THE GLOBAL STEM CELL EVENT

PROGRAM GUIDE

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ISSCR ANNUAL MEETING 2023

14–17 JUNE 2023
BOSTON, USA + VIRTUAL

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Dear Colleagues and Friends:

Whether you flew around the world, dialed-in from your kitchen table, or walked from home, welcome to the 21st ISSCR Annual Meeting. We are glad you are here.

The annual meeting means different things to different people. But, at its heart, this meeting is about transcending borders, backgrounds, and cultures to unite on a single mission: define the future of stem cell science and human health.

For the past two years, the 2023 Program Committee has worked tirelessly in pursuit of a program that represents the breadth of progress in our field – in research, technology, translation, and public service. At the same time, we have been committed to introducing new ways to uncover content and create connections – through one-on-one partnering, member-organized "Science Spotlight" sessions, expanded poster presentations, meet-ups, and late-breaking reports on clinical outcomes. From research in space to standards in research, a week of discovery awaits.

The annual meeting is also a time for celebration as we honor ISSCR's 2023 scientific awardees. Please join us in congratulating ISSCR Outstanding Young Investigator honoree Takanori Takabe, ISSCR Momentum Award recipient Cédric Blanpain, ISSCR Achievement Award winner Tom Rando, and ISSCR Public Service Award recipient Christine Mummery. We commend your contributions to the field!

On behalf of the ISSCR and our community, we thank each of you for making this meeting possible. To the students, attendees, and speakers who are the fabric of this gathering and to co-sponsor BlueRock Therapeutics and all exhibitors and sponsors who generously support the ISSCR mission – we can't do it without you.

The future starts here.

Haifan Lin, PhD
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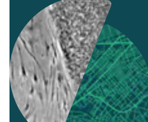
Program Chair



Dear friends and colleagues,

Welcome to the 21st Annual Meeting of the International Society for Stem Cell Research (ISSCR). My colleagues and I from BlueRock Therapeutics are thrilled to welcome you to Boston, which is also the home of BlueRock's global headquarters, and to serve as co-sponsors of this year's meeting which brings together the best and brightest minds in the stem cell field from across the globe.

This is a wonderous time to be working in our field. Today, research in academic labs is providing incredible new insights into the function and power of stem cells and biotech pipelines are rapidly filling with novel therapies that have the potential to change the lives of patients with diseases that have historically had no effective treatment.

We are fortunate to be part of this diverse community of scientific pioneers who share a passion and commitment to harnessing the power of stem cells to transform medical care. This meeting is the world's largest of its kind and is one of many forums provided by ISSCR for scientific exchange, policy dialogue and public education about the impact that stem cell science and medicine is having on the health of mankind.

Over the course of the next five days, you will have the opportunity to explore the latest innovations in our field, catch up with old colleagues, and meet and mingle with the next generation of scientists who are shaping the future. Poster sessions, plenary talks, concurrent sessions, and panel discussions on a wide range of topics abound and I encourage you to dive in, push yourself outside of your comfort zone and engage to expand your horizons. Be sure to also have some fun at some of the networking and social events planned for each day.

Thank you for being here and for being part of this incredible global community of scientists committed to pushing the boundaries of stem cell science in the service of medicine. Enjoy the meeting.

Best,

Stefan Irion
Chief Scientific Officer
BlueRock Therapeutics

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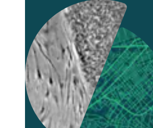

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GENERAL INFORMATION

ONSITE BADGE PICK UP

Pick-up your name badge in the registration area in the North Lobby, Level 1 of the Boston Convention and Exhibition Center (BCEC) during posted hours. Name badges are required for admission to all sessions, social events, and the Exhibit & Poster Hall. Badges may be picked up during the following times:

TUESDAY, 13 JUNE	7:30 am – 6:00 pm
WEDNESDAY, 14 JUNE	7:00 am – 7:45 pm
THURSDAY, 15 JUNE	8:00 am – 6:00 pm
FRIDAY, 16 JUNE	8:00 am – 6:00 pm
SATURDAY, 17 JUNE	8:00 am – 3:30 pm

ONSITE ATTENDEE ORIENTATION (IN PERSON ONLY)

Curious to find out how to best navigate through ISSCR 2023? Join us in the North Lobby, Level 1 at the BCEC for our Attendee Orientation where ISSCR staff will explain the annual meeting's highlights and facilitate attendee introductions before the meeting kicks off. There will be two scheduled Attendee Orientations:

TUESDAY, 13 JUNE	3:00 pm – 3:45 pm
WEDNESDAY, 14 JUNE	7:45 am – 8:30 am

INTERNET ACCESS

Enjoy complimentary Wi-Fi throughout the convention center thanks to our sponsor, STEMCELL Technologies, Inc.

To connect to the Wi-Fi:
Network/SSID: ISSCR2023
Password: stemdiff

ISSCR DIGITAL PLATFORM

All registered attendees have access to the ISSCR 2023 Digital Platform. Click the link and login with your ISSCR credentials. Browse and add sessions to your agenda, live-stream select sessions, interact with other attendees, and more!

NEED VIRTUAL ASSISTANCE?

Click on your profile icon located in the upper right-hand corner of the site to access 'Help Chat' and let us know how we can help. You may also email ISSCRdigital@isscr.org for virtual assistance.

RECORDINGS PROHIBITED

Still photography, screen capture, video and/or audio taping/recording of the sessions, presentations and/or posters at the ISSCR 2023 Annual Meeting is strictly prohibited. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

SMOKING

Smoking or the use of e-cigarettes is prohibited in the Boston Convention and Exhibition Center.

WHERE CAN I FIND...?

SPEAKER READY ROOM

Speakers must review their uploaded presentations at least one hour prior to session start in the Speaker Ready Room (Room 251, Level 2) during the following times:

TUESDAY, 13 JUNE	4:00 pm – 6:00 pm
WEDNESDAY, 14 JUNE	8:00 am – 6:00 pm
THURSDAY, 15 JUNE	7:30 am – 6:00 pm
FRIDAY, 16 JUNE	7:30 am – 6:00 pm
SATURDAY, 17 JUNE	8:00 am – 4:00 pm

Plenary speakers should stop in for a 5-10 minute rehearsal in the Plenary Room (Ballroom, East/West, Level 3) during Technical Rehearsal times:

TUESDAY, 13 JUNE	4:00 pm – 6:00 pm
WEDNESDAY, 14 JUNE	10:00 am – 12:00 pm
THURSDAY, 15 JUNE	1:30 pm – 2:30 pm
FRIDAY, 16 JUNE	1:00 pm – 2:00 pm
SATURDAY, 17 JUNE	7:30 am – 8:30 am

MEDIA OFFICE

Access to the Media Office is available by appointment only. Credentialed members of the media are to contact Kym Kilbourne, ISSCR Director of Media and Strategic Communications, at kkilbourne@isscr.org for instructions on how to access the room.

COAT AND BAGGAGE CHECK

Conveniently located in the North Lobby, Level 1 of the BCEC (next to ISSCR Registration).

TUESDAY, 13 JUNE	7:00 am – 5:30 pm
WEDNESDAY, 14 JUNE	7:00 am – 8:15 pm
THURSDAY, 15 JUNE	7:30 am – 6:30 pm
FRIDAY, 16 JUNE	7:30 am – 6:30 pm
SATURDAY, 17 JUNE	7:30 am – 6:00 pm

NURSING POD

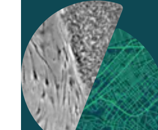
Located on Level 1 of the BCEC (adjacent to Room 159, near the restrooms), there is a Mamava Nursing Pod available throughout the meeting. Mamava Nursing Pods are private and secure, with a roomy bench and a place to plug in your pump.

Download the Mamava App from the AppStore or Google Play to reserve a date and time. Make sure your Bluetooth is on. There is no fee to download the app and to reserve a time slot.

BOSTON INFORMATION DESK

Please stop by the Boston Information desk for information about Boston, places to visit, and dining options in the city. The desk is located in the North Lobby, Level 1 of the BCEC (near ISSCR Registration). The information desk will be staffed during the following times:

WEDNESDAY, 14 JUNE	10:00 am – 5:00 pm
THURSDAY, 15 JUNE	10:00 am – 5:00 pm
FRIDAY, 16 JUNE	10:00 am – 5:00 pm
SATURDAY, 17 JUNE	10:00 am – 5:00 pm



MULTI-FAITH & WELLBEING ROOM

The ISSCR supports attendees who come from all religious and spiritual backgrounds. The Multi-Faith & Wellbeing Room (Room 158, Level 1) is intended to be a quiet shared space away from the bustle of the meeting where attendees have space to pray, reflect, and meditate. The room is open Wednesday, 14 June through Saturday, 17 June from 7:30 AM – 5:00 PM to all. No sign-up in advance is necessary.

LOST AND FOUND

Please bring any found items to the ISSCR Registration desk. If you lost an item, stop by during registration hours for assistance.

PARKING

On-site parking is limited at the BCEC and is available on a first come, first served basis. Click here for directions and more information on parking. In the event that on-site parking has reached capacity, attendees may be directed to an off-site parking lot. All alternate parking lots are also on a first come, first served basis and are within walking distance of the BCEC. Prices will vary. Attendees are responsible for paying their own parking garage fees.

ISSCR MEETING POLICIES

CODE OF CONDUCT

The ISSCR is committed to providing a safe and productive meeting environment that fosters open dialogue and discussion and the exchange of scientific ideas, while promoting respect and equal treatment for all participants, free of harassment and discrimination.

All participants are expected to treat others with respect and consideration, follow venue rules and alert staff or security, if on-site, of any dangerous situations or anyone in distress. Attendees are expected to uphold standards of scientific integrity and professional ethics.

These policies comprise the Code of Conduct for ISSCR Meetings, which will be followed for this event, and apply to all attendees, speakers, exhibitors, staff, contractors, volunteers, and guests at the meeting and related events.

HARASSMENT POLICY

ISSCR prohibits any form of harassment, sexual or otherwise. Incidents should immediately be reported to ISSCR meetings staff at the Registration Desk or isscr@isscr.org.

RECORDING POLICY

By registering for this meeting, you agree to the ISSCR's Recording Policy. It is strictly prohibited to record (photographic, screen capture, audio and/or video), copy, or download scientific results from the sessions, presentations and/or posters at the ISSCR 2023 Annual Meeting. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

EMBARGO POLICY

Abstract content may not be announced, publicized, or distributed before the presentation date and time, in any way, including blogging and tweeting. ISSCR does permit promotion of general topics, speakers, or presentation times. This embargo policy applies to all formats of abstract publication.

ANNUAL MEETING JOB BOARD

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Explore or post open positions in the online Annual Meeting Job Board, sponsored by Stem Cell Network and powered by Scismic, and connect with fellow attendees for academic and industry positions in stem cell science. Included with your annual meeting registration, all attendees are invited to browse open positions OR post open positions in your lab or company. The open positions, like our attendees, are diverse in field, experience, and geography, and represent academia and industry. Take advantage of this week together to make new connections to potentially find your next new PI, employer or lab member. With 4000+ attendees, your next career move or new hire could materialize at ISSCR 2023!

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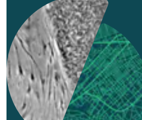
ONE-ON-ONE PARTNERING AT ISSCR 2023

New this year, ISSCR 2023 offers attendees exclusive access to the One-on-One Partnering platform to facilitate new business partnerships on site in Boston during the annual meeting. If you would like to opt-in to partnering at the ISSCR 2023 Annual Meeting before the event, please complete the opt-in questionnaire no later than 13 June. To opt-in during the event on site after 13 June, please visit the One-on-One Partnering Lounge in the Exhibit & Poster Hall.

GAMIFICATION

Earn points for attending sessions and engaging on the ISSCR 2023 Virtual Platform. On the session page for each plenary, track session, poster, special workshop or seminar, exhibitor page, and more, the point value is noted in the top right. You can also see points listed on the agenda page as you build your schedule. Top point earners can win a complimentary registration to the 2024 Annual Meeting or even a Member Spotlight in the ISSCR digital newsletter and on social media. Find out how you rank by visiting the Leaderboard found on the top left of the platform after you click your profile picture.



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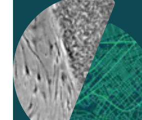

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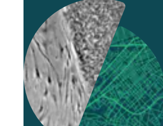

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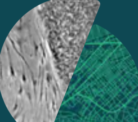

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Milena Bellin
Nissim Benvenisty
Benedikt Berninger
Daniel Besser
Anita Bhattacharyya
Mohammad Firdaus Bin Abdul Aziz
Barak Blum
Vittoria Bocchi
Dario Bonanomi
Dominique Bonnet
Richard Boyd
Catharina Brandsten
Kristen Brennand
Josh Brickman
Justin Brumbaugh
Benoit Bruneau
Francisco Bustos
Massimiliano Caiazzo
Giulia Campostrini
Gonzalo Cancino
Alessio Cantore
Tobias Cantz
Jingli Cao
Shangtao Cao
Rafael Carazo Salas
Charles Chan
Sihem Cheloufi
Jiekai Chen
Christine Cheung
Tom Cheung
Dongho Choi
Konstantinos Chronis
Susana Chuva de Sousa Lopes
Andrew Cohen
April Craft
Kyle Cromer
Brian Davis
Eelco de Koning
Frederic de Sauvage
Raffaella Di Micco
Bruno Di Stefano
Andrea Ditadi
Jeong Tae Do
Claudia Doege
Fiona Doetsch
Peng Du
Nicole Dubois
Connie Eaves
Dieter Egli
Marieke Essers
Jian Feng
Willem Fibbe
Patrick Foong
Valentina Fossati
Misao Fujita
Hironobu Fujiwara
Paul Gadue
Jacques Galipeau
Vivian Gama
Pietro Genovese
Elisa Giacomelli
Casey Gifford
Jeffrey Gimble
Natalia Gomez-Ospina
Anai Gonzalez Cordero
Sofia Grade
Angela Gritti
Mingxia Gu
Shangqin Guo
Shuo Han
David Hay
Mu He
Konrad Hochedlinger
Johan Holmberg
Sara Howden
Ya-Chieh Hsu
Guang Hu
Ping Hu
Meritxell Huch
James Hudson
Samer Hussein
Masaki Ieda
Laertis Ikonomou
Haruhisa Inoue
Shoichi Iriguchi
Tetsuya Ishii
Keisuke Ito
Makiko Iwafuchi
Nisha Iyer
Rajan Jain
Kim Jensen
Sebastian Jessberger
Jianwei JIao
Ying Jin
Leanne Jones
Anna Kajaste-Rudnitski
Keisuke Kaji
Shingo Kajimura
Yonehiro Kanemura
Eyal Karzbrun
Dan Kaufman
Yong Jun Kim
Agnete Kirkeby
Anja Knaupp
Karl Koehler
Bon-Kyoung Koo
Diane Krause
Arnold Kriegstein
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Nico Lachmann
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Fredrik Lanner
Magdalena Laugsch
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Dongwei Li
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Wan-ju Li
Jing Liu
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Jun Lu
Tenneille Ludwig
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Zhen-Ge Luo
Tamra Lysaght
Stephanie Ma
Ilaria Malanchi
Maria Marchetto
Ulrich Martin
Cécile Martinat
Elizabeth Mason
Elvira Mass
Zubin Master
Sandro Matosevic
Kirstin Matthews
Esteban Mazzoni
Philippe Menasche
Viviana Meraviglia
Florian Merkle
Eran Meshorer
Jason Meyer
Sarah Millar
Gabriella Minchiotti
Guo-li Ming
Asuka Morizane
Ryuji Morizane
Samantha Morris
Joanne Mountford
Megan Munsie
Alysson Muotri
Anna Nam
Christian Nefzger
Thao Nguyen
Susie Nilsson
Ryuichi Nishinakamura
Trista North
Michael O'Connor
Il-Hoan Oh
Ryuichi Okamoto
Kenji Osafune
Pierre Osteil
Dmitry Ovchinnikov
Dasaradhi Palakodeti
Nathan Palpant
Athanasia Panopoulos
Mercedes Paredes
In-Hyun Park
Sangbum Park
Francesco Pasqualini
Duanqing Pei
Laura Pellegrini
Guangdun Peng
Martin Pera
Filipe Pereira
Revecca Plew
Alessandro Prigione
Maksymilian Prondzynski
Stephanie Protze
Li Qian
Pengxu Qian
Alireza Rezania
Pamela Robey
Panteleimon Rompolas
Filip Roudnicky
Peter Rugg-Gunn
Sergio Ruiz Macias
Holger Russ
Amy Ryan
Luca Sala
Max Salick
Mootaz Salman
Jayshree Samanta
Tomo Saric
Pierre Savatier
Kazunobu Sawamoto
Edda Schulz
Mark Shackleton
Nika Shakiba
Amar Deep Sharma
Kunyoo Shin
Jian Shu
Robert Signer
José Silva
Kalle Sipila
Matthew Smart
Evan Snyder
Hongjun Song
Abdenour Soufi
Berna Sozen
Lincon Stamp
Jared Sterneckert
Christopher Sturgeon
Jeremy Sugarman
Shigeki Sugii
Ryohichi Sugimura
Yubing Sun
Kazutoshi Takahashi
Minoru Takasato
Yasuhiro Takashima
Takanori Takebe
Nan Tang
Purushothama Rao Tata
Jason Tchieu
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Thorold Theunissen
Junya Toguchida
Mark Tomishima
Kimberly Tremblay
Eirini Trompouki
Tully Underhill
Achia Urbach
Ludovic Vallier
Constanza Vasquez Doorman
Roser Vento-Tormo
Matteo Vietri Rudan
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Daniel Wagner
Hongmei Wang
Sara Wickstrom
Joseph Wu
Jun Wu
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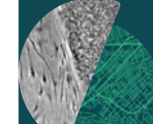
Andrew Xiao
Wei Xie
Yasuhiro Yamada
Nan Yang
Loukia Yiangou
Zheng Yin
Yoshinori Yoshida
Jessica Young
An Zeng
Patricia Zettler
Hui Zheng
Yi Zheng
Hao Zhu
Annika Zink
Thomas Zwaka



JOIN US ON FRIDAY, 16 JUNE FOR THE PRESENTATION OF THE 2023 ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD

ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD

The ISSCR Outstanding Young Investigator Award recognizes exceptional achievements by an ISSCR member and investigator in the early part of their independent career in stem cell research.

The 2023 recipient is Takanori Takebe, MD, PhD, Endowed Chair of Organoid Medicine and Director of Commercial Innovation for Center for Stem Cell and Organoid Medicine (CuSTOM) at Cincinnati Children's Hospital Medical Center, and a Professor at Osaka University, and Tokyo Medical and Dental University.

The Takebe lab develops novel approaches and tools to recapitulate, manipulate, and delineate liver organogenesis, and applies synthetic living tissues to understand the personalized molecular mechanisms that lead to disease. Towards this goal, Dr. Takebe is building translational embryology approaches to engineer hepato-biliary-pancreatic systems using pluripotent stem cells to interrogate previously inaccessible phases of human liver development and disease.

Dr. Takebe will present the ISSCR Outstanding Young Investigator Award Lecture during Plenary IV on Friday, 16 June, 3:15 PM-5:15 PM

JOIN US ON SATURDAY, 17 JUNE FOR THE PRESENTATION OF THE 2023 ISSCR PUBLIC SERVICE, MOMENTUM, AND ACHIEVEMENT AWARDS

ISSCR PUBLIC SERVICE AWARD

The ISSCR Public Service Award is given in recognition of outstanding contributions of public service to the fields of stem cell research and regenerative medicine.

Christine L. Mummery, PhD, Professor of Developmental Biology, Leiden University Medical Center, Netherlands, is being honored with the 2023 ISSCR Public Service Award for her leadership as the founding editor-in-chief of the Society journal, *Stem Cell Reports*, an advocate of the global stem cell field, and a tireless supporter of women scientists.

Dr. Mummery is an internationally recognized scientist in cardiovascular biology, who throughout her 40-year career has contributed revolutionary work that is advancing our understanding of human cardiovascular development and disease. Her research has underpinned her pioneering studies on methods for accurately predicting toxic effects of drugs on the human heart and capturing cardiac disease phenotypes including identifying individual vulnerability. Presently, she leads the disease modeling theme in the Novo Nordisk Foundation project reNEW and the Netherlands NWO-Gravity grant, Organs-on-Chip. She also co-founded the European Organ-on-Chip Society, is a member of the Royal Netherlands Academy of Arts and Sciences, and serves as a member of the board of directors of the ISSCR.

The award will be presented during the Awards and Keynote Session on Saturday, 17 June, 3:15 PM-5:25 PM.

ISSCR MOMENTUM AWARD

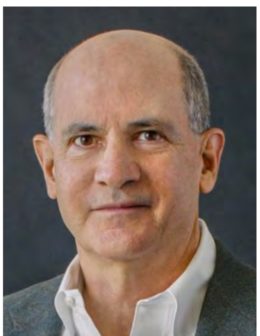
The ISSCR Momentum Award recognizes the exceptional achievements of a mid-career investigator whose innovative research has established a major area of stem cell-related research with a strong trajectory for future success.

The 2023 recipient is Cédric Blanpain, MD, PhD, professor and director of the laboratory of stem cells and cancer at the Université Libre de Bruxelles, Belgium.

Dr. Blanpain's lab uncovered the stem cell dynamic acting during development, homeostasis, and repair of the epidermis and uncovered a novel paradigm of lineage segregation in the mammary gland and prostate. His lab pioneered the identification of the cellular origin of different epithelial cancers and developed novel approaches to unravel tumor heterogeneity and understand the mechanisms regulating the tumor states responsible for tumor growth, metastasis, and resistance to anti-cancer therapy.

Dr. Blanpain will be recognized and deliver the ISSCR Momentum Award Lecture during the Awards and Keynote Session on Saturday, 17 June, 3:15 PM-5:25 PM.

ISSCR ACHIEVEMENT AWARD

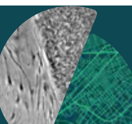


The ISSCR Achievement Award recognizes the transformative body of work of an investigator that has had a major impact on the field of stem cell research or regenerative medicine.

The 2023 recipient is Thomas A. Rando, MD, PhD, director of the Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research and professor of Neurology and of Molecular, Cell, and Developmental Biology, UCLA, USA.

Internationally recognized for his research on muscle stem cell biology, muscle regeneration, and muscular dystrophies, work from Dr. Rando's laboratory has revealed fundamental properties of adult stem cells, identifying key regulators of stem cell quiescence and differentiation. His group has also explored the rejuvenation of aged muscle stem cells by interventions such as parabiosis, diet, and exercise. In addition, his laboratory has advanced preclinical studies of stem cell therapeutics for muscle disorders by combining stem cell biology, bioengineering, and biophysical strategies.

Dr. Rando will be recognized and deliver the ISSCR Achievement Award Lecture during the Awards and Keynote Session on Saturday, 17 June, 3:15 PM-5:25 PM.



CONGRATULATIONS TO THE 2023 TRAVEL AWARD RECIPIENTS

RECIPIENTS OF 2023 ISSCR ZHONGMEI CHEN YONG AWARDS FOR SCIENTIFIC EXCELLENCE

Supported by Chen Yong and the Zhongmei Group, the ISSCR Zhongmei Chen Yong Awards recognize scientific excellence and economic need for Post-docs or students who submit abstracts and present at the ISSCR Annual Meeting.

Samhan Alsolami
Samantha Barton
Gabriele Ciceri
Maud Debaugnies
Ruochen Dong
Jonathan Jung
Rowan Karvas
Taewan Kim
Huanhuan Li
Jeru Manuel
Silvia Marchiano
Mohini Mendiratta
Jitesh Neupane
Miguel Ortiz Salazar
Raquel Perez Fernandez
Serena Scala
Johanna Siehler
Enakshi Sinniah
Dylan Siriwardena
Jan Sokol
Edoardo Sozzi
Qi Sun
Daisylyn Senna Tan
Mengting Wang

RECIPIENTS OF 2023 TRAVEL AWARDS SUPPORTED BY ASTRAZENECA

AstraZeneca

Chloe Baron
Mariana Branco
Barbara Casas
Gabriele Casirati
Kyungtae Lim

RECIPIENTS OF 2023 TRAVEL AWARDS SUPPORTED BY THE BOSTON UNIVERSITY CENTER FOR REGENERATIVE MEDICINE

CReM

Kevin Allan
Clayton Friedman
Caterina Gasperini
Lingli He
Debabrata Jana
Nathan Wang

RECIPIENTS OF TRAVEL AWARDS SUPPORTED BY THE 2023 ISSCR TRAVEL AWARD FUND

ISSCR

Wardiya Afshar-Saber
Thilina Alawathugoda
Troy Anderson
Toshikazu Araoka
Ulgu Arslan
Alexander Atamian
Athina Boumpas
Gabriele Ciceri
Anna Dowbaj
Adhideb Ghosh
Kajal Kamat
Moyra Lawrence
Michal Liput
Yuxin Luo
Sudipta Mahato
Waseem Nasser
ChanWook Park
Qian Hua Phua
Roberta Ragazzini
Daniela Rehakova
Foad Rouhani
Jasper Rubin-Sigler
Kritika Sharma
Minkyoung Shin
Anupong Songsaad
Zhen Sun
Daniel Tavakol
Larissa Traxler
Yi-Hsuan Wu
Isabelle Zaboroski Silva

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Roger A. Barker
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Jennifer Shields
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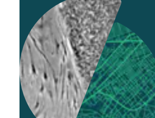
Kenneth S. Zaret
Leonard Zon
Anonymous
Avrobio Inc., Azadeh Golipour
Fate Therapeutics, Bahram Valamehr
Vertex Pharmaceuticals, Gary Meininger
Yale Stem Cell Center, Haifan Lin

2023 ISSCR MERIT ABSTRACT AWARDS

The ISSCR recognizes outstanding abstracts with the ISSCR Merit Abstract Awards. These awards are given to ISSCR Student and Post-doc members who have submitted distinguished abstracts as judged by the ISSCR 2023 abstract reviewers. Award recipients will be recognized in Plenary I on 14 June.

Wardiya Afshar-Saber
Kevin Allan
Thomas Ambrosi
Troy Anderson
Cheen Euong Ang
Toshikazu Araoka
Ulgu Arslan
Alexander Atamian
Chloe Baron
Samantha Barton
Caroline Beyer
Emiliano Bolesani
Gabriele Casirati
Gabriele Ciceri
Joseph Collins
Maud Debaugnies
Ruochen Dong
Anna Dowbaj
Timothy Duerr
Clayton Friedman
Yuya Fujiwara
Caterina Gasperini
Joshua Gershlak
Brandon Gheller
Adhideb Ghosh
Elisa Giacomelli
Lingli He
Yasuaki Iwama
Debabrata Jana
Jonathan Jung
Kajal Kamat
Rowan Karvas
Taewan Kim
Moyra Lawrence
Huanhuan Li
Li Li
Kyungtae Lim
Yuxin Luo
Jeru Manuel
Silvia Marchiano
Waseem Nasser
Jitesh Neupane
Miguel Ortiz Salazar
Raquel Perez Fernandez
ChanWook Park
Qian Hua Phua
Roberta Ragazzini
Foad Rouhani
Jasper Rubin-Sigler
Serena Scala
Kritika Sharma
Minkyoung Shin
Johanna Siehler
Enakshi Sinniah
Dylan Siriwardena
Jan Sokol
Edoardo Sozzi
Zhen Sun
Qi Sun
Daisylyn Senna Tan
Daniel Tavakol
Larissa Traxler
Matheus Victor
Ryan Walsh
Mengting Wang
Bryan Wang
Nathan Wang
Chen Weng
Yi-Hsuan Wu
Atilgan Yilmaz



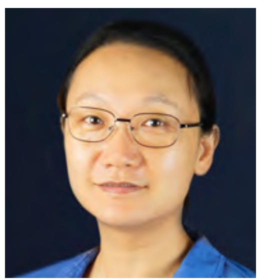
PLENARY I: PRESIDENTIAL SYMPOSIUM

Sponsored by: BlueRock Therapeutics

Wednesday 14 June | 1:00 PM – 3:00 PM

Robert Langer, ScD, Massachusetts Institute of Technology, USA

Robert Langer is one of 12 Institute Professors at the Massachusetts Institute of Technology (MIT) - the highest honor that can be awarded to a faculty member. He has written over 1,500 articles, which have been cited over 377,000 times; his h-index of 306 is the highest of any engineer in history and the 2nd highest of any individual in any field. His patents have been licensed or sublicensed to over 400 companies; he is cofounder of many companies including Moderna. Dr. Langer's over 220 awards include the US National Medals of Science, and Technology & Innovation (one of 3 living individuals to receive both these honors). He holds 40 honorary doctorates and was elected to the National Academies of Medicine, Engineering, Sciences, and Inventors.



Nan Tang, PhD, National Institute of Biological Sciences, China

Nan Tang received her BSc in Medicine from Xian Jiaotong University in China and her PhD in Molecular Pathology from University of California, San Diego. She completed postdoctoral training at University of California, San Francisco, and joined the faculty of the National Institute of Biological Sciences, Beijing.

Employing a convergence of mouse genetics, in vivo live imaging, and mathematical modeling, her lab seeks to ask questions at the interface of cell and developmental biology, specifically, how cellular processes are coordinated by distinct genetic programs and mechanical forces during lung development and adult lung regeneration.

She currently serves on the editorial boards of Developmental Cell, America Journal of Physiology and other journals. She has supported the International Society for Stem Cell Research in various roles.

Magdalena Zernicka-Goetz, PhD, California Institute of Technology, USA

Magdalena Zernicka-Goetz is the Professor of Development and Stem Cells at the University of Cambridge and a Bren Professor of Biology and Biological Engineering at the California Institute of Technology. Spanning the past 25 years, research from the Zernicka-Goetz lab has broken new ground in studies of human embryo development in vitro, cell fate specification in mouse embryos, and the creation of synthetic embryos from multiple stem cell types. The Zernicka-Goetz Lab aims to uncover the fundamental principles and molecular mechanisms that regulate cell identity, pluripotency, and embryo plasticity, size, shape, and self-organization.

ERNEST MCCULLOCH MEMORIAL LECTURE

Wednesday 14 June, Plenary I

Helen M. Blau, PhD, Stanford University School of Medicine, USA

Dr. Helen Blau received her MA and PhD from Harvard University. She is currently the Donald E. and Delia B. Baxter Professor and Director of the Baxter Laboratory for Stem Cell Biology in the Microbiology and Immunology Department and Institute for Stem Cell Biology and Regenerative Medicine, Stanford University. Dr. Blau served on the Ellison Medical Foundation Scientific Advisory Board, Harvard Board of Overseers, is an elected member of the National Academy of Sciences, National Academy of Medicine, American Academy of Arts and Sciences, American Association for the Advancement of Science, National Academy of Inventors and Pontifical Academy of Sciences.

ANNE MCLAREN MEMORIAL LECTURE

Wednesday 14 June, Plenary II

Olivier Pourquié, PhD, Brigham and Women's Hospital and Harvard Medical School, USA

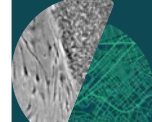
Olivier Pourquié, PhD is the Frank Mallory Burr Professor of Pathology and Professor of Genetics at Brigham and Women's Hospital and Harvard Medical School. The Pourquié laboratory is interested in the development of vertebrate musculo-skeletal axis. Using chicken and mouse embryos as model systems, they combine developmental biology and genomic approaches to study patterning and differentiation of precursors of muscles and vertebrae. They also develop quantitative approaches at the interface with physics to study morphogenesis of the vertebral column. They are also developing protocols to recapitulate these early developmental processes in vitro using mouse and hES or iPS cells. Recently they are focused on development of strategies to produce cells of muscle and vertebral lineages in vitro from pluripotent cells to study human diseases of the musculo-skeletal axis and for cell therapy approaches.

PATIENT ADVOCATE ADDRESS

Saturday 17 June, Plenary VI

Allyson Berent, DVM, Dipl. ACVIM, CSO, Foundation for Angelman Syndrome Therapeutics, USA

Dr. Berent is a veterinary internal medicine specialist/interventionalist who graduated from Cornell University and completed her residency at the University of Pennsylvania, where she served as an Adjunct Assistant Professor before joining the Animal Medical Center in NYC. She is the Director of the Interventional Endoscopy Service, focusing on clinical trials researching medical devices particularly for ureteral and biliary obstructions in animals with naturally occurring diseases. In 2014 Dr. Berent's daughter, Quincy, was diagnosed with Angelman syndrome. In 2015 she joined the Board of Directors for the Foundation for Angelman Syndrome Therapeutics (FAST), becoming the Chief Science Officer. Dr. Berent serves as the co-director of the Angelman Syndrome Biomarker and Outcome Measure Consortium, the co-director for the International Angelman Syndrome Research Council (INSYNC-AS), and is an advisor to numerous pharmaceutical companies working on therapeutic candidates for rare neurodevelopmental disorders. Dr. Berent co-founded GeneTx Biotherapeutics, a company focused on advancing an antisense oligonucleotide therapy for AS, where she was the Chief Operating Officer. GeneTx was acquired in 2022 by Ultragenyx Pharmaceuticals, after launching the Phase1/2 clinical trial, and she now serves as a consultant for Ultragenyx. Dr. Berent is currently the Chief Development Officer at Mahzi Therapeutics advancing gene therapies and disease modifying therapies for rare neurodevelopmental disorders.



JOHN MCNEISH MEMORIAL LECTURE

Saturday 17 June, Plenary VI

Michel Sadelain, MD, PhD, Memorial Sloan-Kettering Cancer Center, USA

Michel Sadelain, MD, PhD, is the Director of the Center for Cell Engineering and the incumbent of the Stephen and Barbara Friedman Chair at Memorial Sloan Kettering Cancer Center. He is a Member of the Immunology Program and the Department of Medicine. Dr. Sadelain's research focuses on human cell engineering and cell therapy to treat cancer and hereditary blood disorders. His laboratory has made several seminal contributions to the field of chimeric antigen receptors (CARs), from their conceptualization and optimization to their clinical translation for cancer immunotherapy. His group was the first to publish dramatic molecular remissions in patients with chemorefractory acute lymphoblastic leukemia following treatment with autologous CD19-targeted T cells.

KEYNOTE ADDRESS

Saturday 17 June, Plenary VII

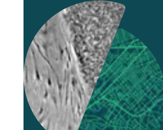
Allan C. Spradling, PhD, Howard Hughes Medical Institute and Carnegie Institution for Science, USA

Allan Spradling heads a research group and is Director Emeritus at the Department of Embryology, Carnegie Institution for Science in Baltimore. He is a Howard Hughes Medical Institute Investigator and Adjunct Professor at Johns Hopkins University. Using both Drosophila and mice, Spradling's group studies how oocytes are constructed and the underlying biology that makes oogenesis possible. Like meiosis itself, they find that many aspects of female gametogenesis are conserved across species. These similarities provide insight into understanding how chromatin organization changes during germ cell development, and how completed oocytes achieve and maintain a quiescent state prior to fertilization. Mature, unfertilized oocytes lack transcription and fully depend on translational regulation of mRNAs that are stored in conserved RNP particles like those located at neural synapses.

Wednesday, 14 June	
7:30 AM – 8:30 AM	Refreshment Break
7:45 AM – 8:30 AM	Attendee Orientation
8:30 AM – 11:00 AM	Focus Sessions
11:45 AM – 12:45 PM	Innovation Showcases
1:00 PM – 3:00 PM	Plenary I: Presidential Symposium
2:30 PM – 7:45 PM	Exhibit & Poster Hall Open
3:00 PM – 3:45 PM	Refreshment Break
3:45 PM – 5:35 PM	Plenary II
6:00 PM – 7:45 PM	Opening Reception
6:00 PM – 7:30 PM	Posters: Cellular Identity, Ethics, Policy & Standards, and Modeling Development & Disease Tracks
6:15 PM – 6:45 PM	Conversation Corner at ISSCR Central
6:15 PM – 7:45 PM	Micro Theaters
6:15 PM – 6:45 PM	Conversation Corner at ISSCR Central
6:30 PM – 7:15 PM	Meet-up Hubs
9:00 PM – 11:00 PM	Early Career Scientists Social Night*

Thursday, 15 June	
8:30 AM – 9:30 AM	Concurrent Track Sessions
9:30 AM – 10:00 AM	Refreshment Break
9:30 AM – 3:30 PM	Exhibit & Poster Hall Open
10:00 AM – 10:30 AM	Conversation Corner at ISSCR Central
10:00 AM – 10:45 AM	Meet-up Hubs
10:00 AM – 11:30 AM	Posters: Tissue Stem Cells & Regeneration Track
10:00 AM – 11:30 AM	Micro Theaters
10:00 AM – 11:40 AM	Concurrent Track Sessions
12:00 PM – 1:00 PM	Innovation Showcases
12:00 PM – 1:15 PM	Equity, Diversity & Inclusion Luncheon*
1:30 PM – 2:00 PM	Conversation Corner at ISSCR Central
1:30 PM – 3:00 PM	Posters: Modeling Development & Disease Track
1:30 PM – 3:10 PM	Concurrent Track Sessions
1:45 PM – 2:30 PM	Meet-up Hubs
1:45 PM – 3:15 PM	Micro Theaters
2:30 PM – 3:00 PM	Conversation Corner at ISSCR Central
3:00 PM – 3:30 PM	Refreshment Break
3:30 PM – 5:10 PM	Plenary III
5:30 PM – 6:00 PM	Innovation Showcases

**Advance registration required*

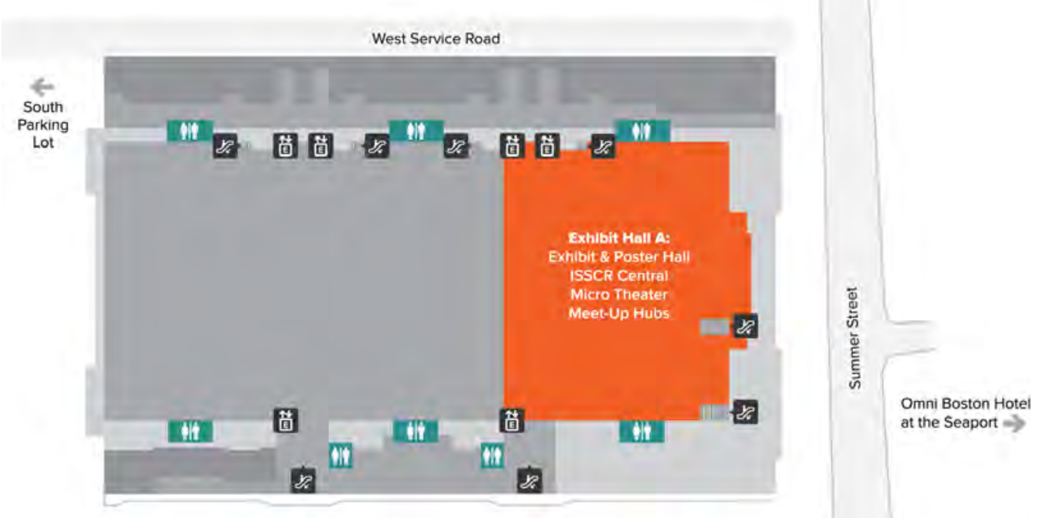


Friday, 16 June	
8:00 AM – 9:00 AM	Science Spotlight Sessions
9:00 AM – 9:30 AM	Refreshment Break
9:00 AM – 3:00 PM	Exhibit & Poster Hall Open
9:30 AM – 10:00 AM	Conversation Corner at ISSCR Central
9:30 AM – 10:15 AM	Meet-up Hubs
9:30 AM – 11:00 AM	Posters: New Technologies Track
9:30 AM – 11:10 AM	Concurrent Track Sessions
9:55 AM – 10:10 AM	Micro Theaters
10:30 AM – 11:00 AM	Conversation Corner at ISSCR Central
11:30 AM – 12:30 PM	Innovation Showcases
11:30 AM – 12:45 PM	Career Panel Luncheon*
1:15 PM – 1:45 PM	Career Exploration at the Micro Theater
1:15 PM – 2:00 PM	Meet-up Hubs
1:15 PM – 2:45 PM	Posters: Clinical Applications Track
1:15 PM – 2:55 PM	Concurrent Track Sessions
2:30 PM – 3:15 PM	Refreshment Break
3:15 PM – 5:15 PM	Plenary IV
5:30 PM – 6:00 PM	Innovation Showcases

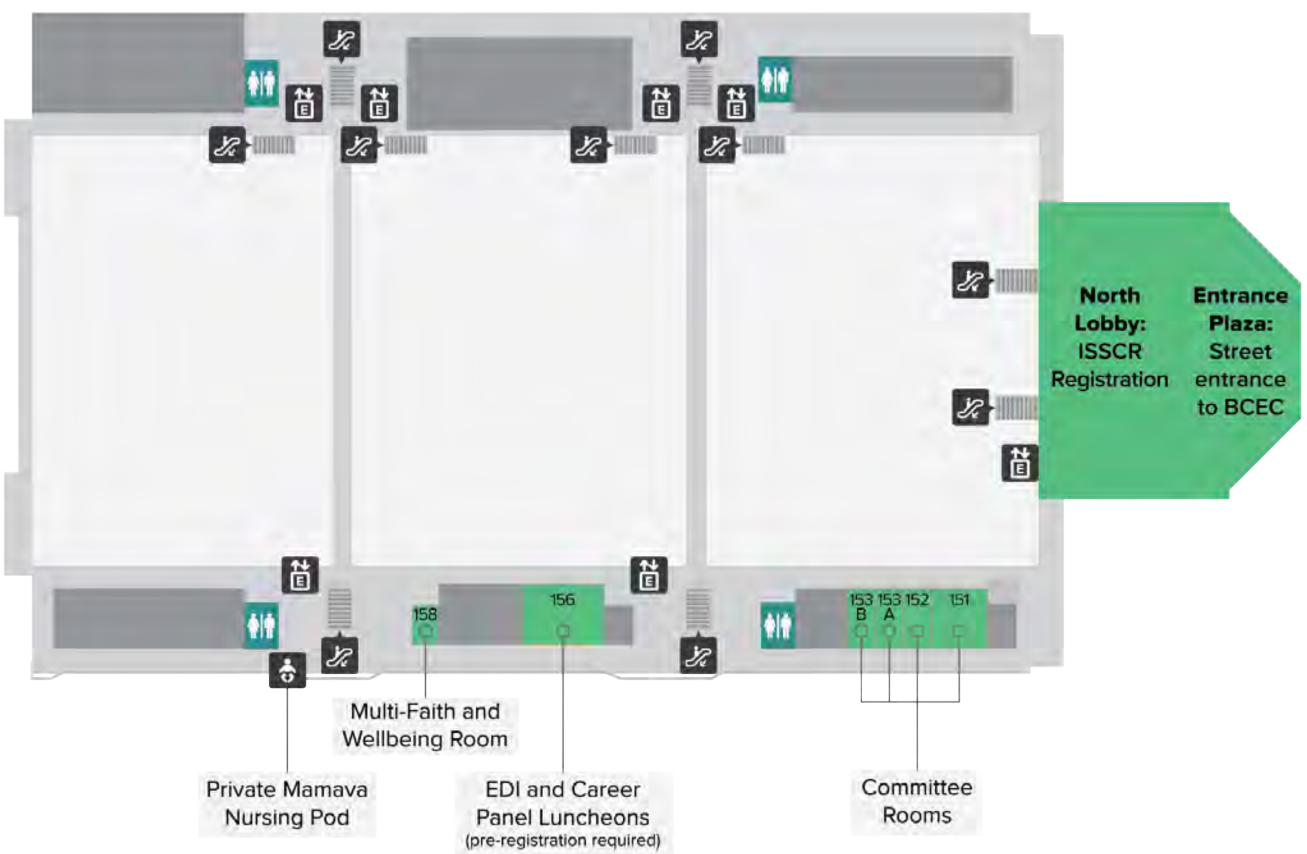
Saturday, 17 June	
7:30 AM – 8:00 AM	Refreshment Break
8:15 AM – 9:55 AM	Concurrent Track Sessions
10:00 AM – 11:25 AM	Plenary V
1:00 PM – 2:40 PM	Plenary VI
2:30 PM – 3:15 PM	Refreshment Break
3:15 PM – 5:25 PM	Plenary VII

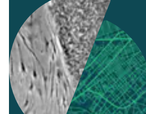
Advance registration required

Exhibit Level

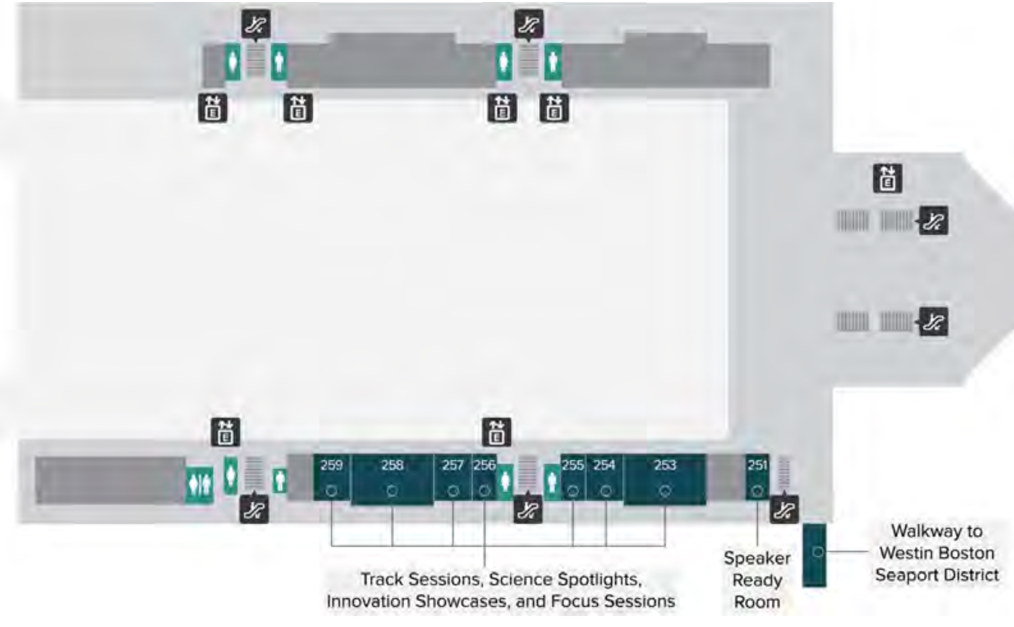


Level 1





Level 2



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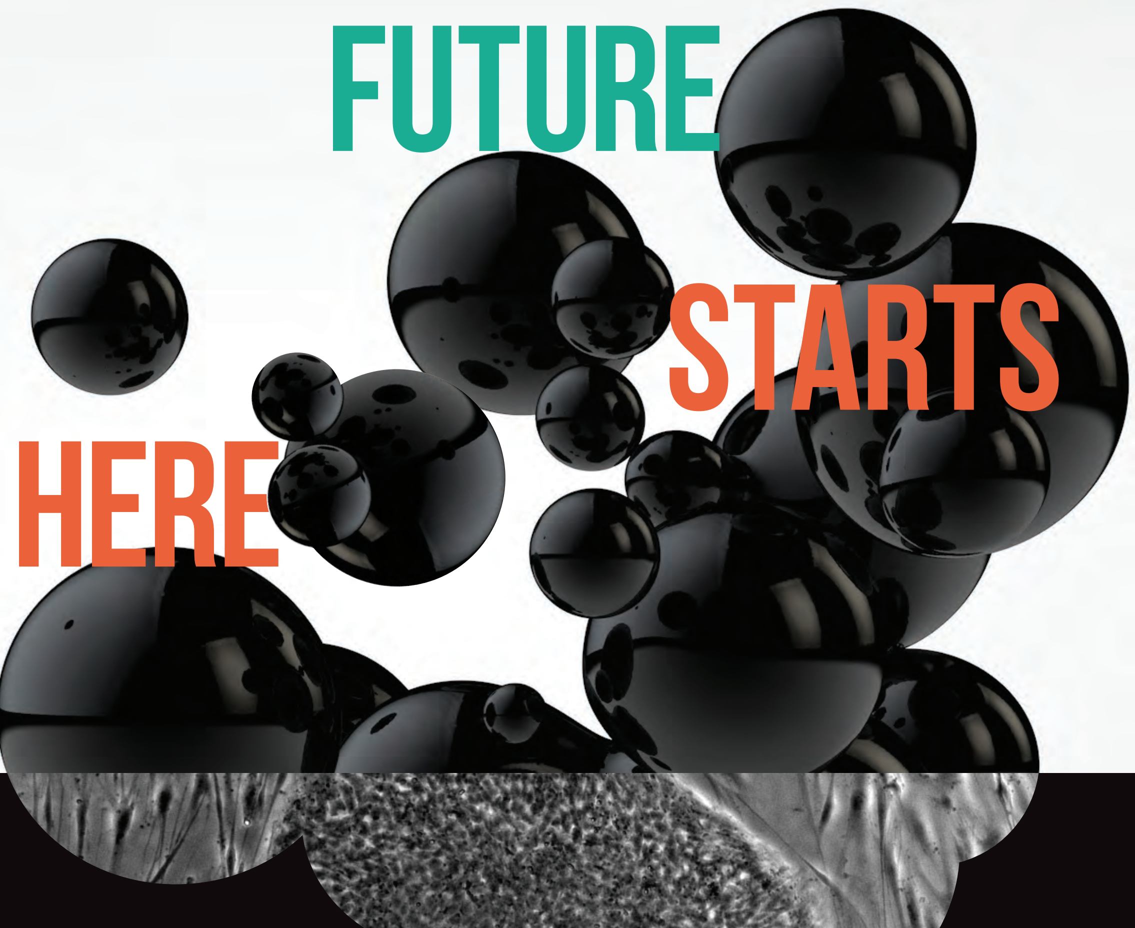

HAMBURG
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THE STEM CELL REPORT

A PODCAST WITH MARTIN PERA

SEASON 2 EPISODE 8
FOCUSING ON THE ABERRATION:
LEARNING FROM PSCS CHROMOSOMAL ABNORMALITIES

IVANA BARBARIC, PHD
UNIVERSITY OF SHEFFIELD, UK

PETE COFFEY, PHD
UNIVERSITY COLLEGE LONDON, UK
AND THE UNIVERSITY OF CALIFORNIA,
SANTA BARBARA, USA

LORIANA VITILLO, PHD
UNIVERSITY COLLEGE LONDON, UK

SEASON 2 EPISODE 9
THE SATELLITE VIEW: MUSCLE STEM CELLS AND MUSCLE DISEASE

AKITSU HOTTA, PHD
KYOTO UNIVERSITY, JAPAN

APRIL PYLE, PHD
UNIVERSITY OF CALIFORNIA,
LOS ANGELES, USA

THOMAS RANDO, MD, PHD
UNIVERSITY OF CALIFORNIA
LOS ANGELES, USA

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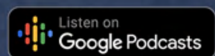


https://thestemcellreport.buzzsprout.com

Photo: NIH

NETWORKING & EVENTS

What better way to nurture your research and career than networking? ISSCR 2023 provides many opportunities for scientists in all stages of their careers to exchange insightful and relevant advice that helps advance their research and lab work. The ISSCR offers various avenues to help scientists foster and strengthen their professional networks.

MEET-UP HUBS

Join your colleagues and engage in conversation and networking at these common interest discussion forums in the Exhibit & Poster Hall.

Industry Scientists Networking

WEDNESDAY, 14 JUNE I 6:30 PM-7:15 PM

The ISSCR Manufacturing, Clinical Translation, and Industry Committee invites interested attendees to join them to network and discuss various industry-related topics, including new developments, collaborations, and potential career paths.

Policy, Ethics, and Regulatory Issues

WEDNESDAY, 14 JUNE I 6:30 PM-7:15 PM

Are you curious about how lawmakers and regulators create the legal frameworks that govern your research? Would you like to know how you can help shape those policies? Join ISSCR's policy team for an open discussion about the legislation, regulation, and ethical issues around the globe impacting stem cell scientists and their work.

Computational Stem Cell Biology

THURSDAY, 15 JUNE I 10:00 AM-10:45 AM

Computational biology is an emerging specialty within the Stem Cell Sciences. Computational stem cell biology invents and applies mathematical approaches to classifying stem cells, predicting cell behaviour, and designing reprogramming strategies or even new cell types. This forum is an opportunity to meet others working in the field, discuss opportunities and challenges for computational stem cell sciences, and highlight resources and standards that we want to work to as a discipline.

(Blue)Rock Your Career!

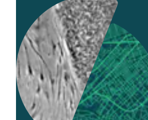
THURSDAY, 15 JUNE I 10:00 AM-10:45 AM

BlueRock Therapeutics is hiring across all functions in the organization. Our Talent Team would love to meet and get to know your interests and experience to either find a fit for a role we have now, or to network to keep you updated on opportunities in the organization in the future.

Meet the Editors of *Stem Cell Reports*

THURSDAY, 15 JUNE I 1:45 PM-2:30 PM

Meet the editors of *Stem Cell Reports* to discuss a potential submission, your paper in review or new trends in scientific publishing, including the growth of open access, the increasing role of preprint servers, and the role of social media in disseminating research findings. There will be an opportunity for you to ask questions about *Stem Cell Reports* and publishing in your society's journal.



German Stem Cell Network

THURSDAY, 15 JUNE I 1:45 PM-2:30 PM

The German Stem Cell Network (GSCN) invites German scientists to join them to get information on what is new in the GSCN and discuss your needs and wishes.

Continue the Conversation: Ethics Track Session

FRIDAY, 16 JUNE I 9:30 AM-10:15 AM

The ISSCR Ethics Committee invites interested attendees to join them for a post-session discussion following the 15 June Ethics Track Session – Ethics and Public Engagement Regarding the 14-Day Rule. Those in attendance will have the opportunity to discuss the important issues tackled during the session as well as additional Ethics Committee work and related topics.

Stem Cell Podcast: Meet the Hosts

FRIDAY, 16 JUNE I 9:30 AM-10:15 AM

Come and meet the hosts of The Stem Cell Podcast, Drs. Daylon James and Arun Sharma, and learn how your research could be featured on a future episode.

Early Career Scientists Networking

FRIDAY, 16 JUNE I 1:15 PM-2:00 PM

Come join the members of the Early Career Scientists Committee as they discuss career transitions. Does change stress you out? Facing career transitions can sometimes feel insurmountable. Students and postdocs who attended the earlier Career Panel luncheon can continue the conversation, and all early career scientists are encouraged to join in and network with your peers. Bring your questions and considerations when searching for and landing a new role. Come join the conversation!

LGBTQ Stem Cell Networking

FRIDAY, 16 JUNE I 1:15 PM-2:00 PM

Join us for an exciting opportunity to connect with like-minded individuals in the stem cell field who identify as LGBTQ or support the LGBTQ community! This meet-up provides a safe and inclusive space to network, discuss current academic and industry trends, and support each other's professional growth. Don't miss out on this chance to build community and advance in your career!

CAREER EXPLORATION AT THE MICRO THEATER

Sponsored by BlueRock Therapeutics

NEW at ISSCR 2023! Career Exploration presentations will take place in the Exhibit Hall Micro Theater and will feature short, 5-10 minute presentations from companies looking to recruit from ISSCR's talented community. The Micro Theater is located at the bottom of the escalators leading into the Exhibit & Poster Hall, Hall A at the Boston Convention and Exhibition Center.

FRIDAY, 16 JUNE | 1:15 PM – 1:25 PM

CAREER EXPLORATION WITH BLUEROCK THERAPEUTICS

1:27 PM – 1:37 PM

CAREER EXPLORATION WITH STEMCELL TECHNOLOGIES

1:39 PM – 1:44 PM

CAREER EXPLORATION WITH SCISMIC

CONVERSATION CORNER AT ISSCR CENTRAL

The Conversation Corners will be held in ISSCR Central on the Exhibit & Poster Hall Floor at the Boston Convention and Exhibition Center.

Networking with Postdocs to Discuss Post-Pandemic Working Environments and University Support

WEDNESDAY, 14 JUNE | 6:15 PM – 6:45 PM

As the co-vice president of CUPS (Columbia University Post-Doc Society), this conversation corner invites Post Docs from other universities to share thoughts and opinions on post-pandemic working environments and support from universities.

Arab Early Career Scientists

WEDNESDAY, 14 JUNE | 6:45 PM – 7:15 PM

This conversation corner is a networking opportunity for Arab early career scientists. This will provide a space for knowledge exchange, as well as potential future collaborations and opportunities in the region.

CIRM Bridges Students, Mentors, Directors and Alumni

THURSDAY, 15 JUNE | 10:00 AM – 10:30 AM

Are you involved in the CIRM Bridges Program? Were you in the past? Come meet others.

What to Look for When Searching for a Postdoctoral Position

THURSDAY, 15 JUNE | 1:30 PM – 2:00 PM

A gathering of prospective postdocs in academia who would like to discuss what kind of factors or criteria should be considered while looking for a postdoctoral position. Postdoc labs and mentors vary, and prospective postdocs should learn how to evaluate whether a specific opportunity fits them. We are hoping to discuss and learn from each other's perceptions and experiences so that everyone can strive towards making a good decision when their time comes.

How Shape Infers Function in Diverse Stem Cell Niches

THURSDAY, 15 JUNE | 2:30 PM – 3:00 PM

Organs evolve and acquire various shapes with specialized functions. How do diverse stem cell niches organize and maintain their unique tissue architecture to regulate stem cell dynamics? This conversation corner will initiate discussions and bring together scientists with shared interests in linking tissue shape and stem cell homeostasis.

Emerging Femtech in Regenerative Medicine

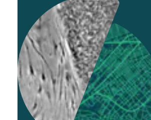
FRIDAY, 16 JUNE | 9:30 AM – 10:00 AM

Welcome to this dedicated corner for individuals who are passionate about women's health, encompassing topics such as fertility, menopause, and more. We invite trainees, researchers, entrepreneurs, health workers, and anyone who shares the common goal of contributing to a better future by advocating for increased resources and research in this field. Together, let us create a community that fosters collaboration and innovation, working towards a brighter and healthier future for all women.

Human iPSC Enthusiasts

FRIDAY, 16 JUNE | 10:30 AM – 11:00 AM

Drop by and enthuse with others about the disease and developmental modeling, regenerative medicine, and cell therapeutic applications of human iPSCs.



EARLY CAREER SCIENTISTS SOCIAL NIGHT

WEDNESDAY, 14 JUNE 9:00 PM-11:00 PM

Start your ISSCR 2023 experience by meeting, mingling, dancing and socializing with fellow young investigators from around the world during the first night of the meeting. Light snacks will be provided.

Venue: Royale Night Club, 279 Tremont Street, Boston, MA 02116
This is a ticketed event that requires pre-registration. ISSCR annual meeting badge and government-issued ID with photo (driver's license, passport, etc.) **is required for entry**. Must be age 21 or older to attend. *Transportation* ***will not*** *be provided by ISSCR to the venue.* Attendees are encouraged to use public transportation, taxi, and/or ride-share service.

This event is for students and postdoctoral fellows.

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EQUITY, DIVERSITY, AND INCLUSION LUNCHEON: CREATING INCLUSIVE TEAM ENVIRONMENTS

THURSDAY, 15 JUNE I 12:00 PM - 1:15 PM

Join us for a discussion focused on creating inclusive team environments where all scientists are able to thrive. Discussion topics include mentorship, allyship, advice on navigating toxic environments, and helpful institutional/lab policies. Organized by the ISSCR and The New York Stem Cell Research Foundation (NYSCF). Advance registration required.

ROOM 156, Level 1

Moderator:

Raeka Aiyer, *The New York Stem Cell Foundation (NYSCF) Research Institute, USA*

Panelists:

Evan L. Graham, *Biosero, a BICO Company, USA*

Valentina Greco, *Yale Medical School, USA*

Shruti Naik, *NYU School of Medicine, USA*

Takanori Takebe, *Cincinnati Children's Hospital Medical Center, USA/Osaka University and Tokyo Medical and Dental University, Japan*

CAREER PANEL LUNCHEON

Transitioning to a New Position: Tools and Take-Aways
FRIDAY, 16 JUNE I 11:30 AM - 12:45 PM

Does change stress you out? While change is an essential part of moving forward in your career, facing career transitions can sometimes feel insurmountable. In this year's Career Panel we will hear about some of the most useful tools our panelists have used to move through the challenges and make the most of the opportunities associated with career transitions. Together, we will also boil down some key take-aways that helped make those transitions successful, and a bit less daunting. This session is designed for post-doctoral fellows and students. Advance registration required.

ROOM 156, Level 1

MODERATORS:
Alessandro Bertero
Università di Torino, Italy

Elisa Giacomelli
Memorial Sloan Kettering Cancer Center, USA

PANELISTS:
Megan Mayerle
Baxter Laboratory for Stem Cell Biology, USA

Nathan Palpant
University of Queensland, Australia

Athanasia Panopoulos
Cedars-Sinai Medical Center, USA

Filipe Pereira
Lund University, Sweden

FOCUS SESSIONS

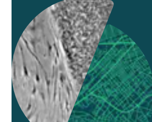
WEDNESDAY, 14 JUNE | 8:30 AM - 11:00 AM

FUNCTIONAL INVESTIGATION AND CLINICAL DEVELOPMENT OF IPSC-BASED THERAPIES
Organized by: Allele Biotech

The field of iPSC-derived cell therapeutics has now moved near or at clinical stages in various disease areas. Building on our previous focus session presentations on resources and industry's GMP capacities, this year's Allele Focus Session will bring in executives from foundations, government agencies, and companies to present their front-line functional results from clinical trials and pre-clinical in vivo studies. In addition, the speakers will share lessons learned from industrial manufacturing, delivery strategy designing, and regulatory communications with the FDA, all of which should prove valuable to the audience who work in the field. More specifically, the focus session attendees will hear first-hand experience from iPSC-based cell therapy developers as to how they chose methodological approaches for such processes as iPSC generation, iPSC differentiation, GMP-compliant manufacturing, pre-clinical and clinical study designing, and clinical-trial management. The current session will also feature inside tales on how to apply recent mRNA advancements into iPSC-based therapeutic development. Following the presentations, a panel discussion featuring a Q&A session will provide an excellent opportunity for the audience to discuss and clarify the best ways for individual iPSC programs you may be interested in and this industry sector as a whole to progress into the next phase.

ROOM 259, Level 2

8:30 AM - 8:35 AM **Jiwu Wang,** *Allele Biotech, USA*
WELCOME AND OVERVIEW



8:35 AM - 8:55 AM	**Kapil Bharti,** *NIH/NEI, USA* CLINICAL MANUFACTURING OF INDUCED PLURIPOTENT STEM CELLS DERIVED RETINAL PIGMENT EPITHELIUM PATCH FOR AUTOLOGOUS CELL BASED THERAPY FOR AGE RELATED MACULAR DEGENERATION
8:55 AM - 9:15 AM	**Tim Klossner,** *HeartWorks, USA* CLINICAL APPLICATION OF AUTOLOGOUS IPSC-DERIVED CARDIAC CELLS IN PATIENTS IN UNIVENTRICULAR CONGENITAL HEART DISEASE
9:15 AM - 9:35 AM	**Andrés Bratt-Leal,** *Aspen Neuroscience, USA* ENABLING AUTOLOGOUS IPSC-DERIVED CELL THERAPIES WITH PREDICTIVE GENOMICS
9:35 AM - 9:55 AM	**Sunny Sun,** *Vita Therapeutics, USA* DEVELOPMENT OF AN IPSC-DERIVED CELL THERAPY FOR LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2A/R1
9:55 AM - 10:15 AM	**Jiwu Wang,** *Allele Biotech, USA* IPSC-DERIVED BETA CELL SPHEROIDS DEVELOPED USING MRNA FOR TREATING DIABETES
10:15 AM - 10:35 AM	**Chunping Xu,** *Trilink Biotechnologies/Maravai LifeSciences, USA* CHEMICAL MODIFICATION OF MRNA FOR BETTER STABILITY AND PROTEIN TRANSLATION
10:35 AM - 11:00 AM	**All Speakers** PANEL DISCUSSION AND Q&A

THE JOURNEY AND OPPORTUNITIES OF DEVELOPING A TRANSFORMATIVE CELL THERAPY

Organized by: BlueRock Therapeutics

Induced pluripotent stem cell-based cell therapies have entered an era of clinical proof-of-concept and safety studies. This advancement illustrates the tremendous potential and opportunities of cell therapies. In recent years, the field made major advances related to defining key attributes of cell therapeutics, and developing at scale processes for cell differentiation and maturation. Commercial practices are constantly evolving to achieve quality control over physical and molecular stability of cells supported by technological advances such as single cell multiomics. In this focus session, we invited distinguished experts from academia, industry, and investor community to share their unique insights into key aspects that propel cell therapies to the clinic.Our speakers will share their experience from matching a cell type to a disease, to defining attributes and efficacy of cell-based products, to manufacturing with consistent, measurable qualities at clinical scale. We would like to shed light on lessons learned from non-stem cell based cell therapies in order to facilitate development in the stem cell field and provide future prospective for what is to come. Our goal is to inspire research and development that may strengthen and refine the next generation of cell therapies and to realize their transformative potential.

ROOM 253, Level 2

8:30 AM - 8:45 AM	**Juliana Hsu**, *BlueRock Therapeutics, USA* **Mathias Pawlak**, *BlueRock Therapeutics, USA* WELCOME AND OVERVIEW
8:40 AM - 9:10 AM	**Catherine Priest**, *Neurona Therapeutics, USA* NRTX-1001: CLINICAL DEVELOPMENT OF AN ALLOGENEIC INTERNEURON CELL THERAPY
9:10 AM - 9:40 AM	**Ralph Brandenberger**, *Nkarta Therapeutics, USA* NATURAL KILLER CELLS – ENGINEERED TO BEAT CANCER
9:40 AM - 9:50 AM	**BREAK**
9:50 AM - 10:20 AM	**Marius Wernig**, *Stanford University, USA* NEXT GENERATION CELL THERAPIES FOR THE BRAIN
10:20 AM - 11:00 AM	**Hosts, speakers, Amir Zamani**, *Bain Capital, USA, and* **Adriana Tajonar**, *Goldman Sachs, USA* PANEL DISCUSSION

ADVANCING DRUG DISCOVERY THROUGH PRECISION MEDICINE

Organized by: Evotec

Development of effective therapeutics for neurological disorders has historically been challenging due to limited understanding of complex disease pathology and lack of accurate model systems in which to investigate disease etiology. Despite major activities over the past decades, one of the major challenges in CNS drug development remains translation. Recent technological advances in the field of multi-omics profiling, patient centric molecular diagnostics, in vitro patient stratification and iPSC disease modelling have now made it possible to identify the variation and mechanisms underlying a patient's disease and hold great promise for the development of more efficacious and safer drugs. With this focus session we would like to give both academic and industry partners the opportunity to share their perspective on this rapidly evolving field of precision medicine that could provide a better understanding of complex diseases on a molecular level and shift the one-fits-all drug discovery paradigm towards precision drugs.

ROOM 254, Level 2

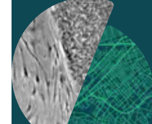
8:30 AM - 8:45 AM	**Bastian Zimmer**, *Evotec, Germany and* **Sandra Lubitz**, *Evotec, Germany* WELCOME REMARKS AND OVERVIEW: ADVANCING DRUG DISCOVERY THROUGH PRECISION MEDICINE
8:45 AM - 9:10 AM	**Tim Ahfeldt,** *Recursion, USA* FROM BIG DATA TO PRECISION MEDICINE DRUG DISCOVERY
9:10 AM - 9:35 AM	**Ian Weidling**, *AbbVie, USA* DEVELOPMENT OF FIRST-IN-CLASS HIPSC-NEURON TAU SEEDING MODELS OF ENDOGENOUS TAU AGGREGATION
9:35 AM - 10:00 AM	**Evangelos Kiskinis**, *Northwestern University, USA* USING PERSONALIZED IPSC MODELS TO REFINE DISEASE MECHANISMS AND THERAPEUTIC APPROACHES IN ALS
10:00 AM - 10:25 AM	**Lorenz Studer**, *MSKCC, USA* TITLE TO BE CONFIRMED
10:25 AM - 10:50 AM	**Abigail Mariga**, *Bristol Myers Squibb, USA* UNLOCKING THE FULL POTENTIAL OF PRECISION MEDICINE APPROACHES TO PATIENT CARE
10:50 AM - 11:00 AM	**Q&A AND SESSION WRAP UP**

FROM THE BENCH TO THE BEDSIDE: MARYLAND'S ACCELERATING CURES INITIATIVE AND BEYOND

Organized by: Maryland Stem Cell Research Fund

In this Focus Session, leaders from the stem cell and regenerative community in Maryland will present their cutting-edge research and latest breakthroughs in the field. The session will highlight how to successfully transition innovative ideas from the benchside to viable cell therapy products at the bedside through MSCRF's accelerating Cures initiative and its seven funding programs. Cell therapy products, including stem cells and CAR-T cells, intended to treat a variety of disease indications will be discussed. Hear from experts on developing, manufacturing, and delivering cell therapies to patients with unmet medical needs.

The Maryland Stem Cell Research Fund (MSCRF) is focused on funding and fostering cutting-edge research and innovation in the field of regenerative medicine in Maryland. Our Accelerating Cures initiative comprises funding programs that help commercialize human stem cell-based technologies as well as mechanisms to build and grow stem cell companies in Maryland. MSCRF has invested over $170 million in accelerating stem cell-based research, commercialization, treatment and cures, in addition to building a collaborative stem cell community in our region. Learn more about our mission and our funding opportunities for faculty, postdoctoral fellows, and cell therapy companies at www.MSCRF.org



ROOM 256, Level 2
****This Focus Session will be available in-person and on the virtual meeting platform.***

8:30 AM - 8:40 AM **Ben Antebi**, *MSCRF, USA*
WELCOME AND OVERVIEW OF MSCRF'S FUNDING PROGRAMS

8:40 AM - 9:03 AM **David Hackam**, *Johns Hopkins University, USA*
DISCOVERY PROGRAM: STEM CELL THERAPEUTIC APPROACHES IN NEONATAL NECROTIZING ENTEROCOLITIS

9:03 AM - 9:26 AM **Jill Fahrner**, *Johns Hopkins University, USA*
LAUNCH PROGRAM: DEVELOPMENT OF PATIENT IPSC-DERIVED ORGANOID MODELS FOR BECK-FAHRNER SYNDROME: PROBING DNA METHYLATION AND ADVANCING TREATMENT

9:26 AM - 9:49 AM **Elias Zambidis**, *Johns Hopkins University School of Medicine, USA*
VALIDATION PROGRAM: COMMERCIAL VALIDATION OF CLINICAL-GRADE PROGENITORS FROM TIRN HUMAN INDUCED PLURIPOTENT STEM CELLS

9:49 AM - 10:12 AM **Bhanu Telugu**, *RenOVAte Biosciences, USA*
COMMERCIALIZATION PROGRAM: PERSONALIZED HUMAN ORGANS FOR TRANSPLANTATION: MEETING A GROWING UNMET NEED

10:12 AM - 10:35 AM **Djordje Atanackovic**, *University of Maryland Greenebaum Comprehensive Cancer Center, USA*
CLINICAL PROGRAM: A PHASE IA STUDY OF LTG2950 TRI-SPECIFIC CD19.20.22 CHIMERIC ANTIGEN RECEPTOR (CAR) T-CELLS FOR PATIENTS WITH RELAPSED/ REFRACTORY B-CELL LYMPHOMAS

10:35 AM - 11:00 AM **Luis Alvarez**, *Theradptive, USA*
MANUFACTURING PROGRAM: MANUFACTURING OF BIO-INSTRUCTIVE IMPLANTS TO ENHANCE STEM CELL THERAPIES

CLINICAL TRANSLATION OF CELL THERAPIES: CHALLENGES OVERCOME, SUCCESSES, AND THE ROAD AHEAD

Organized by: Novo Nordisk A/S

Stem cell-derived cell therapies are moving into the next era of development with several potential product candidates in clinical trials. The field is facing several challenges and opportunities, such as defining the final cell product, mastering product formulation and medical device development. Efforts are also underway to gain a deeper understanding of the processes governing efficient integration of the cell product in the recipient. This session aims at shedding light on some of the challenges and opportunities, how they have been addressed by experts in the field, and how these approaches might pave the way for the next generation of cell therapies. Our examples include the development of investigational stem cell-derived therapies for individuals living with chronic heart failure and Parkinson's disease as well as the importance of including the patient's perspective when developing cell therapies.

ROOM 257, Level 2
****This Focus Session will be available in-person and on the virtual meeting platform.***

8:30 AM - 8:35 AM **Charis Segeritz-Walko**, *Novo Nordisk A/S, Denmark*
WELCOME AND INTRODUCTION

8:35 AM - 9:05 AM **Keiichi Fukuda**, *Heartseed Inc., Japan*
CLINICAL TRIAL OF HIPSC-DERIVED PURIFIED VENTRICULAR CARDIOMYOCYTE TRANSPLANTATION FOR SEVERE CONGESTIVE HEART FAILURE

9:25 AM - 9:30 AM **Henning Kempf**, *Novo Nordisk A/S, Denmark*
THE BUILDING BLOCKS FOR ADVANCING HEART THERAPIES UTILIZING HPSC-DERIVED CARDIOMYOCYTES

9:30 AM - 10:00 AM **Megan Munsie**, *University of Melbourne, Australia*
WHY IT IS IMPORTANT TO THINK ABOUT HOW AND WHEN WE ENGAGE WITH PEOPLE CURIOUS ABOUT STEM CELL TREATMENTS

10:00 AM - 10:30 AM **Malin Parmar**, *Lund University, Sweden*
DEVELOPING A STEM CELL THERAPY FOR PARKINSON'S DISEASE

10:30 AM - 10:55 AM **Fabian Vinzenz Roske**, *Novo Nordisk A/S, Denmark*
HOW DOES NOVO NORDISK CELL THERAPY CMC CONTRIBUTE TO MOVE PROMISING RESEARCH INTO CLINICAL TRIALS?

10:55 AM - 11:00 AM **Brendan Christopher Jones**, *Novo Nordisk A/S, Denmark*
SUMMARY AND CLOSE

EXPANDING BOUNDARIES OF STEM CELL TECHNOLOGIES AND APPLICATIONS

Organized by: ISSCR Industry Subcommittee

New discoveries in stem cell research have rapidly expanded its boundaries of influence, leading to increased interfaces with other fields of science and technology. Unanticipated intersections of scientific disciplines and expertise are now yielding new and exciting applications, ranging from optimizing cell therapy manufacturing and launching stem cells into space, to solving global issues of food production and species conservation. This session will explore how unexpected collaborations across cell and developmental biology, robotic engineering, agricultural farming, bioinformatics, conservation biology, and astronautics have driven the emergence of exciting new avenues for stem cell research and the development of potentially disruptive new technologies and products.

ROOM 255, Level 2

8:30 AM - 9:35 AM **Part 1**
Chair: Felicia Pagliuca, *Vertex Pharamceuticals, USA*

8:30 AM - 8:35 AM **Felicia Pagliuca,** *Vertex Pharmaceuticals, USA*
WELCOME REMARKS AND INTRODUCTION

8:35 AM - 8:55 AM **Masayo Takahashi,** *Vision Care, Japan*
SUSTAINABLE REGENERATIVE MEDICINE AND ROBOTICS

8:55 AM - 9:15 AM **Stefanie Countryman,** *BioServe Space Technologies, USA*
SUPPORTING STEM CELL RESEARCH IN SPACE: TRANSLATING GROUND-BASED EXPERIMENTS TO SPACE-BASED EXPERIMENTS

9:15 AM - 9:35 AM **Tatsuya Shimizu,** *Tokyo Women's Medical University, Japan*
RECENT ADVANCES IN CULTURED MEAT PRODUCTION

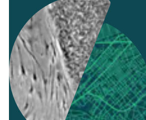
9:35 AM - 9:45 AM **INTERMISSION BREAK**

9:45 AM - 11:00 AM **Part II**
Chair: Nilay Thakar, *ARCH Venture Partners, USA*

9:45 AM - 10:05 AM **Evan Appleton,** *Colossal Bioscience, USA*
STEM CELLS AND SPECIES DE-EXTINCTION

10:05 AM - 10:25 AM **Christopher Austin,** *Vesalius Therapeutics, USA*
CURING COMMON DISEASES

10:25 AM - 11:00 AM **All Speakers**
DISCUSSION PANEL
Moderator: Lee Rubin, *Harvard University, USA*



TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY

Organized by: Stem Cell COREdinates
Supported by: STEMCELL Technologies and Thermo Fisher Scientific

Stem Cell COREdinates (www.COREdinates.org) is an international consortium of human pluripotent stem cell-focused core facilities that share expertise with protocols, reagents, and technological advancements to establish "best practices" in the maintenance, derivation, differentiation and genetic manipulation of human pluripotent stem cells. Each of our member cores plays an important role in the research and educational missions of their respective institutions. The first part of our Focus Session will have selected presentations from Stem Cell COREdinate members and our sponsors. These presentations will cover a number of different areas of expertise including stem cell culture, gene editing and disease modeling. The second part of the session will feature invited speakers with a focus on advances in advancement in making more mature stem-cell derived lineages and tissue/organ engineering.

ROOM 258, Level 2
****This Focus Session will be available in-person and on the virtual meeting platform.***

8:30 AM - 8:35 AM **Wenli Yang,** *University of Pennsylvania, USA*
WELCOME AND OVERVIEW

8:35 AM - 8:50 AM **Xiaoxia Cui,** *Washington University in St. Louis, USA*
SENDAI CLEARANCE IN CLONES REPROGRAMMED WITH CYTOTUNE-IPS 2.0

8:50 AM - 9:05 AM **Azadeh Jadali,** *Sampled Smart Labs, USA*
IDENTIFICATION OF GENOMIC AND TRANSCRIPTOMIC CHANGES THAT OCCUR DURING IPSC REPROGRAMMING AND GENE EDITING

9:05 AM - 9:20 AM **Erik Willems,** *Thermo Fisher Scientific, USA*
THE IMPORTANCE OF PSC CHARACTERIZATION IN KEY PSC-BASED WORKFLOWS

9:20 AM - 9:35 AM **Benjamin Gregor,** *Allen Institute for Cell Science, USA*
AUTOMATED TISSUE CULTURE WORKFLOW FOR PLATING, MAINTENANCE, AND DIFFERENTIATION OF HIPSCS ON GLASS BOTTOM PLATES FOR 3D LIVE CELL MICROSCOPY

9:35 AM - 9:50 AM **Ana Marin Navarro,** *STEMCELL Technologies, USA*
DEVELOPMENT OF IPSCS, DIFFERENTIATED CELLS, AND ORGANOIDS UNDER STRINGENT QUALITY STANDARDS

9:50 AM - 10:05 AM **Taylor Bertucci,** *Neural Stem Cell Institute, USA*
IMPROVED PROTOCOL AND QC TO GENERATE REPRODUCIBLE CEREBRAL ORGANOIDS

10:05 AM - 10:15 AM **BREAK**

10:15 AM - 10:20 AM **Tenneille Ludwig,** *WiCell, USA*
INTRODUCTION OF TOPIC AND SPEAKERS

10:20 AM - 10:40 AM **Nicole Dubois,** *Icahn School of Medicine at Mount Sinai, USA*
APPROACHES TO MATURE HPSC-DERIVED CARDIOMYOCYTES

10:40 AM - 11:00 AM **Kentaro Iwasawa,** *Cincinnati Children's Hospital Medical Center, USA*
MODELING HUMAN STEATOHEPATITIS USING PLURIPOTENT STEM CELL-DERIVED ORGANOIDS TBD

FRIDAY 16 JUNE | 8:00 AM - 9:00 AM

CELL TRANSPLANTATION FOR SPINAL CORD REPAIR

Organized by: Lyandysha Zholudeva, *Gladstone Institutes, USA*
Hideyuki Okano, *Keio University, Japan*
Clive Svendsen, *Cedars Sinai, USA*

Advances in cellular engineering have brought new promise for a myriad of incurable diseases, including spinal cord injury (SCI). This session highlights cutting edge work from research teams focused on applying cell therapy for repair of the injured spinal cord. Topics covered will range from use of pre-clinical SCI animal models to developing clinical studies, that explore donor cell integration and functional connectivity, evaluated using a range of outcome measures. Speakers are represented by senior investigators and leaders in the field of SCI repair, and early career investigators (postdocs and graduate students).

Room 258, Level 2

8:00 AM - 8:03 AM **Lyandysha Zholudeva,** *Gladstone Institutes, USA*
WELCOME

8:03 AM - 8:23 AM **Mark Tuszynski,** *University of California San Diego, USA*
A TRANSLATIONAL PROGRAM OF NEURAL STEM THERAPY FOR SPINAL CORD INJURY

8:23 AM - 8:35 AM **Cameron Hunt,** *The Florey Institute of Neuroscience and Mental Health, Australia*
UTILIZING HIPSCS TO ESTABLISH HIGHLY EFFICIENT DIRECTED DIFFERENTIATION PROTOCOLS AND DEVELOP CHIMERIC MODELS OF SPINAL CORD DEGENERATION

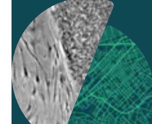
8:35 AM - 8:47 AM **Tara Fortino,** *Drexel University, USA*
ENGINEERED SPINAL INTERNEURON TRANSPLANTS FOR REPAIR OF THE INJURED CERVICAL SPINAL CORD

8:47 AM - 8:59 AM **Lyandysha Zholudeva,** *Gladstone Institutes, USA*
TRANSPLANTED HUMAN SPINAL INTERNEURONS FUNCTIONALLY INTEGRATE WITH THE INJURED SPINAL CORD

INNER EAR ORGANOIDS FOR HEARING AND BALANCE

Organized by: Bryony Nayagam, *The University of Melbourne, Australia*
Alain Dabdoub, *The University of Toronto, Canada*
Jackie Ogier, *The University of Melbourne, Australia*

Human hearing and balance are two of the most poorly understood senses at a molecular level. This is largely the result of inaccessibility to the adult inner ear via biopsy, resulting in a lack of human tissue available for studying the specialised cell types that reside within it. A renewable source of human inner ear cells and tissues could provide an in vitro platform to better understand the molecular and physiological attributes of these sensory cells, and would be of interest to commercial enterprise as a way of screening new drugs and molecules to protect these vulnerable cells. This spotlight will examine the current methods for deriving inner ear sensory cells from organoids and how closely these cells mirror their human tissues counterparts. Our speakers include international leaders and talented ECRs presenting data on both methods for deriving inner ear organoids from pluripotent stem cells and single cell sequencing of both organoid-derived and human-derived inner ear cells. The session will showcase how close the field is to making an “ear on a chip” for both discovery science and for the development of therapeutics for hearing and/or balance restoration.



ROOM 254, Level 2

8:00 AM - 8:05 AM **Bryony Nayagam,** *University of Melbourne, Australia*
WELCOME AND INTRO TO THE INNER EAR

8:05 AM - 8:18 AM **Yoshitomo Ueda,** *Indiana University, USA*
INNER EAR ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS

8:18 AM - 8:31 AM **Sho Kurihara,** *Jikei University, Japan*
OTIC ORGANOIDS CONTAINING SPIRAL GANGLION-LIKE NEURONS

8:31 AM - 8:44 AM **Karl Koehler,** *Boston Children's Hospital and Harvard Medical School, USA*
USING INNER EAR ORGANOIDS TO STUDY CONGENITAL DISEASE

8:44 AM - 8:57 AM **Emilia Luca,** *University of Toronto, Sunnybrook Research Institute, Canada*
THE HUMAN INNER EAR AT SINGLE CELL RESOLUTION

8:57 AM - 9:00 AM **Alain Dabdoub,** *University of Toronto, Sunnybrook Research Institute, Canada*
THANKS AND CLOSING REMARKS

STEM CELL BIOPROCESSING & SCALE UP PRINCIPLES

Organized by: Steve Oh, *Independent Cell Therapy Leader, Singapore*

Human pluripotent stem cell therapies (PSC) have the potential to be curative. However, translating lab based protocols to produce stem cells and their derivatives for preclinical and clinical trials have many bioprocessing and engineering challenges; especially for anchorage dependent progenies like cardiomyocytes, neurons and pancreatic islets. In this session, 3 expert members from the cell & gene therapy industry will candidly share their personal experiences of the problems that they have encountered in developing industry robust protocols. Then we will brainstorm and discuss examples of how to adapt prototype protocols to become feasible, high yielding and reproducible processes at 10L, 100L and even up to 1000L in scale for commercial success. Amongst the many pertinent areas for consideration, panel experts will consider and provide their honest opinions on some the following topics: Selecting robust PSC lines, adaptation of monolayer culture to suspension conditions, when to initiate clinical trials with 2D vs. suspension process, choice of bioreactors/impellers, predicting fluid stresses by scale down models, process intensification options and cost of goods, bubble free aeration systems, modulation of differentiation conditions and cell cycle effects in suspension, cell aggregation and agglomeration, developing efficient harvesting conditions, formulation of cells, analytics and detection of particulates.

ROOM 253, Level 2

8:00 AM - 8:05 AM **Steve Oh,** *Independent Cell Therapy Leader, Singapore*
WELCOME AND OVERVIEW

8:05 AM - 8:10 AM **Joe Yu,** *BlueRock Therapeutics, Canada*
CHALLENGES WITH IPSC BIOPROCESSING

8:10 AM - 8:15 AM **Sofia Hakansson Buch,** *Novo Nordisk, Denmark*
PLURIPOTENT STEM CELL BIOPROCESSING AT NOVO NORDISK

8:15 AM - 8:20 AM **Stefan Braam,** *Ncardia, Netherlands*
CHALLENGES WITH IPSC BIOPROCESSING

8:20 AM - 8:55 AM **All Speakers**
PANEL DISSCUSSION: CHALLENGES OF PSC BIOPROCESSING

8:55 AM - 9:00 AM **Steve Oh,** *Independent Cell Therapy Leader, Singapore*
WRAP UP

STEM CELLS FOR UNRAVELING SEX DIFFERENCES AND FOR GENDER MEDICINE

Organized by: Ithai Waldhorn*, Rambam Health Care Campus, Israel*

Biological sex is a fundamental trait influencing development, reproduction, pathogenesis, and medical treatment outcomes. Stem cells can be highly beneficial for the study of sex differences and for advancing gender medicine. However, the use of stem cells in these fields is still in its infancy. This session will highlight the possible effects of hormones and sex chromosome complement on sex differences, emphasizing the role of stem cells-based models in the study of these differences. In addition, the potential wide applications of stem cells in gender medicine will be discussed.

ROOM 257, Level 2

8:00 AM - 8:03 AM **Ithai Waldhorn,** *Rambam Health Care Campus, Israel*
WELCOME AND OVERVIEW

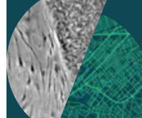
8:03 AM - 8:15 AM **Armin Raznahan,** *National Institute of Mental Health, Intramural Research Program, USA*
SEX CHROMOSOME DOSAGE EFFECTS ON THE HUMAN GENOME

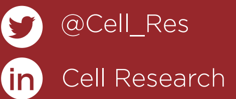
8:15 AM - 8:25 AM **Ithai Waldhorn,** *Rambam Health Care Campus, Israel*
MODELINGS SEX DIFFERENCES IN-VITRO AND IN-VIVO

8:25 AM - 8:35 AM **Joel Berletch,** *University of Washington, USA*
ROLE OF THE X CHROMOSOME IN DIFFERENTIATION AND SEX DIFFERENCES

8:35 AM - 8:45 AM **Iva Kelava,** *Wellcome Sanger Institute, United Kingdom*
HORMONAL EFFECTS ON SEX DIFFERENCES

8:45 AM - 9:00 AM **All Speakers**
PANEL DISCUSSION





Cell Research

Cell Discovery

Editor Emeritus: Gang Pei
Editor-in-Chief: Dangsheng Li

Published in association with Center for Excellence in Molecular Cell Science, Chinese Academy of Sciences and the Chinese Society for Cell Biology

Cell Research is a premium international life science journal with a broad scope in basic molecular and cell biology. The journal publishes original research results that are of unusual significance or broad conceptual or technical advances in all areas of life sciences, as well as authoritative reviews and sharply focused research highlights.
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Editor-in-Chief: Dangsheng Li

Cell Discovery is an open access international journal that publishes results of high significance and broad interest in all areas of molecular and cell biology. The basic bar of acceptance is comparable to the major sister journals of *Cell/Nature/Science*. It is established in 2015 as a sister journal of Cell Research.

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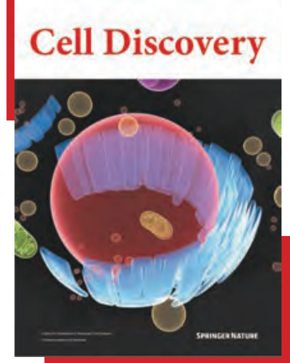


Featured Papers

Activation of lineage competence in hemogenic endothelium precedes the formation of hematopoietic stem cell heterogeneity
Cell Research (2023) 0:1-16; https://doi.org/10.1038/s41422-023-00797-0

Human endoderm stem cells reverse inflammation-related acute liver failure through cystatin SN-mediated inhibition of interferon signaling
Cell Research (2023)33:147–164;https://doi.org/10.1038/s41422-022-00760-5

Two target gene activation pathways for orphan ERR nuclear receptors
Cell Research (2023) 0:1-19;https://doi.org/10.1038/s41422-022-00774-z

Derivation of totipotent-like stem cells with blastocyst-like structure forming potential
Cell Research (2022)32:513–529;https://doi.org/10.1038/s41422-022-00668-0

Generation and characterization of stable pig pregastrulation epiblast stem cell lines
Cell Research (2022)32:383–400;https://doi.org/10.1038/s41422-021-00592-9

SPRINGER NATURE

2023 WORKSHOP DAY

ROOM 253, Level 2

WORKSHOP ON CLINICAL TRANSLATION: HOW TO SUCCESSFULLY CONDUCT A FIRST-IN-HUMAN TRIAL

TUESDAY, 13 JUNE | 8:30 AM - 12:30 PM

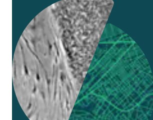
The Workshop on Clinical Translation will feature presentations from scientists and clinician-scientists with experience in critical aspects of first-in-human trials. Topics covered will include manufacturing site logistics, considerations for trial design, decisions in assembling the clinical team and the site(s) and partnering beyond phase I trials.

Organizers:

Roger Barker, *University of Cambridge, UK*
Rajesh Rao, *University of Michigan, USA*

AGENDA

8:30 AM - 8:35 AM	Welcome and Overview, **Rajesh Rao**, *University of Michigan, USA*
8:35 AM - 9:30 AM	MANUFACTURING THE CELLS – THE WHERE, WHY, AND HOW
8:35 AM - 8:40 AM	Session Overview
8:40 AM - 9:00 AM	**Pablo Avalos**, *Cedars Sinai, USA*
9:00 AM - 9:20 AM	**Tenneille Ludwig**, *WiCell Research Institute, USA*
9:20 AM - 9:30 AM	Group Q&A
9:30 AM - 10:20 AM	TRIAL DESIGN AND THE PATIENT POPULATION
9:30 AM - 9:35 AM	Session Overview **Rajesh Rao**, *University of Michigan, USA*
9:35 AM - 9:55 AM	**Catriona Jamieson**, *University of California, San Diego, USA*
9:55 AM - 10:15 AM	**Klara Owen, MD, PhD**, *Novo Nordisk, Denmark*
10:15 AM - 10:25 AM	Group Q&A
10:25 AM - 10:40 AM	Refreshment Break
10:40 AM - 11:35 AM	PUTTING THE TEAM AND CLINICAL SITES TOGETHER
10:40 AM - 10:45 AM	Session Overview **Rajesh Rao**, *University of Michigan, USA*
10:45 AM - 11:05 AM	**Mark Pennesi**, *Oregon Health and Sciences University, USA*
11:05 AM - 11:25 AM	**Graziella Pellegrini**, *University of Modena and Reggio Emilia, Centre for Regenerative Medicine, Italy*
11:25 AM - 11:35 AM	Group Q&A
11:35 AM - 12:30 AM	Beyond Phase I Trials: Partnering with Industry
11:35 AM - 11:40 AM	Session Overview
11:40 AM - 12:00 PM	**Viviane Tabar**, *Memorial Sloan Kettering Cancer Center, USA*
12:00 PM - 12:20 PM	**Steve Harr**, *Sana Biotechnology, USA*
12:20 PM - 12:30 PM	Group Q&A



STEM CELLS IN SPACE WORKSHOP

TUESDAY, 13 JUNE | 1:30 PM - 4:00 PM

Presented by the ISS National Laboratory
Sponsored by: Cedars-Sinai Board of Governors Regenerative Medicine Institute, Rhodium Scientific, and Space Tango
Join the International Space Station National Laboratory, NASA, and industry partners exploring the future of stem cell science, application, and commercialization in space. Learn about research in low earth orbit and funding opportunities across two panels, then enjoy cocktail hour with an astronaut.

1:30 PM - 1:35 PM — **Noor Ward**, *ISS National Laboratory, USA*
WELCOME

1:35 PM - 1:45 PM — **Michael Roberts**, *ISS National Laboratory, USA*
OPENING KEYNOTE

1:45 PM - 2:30 PM — **PANEL 1: STEM CELLS IN SPACE: ADVANCING STEM CELL SCIENCE THROUGH INNOVATION IN MICROGRAVITY**

This panel showcases innovative results from stem cell research in low Earth orbit on the International Space Station where novel insights about stem cell pluripotency and multipotency, proliferation and expansion, genomic and epigenomic integrity, differentiation, and maturation in microgravity promise new benefits for regenerative medicine on Earth. The Panel is comprised of space industry scientists and experts who work to help build the burgeoning LEO economy.

Moderator: Arun Sharma, *Cedars-Sinai, USA*
Panelists:
Heath Mills, *Rhodium Scientific, USA*
Marc Giuliamotti, *Sierra Space, USA*
Pinar Mesci, *Axiom Space, USA*
Stefanie Countryman, *BioServe Space Technologies, USA*
Shelby Giza, *Space Tango, USA*

2:30 PM - 2:40 PM — **QUESTIONS AND ANSWERS FOR PANEL 1**

2:40 PM - 2:45 PM — **Noor Ward**, *ISS National Laboratory, USA*
KEYNOTE INTRODUCTION

2:45 PM - 3:00 PM — **Clive Svendsen**, *Cedars-Sinai Regenerative Medicine Institute, USA*
CEDARS-SINAI KEYNOTE

3:00 PM - 3:40 PM — **PANEL 2: STEM CELLS IN SPACE: FROM BENCH TO BEDSIDE – THE GROWTH OF TRANSLATIONAL R&D IN LEO**

This panel showcases innovative results from stem cell research, biomanufacturing, and the development of next generation tools and models in low Earth orbit on the International Space Station that promise new benefits for regenerative medicine on Earth. The focus will be on ways to translate space findings to serve the needs of the world.

Moderator: Michael Roberts, *ISS National Laboratory, USA*
Panelists:
Catriona Jamieson, *UCSD, USA*
Clive Svendsen, *Cedars-Sinai Regenerative Medicine Institute, USA*
Scott Noggle, *NYSCF, USA*
James Yoo, *Wake Forest University, USA*
Kevin Costa, *Icahn School of Medicine at Mount Sinai, USA*

3:40 PM – 3:50 PM — **QUESTIONS AND ANSWERS FOR PANEL 2**

3:50 PM – 4:00 PM — **Noor Ward**, *ISS National Laboratory, USA*
CLOSING REMARKS AND THANK YOU TO SPONSORS

4:00 PM - 5:00 PM — **STEM CELLS IN SPACE RECEPTION**
Organized by the ISS National Laboratory
Sponsored by Space Tango

Join an astronaut and engage with members of the ISS National Laboratory for cocktails and a networking reception.

PUBLIC SYMPOSIUM: STEM CELLS AT THE PLANETARIUM

A public event
Museum of Science, Boston, 1 Science Park, Boston, MA, USA
TUESDAY, 13 JUNE
7:00 PM – 8:00 PM, free parking

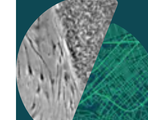
Join host Dr. Insoo Hyun at the Museum of Science's renowned Charles Hayden Planetarium for a specially curated planetarium show, followed by audience discussion with Dr. Arun Sharma.

The International Space Station (ISS) and Low Earth Orbit (LEO) can serve as accessible, unique environments to study human development in microgravity. At the forefront of this new frontier is Dr. Sharma, who led a project that sent human stem cell-derived heart cells to the ISS to study the effects of microgravity on human heart function. Learn how stem cell biomanufacturing in space is being explored through commercial, governmental, and academic collaboration.

To register for this free public event, please use the following link:
https://tickets.mos.org/events/4d5ca3af-92e9-62ba-1892-9b3a52da6f3b

Featuring:
Insoo Hyun
Director, Center for Life Sciences and Public Learning
Museum of Science
Member, Harvard Medical School's Center for Bioethics, USA

Arun Sharma
Stem Cell, Heart, Space Biologist and Assistant Professor,
Cedars-Sinai Medical Center Regenerative Medicine Institute, USA



TUESDAY, 13 JUNE

8:30 AM – 12:30 PM **WORKSHOP ON CLINICAL TRANSLATION: HOW TO SUCCESSFULLY CONDUCT A FIRST-IN-HUMAN (FIH) TRIAL** Room 253, Level 2

1:30 PM – 4:00 PM **STEM CELLS IN SPACE WORKSHOP** Room 253, Level 2
Organized by ISS National Laboratory
Sponsored by Cedars-Sinai Board of Governors Regenerative Medicine Institute, Rhodium Scientific, Space Tango

3:00 PM – 3:45 PM **ATTENDEE ORIENTATION** North Lobby, Level 1

4:00 PM – 5:00 PM **STEM CELLS IN SPACE RECEPTION** Level 2 Foyer
Organized by ISS National Laboratory
Sponsored by Space Tango

7:00 PM – 8:00 PM **PUBLIC SYMPOSIUM: STEM CELLS AT THE PLANETARIUM**
Museum of Science, Planetarium 1 Museum of Science Driveway, Boston, MA

WEDNESDAY, 14 JUNE

7:30 AM – 8:30 AM **REFRESHMENT BREAK** Level 2 Foyer

7:45 AM – 8:30 AM **ATTENDEE ORIENTATION** North Lobby, Level 1

8:30 AM – 11:00 AM **FOCUS SESSIONS: see page 33 for details**

ADVANCING DRUG DISCOVERY THROUGH PRECISION MEDICINE Room 254, Level 2
Organized by Evotec

CLINICAL TRANSLATION OF CELL THERAPIES: CHALLENGES OVERCOME, SUCCESSES, AND THE ROAD AHEAD Room 257, Level 2
Organized by Novo Nordisk
**Presented in-person and on the virtual meeting platform*

THE JOURNEY AND OPPORTUNITIES OF DEVELOPING A TRANSFORMATIVE CELL THERAPY Room 253, Level 2
Organized by BlueRock Therapeutics

TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY Room 258, Level 2
Organized by Stem Cell COREdinates
Supported by STEMCELL Technologies Inc. and Thermo Fisher Scientific
**Presented in-person and on the virtual meeting platform*

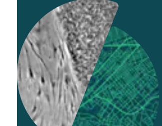
EXPANDING BOUNDARIES OF STEM CELL TECHNOLOGIES AND APPLICATIONS Room 255, Level 2
Organized by The ISSCR Industry Subcommittee

FROM THE BENCH TO THE BEDSIDE: MARYLAND'S ACCELERATING CURES INITIATIVE AND BEYOND Room 256, Level 2
Organized by Maryland Stem Cell Research Fund (MSCRF)
**Presented in-person and on the virtual meeting platform*

FUNCTIONAL INVESTIGATION AND CLINICAL DEVELOPMENT OF IPSC-BASED THERAPIES Room 259, Level 2
Organized by Allele Biotech

WEDNESDAY, 14 JUNE *(continued)*

Time	Session	Location
11:45 AM – 12:45 PM	**INNOVATION SHOWCASES:** **see page 109 for details**	
	MOLECULAR DEVICES: AUTOMATION OF ORGANOIDS CULTURE AND HIGH-CONTENT ANALYSIS OF 3D ORGANOIDS	Room 259, Level 2
	PBS BIOTECH: SCALABLE MANUFACTURING OF IPSC-DERIVED HEMATOPOIETIC PROGENITORS IN A VERTICAL-WHEEL BIOREACTOR TO ENABLE PRODUCTION OF CLINICAL CELL THERAPY PRODUCTS	Room 256, Level 2
	SONY BIOTECHNOLOGY, INC: SONY CGX10 CELL ISOLATION SYSTEM: INTRODUCTION, UTILITY AND ASSESSMENT IN A GMP GRADE ENVIRONMENT FOR MULTI-PARAMETRIC CELL SORTING	Room 257, Level 2 & Virtual
	STEMCELL TECHNOLOGIES INC.: ENHANCING GENETIC STABILITY IN HUMAN PLURIPOTENT STEM CELLS MAINTAINED AS SINGLE CELLS: INTRODUCING ETESR™	Room 253, Level 2 & Virtual
	THE JACKSON LABORATORY: NEW APPROACHES TO THE GENERATION AND USE OF IPSCS TO STUDY NEURODEGENERATIVE DISEASES	Room 255, Level 2
	UBRIGENE BIOSCIENCES INC.: CDMO SERVICE FOR IPSC CELL THERAPY, SCALABLE MANUFACTURE OF CAR-NK CELLS, AND USE OF LIPID NANOPARTICLES TO EXPRESS CARS	Room 254, Level 2
1:00 PM – 3:00 PM	**PLENARY I: PRESIDENTIAL SYMPOSIUM** *Sponsored by BlueRock Therapeutics* **Session Chair: Haifan Lin** *Yale University School of Medicine, USA*	Ballroom East/West, Level 3
1:00 PM – 1:05 PM	**SPONSOR AND OPENING WELCOME REMARKS**	
1:05 PM – 1:12 PM	**Haifan Lin** *Yale University School of Medicine, USA* **PRESIDENTIAL ADDRESS**	
1:12 PM – 1:15 PM	**TRAVEL AND MERIT AWARD RECOGNITIONS**	
1:15 PM – 1:40 PM	**Magdalena Zernicka-Goetz** *California Institute of Technology, USA* **BUILDING EMBRYO MODELS FROM STEM CELLS TO UNDERSTAND SELF-ORGANIZATION**	
1:40 PM – 2:05 PM	**Nan Tang** *National Institute of Biological Sciences, China* **EMPOWER THE DRIVING FORCE OF LUNG REGENERATION**	
2:05 PM – 2:30 PM	**Robert Langer** *Massachusetts Institute of Technology, USA* **DELIVERY SYSTEMS FOR REGENERATIVE MEDICINE**	
2:30 PM – 2:55 PM	**Helen Blau** *Stanford University School of Medicine, USA* **ERNEST MCCULLOCH MEMORIAL LECTURE: REGENERATING AND REJUVENATING AGED TISSUE BY TARGETING A GEROZYME**	
2:30 PM – 7:45 PM	**EXHIBIT & POSTER HALL OPEN**	Exhibit & Poster Hall, Hall A
3:00 PM – 3:45 PM	**REFRESHMENT BREAK** *Sponsored by Notch Therapeutics*	Exhibit & Poster Hall, Hall A



3:45 PM – 5:35 PM	**TRACK: New Technologies (NT)** **PLENARY II: CUTTING EDGE MOLECULAR TECHNOLOGIES** *Sponsored by: BioMarin Pharmaceutical Inc.* **Session Chairs: Helen Blau** *Stanford University School of Medicine, USA* **Ben Simons** *University of Cambridge, UK*	Ballroom East/West, Level 3
3:45 PM – 3:50 PM	**PLENARY INTRODUCTION**	
3:50 PM – 4:10 PM	**Anshul Kundaje** *Stanford University, USA* **DEEP LEARNING THE ROLE OF TRANSCRIPTION FACTOR STOICHIOMETRY AND MOTIF SYNTAX IN SINGLE-CELL CHROMATIN DYNAMICS OF HUMAN SOMATIC CELL REPROGRAMMING**	
4:10 PM – 4:30 PM	**Emma Rawlins** *University of Cambridge, UK* **CRISPR TECHNOLOGY FOR DISCOVERY RESEARCH AND DISEASE MODELLING IN HUMAN FETAL LUNG-DERIVED ORGANOIDS**	
4:30 PM – 4:50 PM	**Jay Shendure** *University of Washington and HHMI, USA* **TOWARDS RECONSTRUCTING MAMMALIAN DEVELOPMENT, ZYGOTE TO PUP**	
4:50 PM – 5:10 PM	**Xiaowei Zhuang** *Harvard University, USA* **SPATIALLY RESOLVED SINGLE-CELL GENOMICS & CELL ATLAS OF THE BRAIN**	
5:10 PM – 5:35 PM	**Olivier Pourquié** *Harvard University and Brigham and Women's Hospital, USA* **ANNE MCLAREN MEMORIAL LECTURE: DECONSTRUCTING HUMAN MUSCULO-SKELETAL DEVELOPMENT IN VITRO**	
6:00 PM – 7:45 PM	**EXHIBIT & POSTER HALL** *Meet-Up Hubs: see page 29 for details* *Micro Theaters: see page 119 for details* *Conversation Corner at ISSCR Central: see page 31 for details*	Exhibit & Poster Hall, Hall A
6:00 PM – 7:45 PM	**OPENING RECEPTION**	
6:00 PM – 6:45 PM	**POSTER SESSION 1 ODD** **TRACK: CELLULAR IDENTITY (CI)** **MODELING DEVELOPMENT AND DISEASE MDD (partial track)** **TRACK: ETHICS, POLICY AND STANDARDS (EPS)**	CI, EPS, MDD Poster Areas
6:15 PM – 6:30 PM	**NITTA GELATIN INC.: BACKFLOW REDUCTION IN LOCAL INJECTION WITH GELATIN FORMULATION**	Micro Theater
6:15 PM – 6:45 PM	**CONVERSATION CORNER: NETWORKING WITH POSTDOCS TO DISCUSS POST-PANDEMIC WORKING ENVIRONMENTS AND UNIVERSITY SUPPORT**	ISSCR Central
6:30 PM – 7:15 PM	**INDUSTRY SCIENTISTS NETWORKING**	Meet-up Hub #1
6:30 PM – 7:15 PM	**POLICY, ETHICS, AND REGULATORY ISSUES**	Meet-up Hub #2

WEDNESDAY, 14 JUNE *(continued)*

6:40 PM – 6:55 PM	**THRIVE BIOSCIENCE: IMAGE DIFFERENTLY - AN OVERVIEW OF A SOLUTION FOR AUTOMATED LIVE CELL IMAGING**	Micro Theater
6:45 PM – 7:15 PM	**CONVERSATION CORNER: ARAB EARLY CAREER SCIENTISTS**	ISSCR Central
6:45 PM – 7:30 PM	**POSTER SESSION 1 EVEN** **TRACK: CELLULAR IDENTITY (CI)** **MODELING DEVELOPMENT AND DISEASE MDD (partial track)** **TRACK: ETHICS, POLICY AND STANDARDS (EPS)**	CI, EPS, MDD Poster Areas
7:05 PM – 7:20 PM	**GETINGE: STIRRED TANK REACTOR PROCESS DEVELOPMENT - SCALE UP FOR CELL AND GENE THERAPY**	Micro Theater
7:30 PM – 7:45 PM	**EOS BIOINNOVATION: ACCELERATING INNOVATION IN REGENERATIVE MEDICINE**	Micro Theater

9:00 PM – 11:00 PM

EARLY CAREER SCIENTISTS' SOCIAL NIGHT
Advance Registration Required
Sponsored by AMSBIO, bit.bio, Sartorius, Scismic, Stem Genomics, Thrive Bioscience, & Watershed Informatics
Offsite: Royale Night Club, 279 Tremont Street
Must be 21 or older to attend. Name badge and government ID with photo required for entry.

THURSDAY, 15 JUNE

CONCURRENT TRACK MINI SESSIONS

8:30 AM – 9:30 AM

TRACK: CLINICAL APPLICATIONS (CA) — Room 258, Level 2

STEM CELLS IN CLINICAL TRIALS
Session Chairs: Luca Biasco
Sana Biotechnology, USA and University College of London, UK
Matthew Porteus
Stanford University School of Medicine, USA

8:30 AM – 8:40 AM

Elisa Mattioli
UKSCB and MHRA, UK
GENERATION OF THE FIRST INTERNATIONAL FLOW CYTOMETRY IDENTITY STANDARD FOR MSCS

8:40 AM – 8:50 AM

Stefan Radtke
Fred Hutchinson Cancer Research Center, USA
CD90-TARGETED VIRAL VECTORS FOR HEMATOPOIETIC STEM CELL GENE THERAPY

8:50 AM – 9:00 AM

Sean Harrington
Sana Biotechnology, USA
IN VIVO DELIVERY OF GENETIC PAYLOADS TO HUMAN HEMATOPOIETIC STEM/PROGENITOR CELLS

9:00 AM – 9:10 AM

Ludi Zhang
Shanghai Institutes for Biological Sciences, China
REVERSAL OF POST-HEPATECTOMY LIVER FAILURE USING A BIOARTIFICIAL LIVER SUPPORTING SYSTEM IMPLANTED WITH CLINICAL-GRADE HUMAN INDUCED HEPATOCYTES

9:10 AM – 9:20 AM

Taewan Kim
Memorial Sloan Kettering Cancer Center, USA
IN VIVO CRISPR/CAS9 SCREEN IDENTIFIES TNF-NFKB-P53 AXIS LIMITING THE SURVIVAL OF HUMAN PSC-DERIVED POSTMITOTIC DOPAMINE NEURON AT TRANSPLANT

8:30 AM – 9:30 AM

TRACK: CELLULAR IDENTITY (CI) — Room 257, Level 2

CELLULAR IDENTITY: MECHANISMS AND APPLICATION

Session Chairs: Hongkui Deng
Peking University, China
Elizabeth Robertson
University of Oxford, UK

8:30 AM – 8:40 AM

Jan Zylicz
University of Copenhagen, Denmark
METABOLIC REWIRING UNDERPINS HUMAN TROPHOBLAST INDUCTION

8:40 AM – 8:50 AM

Graziano Martello
University of Padua, Italy
ESSRB GUIDES NAIVE PLURIPOTENT CELLS THROUGH THE FORMATIVE TRANSCRIPTIONAL PROGRAM

8:50 AM – 9:00 AM

Panagiotis Douvaras
BlueRock Therapeutics, USA
MG01: SINGLE, OFF-THE-SHELF TREATMENT OF CNS PATHOLOGY IN MUCOPOLYSACCHARIDOSES

9:00 AM – 9:10 AM

Jeru Manuel
Universite de Sherbrooke, Canada
FROM A STEM CELL TO A NEURON: HOW ALTERNATIVE RNA SPLICING CONTROLS CELL FATE DECISIONS

9:10 AM – 9:20 AM

Johanna Siehler
Helmholtz Center Munich, Germany
INCEPTOR BINDS AND DIRECTS INSULIN TO LYSOSOMAL DEGRADATION IN STEM CELL-DERIVED PANCREATIC ISLETS

8:30 AM – 9:30 AM

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD) — Room 253, Level 2

REGENERATION AND DISEASES IN A DISH
Session Chairs: Ben Maoz
Tel Aviv University, Israel
Nan Tang
National Institute of Biological Sciences, China

8:30 AM – 8:40 AM

Alessandro Bertero
Università di Torino, Italy
CARDIAC ORGANOIDS REVEAL CHAMBER-SPECIFIC 3D CHROMATIN STRUCTURE MECHANISMS DYSREGULATED IN CONGENITAL HEART DISEASE

8:40 AM – 8:50 AM

Michael Herriges
Boston University, USA
DURABLE ALVEOLAR ENGRAFTMENT OF PSC-DERIVED LUNG TIP-LIKE CELLS INTO IMMUNOCOMPETENT MICE

8:50 AM – 9:00 AM **Mei Lan Li**
Yale University, USA
DYSREGULATED EPITHELIAL-MESENCHYMAL CROSSTALK IN THE STEM CELL NICHE DRIVES INTESTINAL POLYP FORMATION

9:00 AM – 9:10 AM **Ryan Walsh**
Sloan Kettering Institute, USA
GENERATION OF HUMAN CORTICAL ORGANOIDS WITH STRUCTURED OUTER SUBVENTRICULAR ZONE

9:10 AM – 9:16 AM **POSTER TEASERS**

8:30 AM – 9:30 AM **TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)** Room 254, Level 2

AGING, EPIGENETICS, AND PROGENITOR CELL REGULATION
Session Chairs: Lutgarde Arckens
KU Leuven, Belgium
Shruti Naik
NYU School of Medicine, USA

8:30 AM – 8:40 AM **Zhen Sun**
Memorial Sloan Kettering Cancer Center, USA
CHROMATIN REGULATION OF TRANSCRIPTIONAL ENHANCERS AND CELL FATE BY THE SOTOS SYNDROME GENE NSD1

8:40 AM – 8:50 AM **Ruochen Dong**
Stowers Institute for Medical Research, USA
USING SPATIAL TRANSCRIPTOMICS TO REVEAL FETAL LIVER HEMATOPOIETIC STEM CELL-NICHE INTERACTIONS

8:50 AM – 9:00 AM **Fatima Rizvi**
Boston University, USA
VEGFA MRNA-LNPS PROMOTE LIVER PROGENITOR CELL DIFFERENTIATION TO HEPATOCYTES AND RESTORE LIVER FUNCTION IN LIVER INJURY MOUSE MODELS

9:00 AM – 9:10 AM **Shyh-Chang Ng**
IOZ, China
LIN28A MAINTAINS A SUBSET OF ADULT MUSCLE STEM CELLS IN AN EMBRYONIC-LIKE STATE

9:10 AM – 9:16 AM **POSTER TEASERS**

9:30 AM – 3:30 PM **EXHIBIT & POSTER HALL OPEN** Exhibit & Poster Hall, Hall A

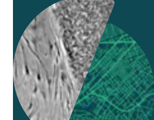
9:30 AM – 10:00 AM **REFRESHMENT BREAK** Exhibit & Poster Hall, Hall A

10:00 AM – 11:30 AM **EXHIBIT & POSTER HALL**
Meet-Up Hubs: see page 29 for details
Micro Theaters: see page 119 for details
Conversation Corner at ISSCR Central: see page 31 for details

10:00 AM – 10:15 AM **DEEPCELL: LABEL-FREE SINGLE CELL IMAGING AND SORTING WITH THE AI-POWERED DEEPCELL PLATFORM** Micro Theater

10:00 AM – 10:45 AM **COMPUTATIONAL STEM CELL BIOLOGY** Meet-up Hub #1

10:00 AM – 10:45 AM **(BLUE) ROCK YOUR CAREER!** Meet-up Hub #2



THURSDAY, 15 JUNE *(continued)*

Time	Session	Location
10:00 AM – 10:45 AM	**POSTER SESSION 2 ODD** **TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)**	TSC Poster Area
10:00 AM – 10:30 AM	**CONVERSATION CORNER: CIRM BRIDGES STUDENTS, MENTORS, DIRECTORS AND ALUMNI**	ISSCR Central
10:25 AM – 10:40 AM	**UNION BIOMETRICA INC.: ANALYSIS, IMAGING AND SORTING OF 3-D CULTURES AND ORGANOID BODIES ON THE COPAS VISION**	Micro Theater
10:45 AM – 11:30 AM	**POSTER SESSION 2 EVEN** **TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)**	TSC Poster Area
10:50 AM – 11:05 AM	**CELLINK: HIGH THROUGHPUT BIOPRINTING OF CELL THERAPY VEHICLES TO TREAT OCULAR DISEASES LIKE CONJUNCTIVAL DISORDER**	Micro Theater
11:15 AM – 11:30 AM	**EPPENDORF BIOPROCESS: IPSC PRODUCTION IN STIRRED-TANK RIGID-WALL SINGLE-USE BIOREACTORS - A SCALABLE APPROACH FOR STEM CELL PROCESSING**	Micro Theater

CONCURRENT TRACK SESSIONS

10:00 AM – 11:40 AM **TRACK: ETHICS, POLICY AND STANDARDS (EPS)** — Room 254, Level 2
STANDARDS FOR HUMAN STEM CELL USE IN RESEARCH

10:00 AM – 10:12 AM
Jack Mosher
ISSCR, USA
INTRODUCTION

10:12 AM – 10:22 AM
Tenneille Ludwig
WiCell Research Institute, USA
STANDARDS: THE SCOPE OF THE PROBLEM

10:22 AM – 10:52 AM
Deepak Mishra
Massachusetts Institute of Technology (MIT), USA
ENGINEERING VASCULARIZED IMMUNOCOMPETENT PROGRAMMABLE ORGANOIDS: LESSONS LEARNED ON STANDARDIZATION

10:52 AM – 11:12 AM
Martin F. Pera
The Jackson Laboratories, USA
REPORTING RECOMMENDATIONS FOR JOURNALS

11:12 AM – 11:40 AM
PANEL DISCUSSION

10:00 AM – 11:40 AM **TRACK: CLINICAL APPLICATIONS (CA)** — Room 258, Level 2
IPS-DERIVED CELLS IN CLINICAL TRIALS
Sponsored by BlueRock Therapeutics
Session Chairs: Deborah French
The Children's Hospital of Philadelphia, USA
Tim Kieffer
University of British Columbia, Canada

10:00 AM – 10:05 AM
TOPIC OVERVIEW

10:05 AM – 10:25 AM
Deborah French
Children's Hospital of Philadelphia, USA
HUMAN PLURIPOTENT STEM CELLS: OVERVIEW OF CLINICAL TRIALS AND STUDIES FOR IMPROVING TRANSFUSION SAFETY

10:25 AM – 10:35 AM

Benjamin Reubinoff
Hadassah Hebrew University Medical Center, Israel
PHASE 1/2A STUDY OF OPREGEN (HUMAN EMBRYONIC STEM CELLS-DERIVED RETINAL PIGMENT EPITHELIAL CELLS) IN AGE-RELATED MACULAR DEGENERATION PATIENTS WITH GEOGRAPHIC ATROPHY

10:35 AM – 10:45 AM

Toshikazu Araoka
Center for iPS Cell Res & Application, Kyoto University, Japan
DEVELOPMENT OF NOVEL CELL THERAPEUTIC STRATEGIES FOR AKI AND CKD USING HUMAN IPSC-DERIVED NEPHRON PROGENITOR CELLS

10:45 AM – 10:55 AM

Anna Smith
Boston University, USA
HOST PRECONDITIONING AND TRANSIENT MITOGEN EXPRESSION VIA MRNA-LNP LEAD TO ROBUST PRIMARY HUMAN HEPATOCYTE ENGRAFTMENT AND TRANSIENT IPSC-DERIVED HEPATOCYTE-LIKE CELL SURVIVAL IN MICE

10:55 AM – 11:05 AM

Sheela Jacob
Vita Therapeutics, USA
DEVELOPMENT OF AN IPSC-DERIVED THERAPY FOR LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2A/R1

11:05 AM – 11:15 AM

Cory Nicholas
Neurona Therapeutics, USA
A PHASE I/II CLINICAL TRIAL OF HPSC-DERIVED INHIBITORY INTERNEURON CELL THERAPY, NRTX-1001, FOR DRUG-REFRACTORY FOCAL EPILEPSY

11:15 AM – 11:35 AM

Timothy Kieffer
University of British Columbia, Canada
PRE-CLINICAL AND CLINICAL TESTING OF STEM CELL DERIVED ISLETS TO TREAT DIABETES

10:00 AM – 11:40 AM

TRACK: CELLULAR IDENTITY (CI) — Room 257, Level 2
MODELING EMBRYONIC CELL FATE SPECIFICATION
Session Chairs: Ivan Bedzhov
Max Planck Institute for Molecular Biomedicine, Münster, Germany
Katerina Hadjantonakis
Sloan Kettering Institute for Cancer Research, USA

10:00 AM – 10:05 AM

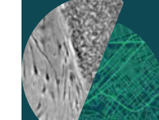
TOPIC OVERVIEW

10:05 AM – 10:25 AM

Anna-Katerina Hadjantonakis
Sloan Kettering Institute for Cancer Research, USA
INTEGRATING IMAGING WITH SINGLE-CELL ‘OMICS TO MAP ENDODERM CELL IDENTITIES IN 3D

10:25 AM – 10:35 AM

Silvia Santos
Francis Crick Institute, UK
NANOG EXPRESSION DURING NAIVE TO PRIME TRANSITION BIASES LINEAGE SPECIFICATION AT GASTRULATION



10:35 AM – 10:45 AM
Miguel Ortiz Salazar
Rice University, USA
ENDOGENOUS NODAL DICTATES ENDODERM VERSUS MESODERM SPECIFICATION IN GEOMETRICALLY CONSTRAINED HUMAN PLURIPOTENT CELLS

10:45 AM – 10:55 AM
Dylan Siriwardena
University of Cambridge, UK
HUMAN AND MARMOSET TROPHOBLAST STEM CELLS RECAPITULATE DIVERGENT MODES OF TROPHOBLAST INVASION AND DIFFER IN SIGNALING REQUIREMENTS

10:55 AM – 11:05 AM
Mengting Wang
Tongji University, China
LOSS OF TET HYDROXYMETHYLATION ACTIVITY CAUSES MOUSE EMBRYONIC STEM CELLS DIFFERENTIATION BIAS AND DEVELOPMENTAL DEFECTS

11:05 AM – 11:15 AM
Kyle Loh
Stanford University, USA
THE BRAIN ARISES FROM TWO SEPARATE EMBRYONIC ORIGINS, WITH IMPLICATIONS FOR DEVELOPMENT, DISEASE, AND EVOLUTION

11:15 AM – 11:35 AM
Ivan Bedzhov
Max Planck Institute for Molecular Biomedicine, Münster, Germany
MOLECULAR KNOBS COORDINATING CELL FATE DYNAMICS AND TISSUE MORPHOGENESIS IN THE EARLY MOUSE EMBRYO

10:00 AM – 11:40 AM
TRACK: MODELING DEVELOPMENT AND DISEASE (MDD) Room 253, Level 2

MODELING THE MICROENVIRONMENT AND CELL-CELL INTERACTIONS
Session Chairs: Ana Paula Pêgo
University of Porto, Portugal
Yi Arial Zeng
Institute of Biochemistry and Cell Biology, Shanghai Institute of Biological Sciences, China

10:00 AM – 10:05 AM
TOPIC OVERVIEW

10:05 AM – 10:25 AM
Ana Paula Pêgo
INEB\i3S, University of Porto, Portugal
IT TAKES TWO TO REMYELINATE: LESSONS LEARNED FROM A MACROGLIA TISSUE ENGINEERED PLATFORM TO STUDY ASTROCYTE-OLIGODENDROCYTE CROSSTALK

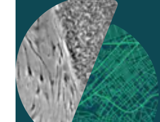
10:25 AM – 10:35 AM
Ulgu Arslan
Leiden University Medical Centre, Netherlands
VASCULARIZED HIPSC-DERIVED 3D CARDIAC MICROTISSUE ON CHIP

10:35 AM – 10:45 AM
Yifei Miao
Cincinnati Children's Hospital, USA
RECONSTRUCTING VASCULARIZED PRIMITIVE GUT TUBE WITH PROPER MESENCHYME IN A DISH

10:45 AM – 10:55 AM
Michal Shoshkes Carmel
The Hebrew University of Jerusalem, Israel
TELOCYTES ARE AN IMPORTANT SOURCE OF WNTS ESSENTIAL FOR HAIR FOLLICLE REGENERATION

10:55 AM – 11:05 AM
Kalle Sipila
King's College London, UK
EMBIGIN IS A FIBRONECTIN RECEPTOR THAT REGULATES THE DIFFERENTIATION AND METABOLISM OF SEBACEOUS PROGENITORS

11:05 AM – 11:15 AM	**Edoardo Sozzi** *Lund University, Sweden* **CO-GRAFT OF DOPAMINE PROGENITORS AND SUPPORTING CELLS TO ENHANCE CELL-BASED THERAPY FOR PARKINSON´S DISEASE**
11:15 AM – 11:35 AM	**Yi Zeng** *Chinese Academy of Sciences, China* **GENERATION OF PANCREATIC ISLET ORGANOIDS USING RESIDENT PROCR PROGENITORS**
10:00 AM – 11:40 AM	**TRACK: NEW TECHNOLOGIES (NT)** Room 259, Level 2 **SINGLE-CELL MULTI-OMICS AND SPATIAL TRANSCRIPTOMICS** *Sponsored by NanoString Technologies* **Session Chairs: Fuchou Tang** *Peking University, China* **Siyuan Wang** *Yale University, USA*
10:00 AM – 10:05 AM	**TOPIC OVERVIEW**
10:05 AM – 10:25 AM	**Siyuan Wang** *Yale University, USA* **IMAGE-BASED SPATIAL GENOMICS IN HEALTH & DISEASE**
10:25 AM – 10:35 AM	**Chen Weng** *Broad Institute/Whitehead Institute, USA* **DECIPHERING CELL STATES AND GENEALOGIES OF HUMAN HEMATOPOIESIS WITH SINGLE-CELL MULTI-OMICS**
10:35 AM – 10:45 AM	**Jan Sokol** *Stanford University, USA* **AN APPROACH FOR UNIQUELY BARCODING CELLS IN A 3D STEM CELL NICHE FOR SPATIAL TRANSCRIPTOMIC DATA COLLECTION**
10:45 AM – 10:55 AM	**Angela Kubik** *Rensselaer Polytechnic Institute, USA* **DECIPHERING TRANSCRIPTOMIC AND FUNCTIONAL DIFFERENCES IN BONE MARROW-DERIVED STEM CELL PROGRESSION IN AGING AND SPACEFLIGHT MODELS**
10:55 AM – 11:05 AM	**Matheus Victor** *MIT, USA* **HUMAN MICROGLIAL STATE DYNAMICS IN ALZHEIMER’S DISEASE PROGRESSION**
11:05 AM – 11:15 AM	**Enakshi Sinniah** *The University of Queensland, Australia* **A CONSERVED GENOME-WIDE EPIGENETIC REPRESSIVE SIGNATURE UNDERPINS CELL IDENTITY**
11:15 AM – 11:35 AM	**Fuchou Tang** *Peking University, China* **A SINGLE MOLECULE SEQUENCING PLATFORM-BASED LONG-READ SINGLE-CELL ATAC-SEQ METHOD TO DETECT CHROMATIN ACCESSIBILITY AND GENETIC VARIANTS SIMULTANEOUSLY WITHIN AN INDIVIDUAL CELL**



THURSDAY, 15 JUNE *(continued)*

Time	Session	Location
12:00 PM – 1:00 PM	**INNOVATION SHOWCASES: see page 109 for details**	
	BIO-TECHNE: UNDERSTANDING THE ROLE OF CULTURE CONDITIONS ON THE GROWTH AND MAINTENANCE OF IPS CELLS	Room 256, Level 2
	BIT.BIO: INDUSTRIALISING CELLULAR REPROGRAMMING: LEVERAGING OPTI-OX™ TECHNOLOGY TO MANUFACTURE HUMAN CELLS WITH UNPRECEDENTED CONSISTENCY	Room 254, Level 2 & Virtual
	CORNING LIFE SCIENCES: PREDICTING DRUG RESPONSES FOR CONVENTIONAL & IO THERAPIES USING MICROORGANOSPHERES™ & IPSC-DERIVED VASCULAR CELLS FOR VASCULARIZATION OF ORGANOIDS & ISCHEMIC TISSUES	Room 255, Level 2
	MAXCYTE: MICRORNA-RESPONSIVE SYNTHETIC MESSENGER RNA AND ITS MEDICAL APPLICATIONS	Room 258, Level 2
	MILTENYI BIOTECH B.V. & CO. KG: PAVING THE WAY TO THE FUTURE: FROM PLURIPOTENT STEM CELL RESEARCH TO TRANSLATION AND MANUFACTURING	Room 259, Level 2 & Virtual
	STEMCELL TECHNOLOGIES INC.: IN VITRO TISSUE MODELING INNOVATIONS: HEPATIC, ALVEOLAR AND INTESTINAL ORGANOIDS	Room 257, Level 2 & Virtual
	THERMO FISHER SCIENTIFIC: DEVELOPING AN IPSC-BASED UNIVERSAL CANCER VACCINE WITH KHLORIS BIOSCIENCES INC.	Room 253, Level 2
12:00 PM – 1:15 PM	**EQUITY, DIVERSITY, AND INCLUSION LUNCHEON** *Organized by the ISSCR and The New York Stem Cell Research Foundation (NYSCF)* *Advanced Registration Required ($30 USD). Seats are limited.*	Room 156, Level 1
1:30 PM – 3:30 PM	**EXHIBIT & POSTER HALL** *Meet-Up Hubs: see page 29 for details* *Micro Theaters: see page 119 for details* *Conversation Corner at ISSCR Central: see page 31 for details*	
1:30 PM – 2:00 PM	**CONVERSATION CORNER: WHAT TO LOOK FOR WHEN SEARCHING FOR A POSTDOCTORAL POSITION**	ISSCR Central
1:30 PM – 2:15 PM	**POSTER SESSION 3 ODD** **TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)**	MDD Poster Area
1:45 PM – 2:00 PM	**STEMBIOSYS, INC.: CELL-DERIVED EXTRACELLULAR MATRICES DRIVE BIOLOGICALLY RELEVANT PHENOTYPES IN MONOLAYER CULTURE**	Micro Theater
1:45 PM – 2:30 PM	**MEET-UP HUB 1: MEET THE EDITORS OF *STEM CELL REPORTS***	Meet-up Hub #1
1:45 PM – 2:30 PM	**MEET-UP HUB 2: GERMAN STEM CELL NETWORK**	Meet-up Hub #2
2:10 PM – 2:25 PM	**SYNTHEGO: IMPROVING LARGE KNOCK-IN EFFICIENCY AND INDUSTRIALIZING METHODS FOR IPSC ENGINEERING USING CRISPR**	Micro Theater
2:15 PM – 3:00 PM	**POSTER SESSION 3 EVEN** **TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)**	MDD Poster Area
2:30 PM – 3:00 PM	**CONVERSATION CORNER: HOW SHAPE INFERS FUNCTION IN DIVERSE STEM CELL NICHES**	ISSCR Central
2:35 PM – 2:50 PM	**V&P SCIENTIFIC, INC.: SPINVESSEL®- MIX WITHOUT A STIR BAR!**	Micro Theater

THURSDAY, 15 JUNE *(continued)*

3:00 PM – 3:15 PM	**PLURISTYX, INC.: NEXT-GENERATION PLATFORM TECHNOLOGIES TO ACCELERATE PLURIPOTENT STEM CELL RESEARCH AND DEVELOPMENT** Micro Theater

1:30 PM – 3:10 PM CONCURRENT TRACK SESSIONS

1:30 PM – 3:00 PM **TRACK: ETHICS, POLICY AND STANDARDS (EPS)** Room 253, Level 2

ETHICS AND PUBLIC ENGAGEMENT REGARDING THE 14 DAY RULE
Session Chairs: Kazuto Kato
Osaka University, Japan
Rosario Isasi
University of Miami, USA

1:30 PM – 1:40 PM **Amander T. Clark**
University of California, Los Angeles, USA
OVERVIEW OF THE ISSCR GUIDELINES

1:40 PM – 1:55 PM **Sarah B. Franklin**
University of Cambridge, UK
THE 14 DAY RULE: A SOCIOLOGICAL ASSESSMENT

1:55 PM – 2:05 PM **Hongmei Wang**
Institute of Zoology, CAS, China
CURRENT STATE OF THE SCIENCE

2:05 PM – 2:15 PM **Amy Wilkerson**
The Rockefeller University, USA
ONE SCRO'S ROUTE TO EXTENDING APPROVAL BEYOND 14 DAYS

2:15 PM – 2:20 PM **Anne Le Goff**
University of California, Los Angeles, USA
POTENTIAL USERS PERSPECTIVES ON IN VITRO GAMETOGENESIS RESEARCH AND APPLICATIONS

2:20 PM – 2:30 PM **Dianne Nicol**
University of Tasmania, Australia
PUBLIC ATTITUDES TOWARDS RESEARCH INVOLVING HUMAN EMBRYOS AND THE 14 DAY RULE IN AUSTRALIA

2:30 PM – 2:55 PM **GENERAL DISCUSSION**

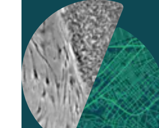
1:30 PM – 3:00 PM **TRACK: CLINICAL APPLICATIONS (CA)** Room 258, Level 2

IN VIVO AND EX VIVO GENE EDITING
Session Chairs: Mark Pennesi
Oregon Health and Science University, USA
Matthew Porteus
Stanford University School of Medicine, USA

1:30 PM – 1:35 PM **TOPIC OVERVIEW**

1:35 PM – 1:55 PM **Mark Pennesi**
Oregon Health and Science University, USA
BRILLIANCE: A PHASE 1/2 SINGLE ASCENDING DOSE STUDY OF EDIT-101, AN IN VIVO CRISPR GENE EDITING THERAPY, IN CEP290-RELATED RETINAL DEGENERATION

1:55 PM – 2:05 PM **Charles E. Murry**
University of Washington, USA
CARDIOMYOCYTE THERAPY WITH ENGINEERED DEOXY-ATP DELIVERY IMPROVES FUNCTION IN CHRONICALLY FAILING HEARTS



THURSDAY, 15 JUNE *(continued)*

2:05 PM – 2:15 PM

Gabriele Casirati
Dana Farber Cancer Institute, USA
EPITOPE EDITED HEMATOPOIETIC STEM CELLS ALLOW IMMUNE-BASED IN VIVO SELECTION OF GENOME-ENGINEERED CELLS

2:15 PM – 2:25 PM

Namita Khajanchi
University of Wisconsin, Madison, USA
CONTROLLING CRISPR-CAS9 GENOME EDITING IN HUMAN CELLS USING A SMALL-MOLECULE INDUCIBLE DEGRADATION STRATEGY

2:25 PM – 2:35 PM

Sonja Schrepfer
Sana Biotechnology Inc., USA
HUMAN HYPOIMMUNE PRIMARY PANCREATIC ISLETS EVADE ALLOGENEIC AND AUTOIMMUNE REJECTION WITHOUT IMMUNOSUPPRESSION AND ALLEVIATE DIABETES IN HUMANIZED MICE

2:35 PM - 2:55 PM

Matthew Porteus
Stanford University School of Medicine, USA
THERAPEUTIC GENOME EDITING TO MAKE SAFE EFFECTIVE STEM CELL THERAPIES

1:30 PM – 3:10 PM

TRACK: CELLULAR IDENTITY (CI) Room 257, Level 2

EMERGENCE OF THE GERMLINE
Session Chairs: Mitinori Saitou
Kyoto University, Japan
Erez Raz
University of Münster, Germany

1:30 PM – 1:35 PM

TOPIC OVERVIEW

1:35 PM – 1:55 PM

Erez Raz
University of Muenster, Germany
THE ROLE OF THE RNA-BINDING PROTEIN DEAD END IN MAINTENANCE OF PRIMORDIAL GERM CELL FATE

1:55 PM – 2:05 PM

Jonathan DiRusso
University of California, Los Angeles, USA
REGULATION OF ENDOGENOUS RETROVIRUSES BY TRIM28 IS NECESSARY TO LICENSE PRIMORDIAL GERM CELLS FOR GAMETOGENESIS

2:05 PM – 2:15 PM

Arend Overeem
Leiden University Medical Centre, Netherlands
EXTRACELLULAR MATRIX IS A CRITICAL FACTOR IN THE DIVERGENCE OF THE GERMLINE AND THE AMNIOTIC LINEAGES

2:15 PM – 2:25 PM

Moyra Lawrence
Kyoto University, Japan
ROADMAP TO THE TOTIPOTENT STATE IN VITRO

2:25 PM – 2:35 PM

Carlos Gantner
University of Cambridge, UK
TRANSGENE DIRECTED INDUCTION OF A STEM CELL-DERIVED EMBRYOID TO MODEL ASPECTS OF HUMAN DEVELOPMENT

2:35 PM – 2:45 PM

Yuxin Luo
Peking University Third Hospital, China
EMPLOYING TOTIPOTENT CELLS TO RECONSTRUCT MOUSE EMBRYOGENESIS

2:45 PM – 3:05 PM **Mitinori Saitou**
Kyoto University, Japan
MECHANISM AND IN VITRO RECONSTITUTION OF MAMMALIAN GERM-CELL DEVELOPMENT

1:30 PM – 3:10 PM **TRACK: NEW TECHNOLOGIES (NT)** Room 259, Level 2

LIVE-IMAGING AND SUPER-RESOLUTION MICROSCOPY
Session Chairs: Joerg Bewersdorf
Yale University, USA
Lucy Erin O'Brien
Stanford University School of Medicine, USA

1:30 PM – 1:35 PM **TOPIC OVERVIEW**

1:35 PM – 1:55 PM **Joerg Bewersdorf**
Yale University, USA
SUPER-RESOLUTION MICROSCOPY OF SINGLE PROTEINS IN THEIR NANOSCALE STRUCTURAL CONTEXT

1:55 PM – 2:05 PM **Sumin Lee**
Tomocube, Inc., Korea
LABEL-FREE 3D SPATIOTEMPORAL ANALYSIS OF CELLULAR DIFFERENTIATION IN LIVE ORGANOIDS USING LOW-COHERENCE HOLOTOMOGRAPHY

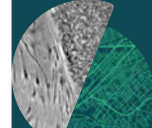
2:05 PM – 2:15 PM **Haoyang Wei**
Yale University, USA
REORGANIZING NICHE ARCHITECTURE STILL PRESERVES ORGAN FUNCTION IN THE HAIR FOLLICLE

2:15 PM – 2:25 PM **Amy Neely**
Northwestern University, USA
NUCLEOPORINS REGULATE EPIDERMAL PROGENITOR FATE DECISIONS THROUGH CHANGES IN COMPOSITION AND CHROMATIN BINDING

2:25 PM – 2:35 PM **Jose Martinez-Sarmiento**
University of Pennsylvania, USA
SUPER-RESOLUTION IMAGING UNCOVERS KEY TEMPORAL CHANGES IN CHROMATIN STRUCTURE AND PLURIPOTENT GENE REACTIVATION IN SINGLE REPROGRAMMING CELLS

2:35 PM – 2:45 PM **Thorsten Schlaeger**
Boston Children's Hospital, USA
SYNTHETIC GENETIC CIRCUITS TO UNCOVER AND ENFORCE THE OCT4 TRAJECTORIES OF SUCCESSFUL REPROGRAMMING OF HUMAN FIBROBLASTS

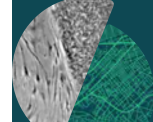
2:45 PM – 3:05 PM **Lucy Erin O'Brien**
Stanford University School of Medicine, USA
HOW STEM CELL PROGENY INTEGRATE INTO MATURE TISSUE ARCHITECTURE: ULTRASTRUCTURAL INSIGHTS FROM FIB-SEM



THURSDAY, 15 JUNE *(continued)*

1:30 PM – 3:10 PM	**TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)** **EPIGENETICS AND TISSUE BIOLOGY** **Session Chairs: Shruti Naik** *NYU School of Medicine, USA* **Xiaohua Shen** *Tsinghua University, China*	Room 254, Level 2
1:30 PM – 1:35 PM	**TOPIC OVERVIEW**	
1:35 PM – 1:55 PM	**Xiaohua Shen** *Tsinghua University, China* **TRANSCRIPTION-RNA METABOLISM COUPLING CONTROLS ZYGOTIC GENOME ACTIVATION AND TOTIPOTENT REPROGRAMMING**	
1:55 PM – 2:05 PM	**Qiao Zhou** *Weill Cornell Medicine, USA* **THE MOLECULAR MACHINERY CONTROLLING STEM CELL AND TISSUE PLASTICITY BETWEEN ADULT COLON AND SMALL INTESTINE**	
2:05 PM – 2:15 PM	**Deniz Goekbuget** *University of California, USA* **TRANSCRIPTIONAL REPRESSION UPON S PHASE ENTRY PROTECTS GENOME INTEGRITY IN PLURIPOTENT CELLS**	
2:15 PM – 2:25 PM	**Mohamad Najia** *Boston Children's Hospital, USA* **TRANSPOSABLE ELEMENTS REGULATE NATURAL KILLER CELL DEVELOPMENT**	
2:25 PM – 2:35 PM	**Laurianne Scourzic** *Weill Cornell Medicine, USA* **REPROGRAMMING AND MULTIOME STUDIES UNCOVER A RARE STEM CELL-LIKE POPULATION OF GERMINAL CENTER B-CELLS**	
2:35 PM – 2:45 PM	**Anna Malkowska** *New York University, USA* **PROMOTERS BECOME ACCESSIBLE DURING STEM CELL QUIESCENCE: SLEEPING WITH ONE EYE OPEN?**	
2:45 PM – 3:05 PM	**Shruti Naik** *NYU School of Medicine, USA* **DEFINING MALADAPTIVE EPITHELIAL PROGRAMS IN INFLAMMATORY DISEASE**	
3:00 PM – 3:30 PM	**REFRESHMENT BREAK**	Exhibit & Poster Hall, Hall A and Level 3 Foyer
3:30 PM – 5:10 PM	**TRACK: CELLULAR IDENTITY (CI)** **PLENARY III: EPIGENETIC REGULATION OF DISTINCT CELL STATES** **Session Chairs: Hongkui Deng** *Peking University, China* **Elizabeth Robertson** *University of Oxford, UK*	Ballroom East/West, Level 3
3:30 PM – 3:45 PM	**ISSCR BUSINESS MEETING**	

3:45 PM – 3:50 PM	**PLENARY INTRODUCTION**
3:50 PM – 4:10 PM	**Kenneth S. Zaret** *Perelman School of Medicine, University of Pennsylvania, USA* **SINGLE MOLECULE DYNAMICS REVEALS EARLY GLOBAL CHROMATIN CHANGES DURING CELLULAR REPROGRAMMING TO PLURIPOTENCY**
4:10 PM – 4:30 PM	**Jeanne B. Lawrence** *University of Massachusetts Medical School, USA* **XIST RNA AND COT-1 RNAS AS ARCHITECTS OF CHROMOSOME REGULATION**
4:30 PM – 4:50 PM	**Wolf Reik** *Altos Labs, UK* **A GENE REGULATORY NETWORK CLOCK OF HUMAN EPIBLAST DEVELOPMENT**
4:50 PM – 5:10 PM	**Yi Zhang** *HHMI and Boston Children's Hospital/Harvard University, USA* **REMOVAL OF FUNCTIONALLY DEFECTIVE HEMATOPOIETIC STEM CELLS RESCUES AGE-RELATED DEFECTS**
5:30 PM – 6:00 PM	**INNOVATION SHOWCASES: see page 109 for details**
	3BRAIN AG: MICROCHIP-BASED FUNCTIONAL SCREENING IN BRAIN ORGANOIDS: MOVING INTO A NEW ERA FROM PLANAR TO 3D TECHNOLOGY Room 254, Level 2
	FEMTOBIOMED: ELECTROPORATION BUFFERLESS MULTIPLEXED CELL ENGINEERING Room 255, Level 2
	NANOSTRING TECHNOLOGIES, INC.: SPATIAL BIOLOGY IS NOW: ACCELERATE YOUR STEM CELL STUDIES WITH SPATIAL MULTI-OMICS Room 253, Level 2 & Virtual
	PEPTIGROWTH: SYNTHETIC PEPTIDE GROWTH FACTORS: FORGING THE PATH FORWARD FOR REGENERATIVE MEDICINE AND CELL THERAPY Room 256, Level 2
	SYNTHEGO: HARNESSING THE POWER OF CRISPR ENGINEERED CELLS FROM SYNTHEGO TO ACCELERATE DISEASE RESEARCH Room 259, Level 2
	THRIVE BIOSCIENCE: IMAGE DIFFERENTLY - A SOLUTION FOR AUTOMATED LIVE CELL IMAGING Room 257, Level 2
	TREEFROG THERAPEUTICS: SCALING-UP IPSC-BASED CELL THERAPIES: REAL-WORLD PROCESSES WITH BIOMIMETIC C-STEM TECHNOLOGY Room 258, Level 2



FRIDAY, 16 JUNE

	SCIENCE SPOTLIGHT SESSIONS: **See page 39 for details**	
8:00 AM – 9:00 AM	**CELL TRANSPLANTATION FOR SPINAL CORD REPAIR** *Organized by* **Lyandysha Zholudeva**, *Gladstone Institutes, USA* **Hideyuki Okano,** *Keio University School of Medicine, Japan* **Clive Svendsen,** *Cedars Sinai, USA*	Room 258, Level 2
	INNER EAR ORGANOIDS FOR HEARING AND BALANCE *Organized by* **Bryony Nayagam**, *The University of Melbourne, Australia* **Jacqueline Ogier,** *The University of Melbourne, Australia* **Alain Dabdoub,** *The University of Toronto, Canada*	Room 254, Level 2
	STEM CELL BIOPROCESSING AND SCALE UP PRINCIPLES *Organized by* **Steve Oh**, *Independent Cell Therapy Leader, Singapore*	Room 253, Level 2
	STEM CELLS FOR UNRAVELING SEX DIFFERENCES AND FOR GENDER MEDICINE *Organized by* **Ithai Waldhorn**, *Rambam Health Care Campus, Israel*	Room 257, Level 2
8:00 AM - 9:00 AM	**TRACK: CLINICAL APPLICATIONS (CA)** **CLINICAL NEWS: IPS CELLS IN CLINICAL TRIALS: OPHTHALMOLOGY** **Session Chairs: Mark Pennesi** *Oregon Health and Science University, USA* **Benjamin Reubinoff** *Hadassah Medical Center, Israel*	Room 259, Level 2
8:05 AM – 8:15 AM	**Jeffrey Stern** *Neural Stem Cell Institute, Rensselaer, NY, USA* **RETINAL PIGMENT EPITHELIAL (RPE) STEM CELL-DERIVED RPE PROGENITOR CELL IMPLANTATION FOR DRY AGE-RELATED MACULAR DEGENERATION (DRY AMD)**	
8:15 AM – 8:25 AM	**Kapil Bharti** *National Eye Institute (NEI), National Institutes of Health (NIH), MD, USA* **A PHASE I/IIA TRIAL TO TEST SAFETY AND FEASIBILITY OF AN AUTOLOGOUS IPS CELL-DERIVED RETINAL PIGMENT EPITHELIUM PATCH IN AGE-RELATED MACULAR DEGENERATION PATIENTS**	
8:25 AM – 8:35 AM	**Masayo Takahashi** *Vision Care, Inc., Kobe, Japan* **THE NEXT STAGE OF RETINAL REGENERATIVE MEDICINE**	
8:35 AM – 8:45 AM	**Jane S. Lebkowski** *Regenerative Patch Technologies, Menlo Park, CA, USA* **LONG-TERM FOLLOW-UP OF SUBJECTS IN A PHASE 1/2A CLINICAL TRIAL OF AN ALLOGENEIC BIOENGINEERED HESC-DERIVED RPE IMPLANT FOR ADVANCED DRY AGE-RELATED MACULAR DEGENERATION**	
8:45 AM – 8:55 AM	**Clive N. Svendsen** *Cedars-Sinai Regenerative Medicine Institute, Los Angeles, CA, USA* **UPDATES ON TWO CLINICAL TRIALS USING HUMAN NEURAL PROGENITORS ALONE OR SECRETING GNDF TO TREAT RETINITIS PIGMENTOSA AND ALS**	
9:00 AM – 9:30 AM	**REFRESHMENT BREAK**	Exhibit & Poster Hall, Hall A
9:00 AM – 3:00 PM	**EXHIBIT & POSTER HALL OPEN**	
9:30 AM – 11:00 AM	*Meet-Up Hubs: see page 29 for details* *Micro Theaters: see page 119 for details* *Conversation Corner at ISSCR Central: see page 31 for details*	

9:30 AM – 10:00 AM	**CONVERSATION CORNER: EMERGING FEMTECH IN REGENERATIVE MEDICINE**	ISSCR Central
9:30 AM – 10:15 AM	**MEET-UP HUB 1: CONTINUE THE CONVERSATION: ETHICS TRACK SESSION**	Meet-up Hub #1
9:30 AM – 10:15 AM	**MEET-UP HUB 2: STEM CELL PODCAST: MEET THE HOSTS**	Meet-up Hub #2
9:30 AM – 10:15 AM	**POSTER SESSION 4 ODD** **TRACK: NEW TECHNOLOGIES (NT)**	NT Poster Area
9:55 AM – 10:10 AM	**PLURISTYX, INC.: NEXT-GENERATION PLATFORM TECHNOLOGIES TO ACCELERATE PLURIPOTENT STEM CELL RESEARCH AND DEVELOPMENT**	Micro Theater
10:15 AM – 11:00 AM	**POSTER SESSION 4 EVEN** **TRACK: NEW TECHNOLOGIES (NT)**	NT Poster Area
10:30 AM – 11:00 AM	**CONVERSATION CORNER: HUMAN IPSC ENTHUSIASTS**	ISSCR Central

CONCURRENT TRACK SESSIONS

9:30 AM – 11:10 AM

TRACK: CLINICAL APPLICATIONS (CA) — Room 258, Level 2

NAVIGATING THE REGULATORY HURDLES IN STEM CELL THERAPIES

Sponsored by WiCell

Session Chairs: Anna Falk

Lund University, Sweden

Peter Marks

FDA Center for Biologics Evaluation and Research, USA

9:30 AM – 9:35 AM

TOPIC OVERVIEW

9:35 AM – 9:55 AM

Anna Falk

Lund University, Sweden

SUSTAINABLE PRODUCTION OF IPSC DERIVED NEUROEPITHELIAL STEM CELLS FOR CLINICAL TRANSLATION OF CELL THERAPY

9:55 AM – 10:05 AM

Elisa Mattioli

UKSCB and MHRA, UK

QUALITY ASSURED PLURIPOTENT STEM CELLS: A JOURNEY FROM BENCH TO BEDSIDE

10:05 AM – 10:15 AM

Jonathan Jung

The Hebrew University, Israel

IDENTIFICATION AND FUNCTIONAL ANALYSIS OF CANCER-RELATED MUTATIONS IN HUMAN PLURIPOTENT STEM CELLS AND THEIR DIFFERENTIATED PROGENIES.

10:15 AM – 10:25 AM

Kevin Ullmann

Hannover Medical School, Germany

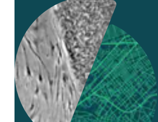
ADVANCED MATRIX-FREE HUMAN PLURIPOTENT STEM CELL MANUFACTURING BY SEED TRAIN APPROACH AND INTERMEDIATE CRYOPRESERVATION

10:25 AM – 10:35 AM

Gal Keshet

The Hebrew University, Israel

EPITYPING - ANALYSIS OF EPIGENETIC ABERRATIONS IN HUMAN PLURIPOTENT STEM CELLS UTILIZED FOR MODELING AND CLINICAL APPLICATIONS



FRIDAY, 16 JUNE *(continued)*

10:35 AM – 10:45 AM
Shinsuke Yoshida
CiRA Foundation, Japan
CONSTRUCTION AND EVALUATION OF A CLINICAL GRADE HLA HAPLOBANK OF IPSCS MATCHING APPROXIMATELY FORTY PERCENT OF THE JAPANESE POPULATION

10:45 AM – 11:05 AM
Peter Marks
US Food and Drug Administration, USA
FDA'S EFFORTS TO HELP FACILITATE THE DEVELOPMENT OF CELLULAR THERAPIES

9:30 AM – 11:10 AM
TRACK: CELLULAR IDENTITY (CI) Room 257, Level 2
CELL IDENTITY DURING REGENERATION AND AGING
Session Chairs: Juan-Carlos Izpisua Belmonte
Altos Labs, USA
Jing Qu
Institute of Zoology, CAS, China

9:30 AM – 9:35 AM
TOPIC OVERVIEW

9:35 AM – 9:55 AM
Jing Qu
Institute of Zoology, CAS, China
ENDOGENOUS RETROVIRUS AS A HALLMARK AND DRIVING FORCE OF CELLULAR SENESCENCE AND TISSUE AGING

9:55 AM – 10:05 AM
Thomas Ambrosi
University of California, Davis, USA
COMBINING HUMAN SKELETAL STEM CELL TRACKING IN VIVO WITH FUNCTIONAL AND TRANSCRIPTIONAL ANALYSIS ON THE SINGLE CELL LEVEL TO IDENTIFY NEW THERAPEUTIC TARGETS THAT PRESERVE STEM CELL DIVERSITY

10:05 AM – 10:15 AM
Larissa Traxler
University of Innsbruck, Austria
NEURONAL FATE INSTABILITY TRIGGERED BY METABOLIC DYSREGULATION OF ALTERNATIVE SPLICING

10:15 AM – 10:25 AM
Amnon Buxboim
The Hebrew University of Jerusalem, Israel
HOW DOES AGEING-RELATED STIFFENING OF BRAIN TISSUE MICROENVIRONMENTS AFFECT THE REGENERATIVE CAPACITY OF CNS PROGENITOR CELLS

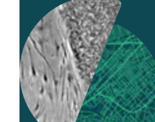
10:25 AM – 10:35 AM
Timothy Duerr
Northeastern University, USA
RETINOIC ACID BREAKDOWN IS REQUIRED FOR POSITIONAL IDENTITY ALONG THE PROXIMODISTAL AXIS OF THE REGENERATING AXOLOTL LIMB

10:35 AM – 10:45 AM
Susanne Rafelski
Allen Institute for Cell Science, USA
INTEGRATED INTRACELLULAR ORGANIZATION AND ITS VARIATIONS IN HUMAN IPS CELLS

10:45 AM – 11:05 AM
Juan Carlos Izpisua Belmonte
Altos Labs, USA
CELL REJUVENATION AND DISEASE

FRIDAY, 16 JUNE *(continued)*

9:30 AM – 11:10 AM	**TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)** **STEM CELLS FOR PERSONALIZED MEDICINE** **Session Chairs: Flora Vaccarino** *Yale University, USA* **Darrell Kotton** *Boston University School of Medicine, USA*	Room 253, Level 2
9:30 AM – 9:35 AM	**TOPIC OVERVIEW**	
9:35 AM – 9:55 AM	**Flora Vaccarino** *Yale University, USA* **ORGANOID MODELING OF GENE REGULATORY EVENTS DURING FOREBRAIN DEVELOPMENT**	
9:55 AM – 10:05 AM	**Richard Davis** *Leiden University Medical Center, Netherlands* **STRAIGHT-IN: A RAPID AND EFFICIENT PLATFORM FOR TARGETED LARGE GENE INSERTIONS IN HUMAN PLURIPOTENT STEM CELLS**	
10:05 AM – 10:15 AM	**Michelle Lohbihler** *McEwen Stem Cell Institute, University Health Network, Canada* **STEM CELL-DERIVED ATRIOVENTRICULAR NODE-LIKE PACEMAKER CELLS FOR APPLICATION AS A BIOLOGICAL PACEMAKER**	
10:15 AM – 10:25 AM	**Xiaofeng (Steve) Huang** *Weill Cornell Medicine, USA* **REDIRECTING DIFFERENTIATION OF HUMAN STOMACH STEM CELLS TO PRODUCE ISLET-LIKE ORGANOIDS FOR DIABETES TREATMENT**	
10:25 AM – 10:35 AM	**Annika Zink** *University Hospital of Düsseldorf and Heinrich Heine University Düsseldorf, Germany* **REPROGRAMMING-DRIVEN DRUG DISCOVERY IDENTIFIES AN EFFICACIOUS REPURPOSING CANDIDATE FOR LEIGH SYNDROME**	
10:35 AM – 10:45 AM	**Anai Gonzalez-Cordero** *Children's Medical Research Institute, Australia* **PROOF-OF CONCEPT GENE THERAPY FOR MOST COMMON INHERITED RETINAL DEGENERATIONS USING RETINAL ORGANOIDS**	
10:45 AM – 11:05 AM	**Darrell Kotton** *Boston University School of Medicine, USA* **RECONSTITUTION OF LUNG PROGENITOR COMPARTMENTS IN VIVO BY ENGRAFTMENT OF DIFFERENTIATED PLURIPOTENT STEM CELLS**	
9:30 AM – 11:10 AM	**TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)** **EMERGING MODEL SYSTEMS** **Session Chairs: Lutgarde Arckens** *KU Leuven, Belgium* **Jenna Galloway** *Massachusetts General Hospital - Harvard Medical School, USA*	Room 254, Level 2
9:30 AM – 9:35 AM	**TOPIC OVERVIEW**	



FRIDAY, 16 JUNE *(continued)*

9:35 AM – 9:55 AM	**Jenna Galloway** *Massachusetts General Hospital, Harvard Medical School, USA* **ENDOGENOUS TENOCYTE ACTIVATION UNDERLIES THE REGENERATIVE CAPACITY OF ADULT ZEBRAFISH TENDON**
9:55 AM – 10:05 AM	**Sangho Lim** *Hubrecht Institute, Netherlands* **ADULT TISSUE-DERIVED THYMIC EPITHELIAL CELL 3D ORGANOIDS RECAPITULATE ITS MORPHOLOGY, HETEROGENEITY, AND FUNCIONALITY**
10:05 AM – 10:15 AM	**Eri Takematsu** *Stanford University, USA* **SKELETAL STEM CELL CONTROLS THE CRANIOFACIAL BONE FATES**
10:15 AM – 10:25 AM	**KuangTse Wang** *Cornell University, USA* **A ROUNDABOUT RECEPTOR REGULATES APPROPRIATE SPATIAL DIFFERENTIATION OF STEM CELLS IN PLANARIANS**
10:25 AM – 10:35 AM	**Helen Miranda** *Case Western Reserve University, USA* **SCALABLE, OPTICALLY-RESPONSIVE HUMAN NEUROMUSCULAR JUNCTION MODEL REVEALS CONVERGENT MECHANISMS OF SYNAPTIC DYSFUNCTION IN FAMILIAL ALS**
10:35 AM – 10:45 AM	**Michinori Mayama** *University of Pennsylvania, USA* **RECONSTITUTION OF HUMAN ADRENOCORTICAL SPECIFICATION AND STEROIDOGENESIS**
10:45 AM – 11:05 AM	**Lutgarde Arckens** *KU Leuven, Belgium* **FACILITATORS AND BRAKES ON SUCCESSFUL NEUROREPAIR: A TURQUOISE KILLIFISH PERSPECTIVE**
11:30 AM – 12:30 PM	**INNOVATION SHOWCASES: see page 109 for details**
	AJINOMOTO CO., INC: ADVANCING CELL THERAPY: INCORPORATING ANIMAL-ORIGIN FREE RECOMBINANT PROTEINS AND CULTURE MEDIA FOR IPSC-BASED CANCER IMMUNOTHERAPY Room 257, Level 2
	BIONANO: OPTICAL GENOME MAPPING - REDEFINING CELL LINE GENOMIC INTEGRITY AND OFF-TARGET CHARACTERIZATION Room 255, Level 2
	CELL MICROSYSTEMS: NOVEL METHODS FOR CULTURE AND DEVELOPMENT OF STEM CELL-DERIVED 2D AND 3D MODELS Room 256, Level 2
	FUJIFILM WAKO PURE CHEMICAL CORPORATION: CEPT COCKTAIL, A NEW CHEMICAL PLATFORM FOR STRESS-FREE AND SAFE CULTURE OF IPSCS Room 259, Level 2
	MAXWELL BIOSYSTEMS AG: ADVANCED FUNCTIONAL CHARACTERIZATION OF IPSC-DERIVED 2D AND 3D IN VITRO MODELS AT THE FRONTIERS OF MOLECULAR BIOSCIENCE Room 253, Level 2
	STEMCELL TECHNOLOGIES INC.: FROM STEM CELL TO IMMUNE CELL: USING DEFINED METHODS TO ENHANCE CONSISTENCY AND PERFORMANCE Room 254, Level 2 & Virtual

11:30 AM – 12:45 PM	**CAREER PANEL LUNCHEON: TRANSITIONING TO A NEW POSITION: TOOLS AND TAKE-AWAYS** *Early career scientists are invited to join the ISSCR Early Career Scientists Committee and a panel of experts for an in-depth discussion in a casual lunch setting. $15 USD additional registration required. Seats are limited. This event is for post doctoral fellows and students.*	Room 156, Level 1
1:15 PM – 3:00 PM	**EXHIBIT & POSTER HALL** *Meet-Up Hubs: see page 29 for details* *Micro Theaters: see page 119 for details* *Conversation Corner at ISSCR Central: see page 31 for details*	
1:15 PM – 2:00 PM	**MEET-UP HUB 1: EARLY CAREER SCIENTISTS NETWORKING**	Meet-up Hub #1
1:15 PM – 2:00 PM	**MEET-UP HUB 2: LGBTQ STEM CELL NETWORKING**	Meet-up Hub #2
1:15 PM – 2:00 PM	**POSTER SESSION 5 ODD** **TRACK: CLINICAL APPLICATIONS (CA)**	CA Poster Area
1:15 PM - 1:25 PM	**CAREER EXPLORATION WITH BLUEROCK THERAPEUTICS**	Micro Theater
1:27 PM – 1:37 PM	**CAREER EXPLORATION WITH STEMCELL TECHNOLOGIES INC.**	Micro Theater
1:39 PM – 1:44 PM	**CAREER EXPLORATION WITH SCISMIC**	Micro Theater
2:00 PM – 2:45 PM	**POSTER SESSION 5 EVEN** **TRACK: CLINICAL APPLICATIONS (CA)**	CA Poster Area

CONCURRENT TRACK SESSIONS

1:15 PM - 2:55 PM	**TRACK: ETHICS, POLICY AND STANDARDS (EPS)** **GLOBAL POLICY INITIATIVES** **Session Chair: Megan Munsie** *University of Melbourne, Australia*	Room 258, Level 2
1:15 PM - 1:20 PM	**TOPIC OVERVIEW**	
1:20 PM - 1:45 PM	**Janet Rossant** *The Gairdner Foundation, Canada* **CHALLENGES IN DEFINING GLOBALLY RELEVANT GUIDELINES FOR STEM CELL AND HUMAN EMBRYO RESEARCH**	
1:45 PM - 2:00 PM	**Ellen Gadbois** *National Institutes of Health, USA* **NIH HUMAN EMBRYO RESEARCH POLICY**	
2:00 PM – 2:15 PM	**Edilene Lopes McInnes** *The University of Adelaide, Australia* **AUSTRALIAN STEM CELL RESEARCHERS PUBLIC ENGAGEMENT: CHALLENGES AND WAYS FORWARD**	
2:15 PM – 2:55 PM	**Jose Polo** *University of Adelaide, Australia* **ADAPTING TO THE POLICIES IN EMBRYO MODELS RESEARCH IN AUSTRALIA**	

1:15 PM – 2:55 PM	**TRACK: CELLULAR IDENTITY (CI)** **GUIDED DIFFERENTIATION OF IPSCS FOR CLINICAL APPLICATIONS** *Sponsored by The Stem Cell Network* **Session Chairs: Gay Crooks** *David Geffen School of Medicine, UCLA, USA* **Lorenz Studer** *Sloan-Kettering Institute for Cancer Research, USA*	Room 257, Level 2
1:15 PM – 1:20 PM	**TOPIC OVERVIEW**	
1:20 PM – 1:40 PM	**Gay Crooks** *University of California, Los Angeles, USA* **GUIDING IPSC-BASED T CELL DIFFERENTIATION THROUGH POSITIVE SELECTION IN THE ABSENCE OF TCR AND HLA EXPRESSION**	
1:40 PM – 1:50 PM	**Nicole Dubois** *Icahn School of Medicine at Mount Sinai, USA* **TRANSIENT NOTCH ACTIVATION ENABLES CONVERSION OF PSC-DERIVED CARDIOMYOCYTES TOWARD A PURKINJE-LIKE FATE**	
1:50 PM – 2:00 PM	**Yuya Fujiwara** *Kyoto University, Japan* **IDENTIFICATION OF CELL ADHESION MOLECULE REGULATING ENGRAFTMENT OF HIPSC-DERIVED CARDIOMYOCYTE TRANSPLANTATION**	
2:00 PM – 2:10 PM	**Wouter van der Valk** *Leiden University Medical Center and Boston Children's Hospital, USA* **SINGLE-CELL LEVEL COMPARISON OF HUMAN INNER EAR ORGANOIDS WITH THE HUMAN COCHLEA AND VESTIBULAR ORGANS**	
2:10 PM – 2:20 PM	**Shoichi Iriguchi** *Center for iPS Cell Research and Application (CiRA), Japan* **GENERATION OF THYMUS-SEEDING PROGENITOR T CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS BY CHEMICALLY DEFINED ENDOTHELIAL-TO-HEMATOPOIETIC TRANSITION CULTURE**	
2:20 PM – 2:30 PM	**Paula Alonso-Guallart** *The New York Stem Cell Foundation Research Institute, USA* **ENGINEERED STEM CELLS FOR IMMUNE EVASION IN A TYPE 1 DIABETES MODEL**	
2:30 PM – 2:50 PM	**Lorenz Studer** *Memorial Sloan Kettering Cancer Center, USA* **Title not available at time of printing**	
1:15 PM – 2:55 PM	**TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)** **ADVANCING IN VITRO MODELS** **Session Chairs: Weida Li** *Tongji University, China* **Ronit Satchi-Fainaro** *Tel Aviv University, Israel*	Room 253, Level 2
1:15 PM – 1:20 PM	**TOPIC OVERVIEW**	
1:20 PM – 1:40 PM	**Weida Li** *Tongji University, China* **DRUG DISCOVERY FOR WOLFRAM SYNDROME USING HESCS-DERIVED SC-B CELLS AND CEREBRAL ORGANOIDS**	

1:40 PM – 1:50 PM **Huanhuan Li**
Guangzhou Laboratory, China
IN VITRO GENERATION OF MOUSE EMBRYOGENESIS FOUNDER CELLS

1:50 PM – 2:00 PM **Portia Smith**
University of Wisconsin, Madison, USA
GENERATION OF "DON'T EAT ME" RECEPTOR KNOCKOUT MACROPHAGES FOR THE TREATMENT OF SOLID TUMORS

2:00 PM – 2:10 PM **Raquel Pérez Fernández**
University of Heidelberg and German Cancer Research Center, Germany
ORGANOID ASSEMBLOIDS MODELING THE ROLE OF SEROTONIN DURING HUMAN CORTICAL DEVELOPMENT

2:10 PM – 2:20 PM **Gabriele Ciceri**
Memorial Sloan Kettering Cancer Center, USA
AN EPIGENETIC BARRIER SETS THE TIMING OF HUMAN NEURONAL MATURATION

2:20 PM – 2:30 PM **Samantha Barton**
The Florey Institute of Neuroscience and Mental Health, Australia
USING HUMAN IPSC-DERIVED ORGANOIDS TO MODEL DEMYELINATION, OLIGODENDROCYTE DYSFUNCTION AND MICROGLIAL TOXICITY IN MULTIPLE SCLEROSIS

2:30 PM – 2:50 PM **Ronit Satchi-Fainaro**
Tel Aviv University, Israel
MANAGING BRAIN MALIGNANCIES IN 3 DIMENSIONS

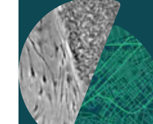
1:15 PM – 2:55 PM **TRACK: NEW TECHNOLOGIES (NT)** Room 259, Level 2
SINGLE-MOLECULE METHODS AND BIOMOLECULAR CONDENSATES
Session Chairs: Srinjan Basu
University of Cambridge, UK
Rong Fan
Yale School of Engineering, USA

1:15 PM – 1:20 PM **TOPIC OVERVIEW**

1:20 PM – 1:40 PM **Srinjan Basu**
University of Cambridge, UK
STICKY PROTEINS AND MOVING GENOMES: TOWARDS A SINGLE-MOLECULE PERSPECTIVE OF INTRA-NUCLEAR DYNAMICS DURING PLURIPOTENT CELL DIFFERENTIATION

1:40 PM – 1:50 PM **Alison Swearingen**
University of Colorado Boulder, USA
H3K36 METHYLATION REGULATES INTESTINAL CELL FATE

1:50 PM – 2:00 PM **Bruno Di Stefano**
Baylor College of Medicine, USA
HIJACKING OF RNA CONDENSATES CORRUPTS CELL IDENTITY AND PROMOTES ONCOGENESIS



FRIDAY, 16 JUNE *(continued)*

2:00 PM – 2:10 PM

Tsuneya Ikezu
Mayo Clinic Florida, USA
PROTEOMIC CHARACTERIZATION OF CELL TYPE-SPECIFIC EXTRACELLULAR VESICLE MOLECULES FROM HUMAN IPSC-DERIVED NEURONS, ASTROCYTES, MICROGLIA, AND OLIGODENDROCYTES

2:10 PM – 2:20 PM

Cheen Euong Ang
Harvard University, USA
SPATIALLY RESOLVED EPIGENOMIC PROFILING OF SINGLE CELLS IN COMPLEX TISSUES

2:20 PM – 2:30 PM

Daisylyn Senna Tan
The University of Hong Kong, Hong Kong
DECODING HOW THE PIONEER FACTOR OCT4 ENGAGES EPIGENETICALLY SILENCED DNA

2:30 PM – 2:50 PM

Rong Fan
Yale University School of Engineering, USA
SPATIAL MULTI-OMICS DRIVING THE NEXT WAVE OF BIOMEDICAL RESEARCH REVOLUTION

1:15 PM – 2:55 PM

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC) Room 254, Level 2
PHYSICAL PROPERTIES AND REGENERATIVE RESPONSES OF PERTURBED TISSUES
Session Chairs: Celeste Nelson
Princeton University, USA
Tien Peng
University of California, San Francisco (UCSF), USA

1:15 PM – 1:20 PM

TOPIC OVERVIEW

1:20 PM – 1:40 PM

Celeste Nelson
Princeton University, USA
THE MECHANICAL LINKS BETWEEN TISSUE MORPHOGENESIS AND PROGENITOR CELL DIFFERENTIATION

1:40 PM – 1:50 PM

Gentaro Ikeda
Stanford University, USA
MITOCHONDRIA-RICH EXTRACELLULAR VESICLES FROM PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES RESTORE ENERGY METABOLISM OF ISCHEMIC MYOCARDIUM IN A PRECLINICAL PORCINE MODEL

1:50 PM – 2:00 PM

Jessie Huang
Boston University, USA
MECHANISMS OF ALVEOLAR EPITHELIAL TYPE 2 CELL SELF-RENEWAL IN LUNG INJURY AND REPAIR

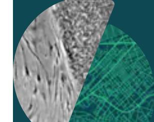
2:00 PM – 2:10 PM

Serena Scala
San Raffaele Scientific Institute, Italy
HEMATOPOIETIC RECONSTITUTION DYNAMICS OF MOBILIZED- AND BONE MARROW-DERIVED HEMATOPOIETIC STEM CELLS AFTER GENE THERAPY

2:10 PM – 2:20 PM

Joseph Collins
University of Pennsylvania, USA
YAP AND TAZ COUPLE OSTEOBLAST PRECURSOR MOBILIZATION TO ANGIOGENESIS AND MECHANOREGULATED BONE DEVELOPMENT

2:20 PM – 2:30 PM	**Mathijs Verhagen** *Erasmus Medical Center, Netherlands* **PANETH CELLS AS THE ORIGIN OF INTESTINAL CANCER IN THE CONTEXT OF INFLAMMATION**
2:30 PM – 2:50 PM	**Tien Peng** *University of California, San Francisco (UCSF), USA* **FRIEND OR FOE: SENESCENCE IN THE STEM CELL NICHE**
2:30 PM – 3:15 PM	**REFRESHMENT BREAK** Exhibit & Poster Hall, Hall A (ends at 3:00 PM) & Level 3 Foyer
3:15 PM – 5:15 PM	**TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)** Ballroom East/West, Level 3 **PLENARY IV: NICHE REGULATION OF DIFFERENTIATION AND REGENERATION** **Session Chairs: Magdalena Goetz** *Helmholtz Zentrum Munchen, Germany* **Jay Rajagopal** *Massachusetts General Hospital and Harvard Stem Cell Institute, USA*
3:15 PM – 3:20 PM	**PLENARY INTRODUCTION**
3:20 PM – 3:40 PM	**Jay Rajagopal** *Massachusetts General Hospital and Harvard Stem Cell Institute, USA* **RARE AIRWAY EPITHELIAL CELLS AND NEW MECHANISMS FOR REGENERATION**
3:40 PM – 4:00 PM	**Kristy Red-Horse** *Stanford University and Howard Hughes Medical Institute, USA* **DEVELOPMENT, REGENERATION, AND REPAIR OF BLOOD VESSELS IN THE HEART**
4:00 PM – 4:20 PM	**Sara Wickström** *Max Planck Institute for Molecular Biomedicine, Germany* **REGULATION OF STEM CELL FATE BY NUCLEAR MECHANOTRANSDUCTION**
4:20 PM – 4:40 PM	**Yukiko Gotoh** *University of Tokyo, Japan* **CHROMATIN-LEVEL REGULATION OF NEURAL STEM CELL FATE DURING MOUSE NEOCORTICAL DEVELOPMENT**
4:40 PM – 5:15 PM	**Takanori Takebe** *Cincinnati Children's Hospital Medical Center, USA, Osaka University, and Tokyo Medical and Dental University, Japan* **ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD LECTURE: UNDERSTANDING INTERCONNECTEDNESS IN LIVER DEVELOPMENT AND DISEASE**
5:30 PM – 6:00 PM	**INNOVATION SHOWCASES: see page 109 for details**
	10X GENOMICS: ORGANOID EXPRESSIONS: USING SPATIAL-OMICS TO VISUALIZE AN ORGANOID TRANSCRIPTOME Virtual
	BAKER COMPANY: OPTIMIZED STEM CELL CULTURE WORKFLOWS IN A FLEXIBLE AND TIGHTLY REGULATED CULTURE ENVIRONMENT FOR ENHANCED CELL PRODUCTION Room 257, Level 2
	CATALENT CELL & GENE THERAPY: NEW DIFFERENTIATION WORKFLOWS AND GMP-COMPLIANT IPSC LINES FOR CELL THERAPY Room 253, Level 2
	IQVIA: DRIVING CELL AND GENE THERAPY DEVELOPMENT FROM "PETRI DISH TO PATIENT" Room 255, Level 2



FRIDAY, 16 JUNE *(continued)*

	LOGOMIX, INC.: PRECISE AND MB-SCALE IPSC GENOME ENGINEERING FOR CELL THERAPY & REGENERATIVE MEDICINE BY LOGOMIX GENO-WRITING™ PLATFORM	Room 254, Level 2 & Virtual
	SCALE BIOSCIENCES: UNLOCKING THE POTENTIAL FOR SINGLE CELL SEQUENCING AT SCALE WITH COMBINATORIAL INDEXING	Room 256, Level 2
	WATERSHED INFORMATICS: SIMPLIFIED LARGE OMICS DATA ANALYSIS FOR EVALUATING CELL THERAPY PRODUCTS	Room 259, Level 2

SATURDAY, 17 JUNE

7:30 AM – 8:00 AM	**REFRESHMENT BREAK**	Level 2 Foyer

CONCURRENT TRACK SESSIONS

8:15 AM – 9:45 AM	**TRACK: CLINICAL APPLICATIONS (CA)** **GENE EDITED ALLOGENEIC T CELLS** **Session Chairs: Chiara Bonini** *IRCCS San Raffaele Scientific Institute, Italy* **Maria Themeli** *Amsterdam Vrije Universiteit, Amsterdam Medical Center*	Room 258, Level 2
8:15 AM – 8:20 AM	**TOPIC OVERVIEW**	
8:20 AM – 8:40 AM	**Maria Themeli** *Amsterdam Vrije Universiteit, Amsterdam Medical Center, Netherlands* **ENGINEERED IPSC AS OFF-THE-SHELF SOURCE OF CAR T CELLS**	
8:40 AM – 8:50 AM	**Miki Ando** *Juntendo University School of Medicine, Japan* **IPSC-DERIVED HYPOIMMUNOGENIC T CELLS ENRICHED WITH TISSUE RESIDENT MEMORY T CELLS POWERFULLY ATTACK CERVICAL CANCER**	
8:50 AM – 9:00 AM	**Teisha Rowland** *Umoja Biopharma, USA* **A SCALABLE, BIOREACTOR-BASED PROCESS UTILIZING A SYNTHETIC CYTOKINE RECEPTOR PLATFORM FOR PRODUCING HIGH YIELDS OF IPSC-DERIVED CYTOTOXIC INNATE LYMPHOCYTES AS AN "OFF-THE-SHELF" CANCER THERAPEUTIC**	
9:00 AM – 9:10 AM	**Julia Bershadsky** *Notch Therapeutics Inc., Canada* **CLINICAL MANUFACTURING PROCESS FOR ENGINEERED CLONAL IPSC LINES**	
9:10 AM – 9:20 AM	**Yasunori Aizawa** *Tokyo Institute of Technology, Japan* **DEVELOPMENT OF MASTER IPSCS WITH SWITCHABLE HLA GENES BY MEGABASE-SCALE GENOME ENGINEERING**	
9:20 AM – 9:40 AM	**Chiara Bonini** *IRCCS San Raffaele Scientific Institute, Italy* **GENOME EDITING OF T CELLS FOR CANCER IMMUNOTHERAPY**	

8:15 AM – 9:55 AM **TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)** Room 253, Level 2

THE USE OF STEM CELLS FOR DISEASE MODELING
Sponsored by bit.bio
Session Chairs: Ya-Wen Chen
Icahn School of Medicine at Mount Sinai, USA
Mingxia Gu
FAHA, Cincinnati Children's Hospital Medical Center, USA

8:15 AM – 8:20 AM **TOPIC OVERVIEW**

8:20 AM – 8:40 AM **Mingxia Gu**
Cincinnati Children's Hospital Medical Center, USA
RECONSTRUCTING ORGANOTYPIC ENDOTHELIUM AND MESENCHYME FROM IPSCS TO STUDY PULMONARY DISEASES

8:40 AM – 8:50 AM **Bryan Wang**
Columbia University, USA
LOSS OF CARDIAC FIBROBLAST BAG3 POTENTIATES TGFBR2 SIGNALING AND FIBROSIS IN DILATED CARDIOMYOPATHY

8:50 AM – 9:00 AM **Mattia Francesco Maria Gerli**
University College London, UK
SINGLE CELL-GUIDED PRENATAL DERIVATION OF PRIMARY EPITHELIAL ORGANOIDS FROM THE HUMAN AMNIOTIC AND TRACHEAL FLUIDS

9:00 AM – 9:10 AM **Shin-Ichi Mae**
Center for IPS Cell Research and Application (CiRA), Kyoto University, Japan
A NOVEL IPSC-DERIVED COLLECTING DUCT CYSTOGENESIS MODEL OF ADPKD FOR DRUG DISCOVERY

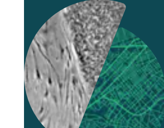
9:10 AM – 9:20 AM **Wardiya Afshar Saber**
Harvard Medical School, USA
USING HUMAN IPSC-DERIVED NEURONS AS A PLATFORM TO INVESTIGATE SUBTYPE SPECIFIC ALTERATIONS IN NEURODEVELOPMENTAL DISORDERS: OUR PROGRESS ON SSADH DEFICIENCY

9:20 AM – 9:30 AM **Alana Van Dervort**
Harvard University, USA
GENERATION OF A DIABETIC IMMUNOPEPTIDOME USING STEM CELL-DERIVED ISLET CELLS

9:30 AM – 9:50 AM **Ya-Wen Chen**
Icahn School of Medicine at Mount Sinai, USA
UNEXPECTED ROLES OF EXTRACELLULAR VESICLES IN SARS-COV-2 INFECTION AND TRANSMISSION

8:15 AM – 9:55 AM **TRACK: NEW TECHNOLOGIES (NT)** Room 259, Level 2

ENGINEERING MODELS OF HUMAN EMBRYOLOGY
Session Chairs: Kathy Niakan
University of Cambridge, UK
Margherita Turco
Friedrich Miescher Institute for Biomedical Research, Switzerland



SATURDAY, 17 JUNE *(continued)*

8:15 AM – 8:20 AM **TOPIC OVERVIEW**

8:20 AM – 8:40 AM **Margherita Turco**
Friedrich Miescher Institute for Biomedical Research, Switzerland
TROPHOBLAST ORGANOIDS FOR THE STUDY OF MATERNAL-FETAL INTERACTIONS IN HUMAN PREGNANCY

8:40 AM – 8:50 AM **Aleksandra Kostina**
Michigan State University, USA
A HUMAN HEART ORGANOID MODEL RECAPITULATING EARLY CARDIAC DEVELOPMENT TO INVESTIGATE THE MECHANISMS OF MATERNAL DIABETES-INDUCED CONGENITAL HEART DEFECTS

8:50 AM – 9:00 AM **Samhan Alsolami**
King Abdullah University of Science and Technology (KAUST), Saudi Arabia
GENERATION OF HUMAN BLASTOIDS FROM SINGLE NAÏVE PSCS IN STIRRED-TANK BIOREACTORS UNDER PHYSIOLOGICAL CONDITIONS FOR HIGH-THROUGHPUT SCREENS

9:00 AM – 9:10 AM **Jitesh Neupane**
University of Cambridge, UK
HUMAN EMBRYO ORGANOIDS AS A MODEL FOR PERI-AND POST-GASTRULATION EMBRYO DEVELOPMENT

9:10 AM – 9:20 AM **Anh Phuong Le**
Boston Children's Hospital, USA
UNDERSTANDING EXTRAEMBRYONIC DEVELOPMENT BY BUILDING HUMAN AMNIOTIC MEMBRANE FROM INDUCED PLURIPOTENT STEM CELLS

9:20 AM – 9:30 AM **Rowan Karvas**
Washington University, USA
3D-CULTURED HUMAN BLASTOIDS MODEL LINEAGE SEGREGATION DURING EARLY POST-IMPLANTATION DEVELOPMENT

9:30 AM – 9:50 AM **Kathy Niakan**
University of Cambridge, UK
UNDERSTANDING MOLECULAR MECHANISMS THAT REGULATE LINEAGE SPECIFICATION IN HUMAN EMBRYOS

8:15 AM – 9:55 AM **TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)** Room 254, Level 2
PHYSIOLOGIC FUNCTION, METABOLISM, AND STEM CELLS
Session Chairs: Andrea Brand
FRS, FMedSCI, NYU Langone, USA
Norbert Perrimon
Harvard University and HHMI, USA

8:15 AM – 8:20 AM **TOPIC OVERVIEW**

8:20 AM – 8:40 AM **Norbert Perrimon**
Harvard University and HHMI, USA
EPITHELIAL CA2+ CURRENTS TRIGGERED BY ENTERIC NEURONS HEAL THE GUT

8:40 AM – 8:50 AM **Silvia Marchiano**
Institute for Stem Cell & Regenerative Medicine at the University of Washington, USA
PREVENTION OF ENGRAFTMENT ARRHYTHMIA FOLLOWING CARDIAC REMUSCULARIZATION WITH GENE-EDITED HUMAN PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

8:50 AM – 9:00 AM

Sarah Millar
Icahn School of Medicine at Mount Sinai, USA
KLF4 MAINTAINS HAIR FOLLICLE STEM CELL QUIESCENCE

9:00 AM – 9:10 AM

Qi Sun
New York University, School of Medicine, USA
MELANOCYTE STEM CELLS ARE MAINTAINED BY DE-DIFFERENTIATION IN A DYNAMIC NICHE

9:10 AM – 9:20 AM

Maud Debaugnies
Université Libre de Bruxelles, Belgium
RHOJ CONTROLS EMT ASSOCIATED RESISTANCE TO CHEMOTHERAPY

9:20 AM – 9:30 AM

Brandon Gheller
Cornell University, USA
CHOLINE METABOLISM MODULATION REDUCES HEMATOPOIETIC CLONAL DOMINANCE

9:30 AM – 9:50 AM

Andrea Brand
NYU Grossman School of Medicine, USA
TIME TO WAKE UP: REGULATION OF NEURAL STEM CELL QUIESCENCE

10:00 AM – 11:25 AM

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD) Ballroom East/West, Level 3
PLENARY V: NEXT GENERATION IN VITRO MODELS
Session Chairs: Ben Maoz
Tel Aviv University, Israel
Nan Tang
National Institute of Biological Sciences, China

10:00 AM – 10:05 AM

PLENARY INTRODUCTION

10:05 AM – 10:25 AM

Roger Kamm
Massachusetts Institute of Technology, USA
VASCULARISED MODELS FOR NEUROLOGICAL DISEASE USING PLURIPOTENT CELLS

10:25 AM – 10:45 AM

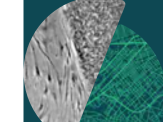
Naomi Moris
The Francis Crick Institute, UK
USING GASTRULOIDS AND EXTENDED MODELS TO EXPLORE PRINCIPLES OF HUMAN DEVELOPMENT

10:45 AM – 11:05 AM

Ryoichiro Kageyama
RIKEN Center for Brain Science, Japan
IMAGING AND QUANTITATIVE ANALYSIS OF SYNCHRONIZED HES7 OSCILLATIONS IN THE MOUSE SEGMENTATION CLOCK

11:05 AM – 11:25 AM

Anna Herland
KTH Royal Institute of Technology, Sweden
COMBINING STEM CELL AND DEVICE ENGINEERING FOR IN VITRO MODELS OF HUMAN PHYSIOLOGY



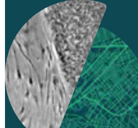
1:00 PM – 2:40 PM	**TRACK: CLINICAL APPLICATIONS (CA)** **PLENARY VI: CLINICAL APPLICATION OF GENE THERAPY AND GENE EDITING** *Sponsored by ElevateBio* **Session Chairs: Giuliana Ferrari** *Ospedale San Raffaele, Italy* **Katherine High** *The Rockefeller University, USA*	Ballroom East/West, Level 3
1:05 PM – 1:25 PM	**Alessandro Aiuti** *San Raffaele Hospital, Italy* **HEMATOPOIETIC STEM CELL GENE THERAPY FOR INBORN ERRORS OF METABOLISM AND IMMUNITY**	
1:25 PM – 1:45 PM	**Selim Corbacioglu** *University Hospital Regensburg, Germany* **EFFICACY AND SAFETY OF A SINGLE DOSE OF EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT B-THALASSEMIA AND SEVERE SICKLE CELL DISEASE**	
1:45 PM – 2:05 PM	**Laura Sepp-Lorenzino** *Intellia Therapeutics, USA* **CLINICAL ADVANCES IN CRISPR-BASED GENOME EDITING FOR TREATMENT OF PATIENTS WITH SEVERE ILLNESS**	
2:05 PM – 2:15 PM	**Allyson Berent** *Foundation for Angelman Syndrome Therapeutics(FAST), USA* **PATIENT ADVOCATE ADDRESS**	
2:15 PM – 2:40 PM	**Michel Sadelain** *Memorial Sloan-Kettering Cancer Center, USA* **JOHN MCNEISH MEMORIAL LECTURE: GENOME-EDITED CAR T CELLS**	
2:30 PM – 3:15 PM	**REFRESHMENT BREAK**	Level 3 Foyer
3:15 PM – 5:25 PM	**PLENARY VII: AWARDS AND KEYNOTE SESSION** *Sponsored by T-CiRA Joint Program* **Session Chairs: Haifan Lin** *Yale University School of Medicine, USA* **David Scadden** *Harvard University and Massachusetts General Hospital, USA*	Ballroom East/West, Level 3
3:15 PM – 3:20 PM	**PLENARY INTRODUCTION**	
3:20 PM – 3:25 PM	**Amander T. Clark** *University of California Los Angeles (UCLA), USA* **ISSCR PRESIDENT-ELECT ADDRESS**	
3:25 PM – 3:35 PM	**Christine L. Mummery** *Leiden University Medical Center, Netherlands* **ISSCR PUBLIC SERVICE AWARD PRESENTATION AND ACCEPTANCE**	
3:35 PM – 4:10 PM	**Cédric Blanpain** *Université Libre de Bruxelles, Belgium* **ISSCR MOMENTUM AWARD LECTURE: MECHANISMS REGULATING TUMOR TRANSITION STATES**	

SATURDAY, 17 JUNE *(continued)*

4:10 PM – 4:45 PM **Thomas A. Rando**
University of California Los Angeles (UCLA), USA
ISSCR ACHIEVEMENT AWARD LECTURE: STEM CELL QUIESCENCE, EVOLUTIONARY TRADE-OFFS, AND TISSUE REGENERATIVE POTENTIAL

4:45 PM – 5:20 PM **Allan Spradling**
Howard Hughes Medical Institute and Carnegie Institution for Science, USA
KEYNOTE ADDRESS: GERM CELLS ILLUMINATE THE BIOLOGY OF HIGHLY POTENT STEM CELLS

5:20 PM – 5:25 PM **POSTER AWARD ANNOUNCEMENTS AND CLOSING**



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Abstracts due 6 July 2023

KEYNOTE SPEAKERS

Christine L. Mummery, PhD
Leiden University Medical Center, The Netherlands

Amander Clark, PhD
University of California, Los Angeles, USA

ELUCIDATING PRINCIPLES OF DEVELOPMENT WITH STEM CELLS

4-6 December 2023
Vienna, Austria
Abstracts due 13 September 2023

SPEAKERS INCLUDE

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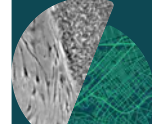

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http://www.allelebiotech.com
Allele Biotechnology (Allele) is a partner for companies creating iPSC-based therapies, providing integrated solutions across engineering, development and cGMP manufacturing. Allele established a core mRNA capability for both iPSC production and iPSC differentiation. The advantages of the use of well-designed mRNA cocktails include precise temporal and stoichiometric control of factors in reprogramming and cell-fate-determination processes. As such, these protocols are generally more robust and consistent than other methods and have readily been standardized for cleanroom operations, and Allele's mRNA-iPSC lines have been shown to have virtually unlimited expansion potentials. Similarly, Allele performs genome-editing services using mRNA-encoded Cas9-like enzymes in iPSCs. The engineered iPSCs can be clonally selected through single-cell sorting with state-of-the-art equipment under cGMP-compliant conditions.

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United States
https://asgct.org
Booth 731
The American Society of Gene & Cell Therapy (ASGCT) is the primary professional organization for individuals working in cell and gene therapy, with a broad membership base including scientists, clinical researchers, physicians, patient advocates, and pharmaceutical and biotechnology professionals. With the support of more than 5,700 members worldwide, the society's mission is to advance knowledge, awareness, and education leading to the discovery and clinical application of genetic and cellular therapies to alleviate human disease. ASGCT's vision is to be a catalyst for bringing together scientists, physicians, patient advocates, and other stakeholders to transform the practice of medicine by incorporating the use of genetic and cellular therapies to control and cure human disease.

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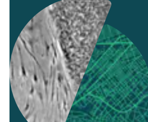

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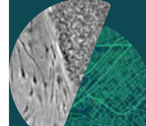

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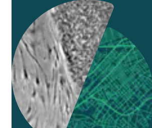

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Clade Therapeutics' mission is to discover and deliver next generation cell medicines to improve the lives of patients in need. Our platform technology "cloaks" human pluripotent stem cells and their adult derivatives enabling the development of immune compatible cell transplantation therapies. The Company is led by a world-class team of company builders and scientific innovators with an unparalleled expertise in generating stem cell-derived adult T, NK and B cells, and is supported by a premier investor syndicate. Clade promises to become a leading innovator in developing widely accessible cell medicines and is initially focused on harnessing the potential of "cloaked" immune cells for cancer treatment. For further information, please visit the company's website at https://www.cladetx.com/.

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https://corebiogenesis.com/
Booth 911
CORE BIOGENSIS provides next-generation recombinant proteins for stem cell research. Rooted by the principles of the bioeconomy, the company delivers its exclusive Ultra-Scalable Biomanufacturing as a Service (UBaaS) platform for the benefit of business leaders, scientists, and ultimately patients in the field of regenerative medicine. Our portfolio has a wide list of growth factors and cytokines for pluripotent, mesenchymal, and immune cells. More importantly, Core Biogenesis supply solutions enable for stock security and long-term batch reservation. Established from scientific rigor, our fast-growing team is fostered by diversity and inclusion in science, business, and technology, and we are fully devoted to help those making the world a better place through the discovery of novel treatments for life devastating diseases.

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https://www.dana-farber.org/
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Founded in Boston in 1947, Dana-Farber Cancer Institute (DFCI) is world-renowned for its leadership in adult and pediatric cancer treatments and research. We develop and disseminate innovative patient therapies and scientific discoveries throughout the world. Within Dana-Farber Cellular Therapies umbrella, there are three FACT accredited programs: DFCI/BWH's Adult program and DFCI/BCH Pediatric program, both of which are accredited for their Transplant Programs and Immune Effector Cell Programs; and the manufacturing laboratory, The Connell & O'Reilly Families Cell Manipulation Core Facility (CMCF), which is accredited for both 361- Minimal Manipulation and 351- More than Minimal Manipulation manufacturing.

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DEFINED BIOSCIENCE INC

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San Diego, CA 92122
United States
https://definedbioscience.com/
Booth 922
Defined Bioscience is a life science company developing cell culture reagents, growth media, and kits to consistently grow high-quality stem cells and stem-derived tissue. We strive to provide improved quality solutions and reduce the production cost of stem cells, stem-derived cells, and tissues for our customers working on life science and cultivated meat solutions. Its flagship products include HiDef-B8, a fully-defined stem cell maintenance medium with weekend-free passaging capabilities, and FGF2-G3, a thermostable variant of FGF2 with a half-life greater than three weeks in mammalian cell culture conditions. Defined Bioscience is located in San Diego, California. For more information, visit us at https://definedbioscience.com.

DENOVOMATRIX

Tatzberg 47
Dresden 1307
Germany
https://www.denovomatrix.com/
Booth 926
denovoMATRIX provides tools for cell manufacturing in higher quality, quantity, and safety. denovoMATRIX supports our customers in cell therapy, cultivated meat, and pharmaceutical research with tools for supporting cell isolation, manufacturing, and differentiation. Our offering is focused on three areas, including tailored biomaterials based on our proprietary platform, stem cell biology & characterization services, and finally high quality cell lines.

DISTEK, INC.

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United States
https://www.distekinc.com/
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Accelerate Process Development with BIOne Benchtop Solutions Distek's bioprocessing solutions offer BIOne benchtop instruments for accelerated process development. With 47 years of experience in biotech and pharma lab testing instruments, Distek's BIOne portfolio comprises the single-use bioreactor for cell culture applications and the BIOne 1250 bioprocess control station, catering to both microbial and mammalian models. The modular and customizable nature of these solutions provides flexibility to support upstream bioprocesses and streamline processes, reducing risk and accelerating tech transfer. The BIOne 1250 control system and BIOne single-use bioreactor are highly adaptable, making them the ideal choice to meet the nuanced requirements of specific upstream bioprocesses.

ELEVATEBIO

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https://elevate.bio/
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ELRIG

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United Kingdom
https://www.elrig.org/
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The European Laboratory Research & Innovation Group (ELRIG) is a leading European not-for-profit organization that exists to provide outstanding scientific content to the life science community. Comprising a global community of over 22,000 life science professionals, participating in our events, whether it be at one of our scientific conferences or one of our networking meetings, will enable any of our community to exchange information, within disciplines and across academic and biopharmaceutical organisations, on an open access basis, as all our events are free-of-charge to attend! Visit our booth to learn more about our free to attend 2023 events.

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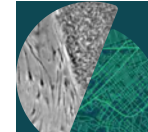

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United States
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Eos BioInnovation is an investment company dedicated to incubating, launching, and building early-stage companies emerging from leading academic labs and research institutions in regenerative medicine.

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Eppendorf is a leading life science company. It was founded in Hamburg, Germany in 1945 and has more than 5.000 employees worldwide. The company has subsidiaries in 25 countries and is represented in all other markets by distributors. Eppendorf – Stimulating Growth. Cultivating Solutions. – Expert Partner in Stem Cell Bioprocessing By exploiting the strong synergies in bioreactor technology and polymer manufacturing, Eppendorf has grown to a global player in the bioprocess marketplace. With a comprehensive offering of single-use and traditional products, the Eppendorf bioprocess portfolio satisfies the demands from research and development through the production of mammalian, microbial, insect, plant and algae cells.

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Essener Bogen 7
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http://www.femtobiomed.com
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Femtobiomed is a cell and gene therapy manufacturing device company based in South Korea. The CellShot® device delivers genetic materials to any cell, including stem cells and innate immunity cells. We are currently in the process of cGMP compliances for clinical use consumables. CellShot® simplified the cell engineering process by eliminating the need of electroporation buffers, permanently reducing the cost and manufacturing timeline. Despite this simplification, the device encompasses all cell types and results high transfection efficiency and cell viability, ultimately a high yield (productivity). It is possible to transfect multiple times sequentially using CellShot®, with minimal impact on cell viability and sustained transfection efficiency. We hope CellShot® support researchers and developers in the field of multiplexed stem cell engineering.

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United States
http://www.fujifilmcdi.com
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FUJIFILM Cellular Dynamics, Inc. (FCDI) is a leading developer and manufacturer of human induced pluripotent stem cells (iPSCs) utilized in drug discovery and cell therapies. The company uses its expertise in iPSC technologies to develop a robust pipeline of cell therapeutics and life science research tools. FCDI offers life science research tools, including iCell® products, that are available in many cell types and sourced from multiple cell lines which can be applied for target identification as well as toxicity testing. Please visit: https://fujifilmcdi.com/

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FUTURE FIELDS

11130 105 Ave NW
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Canada
https://futurefields.io/
Start Up Pavilion Kiosk 9
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GENEMOD

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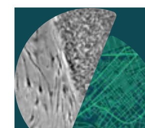
A subsidiary of Nanjing GenScript Biotechnology Co. Ltd., GenScript's dedicated products division, provides extensive product offerings ranging from validated antibodies, stable cell lines, surface marker-based cell separation, encoded-chemical libraries, PCR reagents, gene cloning and gene editing reagents and kits. Furthermore, the products division offers automation solutions and enhanced manual accessories and reagents for western blotting, plasmid and protein purification (resins and AmMag purification technology) and marker-assisted cell separation (CytoSinct cell separation technology). With a commitment to innovation and delivering solutions to unmet scientist needs, GenScript continues to expand its offerings and enhance its solutions.



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Innovative Cell Technologies is the sole manufacturer of all Accutase® sold worldwide. Accutase® is a direct replacement for all cell detachment solutions. With over 22,000 citations to date referencing the use of Accutase® in the culture of stem cells, it is the go-to reagent for stem cell research. It is gentle on stem cells, does not require neutralization and is now available in a cGMP formulation. Stop by booth 230 to sign up to receive a FREE sample.

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KATAOKA-SS AMERICA CORP.

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Carson, CA 90745
United States
https://www.kataoka-ss.co.jp/en/
Booth 232
Kataoka-SS America, a US subsidiary of Kataoka Corporation Kyoto Japan, is the manufacturer of Cell Processor CPD-017. Kataoka`s Cell Processor uses laser and AI technology to scan, identify, and irradiate spontaneously differentiated iPS cells without disassociation or applied stress to the cells. With the CPD-017, the process time of purifying induced pluripotent stem cell (iPSC) is significantly reduced and the adherent cell colonies can maintain a stress-free healthy condition. The CPD-017 uses a unique light-responsive polymer technology to gently and accurately kill the unwanted cells without disturbing the surrounding cells.

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Booth 133
Landmark Bio is a collective endeavor launched by leaders from academia, the life sciences industry, and world-renowned research hospitals to accelerate development and industrialization of next-generation genomic medicine. Inspired by recent advancements in cell and gene therapy, Landmark Bio was established to remove barriers in drug development, create accessible capability, expertise, and solutions, and offer a collaboration platform to advance manufacturing technologies for the new generation of medicines to come. Founding partners include Harvard University, Massachusetts Institute of Technology (MIT), Cytiva, FUJIFILM Diosynth Biotechnologies (FDB), and Alexandria Real Estate Equities, Inc. Other collaborating institutions include Beth Israel Deaconess Medical Center, Boston Children's Hospital, Mass General Brigham, and the Dana-Farber Cancer Institute.

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Japan

https://logomix.bio/
Logomix is a mammalian synthetic biology company developing artificial human cells for new therapeutics based on its pioneering Geno-Writing™ platform technology. Logomix's innovative genome engineering platform Geno-Writing™ is able to write large-scale and complex messages into a genome. It will enable therapy developers to write therapeutics sequences to develop new modalities and cure serious diseases such as cancer, neurodegenerative diseases, and genetic diseases under discovery collaborations with biopharma companies.

LUMINX BIOTECH CO., LTD

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Start Up Pavilion 6
LuminX Biotech is committed to providing preclinical and clinical data required by academic research centers, CROs, and cell therapy-related medical institutions worldwide to build up the "LuminX Cell Therapy Enable Platform". The platform is dedicated to helping customers with cytology, experimental animal model development, evaluation of drug kinetics, efficacy, metabolism, localization tracking of various cellular drugs, and even the "quantitative cellular drug biodistribution," which is considered one of the most difficult tasks in the world. LuminX offers a wide range of professional biochemical and biomedical services to our customers, including molecular biochemistry, high-level analytical services, morphology, extracellular vesicles (EVs & exosome field techniques and analysis), and customized services for in vivo and in vitro model experiments in cell biology.

MARYLAND STEM CELL RESEARCH FUND (MSCRF)

7021 Columbia Gateway
Suite 500
Columbia, MD 21046
United States
https://www.mscrf.org
The Maryland Stem Cell Research Fund (MSCRF) was established in 2006 by the Governor and the Maryland General Assembly through the Maryland Stem Cell Research Act of 2006. The purpose of the Fund is to promote state-funded stem cell research and cures through grants and loans to public and private entities. Our mission is to develop new medical strategies for the prevention, diagnosis, treatment and cure of human diseases, injuries and conditions through human stem cells. MSCRF offers 7 grant programs that help transition human stem cell-based technologies from the bench to the bedside, as well as mechanisms to foster the growth of stem cell companies in Maryland.

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Rockville, MD 20850
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http://www.maxcyte.com
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MAXWELL BIOSYSTEMS

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Zurich 8047
Switzerland
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MaxWell Biosystems is a technology leader providing instrumentation and solutions to boost scientific research and development in neurosciences, stem cell and tissue engineering, ophthalmology, and other fields involving electrogenic cells. The company engineered advanced high-density microelectrode arrays (HD-MEAs) as the core of easy-to-use platforms, MaxOne (single-well) and MaxTwo (multi-well), that equip scientists to record electrical signals of neurons in in-vitro 2D and 3D models. MaxWell Biosystems' HD-MEA technology allows to capture neuronal activity across multiple scales, from sub-cellular to single cells, up to full networks in unprecedented detail. Ultimately, MaxWell Biosystems' platforms facilitate the understanding of neurological diseases, enhance the efficiency of cell-based assays for toxicity and safety pharmacology, and accelerate drug discovery.

MBL INTERNATIONAL CORPORATION

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MEDCHEMEXPRESS

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https://www.miltenyibiotec.com
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MIMETAS B.V.

De Limes 7
Oegstgeest, Zuid-Holland 2342DH
Netherlands
https://www.mimetas.com/en/home/
Booth 833
MIMETAS is a global leader in disease modeling using Organ-on-a-Chip technologies. Founded in 2013 in Leiden, the Netherlands, MIMETAS strives to contribute to ground-breaking therapies with unique human disease biology, revealed by robust, screenable assays in their proprietary platform, the OrganoPlate®. MIMETAS believes that phenotypic tissue-and disease modeling is at the heart of 21st-century therapy development. The OrganoPlate enables the development and high-throughput screening of physiologically relevant disease models for drug discovery and development. By combining technological strengths and expertise, MIMETAS establishes strong drug development partnerships with and offers services to global pharmaceutical companies to develop innovative therapies to target untreatable diseases. The company also provides off-shelf products such as pre-seeded plates through the OrganoReadyTM line and the OrganoTEER® device.

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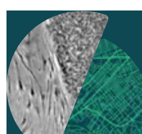
http://www.moleculardevices.com
Booth 305
At Molecular Devices, we enable our customers to unravel the complexity of biological systems. We provide platforms for high-throughput screening, genomic and cellular analysis, colony selection and microplate detection. These leading-edge products empower scientists to improve productivity and effectiveness, ultimately accelerating research and the discovery of new therapeutics.

MONOMER BIO

51 Outlook Circle
Pacifica, CA 94044
United States
http://monomerbio.com
Booth 228
Monomer provides an out-of-the-box automation solution for cell culture workflows designed for volumes that range from as small as 25 uL (in 384-well plates) up to 110 mL in 1-well plate autoflasks. The solution encompasses a software platform layered over commercially available hardware, and a services team of lab automation experts who handle the design, build, configuration, and deployment at customer sites. The Monomer software platform combines a best-in-class execution engine (dynamic scheduling and intuitive operator interfaces) with a robust data platform built for managing, analyzing, and displaying cell culture readouts in realtime. The data platform supports embedded ML algorithms for annotating sophisticated features like contamination and cell morphology.



NACALAI USA, INC.

6625 Top Gun Street
Suite 107
San Diego, CA 92121
United States
http://www.nacalaiusa.com
Booth 201
Nacalai USA, Inc., a wholly owned subsidiary of Nacalai Tesque Inc. (Kyoto, Japan), is based in San Diego, California. Nacalai USA strives to introduce the most innovative and rigorously quality-controlled biochemical reagents and research tools from Japan to the U.S. market, as well as bringing U.S. technologies and products to the Japanese research market. Nacalai USA provides the highest quality research products for Regenerative Medicine Research and Life Science research.

NANOCELLECT BIOMEDICAL

9525 Towne Centre Dr.
Suite 150
San Diego, CA 92121
United States
https://nanocellect.com/
Booth 622
NanoCellect develops innovative solutions for cell sorting based on microfluidic technology. NanoCellect's WOLF and WOLF G2 Cell Sorters provides simple and gentle sorting to maintain cell viability in sterile cartridges. The WOLF is used in many application areas including genomic sample preparation, immunophenotyping, antibody discovery, cell line development, and CRISPR gene editing. Register for the WOLF G2 Cell Sorter digital launch event. Follow us on LinkedIn.

NANOSTRING TECHNOLOGIES

530 Fairview Ave N
Seattle, WA 98109
United States
https://nanostring.com/
Booth 207
NanoString Technologies, a leader in spatial biology, offers an ecosystem of innovative discovery and translational research solutions. The GeoMx® Digital Spatial Profiler is a flexible solution combining the power of whole tissue imaging with gene expression and protein data for spatial whole transcriptomics and proteomics from one FFPE slide. The CosMx™ Spatial Molecular Imager (SMI) is an FFPE-compatible, single-cell imaging platform powered by spatial multiomics enabling researchers to map single cells in their native environments. The AtoMx™ Spatial Informatics Platform (SIP) is a cloud-based informatics solution with advanced analytics and global collaboration capabilities, enabling spatial biology insights anytime, anywhere. www.nanostring.com.

NEST SCIENTIFIC USA

3 Convery Blvd Ste 600
Woodbridge, NJ 07095
United States
http://www.nestscientificusa.com/
Booth 206
NEST is dedicated to researching and developing innovative plastic consumables suitable for life sciences research and medical establishments. There are more than 600 plastic consumables that can be widely used for cell culture, molecular biology, immunoassays, liquid handling, and storage such as cell culture plates, Erlenmeyer flasks, BioFactory, pipette tips, etc. More than 100 medical plastic consumables and reagents can be used in molecular diagnosis and vaccination, such as disposable samplers, transport media, swabs, nucleic acid extraction kits, and disposable intranasal atomization devices. In order to provide a more comprehensive and convenient service, we work closely with our affiliated company Wuxi Tech-star Technology Co., Ltd. We also provide lab instruments such as centrifuges, metal baths, BioBank, etc.

NEUCYTE

319 N Bernardo Avenue
Mountain View, CA 94043
United States
https://www.neucyte.com/
Booth 932
NeuCyte is an innovative biotechnology company focused on CNS drug discovery. Based on its proprietary SynFire® technology for generating human iPSC-derived neurons, NeuCyte has developed a highly functional in vitro platform for target identification and validation, compound efficacy testing, neurotoxicity assessment, and disease modeling. The team is actively pursuing drug discovery programs on Alzheimer's disease, ALS, Epilepsy, Fragile X Syndrome, and more.

NIPPI, INC.

1-1-1 Sonju, Midori-cho,
Adachi, Tokyo 120-8601
Japan
https://www.nippi-inc.co.jp/english/business_outline/tabid/212/Default.aspx
Booth 422
Nippi Inc., based out of Tokyo, Japan, has been doing business for well over 100 years producing collagen and gelatin products for various industries. With the creation of the Nippi Research Institute of Biomatrix, Nippi has begun innovating in the biotech space with products like MatriMix™ and utilizing technologies such as spERt™, while differentiating ourselves with medical-grade collagen and gelatin products. Matrixome, Inc. is a venture company born out of Osaka University and over 20 years of ECM research by Professor Sekiguchi. With the creation of the laminin E8 fragment, a unique product line was created called iMatrix™ with numerous advantages over other cell culture substrates. iMatrix-511, available in clinical and research grades, has already been utilized in clinical trials.

NISSAN CHEMICAL AMERICA CORPORATION

10333 Richmond Ave
Suite 1100
Houston, TX 77042
United States
https://nissanchem-usa.com/
Booth 531
Nissan Chemical Corporation has been a leading producer of fine chemicals for more than 100 years. Since our company was founded in 1887, our mission has been to explore the limitless possibilities of chemical science to create safe, valuable, reliable products that satisfy customer demands, and pave the way for a brighter future. In the Healthcare business development department, we have combined our unparalleled expertise in organic synthesis, polymer design, nanoparticle technology, and biological evaluation to develop game-changing innovations for the fields of regenerative medicine, drug discovery, and several other life sciences industries. Our materials provide new solutions for cell spheroids/organoids manufacturing and room temperature transportation methods for research and clinical development of cell therapy.

NITTA GELATIN

Contributing Sponsor
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Ste 900
Morrisville, NC 27560
United States
https://bematrixbiomedical.com/
Booth 624
Nitta Gelatin Inc. was founded 1918 and is a world-leading gelatin manufacturer with proprietary technology to quickly and efficiently service global customers. Our products include ultra-pure collagen applied in regenerating human tissue, biomaterial, and gelatin for the pharmaceutical industry. We also have a long history of research and development in unlocking the potential of collagen and gelatin for medical applications, in various fields, including medical device, cell therapy, gene therapy, and virotherapy. We thrive to support a dramatic reduction of challenging hurdles of overhead costs associated with cold chain logistics in virus stability and backflow (leakage) in local injection through our patented technologies, using our up-to-date gelatin formulations with pharmaceutical grade and registered trademark products from the beMatrix series.

NORDMARK PHARMA GMBH

Pinnauallee 4
Uetersen, Schleswig-Holstein 25436
Germany
http://www.nordmark-biochemicals.com
Booth 113
Nordmark, one of the world's largest manufacturers of pharmaceutical collagenases, develops and produces translational enzymes - research and GMP grade collagenases and neutral proteases – to simplify the path from research to the clinic. Our Nordmark Biochemicals division offers products for cell isolation from a variety of tissues and extensive support for both research and clinical applications. Our Collagenase NB 6 GMP Grade is a fast and reliable tool for cell isolation of many cell types. Additionally, we provide highly purified, animal-free Collagenase AF-1 GMP Grade and Neutral Protease AF GMP Grade.

NOTCH THERAPEUTICS

887 Great Northern Way
Suite 500
Vancouver, BC V5T 4T5
Canada
http://www.notchtx.com
Notch is a biotech company working to maximize the benefit of cell therapies for cancer. The company is generating functional T cells from renewable induced pluripotent stem cells with unprecedented function. This is made possible by the company's proprietary stir-tank bioreactor process for controlling notch and other signaling pathways during cell manufacturing. In the pursuit of true 'off the shelf' cell therapy, Notch is using open clinical data, artificial intelligence, and computational biology to produce an unlimited supply of therapeutic T cells.

NOVARTIS INSTITUTES FOR BIOMEDICAL RESEARCH

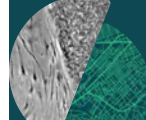
https://www.novartis.com/
Our mission is to discover new ways to improve and extend people`s lives. Our vision is to be a trusted leader in changing the practice of medicine. We use science-based innovation to address some of society's most challenging healthcare issues. We discover and develop breakthrough treatments and find new ways to deliver them to as many people as possible.

NOVOHEART

5171 California Avenue, Ste 150
Irvine, CA 92617
United States
https://www.medera.bio/
Booth 905
Novoheart is a global stem cell biotechnology company pioneering an array of next-generation human heart tissue prototypes. Through its MyHeart Platform of bioengineered 2D and 3D heart tissue constructs including organoid chambers, Novoheart aspires to revolutionize drug discovery, helping to save time and money for developing new therapeutics by offering accurate, sensitive and reliable drug screening and disease modelling tools.

NOVO NORDISK

https://www.novonordisk.com/
Booth 323
Novo Nordisk is a leading global healthcare company, founded in 1923 and headquartered in Denmark. Our Rare Disease division is focused on generating scientific and technological breakthroughs for people living with a rare disease through the discovery and development of integrated therapeutic solutions and novel indications of established medicines in rare and ultra-rare blood, endocrine and renal disorders. Novo Nordisk employs about 54,400 people in 80 countries, of which 3,300 work with rare diseases.



OMEGA BIO-TEK

400 Pinnacle Way, Ste 450
Norcross, GA 30071
United States
https://www.omegabiotek.com/
Booth 306
Omega Bio-tek, founded in 1998, is an ISO 9001:2015 and ISO 13485:2016 certified, industry-leading manufacturer of DNA/RNA purification kits for clinical, biotechnology, and genomics research. With a diversified product portfolio for low-throughput to high-throughput purification, Omega Bio-tek kits purify high-quality nucleic acids from a wide variety of samples. Omega Bio-tek's products and services are used in thousands of universities and research institutes in over 100 countries worldwide.

ORFLO TECHNOLOGIES

260 Northwood Wy
Ketchum, Idaho, ID 83340
United States
http://www.orflo.com/
Booth 930
ORFLO Technologies is a life sciences company that develops fast and accurate personal systems for cellular analyses. 'Increasing your pace of discovery' has always been our mission. ORFLO has revolutionized cell analysis by integrating fluorescence with Coulter Principle for accurate cell counting and sizing, helping scientists accelerate discoveries. Our powerful solutions include industry-leading cell counters and personal cell analysis systems.

PBS BIOTECH INC.

4721 Calle Carga
Camarillo, CA 93012
United States
http://www.pbsbiotech.com
Booth 825
PBS Biotech is a leading manufacturer of single-use bioreactor systems and provider of process development services. PBS bioreactors utilize proprietary Vertical-Wheel® technology to create homogeneous and scalable mixing conditions for a variety of sensitive cell therapy products and cell culture applications. PBS Biotech's vision is to become the world's standard manufacturing platform for allogeneic cell-based therapies. To learn more, visit pbsbiotech.com or contact sales@pbsbiotech.com.

PEPROTECH, PART OF THERMO FISHER SCIENTIFIC

5 Cedarbrook Drive
Cranbury, NJ 08512
United States
http://www.thermofisher.com/peprotech
Booth 515
PeproTech is a business unit within the Thermo Fisher Scientific Biosciences Division, specializing in manufacturing high quality cytokine products and providing exceptional service to the global life science and cell therapy markets. Our products include Recombinant Human, Murine and Rat Cytokines, Animal-Free Recombinant Cytokines, GMP Cytokines, Antibodies and ELISA Kits.

PEPTIGROWTH

411, Hackensack Ave,
Suite 901,
Hackensack, NJ 07601
United States
https://peptigrowth.com/en/
Booth 410
PeptiGrowth was established in April 2020 as a joint venture between Mitsubishi Corporation and PeptiDream Inc. Its mission is to contribute to the growth of the regenerative medicine and cell therapy industry through innovative solutions. Since its foundation, PeptiGrowth has been developing a series of synthetic peptides that have the same functions as the conventional growth factors and cytokines by joint development with PeptiDream. Following HGF-Alternative Peptide (PG -001), TGFβ1 inhibitor (PG -002), Trk-b, BDNF -alternative peptide (PG -003), Noggin-alternative peptide (PG-004), Noggin- BMP4 specific peptide(PG -005), and Noggin- BMP7 specific peptide(PG -006). PeptiGrowth plans to launch the next series of key growth-factor alternatives in 2023 to serve the cell-culture business.

PHASE HOLOGRAPHIC IMAGING

Skiffervägen 48
Lund, Skane Lan 22478
Sweden
https://phiab.com/
Booth 430
Phase Holographic Imaging (PHI) aims to empower any lab to work cell-friendly by developing and marketing innovative tools for non-invasive time-lapse imaging and analysis of cells. The company's HoloMonitor product line is used by researchers worldwide for long-term, quantitative analysis of living cell cultures, particularly in preclinical research, stem cell studies and regenerative medicine. PHI is based in Lund, Sweden and Boston, Massachusetts.

PLURISTYX

3000 Western Avenue
Seattle, WA 98121
United States
http://www.pluristyx.com
Booth 626
A fully integrated Pluristyx and panCELLa offer an enlarged portfolio and aims to become the leading provider of iPSC and cell therapy services and solutions. The combined product and service offerings provide clients with the fastest speed to clinic and the best route to commercialization. Pluristyx today offers a portfolio of iPSC-based products and services to provide end-to-end client support in early product development, while PanCella offers an array of unique and effective technologies with particular strength in gene editing. The long-term focus of the combined company is to offer an expanding technology base and products and deepen operating capabilities to become the global leader in clinical-grade, genetically modified iPSCs with the lowest barrier to entry for cell therapy development.

PROTEINTECH GROUP INC.

5500 Pearl Street
Suite 400
Rosemont, IL 60018
United States
https://www.ptglab.com/
Booth 300
Proteintech is a leading manufacturer of life science reagents with the largest proprietary portfolio of self-manufactured antibodies. With over 150,000 publications, Proteintech offers antibodies and immunoassays across research areas. In addition, Proteintech produces cytokines, growth factors and other proteins that are human expressed, bioactive and cGMP-grade. ChromoTek is part of Proteintech and is a pioneer in the development and commercialization of innovative reagents based on camelid Nanobodies.

QKINE

Unit 1 Murdoch House
30 Garlic Row
Cambridge, England CB5 8HW
United Kingdom
http://www.qkine.com
Booth 709
Qkine manufactures high-purity, animal-free growth factors, cytokines, and other complex proteins for stem cell, organoid culture, and regenerative medicine. Our ISO9001: 2015 certified facility is based in Cambridge, UK, and Qkine combines proprietary production processes with protein engineering technology to tackle fundamental biological and scale-up challenges. We aim to provide the highest purity, bioactive proteins to support our customers and maximize the impact of their science. We are leaders in protein innovation and have developed a portfolio of growth factors for use in the most popular pluripotency media recipes and organoid cultures. Unique products available from Qkine include thermostable FGF2-G3 and the first animal-free TGF-β1 for chemically defined stem cell media. For more information, please email info@qkine.com.

REPROCELL USA INC.

9000 Virginia Manor Rd.
Suite 207
Beltsville, MD 20705
United States
https://www.reprocell.com
Booth 414
Our corporate vision is to promote human health by providing cutting-edge products and services that advance the future of Regenerative Medicine. Our RNA-based GMP iPSC – Master Cell Bank manufacturing is compliant with regulatory standards of FDA, EMA, and PMDA. For drug discovery, REPROCELL's pre-clinical service is uniquely positioned to provide custom assay services using functional human tissues or 3D tissue models to demonstrate the efficacy and safety of investigational drugs prior to costly clinical trials. Established in 2003, REPROCELL became the first stem cell research company in Japan. In recent years, the REPROCELL group expanded through a series of acquisitions globally creating a workflow including human tissue acquisition (BioServe®), RNA reprogramming (Stemgent®), 3D technologies (Alvetex®) and drug discovery (Biopta®).

REVVITY

940 Winter Street
Waltham, MA 02451
United States
https://www.revvity.com/
Booth 832
Revvity provides health science solutions, technologies, expertise, and services that deliver complete workflows from discovery to development, and diagnosis to cure. Revvity is pushing the limits of what's possible in healthcare, with specialized focus areas in translational multi-omics technologies, biomarker identification, imaging, prediction, screening, detection and diagnosis, informatics, and more. With a robust global network and localized agility, we serve a diverse range of organizations from pharmaceutical and biotech, to clinical labs, academia, and governments. Together with our customers and partners, we are united in impact, embracing the impossible to improve lives everywhere.

ROCKEFELLER UNIVERSITY PRESS

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United States
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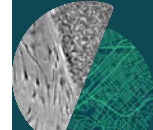
Rockefeller University Press publishes Journal of Cell Biology (JCB), Journal of Experimental Medicine (JEM), Journal of General Physiology (JGP), and co-publishes Life Science Alliance (LSA). RUP journals publish groundbreaking research in the life sciences and biomedicine from leading investigators around the world and serve as a valued resource to those engaged in cutting-edge research and who train future generations of scientists. RUP journals were established by the research community, and editorial decisions and policies continue to be driven by scientists who actively contribute to their fields, appreciate the value of peer review, and desire a better publication experience for all. Join us at our booth to learn more and speak with an editor about your research.

RWD LIFE SCIENCE CO. LTD.

6540 Lusk Blvd
Suite C161
San Diego, CA 92121
United States
http://www.rwdstco.com
Booth 103
Contributing wits and powers to enhance the quality of life has always been the vision of RWD Life Science. By providing competitive instruments, solutions and services for Industry-Academia-Research of life science, RWD helps researchers in the life science field achieve success. Our products and solutions have been delivered to over 100 countries, helping more than 1000 research institutions, 6000 universities and 700 hospitals to achieve success. Our products and solutions have fully covered in the fields of neuroscience, immunology, lab animal research, cell and molecular biology, histopathological diagnosis and veterinary medical. As a leading instruments and equipment provider, RWD is actively carrying out joint innovation with customers, hoping to become a powerful enabling platform for "industry-academia-research-application" in life science.



S-BIO, SUMITOMO BAKELITE CO., LTD.

20 Executive Dr
Hudson, NH 03051
United States
http://www.s-bio.com
Booth 808
S-BIO specializes in providing high-performance and highly quality-controlled labware for Drug Screening and Regenerative Medicine. 3D-cell culture PrimeSurface® ULA plates are used in cancer spheroid culturing and organoid formation. Low Bind Proteosave and Stemfull tubes are used to block any non-specific binding thus preventing sample loss and increasing recovery of DNA, RNA, proteins, peptides, and cells. SuperQuality, high-quality-controlled labware products are manufactured especially for regenerative medicine and cell manufacturing facilities. Labware includes flasks, pipettes, plates, and tubes that are triple-packed with advanced quality control to minimize foreign particle adhesion in labware. S-BIO's most recent development to advance research in the pharmaceutical industry is a versatile micro-physiological system that will assist in bridging the gap between animal studies and clinical trials.

SARTORIUS

Contributing Sponsor
565 Johnson Ave.
Bohemia, NY 11716
United States
https://www.sartorius.com
Booth 533
We empower scientists and engineers to simplify and accelerate progress in life science and bioprocessing, enabling the development of new and better therapies and more affordable medicine. The CellCelector Flex platform is a fully automated cell imaging and picking system developed for the screening, detection, selection and isolation of single cells, clusters, spheroids and organoids, as well as single cell clones and adherent colonies. It is widely used in a multitude of research areas, including stem cell research. The Incucyte® Live-Cell Analysis System automatically acquires and analyzes images around the clock, providing an information-rich analysis that is easy to achieve. Monitor stem cell reprogramming and differentiation events from your desktop without removing cells from the incubator.

SCALE BIOSCIENCES

1440 O'Brien Dr.
Menlo Park, CA 94025
United States
http://www.scale.bio
Booth 915
At ScaleBio, we leverage the cell as the compartment to employ combinatorial indexing single-cell profiling solutions. This method enables increased levels of sample multiplexing, increased cell throughput, and support for a broad range of single-cell genomics applications. Numbers of cells or nuclei can be scaled exponentially to enable single-cell experiments with 100s of thousands to millions of cells, at a fraction of the cost of on-market single-cell isolation instruments. We currently have products to support scRNAseq, scATACseq, and are developing applications for single-cell methylation, protein, and multi-omic analysis.

SCELLEX

Tukholmankatu 8
Biomedicum 2U
Helsinki, Uusimaa 00290
Finland
https://www.scellex.com/
Start Up Pavilion Kiosk 11
SCellex Oy is a Finnish biotech company that develops novel solutions for spatial single cell analysis. Our unique, patented technology is based on oligo-tagged microbeads in 20 different sizes and colours, which form over million random but unique, microscopically visible combinations in picowell arrays. Image is analyzed with AI model that creates spatial coordinates matching the picowells with the RNAseq profiles of the cells or tissues sequenced from each well. Our method works in various applications and is suitable both for tissue cryosections and cell suspensions, allowing also functional cell assays and single cell cultures in the picowells. The colour microbeads can be also used with third party arrays such as Singleron Biotechnologies GEXSCOPE and BD Rhapsody.

SCIENCELL RESEARCH LABORATORIES

1610 Faraday Ave
Carlsbad, CA 92008
United States
http://www.sciencellonline.com
Booth 432
ScienCell is the world's largest cell provider. We enable the scientists of today to discover the science of tomorrow by providing a variety of high-quality normal human and animal cells, cell culture media and reagents, gene analysis tools, cell-derived molecular biology products, cell-based assay kits, and stem cell products for the research community.

SCISMIC

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625 Massachusetts Avenue
Cambridge, MA 23188
United States
http://www.scismic.com
Start Up Pavilion Kiosk 7
Scismic is a skills-based talent matching platform that places the right STEM candidates in the right jobs. We use tech to pre-qualify candidates so only those with the right skills and experiences apply. We support STEM jobseekers with resume reviews, webinars on career advancement, and networking opportunities. We support STEM-Tech companies with hiring and best practices for equitable evaluation practices and first class customer support.

SEED BIOSCIENCES SA

Rt de la Corniche 6
Bldg Serine
Epalinges, Vaud 1066
Switzerland
https://seedbiosciences.com/
Booth 529
By accelerating the use of precision medicine in personalized therapies, SEED Biosciences aims to set new standards in single-cell biology to benefit patients. To do this, we provide scientists with innovative tools that are gentle with cells, affordable, intuitive and – most importantly – compliant with the most stringent regulatory demands. Our first product, DispenCell™, enables scientists to isolate single cell lines three times faster and ten times cheaper than existing solutions. The award-winning company is headquartered in Switzerland. Visit SEED Biosciences at www.seedbiosciences.com.

SONY BIOTECHNOLOGY INC.

1730 N. First St.
San Jose, CA 95112
United States
https://www.sonybiotechnology.com/us/
Booth 623
Sony Biotechnology Inc. is dedicated to helping the scientific community, researchers, laboratory professionals, and institutions achieve the best scientific results possible. By leveraging Sony's comprehensive expertise in electronics innovation and design and with our technological assets we are accelerating development of next-generation cell analysis systems. We bring a unique perspective to science's high-level instrumentation and are creating innovative products to address our customer's challenges.

STEM CELL NETWORK

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501 Smyth Road
Box 511
Ottawa, ON K1H 8L6
Canada
http://www.stemcellnetwork.ca
The Stem Cell Network (SCN) is a national not-for-profit organization that supports three main objectives: stem cell and regenerative medicine research; training the next generation of highly qualified personnel; and supporting the knowledge mobilization and transfer of stem cell and regenerative medicine research. From the lab to the clinic, SCN's goal is to power life-saving therapies and technologies through regenerative medicine research for the benefit of all. With support from the Government of Canada, the Network has grown from a few dozen labs to over 230 world-class research groups, supporting 225+ research projects and more than 25 clinical trials. Since inception, over 20 biotech companies have been catalyzed or enhanced and more than 5,000 highly qualified personnel have been trained.

STEM CELL PODCAST

1618 Station St
Vancouver, BC V6A1B6
Canada
https://stemcellpodcast.com/
Booth 906
Launched in 2013, the Stem Cell Podcast is an accessible and entertaining resource that allows scientists to stay current with the latest developments in stem cell research. Listen bi-weekly as hosts Drs. Daylon James and Arun Sharma discuss recent publications and talk with stem cell biologists about their research and perspectives on the field. The Stem Cell Podcast is owned and produced by STEMCELL Technologies as part of its commitment to helping scientists stay current and connected with science and with each other. The Stem Cell Podcast is available wherever you get your podcasts.

STEM CELL REPORTS

https://www.cell.com/stem-cell-reports/home
Virtual only exhibit
Stem Cell Reports, the official journal of the ISSCR, is an online, open access forum communicating basic discoveries-in stem cell research, in addition to translational and clinical studies. The journal also produces a podcast, The Stem Cell Report, a Podcast with Martin Pera available on iTunes, Spotify and other podcast platforms.

STEM GENOMICS

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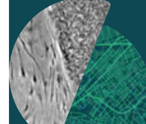
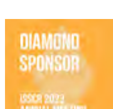
Institute for Regenerative Medecine & Biotherapy
Hôpital Saint Eloi
80 avenue Augustin Fliche
Montpellier Cedex 5, Languedoc-Roussillon 34295
France
http://www.stemgenomics.com
Booth 707
Stem Genomics designs innovative testing solutions for research scientists working on Stem Cells. We offer a range of innovative tests for various cell types with clients based all around the world. Our flagship assay uses digital PCR and a panel of specific probes to detect most of the recurrent genetic abnormalities observed in stem cells. This innovation, called iCS-digital™, is rapid, robust, and cost-effective. It can be performed on genomic DNA, cell pellets and cells in fresh culture media (or in cell culture supernatant).



STEMBIOSYS, INC

Contributing Sponsor
3463 Magic Drive
Suite 110
San Antonio, TX 78229
United States
http://www.stembiosys.com
Booth 317
StemBioSys offers a range of cell derived microenvironments which offer multiple advantages for cell culture in research settings. The centerpiece of these technologies is our CELLvo™ Matrices. These tissue-specific, cell-derived microenvironments elicit biologically relevant phenotypes from a variety primary and stem cell-derived cell types. The company also has several cell products isolated and expanded on our matrix In November 2020, we published a paper in Nature Scientific Reports that described an important application of our technology that improves assays for cardiac safety testing of drugs in development. Our product is currently being used by multiple pharmaceutical companies. Additional applications will be announced in 2023.

STEMCELL TECHNOLOGIES INC.



1618 Station St.
Vancouver, BC V6A 1B6
Canada
https://www.stemcell.com/
Booth 401
At STEMCELL, science is our foundation. Driven by our mission to advance research globally, we offer over 2,500 tools and services supporting discoveries in stem cell research, regenerative medicine, immunotherapy and disease research. By providing access to innovative techniques like gene editing and organoid cultures, we're helping scientists accelerate the pace of discovery. Inspired by knowledge, innovation and quality, we are Scientists Helping Scientists.

STEMCULTURES

1 Discovery Dr.
Rensselaer, NY 12144
United States
https://stemcultures.com/
Booth 412
StemCultures provides controlled-release growth factor media additives for iPSC culture. This technology overcomes the fluctuations in growth factor levels due to half short half-life, eliminating the need for daily feeding and unknown growth factor concentrations in media. Providing stable FGF2 levels reduces feeding to 2-3x a week, saving on media and labor. This reduces unwanted spontaneous differentiation while enhancing pluripotency to improve differentiation efficiency and organoid production.

STREX

10060 Carroll Canyon Road
San Diego, CA 92131
United States
https://strexcell.com/
Booth 428
Strex manufacturers "LN2 Free Controlled Rate Freezers, Mecahnotransduction Stress Systems, and Cell Pressurizing Systems for iPS/ES cells. We are constantly developing new cutting edge technology in the fields of cell biology, regenerative medicine, and tissue engineering. Come visit our booth so you can take your research to the next phase by studying cells in their physiological state during your journey to discovery.

SYNTHEGO

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3696 Haven Ave
Suite A
Redwood City, CA 94063
United States
http://www.synthego.com

Booth 713
Synthego is a genome engineering company that enables life science research and the development of new therapeutics and genomic medicines. Our mission is to increase access to CRISPR-based technologies and therapeutics for all scientists and patients. With unparalleled CRISPR expertise, state-of-the-art cell engineering and GMP capabilities, and a continuum of product offerings, Synthego supports the development of new therapeutics and genomic medicines at every step, from R&D through IND submission to first-in-human clinical trials.

SYSTEMIC BIO A 3D SYSTEMS COMPANY

333 3D Systems Circle
Rock Hill, SC 29730
United States
https://systemic.bio/
Booth 903
Allevi became part of the 3D Systems family in 2021 as part of the company's strategic growth in advanced bioprinting & regenerative medicine. Our 3D bioprinters & bioinks are used by leading researchers worldwide to find solutions to humanity's most difficult problems—to cure disease, to test novel drugs, to eliminate the organ waiting list, to build with life. Allevi by 3D Systems builds tools to design & engineer with life. Our desktop 3D bioprinters are the most versatile, powerful, & easy-to-use bioprinters on the market. Allevi is trusted by leading researchers & industry giants in hundreds of labs worldwide. We are constantly inspired by our community of users who are performing world-class research on our platform.

T-CIRA JOINT PROGRAM

26-1 Muraoka-Higashi 2 Chome
Fujisawa, Kanagawa 251-0038
Japan
https://www.takeda.com/what-we-do/t-cira/

T-CiRA is a unique, long-term joint research program that was established in 2016 by Takeda and the Center for iPS Cell Research and Application (CiRA), Kyoto University. From our research facilities in Shonan Health Innovation Park (iPark) in Japan, the program is led by Professor Shinya Yamanaka, Director Emeritus of CiRA and recipient of the 2012 Nobel Prize in Physiology or Medicine. Over a 10-year period, the program is mapping uncharted territory to explore breakthrough clinical applications by use of evolving technologies with iPS cells. The ultimate aim is to develop innovative treatments, alongside cell and gene therapies, that address unmet patient need in neuro-psychiatric conditions, cancer, complex muscle diseases, complication of heart function with genetic causalities and gastrointestinal disorders.

THE COMPANY OF BIOLOGISTS

Bidder Building, Station Rd,
Histon,Cambridge, England CB249LF
United Kingdom
https://www.biologists.com/
Booth 203

The Company of Biologists is a not for profit publishing organization dedicated to supporting and inspiring the biological community. The Company publishes five specialist peer-reviewed journals: Development, Journal of Cell Science, Journal of Experimental Biology, Disease Models & Mechanisms and Biology Open. It offers further support to the biological community by facilitating scientific meetings and communities, providing travel grants for researchers and supporting research societies.

THE JACKSON LABORATORY

600 Main Street
Bar Harbor, ME 04609
United States
http://www.jax.org

The Jackson Laboratory (JAX) is a nonprofit biomedical research institution, with more than 2,400 employees. A pioneer in genetics and mouse model research, JAX has been empowering researchers worldwide for over 90 years with a broad range of in-vitro and in-vivo models of human disease and preclinical research services such as model and cohort generation, biospecimens, and therapeutic safety and efficacy testing. In addition to the largest repository of genetically modified mouse models, JAX now also offers genetically engineered human iPS and mouse ES cells. JAX is committed to supporting the next generation of scientists with access to online databases and education, and training such as in-person courses and workshops. For more information, please visit our website at www.jax.org.

THE NEW YORK STEM CELL FOUNDATION (NYSCF) RESEARCH INSTITUTE

619 West 54th Street
3rd Floor
New York, NY 10019
United States
https://nyscf.org/
Booth 822

The New York Stem Cell Foundation (NYSCF) Research Institute is an independent non-profit with the mission to accelerate cures for the major diseases of our time through stem cell research and technology innovation. NYSCF has developed a high-throughput, automated platform for standardized iPSC derivation, differentiation, and quality control (The NYSCF Global Stem Cell Array®), which has generated a repository of thousands of lines used by laboratories worldwide. We are committed to "team science" — collaborating with and funding leaders in the stem cell community to advance the understanding and treatment of disease. NYSCF also hosts a comprehensive education and outreach program to bring the excitement of science to all audiences, and an annual conference showcasing the latest translational stem cell research.

THERMO FISHER SCIENTIFIC

168 Third Avenue
Waltham, MA 02451
United States
http://www.thermofisher.com

Booth 415

Thermo Fisher Scientific supplies innovative solutions for the world's stem cell research. With applications that span basic research and commercial scale-up to disease modeling and downstream clinical research – we provide a broad range of products and services including high quality media, non-integrating reprogramming technologies, reagents and instruments for characterization and analysis, and cutting edge plastics.

THEWELL BIOSCIENCE INC.

675 US Highway 1
Suite 120
North Brunswick, NJ 08902
United States
http://www.thewellbio.com
Booth 705

TheWell Bioscience – developer of VitroGel®, an animal-free synthetic biofunctional hydrogel, enables scientists to shift from 2D to 3D cell culture and help drive innovations for precision medicine, cell therapy, and biomanufacturing by getting faster and more accurate data than animal-based systems. Explore an array of high-throughput automation-capable hydrogels and bioinks that can open the door to 3D cell models for preclinical and clinical applications and how VitroGel can help researchers improve personalized medicine globally. Visit www.thewellbio.com to explore our technology and solutions.

THRIVE BIOSCIENCE

100 Cummings Center
Suite 306-P
Beverly, MA 01915
United States
http://thrivebio.com
Booth 423
Thrive Bioscience (thrivebio.com), located in the Greater Boston Area, manufactures and sells to researchers a family of instruments with extensive software tools that provide previously unavailable live cell imaging, analytics, and automation for reproducible cell culture imaging for improved processes and breakthrough insights. Thrive's products enable biologists to deliver reproducible cell culture and experiment results by leveraging microscopy, robotics, and fluidics to automatically capture and build a database of terabytes of high-resolution images and data. The principal markets are drug discovery, drug development, regenerative medicine, basic research, and infectious disease research. Learn more about Thrive Bioscience: https://www.thrivebio.com/

TOKAI HIT USA INC

Two Bala Plaza
Suite 300
Bala Cynwyd, PA 19004
United States
http://www.tokaihit.com
Booth 204
Tokai Hit offers various Dynamic culturing systems for many applications, such as live-cell imaging, organoid research, drug discovery, and tissue culture. We will exhibit some fluidic solutions that can be used on the microscope stage or inside the CO2 incubator. And those perfusion, medium exchange, and pressure control devices are for MPS, Organ-on-a-chip, and other marketed dishes. With more than 28 years of experience in live-cell incubation systems: from compact Stage Top Incubator, Warming Box (Enclosure Incubator), and PureBox (high-end clean enclosures) We support your cell culturing from static to Dynamic culturing! Keywords: Live-cell imaging, MPS, Perfusion, Pressure control, Share stress, Hypoxia, MEA

TOMOCUBE

Sinseong-ro 155
4rd floor
Yuseong-gu, Daejeon
Republic of Korea
http://www.tomocube.com
Booth 107
Tomocube is dedicated to delivering label-free 3D live cell imaging and AI-enabled analysis to innovate basic research, biological processes, and disease diagnosis. Tomocube's Holotomography (HT) products provide a unique combination of high-resolution 3D imaging to analyze real-time subcellular dynamics and advanced quantification capabilities of volume and dry mass of individual cells and multicellular specimens such as tissues and organoids.

TOYO SEIKAN GROUP HOLDINGS, LTD.

2-18-1 Higashi-Gotanda
Osaki Forest Bldg
Shinagawa-ku, Tokyo 141-8627
Japan
http://www.tskg-hd.com/en/
Booth 824
Toyo Seikan Group is a company that utilizes materials such as metal, plastic, paper, and glass to provide the world with high-quality, highly functional containers. WELLBAG introduced here is an innovative spheroid culture tool, which can easily produce a large number of uniform size spheroids. The well-gas-permeable film used in the WELLBAG enables the supply of oxygen to cells and the discharge of carbon-dioxide accumulated in the bag. Furthermore, the high safety levels required for the cell culture bag is achieved. We will be exhibiting a standard-sized WELLBAG, an automatic culture medium changer under development, and a large-sized WELLBAG for scale-up. We are looking for the distributors of our products.

TREEFROG THERAPEUTICS

Contributing Sponsor
30 Avenue Gustave Eiffel, Bat A
Pessac, Aquitaine 33600
France
https://treefrog.fr/
TreeFrog Therapeutics is an international cell therapy company that leverages biophysics to overcome the major bottlenecks of the industry, introducing new standards in terms of scalability, cell quality, transplantation efficiency and safety/functionality of cell therapy products. Headquartered in France, with offices and labs in the USA and Japan, TreeFrog is advancing a pipeline of therapeutic candidates in regenerative medicine and immuno-oncology based on a disruptive 3D cell culture platform: C-Stem™.

UBRIGENE BIOSCIENCES INC.

3800 Wesbrook Mall
421
Vancouver, BC V6S 2L9
Canada
http://ubrigene.com
Booth 804
uBriGene Bioscience Inc. is a leading contract development and manufacturing organization (CDMO), specializing in development and application of cell and gene therapy technologies. uBriGene provides clients with end-to-end cell and gene therapy support and is committed to driving innovation in biologics development and to accelerating cell and gene therapy processes from concept to commercialization. By ensuring the highest quality of products and services, uBriGene's goal is to optimize time and cost efficiencies for its clients.

UNION BIOMETRICA, INC.

84 October Hill Rd.
Holliston, MA 01746
United States
http://www.unionbio.com
Booth 723
Union Biometrica COPAS FP™ and BioSorter® Large Particle Flow Cytometers automate analysis and sorting of objects too big/fragile for traditional cytometers, e.g., large cells/clusters, cells in/on beads and small model organisms (5-1500 micron diameter). The COPAS VISION cytometer adds brightfield image capture on the fly for convenient identification of objects.

V&P SCIENTIFIC, INC.

Contributing Sponsor
9823 Pacific Heights Blvd.
Ste T
San Diego, CA 92121
United States
http://vp-sci.com
Booth 902
We work with scientists to design and develop cutting edge innovative tools for biological, chemical, genetic, and materials research; from basic studies to pharmaceutical and industrial applications. With our 44 years of knowledge in scientific research, we can solve your application problems and save you money.

VECTORBUILDER INC.

1010 W 35th St
Ste 515
Chicago, IL 60609
United States
https://vectorbuilder.com/
Booth 101
VectorBuilder is a global leader in gene delivery technologies. As a trusted partner for thousands of labs and biotech/pharma companies across the globe, VectorBuilder offers a full spectrum of gene delivery solutions covering virtually all research and clinical needs from design to therapy.

VERTEX PHARMACEUTICALS

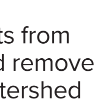
50 Northern Avenue
Boston, MA 02210
United States
https://www.vrtx.com/
Vertex creates new possibilities in medicine to cure diseases and improve people's lives. It invests in cutting-edge science and innovation, including small molecules and cell and genetic therapies, to tackle cystic fibrosis, sickle cell disease, type 1 diabetes and other serious diseases. Learn more at www.vrtx.com.

WAISMAN BIOMANUFACTURING

1500 Highland Avenue
Madison, WI 53705
United States
http://www.gmpbio.org
Booth 402
Strategically part of the University of Wisconsin-Madison, Waisman Biomanufacturing maintains industry-standard facilities, equipment, and quality systems with a scientific staff that provide a highly flexible and collaborative project management approach. WB has a proven track record for producing high-quality clinical trial material for both large and small biotech companies, universities, and federal agencies for regulatory filings in the US and other global markets. Waisman Biomanufacturing has manufactured hundreds of clinical grade products since inception in 2001 and has earned a reputation as a strategic partner for cost effective and timely delivery. We strive to meet these high standards with each manufacturing campaign or development program.

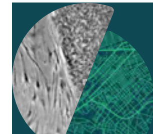
WATERSHED INFORMATICS

64 Sidney St
Cambridge, MA 02139
United States
https://www.watershed.ai/
Start Up Pavilion Kiosk 1
We empower scientists to organize and distill insights from the deluge of new data from lab instrumentation and remove the paralysis caused by fragmented tooling. The Watershed Omics Bench provides biologists and bioinformaticians a unified workspace to design, execute, and iterate through multi-omics analyses on the cloud, enabling more efficient and effective experimentation in today's therapeutic discovery programs.



WICELL

504 S Rosa Rd
Suite 101
Madison, WI 53719
United States
http://www.wicell.org
Booth 501
Headquartered in Madison, Wisconsin, WiCell is a supporting organization of the University of Wisconsin–Madison, a world leader in the area of human pluripotent stem cell research. WiCell is a nonprofit organization established in 1999 to advance stem cell technologies. The global leader in cell banking, characterization testing, and distribution of stem cell lines, WiCell builds on these core strengths by also providing characterization testing including non-cGMP and cGMP-compliant testing for a wide variety of cell types, clinical grade stem cell lines, quality control testing, contract cell banking, and long-term LN2 storage services.



WORTHINGTON BIOCHEMICAL CORPORATION

730 Vassar Ave
Lakewood, NJ 08701
United States
http://Worthington-Biochem.com
Booth 123
Register to Win an iPAD When You Stop By Booth# 123 New Products, New Catalog, New Website Worthington is an ISO9001 certified primary producer of enzymes and biochemicals for primary & stem cell isolation, bioprocessing, biopharm and related applications. Products include Animal/Xeno Free STEMxyme® Collagenase/Neutral Protease Blends, Collagenases, DNAses, RNAses and Proteases for primary/stem cell isolation. Request a New Catalog, Enzyme Manual, Cell Isolation/Tissue Guide and FREE Collagenase Sampling Program. To stay informed on new products and services, open an account at the new Worthington-Biochem.com website.

X-THERMA INC.

2600 Hilltop Drive Suite B220
Richmond, CA 94806
United States
http://www.x-therma.com
Booth 214
X-Therma is headquartered in Richmond, San Francisco Bay Area, and pioneers ground-breaking cold chain technology via a convergent biopreservation platform, to advance Regenerative Medicine and make available safe and on-demand organs, engineered tissues, cell & gene therapies, vaccines, and beyond. X-Therma's technology makes worldwide organ sharing possible and eliminates organ waiting lists. X-Therma has been a selected Industrial User at the Lawrence Berkeley National Laboratory and received over $11M contracts and grant support from the U.S. Department of Defense, the National Science Foundation, and the California Institute for Regenerative Medicine. The company closed an oversubscribed Series A of $13M. The FDA has granted its proprietary organ preservation solution, XT-ViVo®, and TimeSeal® Organ Transport Device, Breakthrough Device status.

ZEN-BIO, INC

3920 South Alston Avenue
Durham, NC 27713
United States
http://www.zen-bio.com
Booth 125
Zen-Bio is a leading global provider of advanced cell-based solutions and services to the life science, cosmetics, and personal care communities. The company, founded in 1995, was a pioneer in adipose derived stem cells (ASCs) and continues this legacy by providing cutting edge human primary cell culture products and services. Our mission is to provide the highest quality human cell systems, reagents, blood products and contract services to our research partners; to develop and commercialize innovative research tools; and to leverage our expertise through research and development and strategic alliances that accelerate discovery.

INNOVATION SHOWCASES

WEDNESDAY, 14 JUNE

11:45 AM - 12:45 PM

AUTOMATION OF ORGANOIDS CULTURE AND HIGH-CONTENT ANALYSIS OF 3D ORGANOIDS

PRESENTED BY MOLECULAR DEVICES

Room 259, Level 2

Three-dimensional (3D) organoid models representing various tissues are being successfully used for modeling complex biological effects. However, the complexity of 3D models remains a hurdle for their wider adoption in drug screening. We describe an integrated system that allows the automation of complex organoid workflow that includes assay set-up, maintenance, characterization of organoid development, and includes methods for testing the efficacy of various compounds. This integrated system includes an incubator, liquid handler, imaging system, and scheduling and image analysis software. We demonstrate organoid culture and assay automation and propose analysis approaches and descriptors that better convey information about phenotypic changes and the morphology of 3D organoids.

PRESENTER:

OKSANA SIRENKO, PHD, *MOLECULAR DEVICES, USA*

11:45 AM - 12:45 PM

SCALABLE MANUFACTURING OF IPSC-DERIVED HEMATOPOIETIC PROGENITORS IN A VERTICAL-WHEEL BIOREACTOR TO ENABLE PRODUCTION OF CLINICAL CELL THERAPY PRODUCTS

PRESENTED BY PBS BIOTECH

Room 256, Level 2

Allogeneic iPSC-derived iNK and iT cell therapies have shown encouraging pre-clinical and clinical promise. These therapies have the potential to treat a wide range of indications and provide a limitless source of readily available doses to numerous patients. As therapeutic technologies progress, the requirement for the development to adequately support clinical to commercial scale production becomes more critical. To that end, this presentation will first explain the importance of hydrodynamic relationships to control PSC aggregate morphology, size, and density in bioreactor culture to designing processes that maximize yields and directed differentiation efficiencies. Secondly, we shall highlight the use of PBS Biotech's Vertical-Wheel bioreactor platform to facilitate iPSC differentiation, downstream processing, purification, and formulation strategies of hematopoietic cells intermediates and T-cell therapies to meet the requirements of both patients and cell therapy manufacturers.

PRESENTERS:

BREANNA BORYS, PHD, *PBS BIOTECH, USA*

JAY MILLS, PHD, *CENTURY THERAPEUTICS, USA*

11:45 AM - 12:45 PM

SONY CGX10 CELL ISOLATION SYSTEM: INTRODUCTION, UTILITY AND ASSESSMENT IN A GMP GRADE ENVIRONMENT FOR MULTI-PARAMETRIC CELL SORTING*

PRESENTED BY SONY BIOTECHNOLOGY INC.

Room 257, Level 2

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

CGX10 Cell Isolation System from Sony is a unique GMP ready cell sorting instrument with "closed" single unit disposables, that can enable multi-parametric isolation of rare/desired target cell types by fluorescence-activated cell sorting. In this presentation we will talk about CGX10 cell isolation system benefits, features and utility in manufacturing of iPSC Derived Cell Therapies. We will also share the data generated during comprehensive assessment of CGX10 in a grade B GMP environment at Center for Commercialization of Regenerative Medicine (CCRM), Toronto, Canada.

PRESENTERS:

JERRY BARNHART, *SONY BIOTECHNOLOGY INC., USA*

MANOJA ESWARA, PHD, *CCRM, CANADA*

11:45 AM - 12:45 PM

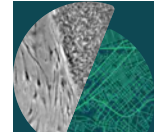
ENHANCING GENETIC STABILITY IN HUMAN PLURIPOTENT STEM CELLS MAINTAINED AS SINGLE CELLS: INTRODUCING ETESR™*

PRESENTED BY STEMCELL TECHNOLOGIES INC.

Room 253, Level 2

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

Genetic instability in human pluripotent stem cells (hPSCs) can be exacerbated by prolonged in vitro culture or cellular stress, including the use of routine single-cell passaging. However, single-cell passaging may be required for obtaining higher-density cultures, or compatibility or familiarity with single-cell workflows. In this talk, we introduce eTeSR™, a novel hPSC maintenance medium developed specifically to maintain cell quality when passaging hPSCs as single cells. The formulation is optimized to support hPSC expansion while reducing cellular stress. When tested against other commercially available media, hPSCs routinely maintained as single cells in eTeSR™ demonstrate higher genetic stability. When passaging hPSCs as single cells with



eTeSR™, researchers maintain key hPSC quality attributes, achieve improved growth rates, and retain compatibility with downstream applications including differentiation, gene editing, and cloning.

PRESENTER:

ADAM HIRST, PHD, *STEMCELL TECHNOLOGIES INC., UK*

11:45 AM - 12:45 PM

NEW APPROACHES TO THE GENERATION AND USE OF IPSCS TO STUDY NEURODEGENERATIVE DISEASES

PRESENTED BY THE JACKSON LABORATORY

Room 255, Level 2

Human induced pluripotent stem cells (iPSCs) have become a powerful tool to study development and disease in-vitro. However, there is huge variation in currently available iPSC lines with regard to genetic background and depth of characterization, making it difficult for the scientific community to replicate and compare key findings.
In this session, Prof. Bill Skarnes will present on the characterization efforts undertaken as part of the NIH-funded iPSC Neurodegenerative Disease Initiative (iNDI) that led to the identification of KOLF2.1J as a suitable reference iPSC line for this project and the neuroscience community, in general. KOLF2.1J was used to generate hundreds of variants relevant to Alzheimer's disease (AD) and related dementias through high-throughput CRISPR-Cas gene editing. Bill will discuss some of the methodology used in his lab to enhance homology-directed repair and improve precision and efficiency of the engineering platform.
In the second part of this session, Dr. Julia TCW will talk about various iPSC model systems her lab is using to study AD ranging from 2D, 3D organoid in-vitro cultures to sophisticated in-vivo iPSC/mouse chimeric models. She will describe some of the omics approaches and computational pipelines her lab has developed to identify new targets for AD therapeutics.

PRESENTERS:

WILLIAM C. SKARNES, PHD, *THE JACKSON LABORATORY, USA*

JULIA TCW, PHD, *BOSTON UNIVERSITY CHOBANIAN & AVEDISIAN SCHOOL OF MEDICINE, USA*

11:45 AM - 12:45 PM

CDMO SERVICE FOR IPSC CELL THERAPY, SCALABLE MANUFACTURE OF CAR-NK CELLS, AND USE OF LIPID NANOPARTICLES TO EXPRESS CARS

PRESENTED BY UBRIGENE BIOSCIENCES INC.

Room 254, Level 2

uBriGene Biosciences is a global Contract Development & Manufacturing Organization (CDMO) that provides one-stop services for Cell and Gene Therapy (CGT) through our integrated innovative CDMO platforms. Our expertise lies in iPSC cell reprogramming, cell banking establishment, reprogrammed iPSC cell expansion, GMP iPSC cell manufacturing as well as Cas9/Cas12 protein, gRNA and DNA donor GMP manufacturing. We possess extensive regulatory filing expertise and experience in data compilation and IND filings with the FDA and CDE. Guest speaker 1: Hebecell developed a proprietary scalable 3D iPS-NK manufacture platform with defined, serum-free and feeder-free conditions: pure and strong functional iPS-NK with CD8+ effector cell identity for immunotherapy, a truly viable unlimited/renewable source of immune cells with improved potency and simplified manufacture process. Guest speaker 2: As immunotherapy evolves, scientists are looking for ways to express chimeric antigen receptors (CARs) on multiple types of immune cells, including NK cells, dendritic cells and macrophages. Promab Biotechnologies has developed a platform to generate lipid nanoparticles (LNPs) containing mRNAs for CARs and other immune modulators. When these LNPs are added to primary immune cells in culture, 50% - 95% of the cells express the CAR, depending on the CAR and the cell type.

PRESENTERS:

XIULIAN SUN, PHD, *UBRIGENE BIOSCIENCES INC., CHINA*

ALLEN FENG, PHD, *HEBECELL CORP., USA*

JOHN LU, PHD, *HEBECELL CORP., USA*

ROBERT BEHAROVICH, PHD, *PROMAB BIOTECHNOLOGIES, USA*

THURSDAY, 15 JUNE

12:00 PM - 1:00 PM

UNDERSTANDING THE ROLE OF CULTURE CONDITIONS ON THE GROWTH AND MAINTENANCE OF IPS CELLS

PRESENTED BY BIO-TECHNE

Room 256, Level 2

Human induced pluripotent stem cells (iPSC) are critical for ex vivo models for studying development, disease mechanisms, performing drug discovery and other evolving stem cell applications. However, many iPSC workflows involve undefined culture surfaces and cell medium with lot-to-lot variability and animal components that can limit data reproducibility or hamper transition to the clinic. It is critical to overcome these obstacles by creating an animal free and fully defined workflow that ensures validity, reproducibility of results and easier compliance with cGMP standards. In this session, we will highlight recent developments that move the stem cell industry towards this goal with animal component free ExCellerate™ iPSC medium and animal-free Vitronectin. Additionally, we will showcase data that demonstrates usage of these products along with our animal free proteins

and small molecules in the generation of human iNKs for potential clinical application. These results demonstrate the feasibility of a standardized defined and reproducible process for iPSCs research and other relating applications.

PRESENTERS:

YAS HEIDARI, PHD, *BIO-TECHNE, UK*

MEHRNAZ GHAZVINI, PHD, *ERASMUS MC, NETHERLANDS*

ELI PERR, PHD, *BIO-TECHNE, USA*

12:00 PM - 1:00 PM

INDUSTRIALISING CELLULAR REPROGRAMMING: LEVERAGING OPTI-OX™ TECHNOLOGY TO MANUFACTURE HUMAN CELLS WITH UNPRECEDENTED CONSISTENCY*

PRESENTED BY BIT.BIO

Room 254, Level 2

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

Transcription factor-mediated cellular reprogramming has emerged as a groundbreaking paradigm in developmental biology, challenging traditional theories and opening new avenues for further scientific innovations. Prof Wernig will discuss his pioneering work on cellular reprogramming, which opened up a new paradigm for cell identity, in which cellular states are driven by transcriptional events. His laboratory developed the first across germ layer reprogramming protocols highlighting the potential generalisability of this concept. His group demonstrated how transcription factor combinations are able to dictate cellular states and sub-cell identities. Based on this new paradigm, he developed new cellular models for translational research and outlined how reprogrammed cells could be used for therapeutic applications. Despite the benefits of cellular reprogramming, several challenges associated with conventional vector-based methods of transgene expression impact the efficiency, consistency and purity of the resulting cell populations, all of which need to be addressed for its potential to be truly realised in regenerative medicine. As Dr Kotter will outline, many of these challenges can be addressed by expressing reprogramming cassettes via genomic safe harbour (GSH) sites. GSH-mediated optimised inducible over-expression (opti-oxTM) enables highly controlled, consistent and scalable manufacturing of human iPSC-derived cells. Further, he will discuss how bit.bio has generalised this paradigm to generate cells from all three germ layers. The integration of opti-ox technology ensures increased precision and inducible control of transcription factor expression, setting a new standard for consistency in cell manufacturing. This breakthrough enables the manufacture of trillions of human cells with unprecedented consistency offering the potential to transform the field of regenerative medicine and accelerate advancements in cell-based therapies.

PRESENTERS:

MARIUS WERNIG, MD, PHD, *STANDFORD UNIVERSITY, USA*

MARK KOTTER, MD, PHD, *BIT.BIO, UK*

12:00 PM - 1:00 PM

PREDICTING DRUG RESPONSES FOR CONVENTIONAL & IO THERAPIES USING MICROORGANOSPHERES™ & IPSC-DERIVED VASCULAR CELLS FOR VASCULARIZATION OF ORGANOIDS & ISCHEMIC TISSUES

PRESENTED BY CORNING LIFE SCIENCES

Room 255, Level 2

Clinical therapies are currently physician's choice and often driven by the patient's performance status or molecular testing. However, biomarkers can fail to robustly predict therapy success prior to therapy start. Dennis Plenker, Ph.D. will discuss how MOS technology tumor samples are grown ex vivo and tested against chemotherapies, targeted agents, IO drugs or any available clinical options. The in vitro responses can inform phenotypically if a sample responds to therapy and might be an effective patient therapy. MOS technology is a promising option to stratify patients to effective treatments and is currently evaluated for clinical feasibility.
Vascular cells hold great potential for treating vascular disease, engineering vascularized organoids and tissues for transplantation. Dr. Zhou's team developed a robust protocol to differentiate hPSCs into endothelial cells and vascular smooth muscle progenitor. These cells formed tubes on Corning® Matrigel® matrix in vitro. The endothelial cells derived from hPSCs generated functional blood vessels connected to host vasculature in ischemic limbs of immune deficient mice. When cultured with hPSC-derived hepatocytes progenitors on solidified Matrigel matrix, liver organoids formed. These organoids displayed liver specific expression and maintained transplanted iPSC-derived endothelial cells two months after transplantation into mice. Our study suggests broad hPSC-derived vascular cells applications.

PRESENTERS:

CATHERINE SILER, PhD, *CORNING LIFE SCIENCES, USA*

DENNIS PLENKER, PHD, *XILIS INC., USA*

PING ZHOU, PHD, *UNIVERSITY OF CALIFORNIA DAVIS MEDICAL CENTER, USA*

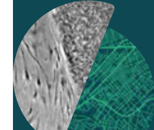
12:00 PM - 1:00 PM

MICRORNA-RESPONSIVE SYNTHETIC MESSENGER RNA AND ITS MEDICAL APPLICATIONS

PRESENTED BY MAXCYTE

Room 258, Level 2

Identifying and purifying specific cell types are essential for basic biological research and cell therapy (e.g., transplantation of purified cells in regenerative medicine).



MicroRNA (miRNA) is a class of small non-coding RNAs that regulates gene expression post-transcriptionally and can serve as a cell type-specific marker. We have previously developed the miRNA switch, a miRNA-responsive modified RNA (modRNA) transcribed in vitro, to identify and purify specific cell types. miRNA switch enabled FACS-free elimination of contaminating human induced pluripotent stem cells (iPSCs) from iPSC-derived cardiomyocytes. Although lipid-based transfection delivers modRNAs into cells efficiently, it remains challenging to transfect several types of cells (e.g., hematopoietic stem cells; HSCs). Recently, we have been employing MaxCyte® electroporation system that delivers modRNAs efficiently into hard-to-transfect cells, to purify hematopoietic stem cells (HSCs) with miRNA switches. In this session, I will share our recent progress in cell purification for regenerative medicine using miRNA switches.

PRESENTERS:

HIROKI ONO, PHD, *CENTER FOR IPS CELL RESEARCH AND APPLICATION (CIRA) AT KYOTO UNIVERSITY, JAPAN*

JESSICA MCCLURE, *MAXCYTE, USA*

12:00 PM - 1:00 PM

PAVING THE WAY TO THE FUTURE: FROM PLURIPOTENT STEM CELL RESEARCH TO TRANSLATION AND MANUFACTURING*

PRESENTED BY MILTENYI BIOTEC B.V. & CO. KG

Room 259, Level 2

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

In the first part of the talk, Sebastian Knöbel, PhD, Senior R&D Manager at Miltenyi Biotec will present solutions that cover the whole journey from bench to bedside. These include new product developments for mRNA-based reprogramming, PSC expansion, differentiation, and characterization. He will highlight how manual PSC workflows can benefit from these developments and pave the way for manufacture in the closed CliniMACS Prodigy® Adherent Cell Culture process. Furthermore, he will present how cell sorting with the MACSQuant® Tyto® and light sheet imaging with the UltraMicroscope Blaze™ can facilitate preclinical and translational research.
Afterward, Dr Chan from Xellera Therapeutics will discuss how cell therapies have emerged as a promising next-generation modality for many incurable diseases. In her talk on "Establishing the first southern Chinese haplobank of clinical-grade hIPSC lines for cell-based therapies", she will illustrate how Xellera has established the first commercial cGMP facility for cell and gene products according to PIC/S in Hong Kong. By analyzing the HLA diversity of the southern China population, Xellera has identified donors that are homozygous for the most frequent HLA-A,B,C and DRB1 combination. The top three iPSC lines of the haplobank are expected to cover approximately 50% of the Chinese population, offering an off-the-shelf approach for allogeneic transplantation of iPSC-derived cell therapies.

PRESENTERS:

CAMIE CHAN, DR, *XELLERA THERAPEUTICS LIMITED, HONG KONG SAR*

SEBASTIAN KNÖBEL, PHD, *MILTENYI BIOTEC, GERMANY*

12:00 PM - 1:00 PM

IN VITRO TISSUE MODELING INNOVATIONS: HEPATIC, ALVEOLAR AND INTESTINAL ORGANOIDS*

PRESENTED BY STEMCELL TECHNOLOGIES INC.

Room 257, Level 2

**This Innovation Showcase will be available in-person and on the virtual meeting platform..

Advances in tissue model techniques are increasing the relevance of in vitro approaches to research questions. This presentation introduces new, advanced culture systems for hepatic, alveolar, and intestinal cells. We describe an efficient, serum-free system for generating hepatocyte-like cells and mature liver organoids from human pluripotent stem cells (hPSCs). These are useful for various applications, including studying human liver development and disease, and assessing hepatotoxicity. We introduce an optimized culture system for efficiently expanding human alveolar type 2 cells and subsequently differentiating into type 1 cells. This system addresses current respiratory research challenges by allowing type 2 cells to maintain their phenotype and ability to self-renew without support from stromal or feeder cells. We also detail an intestinal organoid differentiation medium that matures cultures from an undifferentiated, proliferative state to functional cultures incorporating mature enterocyte, goblet cell and enteroendocrine cell populations, all while maintaining a small Lgr5+ stem cell population.

PRESENTERS:

RIYA SHARMA, BSC, *STEMCELL TECHNOLOGIES INC., CANADA*

RYAN CONDER, PHD, *STEMCELL TECHNOLOGIES INC., CANADA*

12:00 PM - 1:00 PM

DEVELOPING AN IPSC-BASED UNIVERSAL CANCER VACCINE WITH KHLORIS BIOSCIENCES INC.

PRESENTED BY THERMO FISHER SCIENTIFIC

Room 253, Level 2

Khloris Biosciences Inc. is the first company to develop an iPSC-based whole cell vaccine for the treatment of cancer and will present on the basic science and clinical translation of their product. Fundamentally differentiated from previous cancer vaccinations, iPSC vaccination combines key mechanistic elements to boost anti-tumor immunity.

Presenting a broad spectrum of oncofetal and other cancer-related antigens, iPSC vaccination fully mobilizes the immune system in targeting multiple cancer types.

PRESENTERS:

LYNNE A. BUI, MD, PHD, *KHLORIS BIOSCIENCES, INC., USA*

NIGEL KOOREMAN, MD, PHD, *KHLORIS BIOSCIENCES, INC., USA*

5:30 PM - 6:00 PM

MICROCHIP-BASED FUNCTIONAL SCREENING IN BRAIN ORGANOIDS: MOVING INTO A NEW ERA FROM PLANAR TO 3D TECHNOLOGY

PRESENTED BY 3BRAIN AG

Room 254, Level 2

Human-derived iPCS model systems like brain organoids offer to recapitulate the complexity and functionality of human tissues. Microchip-based technologies that can directly access the functional activity of 3D neuronal assemblies hold promise to be the next gold-standard technique for non-invasive, kinetic, or long term measurements of physiological and pathological phenotypes. However, many current approaches struggle to fulfil accuracy, precision, sensitivity, reproducibility and throughput requirements. For 3D model systems specifically, current microchips have limited capability to record physiologically relevant cells and endpoints, causing a bottleneck in a wider adoption and research utility.
In this innovation showcase, 3Brain will present their CMOS-powered cell-electronic biointerface solutions for high-content screening, cell-based assays and drug discovery. The showcase will highlight several advantages and capabilities of our first-in-class Accura-3D microchip, using thousands of electrodes mounted on ultrathin microneedles to gain unprecedented access to the inner layers of structured tissue. Accura-3D allows for non-destructive, label-free, real-time and parallel recording of thousands of neurons and provides a detailed granular description of the complex functional activity expressed by iPSC-derived brain organoids. By increasing data quality and reducing experimental variability, Accura-3D makes a technological leap toward mass adoption of brain organoids for studying neurodegenerative disease or drug discovery pipelines.

PRESENTERS:

MAURO GANDOLFO, PHD, *3BRAIN AG, SWITZERLAND*

ALESSANDRO MACCIONE, PHD, *3BRAIN AG, SWITZERLAND*

5:30 PM - 6:00 PM

ELECTROPORATION BUFFERLESS MULTIPLEXED CELL ENGINEERING

PRESENTED BY FEMTOBIOMED

Room 255, Level 2

Cell therapy development has led to an increasing need for delivering multiple genetic materials into a single cell. This unmet need has been repeatedly raised by fields such as iPSC reprogramming. Electroporation is a widely used method for delivering DNA/RNA into various cells, but it has limitations due to cell damage and death caused by injection of genetic material via an electric field. To overcome the conventional constraints of electroporation, the CellShot platform eliminated the need for a specific electroporation buffer based on the Partitioned Flow Transfection technology. It minimizes cell loss and damage on top of the simplified the process, resulting in efficient delivery and high cell viability in various cells, including fibroblasts and human iPSCs. CellShot is a powerful tool for stem cell therapy research and production processes that require repeated delivery of various genetic materials into cells. It is expected to provide more flexibility in selecting source cells, especially for blood-derived cells. Overall, the transfection process with CellShot may also reduce the production cost of cell therapy using iPSCs/MSCs. Currently, strategic partnerships with institutions and companies are ongoing for MSC, iPSC reprogramming and differentiation, PBMC, T and NK cell research, evaluating the feasibility of therapeutic applications.

PRESENTERS:

JINOOK LEE, MENG, *FEMTOBIOMED, SOUTH KOREA*

JONGSEON CHOI, PHD, *FEMTOBIOMED, SOUTH KOREA*

5:30 PM - 6:00 PM

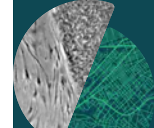
SPATIAL BIOLOGY IS NOW: ACCELERATE YOUR STEM CELL STUDIES WITH SPATIAL MULTI-OMICS*

PRESENTED BY NANOSTRING TECHNOLOGIES, INC.

Room 253, Level 2

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

Biology is inherently spatial, so why study stem cells in isolation? Join us to learn about the spatial biology revolution and how you can get high plex RNA and protein expression data in situ in stem cell-derived tissues. Gain a deeper understanding of stem cell differentiation and optimize organoid formation with the CosMx™ Spatial Molecular Imager (SMI) and the GeoMx® Digital Spatial Profiler (DSP). Track the differentiation of stem cells into organoid tissue by spatially profiling the expression of up to 6000 RNAs and 64 proteins at the single cell and subcellular level with CosMx SMI. Then, separately profile the whole transcriptome and select RNAs and proteins in distinct tissue



compartments with GeoMx DSP. Store and analyze data with the AtoMx™ Spatial Informatics Platform, a scalable, cloud-based spatial informatics solution that lets you collaborate with your colleagues.
Hear how the GeoMx Whole Transcriptome Atlas was used to study the infection of SARs-CoV-2 in brain organoids, revealing that the virus likely infects astrocytes through the NRP1 receptor. Infection led to an increase in expression of genes associated with the Type 1 interferon response, chromatic remodeling, and apoptosis, creating an environment that promotes neuronal dysfunction and may underlie CNS symptoms of COVID-19.

IN-PERSON PRESENTER:

SEAN GERRIN, *NANOSTRING TECHNOLOGIES, INC., USA*

VIRTUAL PRESENTERS:

SEAN GERRIN, *NANOSTRING TECHNOLOGIES, INC., USA*

WEILI KONG, PHD, *THE GLADSTONE INSTITUTES, USA*

5:30 PM - 6:00 PM

SYNTHETIC PEPTIDE GROWTH FACTORS: FORGING THE PATH FORWARD FOR REGENERATIVE MEDICINE AND CELL THERAPY

PRESENTED BY PEPTIGROWTH

Room 256, Level 2

Conventional growth factors and cytokines in the manufacturing of regenerative medicine, cell therapy products, and cultivated meat industry are facing various challenges such as lot-to-lot quality variations, potential contamination with biological impurities, low stability, and high manufacturing cost. PeptiGrowth Inc. has been working on developing a series of synthetic peptides that can offer a potential solution to all of these challenges. Our synthetic peptides possess the same capabilities for receptor activation, cell proliferation and differentiation as conventional growth factors. Along with greater ease of use, longer shelf life, and non-contamination by biological components, they provide consistent quality that can improve efficiency and data reproducibility, and thus, reduce the cost of R&D, manufacturing, and quality control of cell therapy and regenerative medicine products. We have launched our hepatocyte growth factor (HGF) alternative peptide, TGF-β1 inhibitory peptide, brain-derived neurotrophic factor (BDNF) alternative peptide, and BMP4/7 inhibitor peptide (Noggin-like peptide) as well as BMP 4 or BMP7 selective inhibitor peptides in the market. In this seminar, we will be sharing some application examples of our synthetic peptides in cell culture models. We believe that these synthetic peptides have the potential to boost the growth of the industry and we are excited to share our innovation with you.

PRESENTERS:

KOSUKE MINAMIHATA, PHD, *PEPTIGROWTH, JAPAN*

JES KURUVILLA, PHD, *MIFI BIOCEUTICALS, USA*

5:30 PM - 6:00 PM

HARNESSING THE POWER OF CRISPR ENGINEERED CELLS FROM SYNTHEGO TO ACCELERATE DISEASE RESEARCH

PRESENTED BY SYNTHEGO

Room 259, Level 2

Synthego's CRISPR Engineered Cells are powerful tools for accelerating disease research by providing precise editing of genes with unprecedented speed and accuracy. Additionally, Synthego's CRISPR Discovery Partner ecosystem provides access to cutting-edge technologies and expertise to accelerate scientific discovery. In this presentation, we will discuss the integration of the Engineered Cells portfolio with the CRISPR Discovery Partner ecosystem and how it can revolutionize drug discovery and functional genomics studies. We will highlight the benefits of these partnerships, including access to a network of leading experts in small molecule screening, cell-based assays, high content imaging, iPSC differentiation, and multi-omics. We will also share examples of how Synthego's CRISPR Engineered Cells platform has been used to accelerate research in various disease areas, including cancer, neurological disorders, and rare genetic diseases. Finally, we will discuss the future directions of the portfolio and how it can continue to transform disease research in the years to come.

PRESENTER:

TRAVIS HARDCASTLE, MS, *Synthego, USA*

5:30 PM - 6:00 PM

IMAGE DIFFERENTLY - A SOLUTION FOR AUTOMATED LIVE CELL IMAGING

PRESENTED BY THRIVE BIOSCIENCE

Room 257, Level 2

The Thrive Bioscience CellAssist System is a tightly integrated hardware and software solution for acquiring, analyzing, storing and visualizing live cell images. In addition to phase contrast and bright field images, the Thrive analysis software computes Quantitative Phase Images (QPI) for robust identification and quantification of individual cells. Expandable from a single bench-top unit to a global network of automated, environmentally controlled imagers, it elevates imaging of live cells in culture from an occasional, manual process with sporadic documentation, to a reproducible, routine, automated process that provides unparalleled insight into your cells' behavior. With the ability to collect up to 100+ focal planes spanning a z-range of 4.0 mm, the CellAssist is also uniquely suited to the demands of imaging spheroids, organoids, and cells in suspension. The CellAssist family of instruments are designed to be easily integrated into existing cell culture workflows. An open API, easy export of all images, metadata, and analysis output, coupled with powerful control, database, and visualization software make the CellAssist the imager of choice for industrial live cell imaging.

PRESENTERS:

THOMAS FARB-HORCH, *THRIVE BIOSCIENCE, INC., USA*

MICHAEL MOODY, MS, *THRIVE BIOSCIENCE, INC., USA*

5:30 PM - 6:00 PM

SCALING-UP IPSC-BASED CELL THERAPIES: REAL-WORLD PROCESSES WITH BIOMIMETIC C-STEM TECHNOLOGY

PRESENTED BY TREEFROG THERAPEUTICS

Room 258, Level 2

For the past 10 years, developmental biologists have explored novel approaches to mimic the in vivo niche and 3D architecture of human pluripotent stem cells (hPSCs). Taniguchi et al. (2015, 2017) demonstrated that, in permissive in vitro conditions, PSC colonies spontaneously self-organize and polarize in 3D around a central lumen, promoting PSC proliferation, homogeneous pluripotency, and maintenance of genomic integrity [Kim et al. 2021; Knouse et al., 2018; Hashimoto et al., 2019]. Based on high-speed cell encapsulation microfluidics, Treefrog proprietary GMP-compliant C-Stem technology enables the expansion of high quality 3D hiPSC lumenized rosettes protected within an alginate shell. This presentation aims to show C-Stem-based processes for the mass-production and differentiation of iPSC into neural microtissues for the treatment of Parkinson's disease and other cell therapy products.

PRESENTERS:

MAXIME FEYEUX, PHD, *TREEFROG THERAPEUTICS, FRANCE*

KEVIN ALESSANDRI, PHD, *TREEFROG THERAPEUTICS, FRANCE*

EMILIE FAGGIANI, PHD, *TREEFROG THERAPEUTICS, FRANCE*

FRIDAY, 16 JUNE

11:30 AM - 12:30 PM

ADVANCING CELL THERAPY: INCORPORATING ANIMAL-ORIGIN FREE RECOMBINANT PROTEINS AND CULTURE MEDIA FOR IPSC-BASED CANCER IMMUNOTHERAPY

PRESENTED BY AJINOMOTO CO., INC.

Room 257, Level 2

The utilization of Animal-Origin Free (AOF) ancillary materials provides multiple benefits, such as the elimination of contamination risks from adventitious agents and extraneous materials, ensuring consistent performance, and simplifying cell production workflows. In this showcase, we will discuss how Ajinomoto is accelerating iPSC-based cell therapy by developing innovative ancillary materials – StemFit™ , a chemically defined AOF media, and StemFit Purotein™, a series of recombinant proteins that include growth factors, cytokines, and scaffolds.

The showcase will then highlight Ajinomoto's collaborator, Professor Takashi Aoi from Kobe University, who has succeeded in differentiating iPSCs into a variety of cell types, including Leydig cells, esophageal epithelium, bladder epithelium, gastric organoid, melanocyte precursor, neuron, cardiomyocyte, and hematopoietic cells, using StemFit. Professor Aoi will feature his work on establishing a differentiation process to generate immunogenic γδT cells from hematopoietic cells using AOF ancillary materials. This study provides compelling evidence that AOF ancillary materials are a safe and effective alternative for cancer immunotherapy.

PRESENTERS:

TAKASHI AOI, PHD, *KOBE UNIVERSITY, JAPAN*

TAKAYUKI ITO, PHD, *AJINOMOTO CO., INC., JAPAN*

11:30 AM - 12:30 PM

OPTICAL GENOME MAPPING - REDEFINING CELL LINE GENOMIC INTEGRITY AND OFF-TARGET CHARACTERIZATION

PRESENTED BY BIONANO

Room 255, Level 2

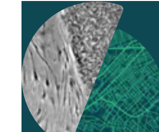
Optical genome mapping (OGM) is a transformative solution for genomic integrity and off-target characterisation in cell lines. In this informative one hour session, Bionano will present three leading experts to share their experiences and data using the Bionano Saphyr® platform in their R&D and manufacturing processes. Jeanne Loring, PhD (Scripps Research Institute) will first discuss the use of OGM for assessing genomic integrity in iPSC culture and engineering. Suk See De Ravin, MD, PhD (NIH) will present OGM's capabilities for the detection of off- and on-target structural variants in CRISPR/Cas and base editing research. The session will round off with Travis Hardcastle, MS (Synthego) presenting on applying OGM for QC of cell biorepositories in a more high throughput, industrial setting. Overall, this session will demonstrate the potential of Bionano's unique OGM technology in cell & gene therapy R&D, and how it can significantly improve the quality, safety, and overall risk profile of next-generation therapy development & manufacturing.

PRESENTERS:

ALEX HASTIE, PHD, *BIONANO, USA*

SUK SEE DERAVIN, MD, PHD, *NATIONAL INSTITUTES OF HEALTH, USA*

TRAVIS HARDCASTLE, MS, *SYNTHEGO, USA*



11:30 AM - 12:30 PM

NOVEL METHODS FOR CULTURE AND DEVELOPMENT OF STEM CELL-DERIVED 2D AND 3D MODELS

PRESENTED BY CELL MICROSYSTEMS

Room 256, Level 2

Stem cells are an invaluable tool for generating multiple cell types from individual patients. However, the workflows associated with growing, CRISPR gene editing, and differentiating iPSCs in 2D and 3D culture are inefficient and low-throughput, costly, time-consuming, and manually labor-intensive. Dr. Allysa Stern will discuss workflows that span the breadth of iPSC biology from reprogramming to monoclonal edited colony formation to 3D models for disease. She will share newly generated iPSC data and demonstrate a protocol that helps to get to the desired clone in the shortest time possible with a demonstrated savings of valuable reagents, media, and plastic. With this protocol, you can:

- Generate 100s of monoclonal iPSC lines in under two weeks (with proof of monoclonality)
- Achieve >90% clonal outgrowth by automated isolation of monoclonal colonies
- Enable all iPSC workflows from reprogramming to differentiation on one consumable
- Optimize your iPSCs for 2D and 3D culture via established protocols and methods in our lab

PRESENTER:

ALLYSA STERN, PHD, *CELL MICROSYSTEMS, USA*

11:30 AM - 12:30 PM

CEPT COCKTAIL, A NEW CHEMICAL PLATFORM FOR STRESS-FREE AND SAFE CULTURE OF IPSCS

PRESENTED BY FUJIFILM WAKO PURE CHEMICAL CORPORATION

Room 259, Level 2

Human induced pluripotent stem cells (iPSCs) offer unprecedented opportunities for biomedical research, drug discovery, and regenerative medicine. However, to fully capitalize on the potential of iPSCs, it is necessary to culture and differentiate them under appropriate conditions. Poor cell survival, cell stress, and accumulation of genetic abnormalities have been long-standing challenges. This webinar will introduce and discuss the discovery and application of CEPT, a four-part small molecule cocktail for cytoprotective and stress-free cell culture. CEPT represents a novel end-to-end solution for iPSCs and other sensitive cell types and can be utilized for routine cell passaging, cryopreservation/thawing, single-cell cloning, gene editing, and organoid formation. At this webinar, Dr. Ilyas Singeç, who led the discovery of CEPT at the National Institutes of Health (NIH) and is currently the Chief Scientific Officer of FUJIFILM Cellular Dynamics Inc., will discuss the scientific rationale and practical advantages of using the CEPT cocktail.

PRESENTER:

ILYAS SINGEÇ, MD, PHD, *FUJIFILM CELLULAR DYNAMICS, INC., USA*

11:30 AM - 12:30 PM

ADVANCED FUNCTIONAL CHARACTERIZATION OF IPSC-DERIVED 2D AND 3D IN VITRO MODELS AT THE FRONTIERS OF MOLECULAR BIOSCIENCE

PRESENTED BY MAXWELL BIOSYSTEMS AG

Room 253, Level 2

Two-dimensional (2D) or three-dimensional (3D) cell cultures are currently widely used in stem cell research. They aim to be as close to in vivo conditions to varying degrees, and, when derived from human induced pluripotent stem cells (iPSCs), provide a valuable alternative to animal models. Cell shape, differentiation, and proliferation, drug sensitivity and response to stimuli are among the characteristics guiding researchers to prefer one method to the other based on the scientific question and application. Considering that both 2D and 3D in vitro cellular models can serve as equally valuable tools to overcome the current barriers in stem cell research and further advance the field, we invited three speakers to spotlight on novel applications and methods to functionally characterize iPSC-derived cellular models. Scientific presentations will be followed by Q+A session and panel discussion to shine the light on current opinions about this controversial and highly relevant topic.

PRESENTERS:

JENNIFER ERWIN, PHD, *LIEBER INSTITUTE FOR BRAIN DEVELOPMENT, USA*

CHANGHUI PAK, PHD, *UNIVERSITY OF MASSACHUSETTS, USA*

MARIA SUNDBERG, PHD, *BOSTON CHILDREN'S HOSPITAL, USA*

LAURA D'IGNAZIO, PHD, *MAXWELL BIOSYSTEMS, SWITZERLAND*

11:30 AM - 12:30 PM

FROM STEM CELL TO IMMUNE CELL: USING DEFINED METHODS TO ENHANCE CONSISTENCY AND PERFORMANCE*

PRESENTED BY STEMCELL TECHNOLOGIES INC.

Room 254, Level 2

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

Obtaining a high yield of immune cells for cell therapy research and immunotherapy development can be challenging. Current workflows are often sub-optimal; their reliance on the use of serum and feeder cells leaves them prone to variability. In addition, the need for autologous cell sources adds further uncertainty and complexity. This can increase the risk of delays, high costs, and issues with

getting approvals from regulatory bodies. Researchers must consider every step of their workflow when optimizing protocols to enhance consistency and performance. In this talk, we will introduce tools from STEMCELL Technologies that offer optimal conditions for generating immune cells from alternative cell sources including cord blood-derived hematopoietic stem & progenitor cells or pluripotent stem cells. Our media and supplements have been developed using defined materials and protocols without the use of serum or feeder cells, facilitating the generation of high-quality cell products required in clinical applications.

PRESENTERS:

NOOSHIN TABATABAEI-ZAVAREH, PHD, *STEMCELL TECHNOLOGIES INC., CANADA*

PATRICK BRAUER, PHD, *STEMCELL TECHNOLOGIES INC., CANADA*

5:30 PM - 6:00 PM

ORGANOID EXPRESSIONS: USING SPATIAL-OMICS TO VISUALIZE AN ORGANOID TRANSCRIPTOME*

PRESENTED BY 10X GENOMICS

Virtual

* This Innovation Showcase will only be available on the virtual meeting platform.

Cellular function and identity are linked with tissue and organ function via their location and structural relationships. This natural relationship is often lost in the 2 dimensional cell culture systems that predominate cell biology studies. Organoids, simple 3D cell culture structures, have become increasingly useful as a tool for studying cellular identity and function within the more natural context of a 3D environment. New methods in spatial omics combine imaging and nucleotide sequencing to allow a comprehensive look at the transcriptome and proteome of cultured organoids. Please join us as we review some of the novel ways spatial transcriptomics are being used to look at gene expression in organoids.

PRESENTER:

JEFF BYLUND, PHD, *10X GENOMICS, USA*

5:30 PM - 6:00 PM

OPTIMIZED STEM CELL CULTURE WORKFLOWS IN A FLEXIBLE AND TIGHTLY REGULATED CULTURE ENVIRONMENT FOR ENHANCED CELL PRODUCTION

PRESENTED BY BAKER COMPANY

Room 257, Level 2

Stem cells are highly sensitive to their environment. Not only do changes in their culture conditions such as media components and cell density trigger or stop self-renewal and critical stages of differentiation, but changes in environmental conditions like temperature and oxygen levels also have a significant impact on cell behavior. Baker's SCI-tive is a physiological workstation designed to mimic in-vivo conditions by providing a continuous cell culture environment with an accurate, homogeneous biological atmosphere including tight control over oxygen, carbon dioxide, temperature, and humidity levels. Manipulating cells in the SCI-tive is not that different from working in a standard biosafety cabinet. However, the advantage of the SCI-tive is continuous control over the cell culture environment. There are no fluctuations in oxygen, carbon dioxide, temperature, or humidity during incubator door openings, media changes, passaging, and even imaging. EverCell Bio has translated many of the most common stem cell culture workflows within the SCI-tive to allow for easy and productive manipulation of cells. The key is to plan ahead, protecting the environment and preventing any unintended shocks to the cells, which will ultimately lead to an increase in a more robust stem cell.

PRESENTERS:

KARA HELD, PHD, *THE BAKER COMPANY, USA*

NATASHA ARORA, PHD, *EVERCELL BIO, INC., USA*

PHILIP MANOS, *EVERCELL BIO, INC., USA*

5:30 PM - 6:00 PM

NEW DIFFERENTIATION WORKFLOWS AND GMP-COMPLIANT IPSC LINES FOR CELL THERAPY

PRESENTED BY CATALENT CELL & GENE THERAPY

Room 253, Level 2

Human induced pluripotent stem cells (iPSCs) are emerging as a cornerstone for successful cell therapies, requiring manufacturing processes that adhere strictly to good manufacturing practice (GMP) guidelines. We have established a GMP process for manufacturing clinical-grade iPSC lines and continue to produce new cell lines that are both commercially exploitable and EMA/FDA-compliant from a regulatory standpoint. The cells display full acquisition of pluripotency and a low mutational burden reflecting their neonatal origin, cord blood. In parallel efforts, we have been developing improved clean room-friendly and weekend-free iPSC differentiation protocols, similar to the iPSCs, offered through an "open source" licensing model. These imply new workflows for generating retinal pigment epithelium (RPE cells), mesenchymal stromal cells (MSCs), cardiomyocytes, and immune cells in a streamlined manner through directed instruction and natural selection. The underlying protocols generate these cell types at high purities and under defined conditions and may imply inherent upscaling strategies. Catalent's iPSC-derived hematopoietic precursor cells hold immense promise as a universal and versatile platform for allogeneic cell therapies in immuno-oncology.

PRESENTER:

BORIS GREBER, PHD, *CATALENT CELL & GENE THERAPY, GERMANY*

5:30 PM - 6:00 PM

DRIVING CELL AND GENE THERAPY DEVELOPMENT FROM "PETRI DISH TO PATIENT"

PRESENTED BY IQVIA

Room 255, Level 2

The development of cell and gene therapies (CAGTs) faces many hurdles: complex preclinical development, constrained GMP manufacturing capacity, limited qualified clinical sites, an evolving regulatory landscape and an unclear pathway for pricing and market access. Join us to learn how we accelerate cell and gene therapy translation for companies and academic institutions through our end-to-end data solutions, innovations and partnerships.

The IQVIA Cell and Gene Therapy Center serves as a specialized hub to support preclinical/clinical development, and commercialization of CAGTs. In this session, we discuss key challenges and considerations in translating a discovery to a product and we provide tools to address critical gaps in the CAGT development process such as our data and logistics solutions as well as our evidence engine, that uses AI/ML to reveal hidden causes of variability in patient responses to CAGT.

PRESENTER:

AMRITHA JAISHANKAR, PHD, *IQVIA, USA*

5:30 PM - 6:00 PM

PRECISE AND MB-SCALE IPSC GENOME ENGINEERING FOR CELL THERAPY & REGENERATIVE MEDICINE BY LOGOMIX GENO-WRITING™ PLATFORM

PRESENTED BY LOGOMIX, INC.

Room 254, Level 2

*This Innovation Showcase will be available in-person and on the virtual meeting platform.

Geno-Writing™ is our genome-writing platform that grants unprecedented freedom to screen, design and write-in large-scale genomic alterations in cells and create new cell types with desired functions. By applying this genome engineering platform, we recently established two types of the master iPSC lines. The first master cell (HLA-I free master iPSCs) has ~800 kb deletion of all the six HLA class I gene loci and integration of the genomic landing pads called UKiS donors at both alleles, whereas the second one (All HLA free master iPSCs) has ~2.0 Mb deletion of all of the HLA class I and all the HLA class II gene loci and integration of the UKiS donors at both alleles. The UKiS donor alleles can be efficiently replaced with any gene cassettes of your interests. In this presentation, we will show our data on the genomic quality and functionality of the master iPSCs with different gene cassettes installed so as to demonstrate that these master iPSCs are advantageous in investigating the HLA-mediated interaction rules between immune cells and their target cells as well as in developing new types of cell modality for allogeneic cell therapy and regenerative medicine.

IN-PERSON PRESENTER:

YASUNORI AIZAWA, PHD, *LOGOMIX, INC., JAPAN*

VIRTUAL PRESENTER:

TOMOKI OTANI, PHD, *LOGOMIX, INC., JAPAN*

5:30 PM - 6:00 PM

UNLOCKING THE POTENTIAL FOR SINGLE CELL SEQUENCING AT SCALE WITH COMBINATORIAL INDEXING

PRESENTED BY SCALE BIOSCIENCES

Room 256, Level 2

Combinatorial indexing technology enables cost-effective single-cell profiling and increased levels of throughput for larger, more complex single cell studies. Leveraging the cell as the reaction compartment, this method enables increased sample multiplexing and a reduced cost per cell, as well as a 2-day, instrument-free, accessible workflow. In this presentation, we will provide a brief introduction to the technology and our ScaleBio Single Cell RNA Sequencing Kit, which enables the processing of up to 96 samples and 125,000 cells per experiment. We will then invite Dr. Cole Trapnell (University of Washington) to present his recent implementation of combinatorial indexing for single-cell transcriptomic profiling.

PRESENTERS:

JASON KOTH, *SCALE BIOSCIENCES, USA*

COLE TRAPNELL, PHD, *UNIVERSITY OF WASHINGTON, DEPARTMENT OF GENOME SCIENCES, USA*

5:30 PM - 6:00 PM

SIMPLIFIED LARGE OMICS DATA ANALYSIS FOR EVALUATING CELL THERAPY PRODUCTS

PRESENTER BY WATERSHED INFORMATICS

Room 259, Level 2

The significant reduction of costs for NGS and similar technologies in recent years has led to an explosion of genomic, epigenetic, transcriptomic, proteomic, and metabolomic data that can be generated in record time. This has driven an increased demand for inclusion of such data in the rigorous evaluation of cell therapy products, however, processing and interpreting the data present significant challenges. Omics Bench aims to address these issues by accelerating, streamlining, and simplifying data analysis for bioinformaticians and biologists alike. By democratizing access to powerful analytical tools, Omics Bench enables consistent, transparent, easily interpretable, and well-documented data processing. In so doing, we aim to facilitate the rapid iterations on actionable results that are key to driving faster development of impactful cell therapies.

PRESENTER:

STEFANIE MORGAN, PHD, *WATERSHED INFORMATICS, USA*

MICRO THEATER

Micro Theater is located at the bottom of the escalators leading into the Exhibit & Poster Hall, Hall A at the Boston Convention and Exhibition Center (BCEC).

WEDNESDAY, 14 JUNE

6:15 PM – 6:30 PM

BACKFLOW REDUCTION IN LOCAL INJECTION WITH GELATIN FORMULATION

PRESENTED BY NITTA GELATIN INC.

The local injection of therapeutic drugs, including cells into different organs, is a delivery method to achieve high drug exposure at the site of action. However, backflow (reflux) and side effect reactions can occur. In fact, a degree of backflow was reported in all cases in a previous experimental trial of cell delivery in intravitreal injection. Hence, we investigated gelatin potential to reduce backflow in local injection. Gelatin was injected into tissue models, including versatile training tissue and chicken muscle, using needles of different gauges. The backflow fluid was collected with filter paper, and the backflow fluid rate was determined. The backflow rate was significantly reduced with gelatin concentrations up to 5%. Additionally, the backflow rate was influenced gelatin molecular weights. Our findings from this proof-of-concept study imply that gelatin can prevent backflow in local injection, and further investigations are necessary to evaluate its applicability in clinical research to solve backflow issues in medical application including cell and gene therapies.

PRESENTER:

FRANCOIS MARIE NGAKO KADJI, PHD, *NITTA GELATIN INC., JAPAN*

6:40 PM – 6:55 PM

IMAGE DIFFERENTLY - AN OVERVIEW OF A SOLUTION FOR AUTOMATED LIVE CELL IMAGING

PRESENTED BY THRIVE BIOSCIENCE

This talk offers an overview of the comprehensive presentation, Image Differently - A Solution For Automated Live Cell Imaging, presented on June 15th, 2023 from 5:30pm - 6:00pm.

Learn how the Thrive Bioscience CellAssist System elevates live cell imaging to an automated, reproducible process while allowing users to capture extensive databases of information about their live cells in culture. With its ability to capture many 1,000s of images per scan with up to 100+ focal planes spanning a z-range of 4.0 mm, the CellAssist is uniquely suited to the demands of imaging spheroids, organoids, and cells in suspension. The CellAssist is a tightly integrated hardware and software solution for acquiring, analyzing, storing, and visualizing live cell images. Expandable from a single bench-top unit to a global network of automated, environmentally controlled imagers, it elevates imaging of live cells in culture from an occasional, manual process with sporadic documentation, to a reproducible, routine, automated process that provides unparalleled insight into your cells' behavior. This talk demonstrates the CellAssist's unique capabilities for imaging spheroids, organoids, and cells in suspension by taking up to 100+ focal planes. Discover why the CellAssist is the imager of choice for industrial live cell imaging applications.

PRESENTERS:

THOMAS FARB-HORCH, *THRIVE BIOSCIENCE, INC., USA*

MICHAEL MOODY, MS, *THRIVE BIOSCIENCE, INC., USA*

7:05 PM – 7:20 PM

STIRRED TANK REACTOR PROCESS DEVELOPMENT – SCALE UP FOR CELL AND GENE THERAPY

PRESENTED BY GETINGE

Scale Up is an important procedure in the development of stirred tank reactor processes for commercialization of Cell and Gene Therapy.

Cell and Gene Therapy Process Development focus typically moves from 2D to 3D culture formats as product demand exponentially increases from development to pre-clinical to clinical and then to commercial production. Suspension culture in stirred tank bioreactors is the most common format for these later stages of the manufacturing process. The development process will typically move in discrete steps from small volume reactors to increasingly larger reactors and is evaluated at each step for efficiency, consistency, and successful maintenance of key Critical Product Attributes. This process is known as Scale Up.

Critical Process Parameters in stirred tank bioreactors which are affected by vessel volume and which need to be scaled to maintain uniform culture conditions at each vessel size are impeller diameter, impeller tip speed, impeller rotation speed, vessel geometry, working volume, and gas addition rates. These Critical Process Parameters and their effect on Critical Product Attributes in Scale Up will be discussed.

PRESENTER:

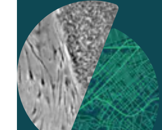
GEORGE BARRINGER, PHD, *GETINGE LIFE SCIENCES, USA*

7:30 PM – 7:45 PM

ACCELERATING INNOVATION IN REGENERATIVE MEDICINE

PRESENTED BY EOS BIOINNOVATION

Eos BioInnovation is a new venture investment company dedicated to enabling the commercialization of compelling



ideas from academic labs in the regenerative medicine field. We work closely with academic founders to incubate and launch companies that have the potential to develop curative therapies across different modalities and disease areas. Our partners' experiences in managing a leading academic research center, the Harvard Stem Cell Institute, that had commercial successes as well as in the venture capital field gives us the right perspective, skill set and experience to accomplish this. This talk will discuss the challenges in the field and our approach.

PRESENTER:

BROCK REEVE, MPHIL, MBA, *EOS BIOINNOVATION, USA*

THURSDAY, 15 JUNE

10:00 AM – 10:15 AM

LABEL-FREE SINGLE CELL IMAGING AND SORTING WITH THE AI-POWERED DEEPCELL PLATFORM

PRESENTED BY DEEPCELL

Like molecular analytes, cell morphology is a rich source of biological information that is indicative of phenotype and function. To unlock the insights embedded in cell morphology, multi-dimensional morphological traits must be turned into a quantitative, high-dimensional "-ome", the morpholome.

The Deepcell platform combines high-resolution brightfield imaging of single cells in flow with deep learning foundation models to analyze cell morphology. The high-dimensional descriptions of cell features are projected onto morphology UMAPs for visualization and unbounded exploration of cell groups. This technology can be used to assess morphological changes at the single cell level, including stem cell differentiation, cellular identity during regeneration and aging, and disease modeling with stem cells.

Come hear about the latest developments on the Deepcell platform and learn what the morpholome can reveal!

PRESENTER:

COURTNEY ANDERSON, PHD, *DEEPCELL, USA*

10:25 AM – 10:40 AM

ANALYSIS, IMAGING AND SORTING OF 3-D CULTURES AND ORGANOID BODIES ON THE COPAS VISION

PRESENTED BY UNION BIOMETRICA, INC.

Large particle flow cytometers from Union Biometrica provide automation for the analysis and dispensing of cell clusters. Research using stem cell clusters, organoids, tumor spheres and other types of 3D cultures are important biological systems for the discovery of signals responsible for normal development as well as abnormal disease states, such as that of solid tumors. Many cell types self-assemble to form cell clusters when given the opportunity. Appropriate cell-cell interactions occur and provide biological insights otherwise missed when studying flat sheets of cells growing on plastic surfaces or as cells grow in isolation. Furthermore, transgenics expressing fluorescent proteins from promoters of interest reveal expression of various developmental pathways occurring within the cell clusters. Researchers can use these to track different cell types and identify when a cell or group of cells has transitioned to a different state. Organoids can be generated by different methods such as microcavity plates (Corning™) or bioreactors (CelVivo™). The COPAS Vision can analyze and image these cell clusters, as well as sort these individually into wells of multiwell plates for high throughput assays and analysis.

PRESENTER:

ROCK PULAK, PHD, *UNION BIOMETRICA, INC, USA*

10:50 AM – 11:05 AM

HIGH THROUGHPUT BIOPRINTING OF CELL THERAPY VEHICLES TO TREAT OCULAR DISEASES LIKE CONJUNCTIVAL DISORDER

PRESENTED BY CELLINK

Conjunctival disorder is an ocular surface disease that can severely affect patients' vision. Stem cell therapies using conjunctival stem cells (CjSCs) have become a promising approach to treat conjunctival disorder. However, studies on the culturing of CjSCs and minimally invasive CjSCs transplantation are still insufficient. To address this gap, we developed a method leveraging the BIONOVA X 3D bioprinter to produce CjSC-loaded hydrogel micro-constructs that can be delivered to patients via injection. The bioprinted hydrogel micro-constructs can support CjSCs viability, stem cell phenotype, and differentiation potency into conjunctival goblet cells. In this presentation we dive into:

- How bioprinting can be used to develop minimally invasive stem cell therapies
- The impact of tunable stiffness for differentation potency
- Downstream processes that enable high throughput biofabrication

PRESENTER:

WEI ZHU, PHD, *CELLINK, USA*

11:15 AM – 11:30 AM

IPSC PRODUCTION IN STIRRED-TANK RIGID-WALL SINGLE-USE BIOREACTORS – A SCALABLE APPROACH FOR STEM CELL PROCESSING

PRESENTED BY EPPENDORF BIOPROCESS

Cell therapy is an advanced and promising field with the potential to transform modern medicine and bring therapeutic benefits to patients in different disease areas with unmet medical needs. Autologous cell therapy is a novel intervention in which cells are collected from individual patient, expanded ex vivo, and reinfused into the same patient. This approach reduces the risk of immune rejection and the need for immunosuppressive drugs. However,

the high costs, the scale-up complexity process, and the prolonged time to manufacture the final product for each patient present several challenges that prevent it from reaching its full potential. Allogeneic cell therapy follows the same manufacturing process as the autologous strategy except that the cells are collected from a healthy donor and used in patients with different medical conditions. In this sense, induced pluripotent stem cells (iPSCs) could provide an inexhaustible source of cells. Nevertheless, scalability requirements are some of the main challenges in supporting cell growth for a large group of patients. In this talk, we will show how we have generated embryoid bodies (EBs) from iPSC in 1 L bioreactors controlled by the parallel bioreactor control system SciVario® twin and highlight the benefits of single-use stirred-tank bioreactors in iPSC scale-up processes.

PRESENTER:

PHILIPP NOLD, PHD, *EPPENDORF BIOPROCESS, GERMANY*

1:45 PM – 2:00 PM

CELL-DERIVED EXTRACELLULAR MATRICES DRIVE BIOLOGICALLY RELEVANT PHENOTYPES IN MONOLAYER CULTURE

PRESENTED BY STEMBIOSYS, INC.

Human cells naturally secrete bioactive matrices in vitro that retain properties of the tissue of origin of the cells used to produce the matrix. These tissue-specific extracellular matrices may be used to elicit biologically-relevant phenotypes from human primary and iPSC-derived somatic cells. Previously, we have reported that CELLvo Matrices may be used to rapidly mature iPSC-derived cardiomyocytes in monolayer culture with implications for drug discovery and toxicity test. Here, we expanded on those findings with evidence that we can mature chamber specific cardiomyocytes and show that the approach may be generalized for producing biologically-relevant phenotypes from iPSC-derived neurons, hepatocytes, and islets. Cell-derived matrices are highly reproducible, versatile, easy-to-use and are compatible with high throughput plate formats.

PRESENTER:

TRAVIS BLOCK, PHD, *STEMBIOSYS, INC., USA*

2:10 PM – 2:25 PM

IMPROVING LARGE KNOCK-IN EFFICIENCY AND INDUSTRIALIZING METHODS FOR IPSC ENGINEERING USING CRISPR

PRESENTED BY SYNTHEGO

Specific genetic alterations can be engineered into pluripotent stem cells using CRISPR technology to generate more approximate models of human disease than provided by immortalized cell lines. There is also great promise in utilizing iPSCs as cellular therapies for genetic diseases. Synthego has developed automated platforms for synthesizing CRISPR sgRNAs at both RUO and GMP standards, and for applying these to engineer iPSC lines at scale. Since 2019, Synthego has completed over 1,500 gene editing projects (knockouts, SNVs, tags) in more than 400 customer-supplied iPS lines, and participated in large scale engineering projects such as the NIH's iPSC Neurodegenerative Disease Initiative (iNDI). Now we show how Synthego is pioneering efforts to efficiently generate challenging, large cargo (>1kb) knock-ins in iPSCs using non-viral approaches.

PRESENTER:

CAMILLE SINDHU, PHD, *SYNTHEGO, USA*

2:35 PM – 2:50 PM

SPINVESSEL® – MIX WITHOUT A STIR BAR!

PRESENTED BY V&P SCIENTIFIC, INC.

Keeping particulates such as agarose beads, cells or magnetic beads in uniform suspension while dispensing to microplates has been one of V&P's strengths. We have made a variety of stirring units and many different shapes and sizes of stir elements or stir bars for all types of containers. One of the common questions we always get is, "Can I stir without a stir bar?" The answer is YES with our new patented product, the SpinVessel®. The main concern is contamination or carryover if the stir bar is being reused. Also, creating a vortex in a particulate solution may not always result in a homogenous solution. And, finally, mixing with a stir bar can damage the particulates in the solution. V&P has developed the SpinVessel® to gently mix solutions containing particulates and keep them homogenously suspended, WITHOUT a stir bar. This system uses modified vessels and a rotating motion to mix and suspend particulates in solution. With this system, the concern of contamination or carry-over or damage is eliminated while providing a simple way to uniformly aliquot particulate samples into microplates.

PRESENTER:

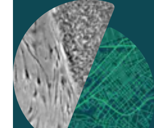
KRISTI MYERS, MS, *V&P SCIENTIFIC, INC., USA*

3:00 PM – 3:15 PM

NEXT-GENERATION PLATFORM TECHNOLOGIES TO ACCELERATE PLURIPOTENT STEM CELL RESEARCH AND DEVELOPMENT

PRESENTED BY PLURISTYX, INC.

Pluripotent stem cells promise to revolutionize future medicine by eliminating or replacing organs, tissues, and cells compromised by disease or old age. The timeframe to realize these medical advances is currently decades due to the complexity and inherent variability between stem cell lines and the lack of uniform technologies to prevent transplant rejection and introduce safety switches that prevent aberrant transplant function. There are no current standards to these development hurdles, forcing groups to expend precious time and resources addressing transplant rejection and introduce technologies in isolation, lengthening the translation from the bench to the bedside.



This presentation will introduce the audience to some of the challenges of pluripotent stem cell products, as well as how Pluristyx tackles these challenges to accelerate development and regulatory approval through the use of genetically-modified platform stem cell lines and gene editing solutions.

PRESENTER:

BRIAN HAWKINS, PHD, *PLURISTYX, INC., USA*

FRIDAY, 16 JUNE

9:55 AM – 10:10 AM

NEXT-GENERATION PLATFORM TECHNOLOGIES TO ACCELERATE PLURIPOTENT STEM CELL RESEARCH AND DEVELOPMENT

PRESENTED BY PLURISTYX, INC.

Pluripotent stem cells promise to revolutionize future medicine by eliminating or replacing organs, tissues, and cells compromised by disease or old age. The timeframe to realize these medical advances is currently decades due to the complexity and inherent variability between stem cell lines and the lack of uniform technologies to prevent transplant rejection and introduce safety switches that prevent aberrant transplant function. There are no current standards to these development hurdles, forcing groups to expend precious time and resources addressing transplant rejection and introduce technologies in isolation, lengthening the translation from the bench to the bedside. This presentation will introduce the audience to some of the challenges of pluripotent stem cell products, as well as how Pluristyx tackles these challenges to accelerate development and regulatory approval through the use of genetically-modified platform stem cell lines and gene editing solutions.

PRESENTER:

BRIAN HAWKINS, PHD, *PLURISTYX, INC., USA*

CAREER EXPLORATION AT THE MICRO THEATER

SPONSORED BY BLUEROCK THERAPEUTICS

NEW at ISSCR 2023! Career Exploration presentations will take place in the Exhibit Hall Micro Theater and will feature short, 5-10 min presentations from companies looking to recruit from ISSCR's talented community. The Micro Theater is located at the bottom of the escalators leading into the Exhibit & Poster Hall, Hall A at the Boston Convention and Exhibition Center.

1:15 PM – 1:25 PM

CAREER EXPLORATION WITH BLUEROCK THERAPUTICS

1:27 PM – 1:37 PM

CAREER EXPLORATION WITH STEMCELL TECHNOLOGIES

1:39 PM – 1:44 PM

CAREER EXPLORATION WITH SCISMIC

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SPEAKER ABSTRACTS

WEDNESDAY, 14 JUNE

PLENARY I: PRESIDENTIAL SYMPOSIUM

Sponsored by: BlueRock Therapeutics

1:00 PM – 3:00 PM

Ballroom East/West, Level 3

1:15 PM – 1:40 PM

BUILDING EMBRYO MODELS FROM STEM CELLS TO UNDERSTAND SELF-ORGANIZATION

Zernicka-Goetz, Magdalena

Biology and Biological Engineering, California Institute of Technology, Pasadena, CA, USA

I will talk about our lab's work to establish methods for culturing human and mouse embryos beyond implantation in vitro and how results coming from these studies enabled us to put together multiple stem cell types, programmed to form embryonic and extra-embryonic tissues, to self-organise into complete embryo-like structures. I will detail how we are using these complete mouse and human embryo models to determine the mechanisms behind embryo self-organisation, bringing insight into the cellular and molecular mechanisms that control previously unexplored aspects of early mammalian development until early organogenesis.

Keywords: stem cell, embryo model, embryogenesis

1:40 PM – 2:05 PM

EMPOWER THE DRIVING FORCE OF LUNG REGENERATION

Tang, Nan

National Institute of Biological Sciences, Beijing, China

Lung diseases are the leading causes of morbidity and mortality worldwide. The lung epithelium is not only essential for lung gas exchange function, it also acts as an important barrier to protect our body from harm. In response to injuries, the lung epithelium is able to rapidly repair and regenerate to restore an intact epithelial barrier and recover normal lung function. Using a convergence of mouse genetics, cell biology, intravital live imaging, and state-of-the-art sequencing technology, we aim to investigate the genetic and cellular mechanisms underlying the complex orchestration of lung regeneration. We demonstrate pulmonary alveolar development and regeneration are synergistically controlled by mechanical forces, local growth factors, and niche cell interactions. We have established a direct mechanistic link between impaired alveolar regeneration, mechanical tension, and progressive lung fibrosis. Our studies will provide insights to develop therapeutic strategies to induce lung tissue repair and regeneration in diseased lungs.

Keywords: Lung regeneration, mechanical force, live imaging

2:05 PM – 2:30 PM

DELIVERY SYSTEMS FOR REGENERATIVE MEDICINE

Langer, Robert

ChemE, Massachusetts Institute of Technology, Cambridge, MA, USA

Informational molecules regulate numerous processes in the body. However, most of these —if used therapeutically—are difficult to deliver safely and effectively to patients. Our work in this area started in 1974 with our studies on isolating the first angiogenesis inhibitors and has continued to this day and includes developing approaches to deliver substances that can regulate stem cell behavior. Applications range from cancer treatments, to COVID vaccines, to regenerative medicine, to creating new tissues and organs in humans or on chips.

2:30 PM – 2:55 PM

ERNEST MCCULLOCH MEMORIAL LECTURE: REGENERATING AND REJUVENATING AGED TISSUE BY TARGETING A GEROZYME

Blau, Helen M.

Microbiology and Immunology/Baxter Laboratory for Stem Cell Biology, Stanford University School of Medicine, Stanford, CA, USA

Helen M. Blau, PhD, is the Donald E. and Delia B. Baxter Foundation Professor and Director of the Baxter Laboratory for Stem Cell Biology at Stanford University. Blau is world-renowned for her early work on nuclear reprogramming and demonstration of the plasticity of cell fate using cell fusion. Her lab has embraced multidisciplinary approaches to characterize the potent muscle stem cell (MuSC) population that is poised to repair muscle throughout life. By designing biomaterials to mimic the in vivo muscle stem cell niche, they were able to maintain the stem cell state in vitro. Blau's lab forged methods to prospectively isolate MuSCs using fluorescence activated cell sorting (FACS), employed high-resolution lineage mapping by single-cell mass cytometry (CyTOF) to resolve a dysfunctional MuSC subset in aging, and monitored the dynamics of stem cell expansion during regeneration by bioluminescence imaging (BLI). Blau's lab discovered that aged muscle stem cells and tissues can be rejuvenated by targeting a single enzyme, 15-PGDH, the Prostaglandin E2 degrading enzyme, which she named a "gerozyme", a pivotal molecular determinant of aging. Remarkably, 15-PGDH overexpression triggers atrophy in young muscles, whereas its inhibition strengthens aged muscles. The potency of PGE2, which accumulates following enzyme inhibition, arises from its dual targets: muscle stem cells and mature myofibers. These findings hold promise for translation to the clinic to augment strength in patients with muscular dystrophies, disuse atrophy, and sarcopenia, the debilitating loss of muscle function with aging for which there currently is no treatment. Dr. Blau is a co-inventor on 20 patents. She is a member of the Board of Directors and program committee of ISSCR. She is an elected member of American Academy of Arts and Sciences, Pontifical Academy of Sciences, National Academy of Medicine, and National Academy of Sciences.

Keywords: Gerozyme, Rejuvenation, Muscle

TRACK: NEW TECHNOLOGIES (NT)

PLENARY II: CUTTING EDGE MOLECULAR TECHNOLOGIES

Sponsored by: BioMarin Pharmaceutical Inc.

3:45 PM – 5:35 PM
Ballroom East/West, Level 3

3:50 PM – 4:10 PM

DEEP LEARNING THE ROLE OF TRANSCRIPTION FACTOR STOICHIOMETRY AND MOTIF SYNTAX IN SINGLE-CELL CHROMATIN DYNAMICS OF HUMAN SOMATIC CELL REPROGRAMMING

Kundaje, Anshul
Genetics, Computer Science, Stanford University, CA, USA

In this study, we investigate the role of continuous OSK stoichiometry variation in shaping the chromatin and gene expression landscape during the reprogramming of differentiated cells into induced pluripotent stem cells at single-cell resolution. Utilizing deep neural networks, we predict cell-state-specific ATAC-seq signals derived from the underlying DNA sequence, decoupled from Tn5's intrinsic sequence preference. This approach allows us to identify and interpret context-specific regulatory motifs crucial in progressive cell states. We observe that initial diversification into a reprogramming trajectory and non-reprogramming keratinocyte- and fibroblast-like fates stems from stochastic variation in the stoichiometry of OSKM. In cells with supraphysiological overexpression, OSK takes over the chromatin landscape by engaging and opening closed chromatin. Our findings reveal that a significant fraction of opened cis-regulatory elements (CREs) contain low-affinity OSK motifs, including a novel partial POUS-HMG OCT-SOX motif. Interestingly, we note that CREs with weaker motifs are progressively released as OSK concentration reduces, suggesting a simple mechanism for silencing early transient CREs. Our deep learning models reveal that single-cell ATAC-seq encodes differences in transcription factor (TF) footprint depths correlating with TF stoichiometry and motif affinity. We also observe that temporally restricted expression of pioneer TFs like TFAP2C drives secondary transient effects. Lastly, we elucidate how OSK stoichiometry affects somatic silencing by tuning the ability to sequester away somatic TFs such as AP1 to transient CREs. Our approach outlines a powerful paradigm for interrogating sequence determinants of accessibility in trajectories with continuous variation in TF concentrations. In summary, our findings provide valuable insights into sequence determinants of accessibility in trajectories with continuous TF concentration variations. By connecting TF stoichiometry over the course of reprogramming to diversification of trajectories, low-affinity motif binding, differential footprinting, CRE selection, and somatic silencing, we contribute to a deeper understanding of the complex process of cellular reprogramming.

Keywords: reprogramming, deep learning, gene regulation, cis-regulatory code, single cell, chromatin accessibility, transcription factors

4:10 PM – 4:30 PM

CRISPR TECHNOLOGY FOR DISCOVERY RESEARCH AND DISEASE MODELLING IN HUMAN FETAL LUNG-DERIVED ORGANOIDS

Rawlins, Emma L.[1], Lim, Kyungtae[2], Sun, Dawei[2], Rutherford, Eimear[2] and Dickens, Jennifer[2]
[1]*Gurdon Institute and Department Physiology, Development and Neuroscience, University of Cambridge, UK,* [2]*The Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge, UK*

Organoids derived from primary human tissues retain key functional characteristics of the tissue of interest and have the potential to improve in vitro assays used for disease modelling and drug development. However, the burgeoning CRISPR toolkits have not yet been widely applied to human organoids. We have developed efficient methodologies for the use of CRISPR techniques in primary human embryonic lung organoids. These will be widely adaptable to other human organoid systems and include homology directed repair, CRISPRi, CRISPRa and drop-out screens. This talk will illustrate how we have applied these systems to develop new human lung organoid models for fundamental and disease research.

Keywords: Human, organoids, CRISPR

4:30 PM – 4:50 PM

TOWARDS RECONSTRUCTING MAMMALIAN DEVELOPMENT, ZYGOTE TO PUP

Shendure, Jay A.
Genome Sciences, University of Washington/HHMI, Seattle, WA, USA

Our long-term dream is to comprehensively reconstruct the unfolding of mammalian development, all the way from a single cell zygote to a free-living pup. In this talk, I will describe recently developed technologies for time-resolved lineage and molecular recording, called DNA Typewriter and ENGRAM, that are relevant to this goal.

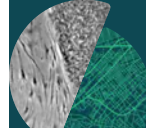
Keywords: Towards a DNA Typewriter for recording mammalian development

4:50 PM – 5:10 PM

SPATIALLY RESOLVED SINGLE-CELL GENOMICS & CELL ATLAS OF THE BRAIN

Zhuang, Xiaowei
Harvard University, MA, USA

Inside living organisms, thousands of different genes function collectively to give rise to cellular behavior and tissue function. Understanding the behaviors and functions of cells and tissues thus require imaging at the genome scale, which will advance our understanding in many areas of biology, ranging from the regulation of gene expression in cells to the development of cell fate and the organization of cell types in complex tissues. We developed a single-cell transcriptome and genome imaging method, multiplexed error-robust fluorescence in situ hybridization (MERFISH), which allows RNA, DNA, and epigenetic marks to be imaged at the genome scale. This approach enabled spatially resolved transcriptomic profiling, epigenomic profiling, and 3D-genome organization mapping in single cells. The ability to perform single-cell gene expression profiling in intact tissues further enabled the identification, spatial mapping, and functional annotation of distinct cell types in intact tissues. In this talk, I will describe the MERFISH technology and its applications, with a focus on mapping the molecular, spatial, and functional organizations of cell types in the mouse and human brain.



5:10 PM – 5:35 PM

ANNE MCLAREN MEMORIAL LECTURE: DECONSTRUCTING HUMAN MUSCULO-SKELETAL DEVELOPMENT IN VITRO

Pourquié, Olivier
Harvard University/Brigham and Women's Hospital, Boston, MA, USA

Skeletal muscles and vertebrae derive from precursors located in the embryonic segments called somites. These structures form periodically from a posterior tissue called Presomitic Mesoderm (PSM). The rhythmic formation of somites involves a molecular oscillator called segmentation clock which drives pulses of Notch, Wnt and FGF signaling in the PSM. Virtually nothing is known on human somitogenesis as it proceeds between 3- and 5-weeks post conception when embryos are extremely difficult to access. We have developed protocols to differentiate human pluripotent stem cells (ES/iPS) in vitro into PSM. Single cell RNA-sequencing comparison of these human cells differentiating in vitro with mouse embryo PSM reveals that they faithfully recapitulate the PSM differentiation sequence in vitro. Using our in vitro system as a proxy for human somitogenesis, we were able to demonstrate that human iPS reporter cells harboring a HES7 fluorescent reporter differentiated to PSM exhibit 5-hour oscillations, thus identifying the human segmentation clock. We have also succeeded in generating PSM organoids that can sequentially form somites exhibiting a normal antero-posterior pattern in vitro. By mimicking key signaling events leading to muscle formation in the embryo, we developed directed differentiation protocols which recapitulate the developmental sequence of myogenesis. We then used these cells to generate new in vitro models of Duchenne Muscular Dystrophy and to pioneer the production of human satellite cells for cell therapy strategies for muscular dystrophies. Our work provides a framework to study early stages of human myogenesis which are poorly accessible in the embryo.

Keywords: organoids, mesoderm, skeletal muscle

THURSDAY, 15 JUNE

CONCURRENT TRACK MINI SESSIONS

8:30 AM – 9:30 AM

TRACK: CLINICAL APPLICATIONS (CA)

STEM CELLS IN CLINICAL TRIALS

8:30 AM – 9:30 AM
Room 258, Meeting Level 2

8:30 AM – 8:40 AM

GENERATION OF THE FIRST INTERNATIONAL FLOW CYTOMETRY IDENTITY STANDARD FOR MSCS

Mattioli, Elisa[1], Konstantinidou, Chrysoula[2], Lindsay-Hill, Luke[2], Choy, Andrew[2], Zarzoso, Adrian[2], Prince, Judith[2], Perfect, Leo[2], Wise, Clare[3], Burns, Chris[3], Carpenter, Lee[3] and Warre-Cornish, Katherine[2]
[1]UKSCB, UKSCB/MHRA, Potters Bar, UK, [2]UKSCB, NIBSC/MHRA, London, UK, [3]UKSCB, UKSCB/MHRA, London, UK

There are currently over 1000 Mesenchymal Stromal Cell (MSC) clinical trials registered for a large variety of diseases. MSCs have shown promise in the treatment of a wide range of disorders including auto-immune diseases such as Crohn's disease and systemic lupus erythematosus, conditions involving tissue damage such as chronic obstructive pulmonary disease and diseases of uncontrolled inflammation such as graft versus host disease. Despite this progress, a lack of standardisation has limited the development of MSC-based therapies in an attempt to harmonise the field, the International Society for Cellular Therapy (ISCT) issued recommendations defining minimal criteria for MSC identity. These include ≥95% of the cell population expressing MSC positive markers, CD73, CD90 and CD105 and ≤2% of the cell population expressing MSC negative markers CD45, CD34, CD14, CD11b, CD19 and HLA-DR, as assessed by flow cytometry. The UK Stem Cell Bank aims to build on these efforts by developing the world's first international reference reagents for MSCs, designed to increase confidence in critical quality data. The bank conducted a successful pilot WHO collaborative study for a reference reagent for flow cytometry in 2018-2019. Fixed, freeze-dried MSCs derived from human pluripotent stem cells were distributed to collaborators and tested for MSC markers using in-house flow cytometry protocols. Results were highly consistent between participants and compliant with ISCT identity requirements. Further characterisation is underway to investigate stability and quality. This work includes comparison of the ISCT expression profiles with the MRC-5 cell line and primary umbilical cord-derived MSCs, and the assessment of formaldehyde-based versus formaldehyde-free fixative reagents. Results assured fidelity of the product with other MSC cell types, consistency between biological and technical replicates and indicated more consistent results with formaldehyde fixed MSCs. This reference reagent could be used to increase confidence in identity assessment of MSC products for clinical applications. It will enable comparison between batches of MSCs and promote consistency in flow cytometry assessment between different laboratories, despite differing equipment, reagents, instrument settings and data analysis strategies

Keywords: Mesenchymal Stromal Cells (MSCs), Flow Cytometry Standard, MRC-5

8:40 AM – 8:50 AM

CD90-TARGETED VIRAL VECTORS FOR HEMATOPOIETIC STEM CELL GENE THERAPY

Radtke, Stefan[1], Berckmueller, Kurt[2], Kiem, Hans-Peter[2] and Thomas, Justin[2]
[1]Fred Hutchinson Cancer Research Center, Seattle, WA, USA, [2]Translational Science and Therapeutics Division, Fred Hutchinson Cancer Center, Seattle, WA, USA

Hematopoietic Stem Cell (HSC) gene therapy is a promising route to curing patients with a variety of hematologic diseases and disorders. HSC gene therapy is currently performed ex vivo and requires highly sophisticated infrastructure similar to bone marrow transplantation. Application of gene therapy agents directly in the patient (in vivo) would overcome this bottleneck. The Kiem lab has previously shown that CD90+ HSCs contribute to early recovery and form long-term persisting clonal pools after transplantation. Here we designed CD90-targeted lentiviral vectors for the ex vivo as well as in vivo delivery of transgenes into this refined HSC population. We initially developed and attached a CD90 scFv to the viral envelop. Surface-engineered VSVG-, Cocal-, and Measles-based viral vectors showed no impairment in the number of secreted viral particles from HEK293T producer cells and mRNA-loading was comparable to wildtype virus. Functionality of all three engineered vectors was evaluated on CD90-expressing Jurkat cells demonstrating successful transduction and transgene expression. To evaluate specificity, Jurkat cells were diluted with CD90-lacking K562 cells demonstrating highly specific transduction of on-target cells in comparison to wildtype virus. Most importantly, CD90-targeted vectors were ap-

plied to CD34+ hematopoietic stem and progenitor cells showing enhanced transgene expression in human HSCs with secondary colony-forming potential. Here we show that CD90-targeted viral vectors are functional and taken up by target cells. Targeted vectors showed greater specificity for CD90 expressing Jurkat cells as well as CD90+ HSCs ex vivo. Experiments in humanized mice are ongoing to test the targeting efficiency of vectors in vivo. In contrast to other approaches, this new viral vector will be capable of improving ex vivo therapies and overcoming the hurdles in vivo therapies still have. The development of targeted viral vectors has the potential to increase the on-target efficiency and safety of in vivo HSC gene transfer and will be a crucial step in democratizing access to gene therapies.

Keywords: Hematopoietic stem cells (HSCs), CD90-targeted viral vectors, Gene Therapy

8:50 AM – 9:00 AM

IN VIVO DELIVERY OF GENETIC PAYLOADS TO HUMAN HEMATOPOIETIC STEM/PROGENITOR CELLS

Harrington, Sean[1], Botchkarev, Vladimir[1], Justen, Alex[1], Kimber, Casey[1], Kapuria, Anjali[1], Jain, Suvi[2], Zeballos, Gonzalo[3], Adewale, Funmi[4], Haugh, Kelsey[1], Crocker, Samantha[3], Liang, Anna[3], Joyce, Shannon[3], Ferland, Ben[3], Chandra, Sundeep[3], Daniels, Kathy[4], Stoppato, Matteo[1], Trudeau, Kyle[1], Rebar, Ed[5], Shah, Jagesh[1] and Biasco, Luca[1]
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Achieving in vivo genetic engineering of hematopoietic stem/progenitor cells (HSPC) could dramatically expand patients' access to gene therapy. However, preclinical development is complicated by the fact that mouse hematopoiesis differs from human and is not permissive to all human-compatible vector pseudotypes. We have developed a strategy to measure in vitro and in vivo access to human HSPC and achieved efficient genetic engineering of these cells using lentiviral vectors (LV) without relying on high vector doses or selective enrichment. We initially conducted a high-resolution characterization of access to unstimulated HSPC and resting individual HSPC subtypes in vitro. Using BaEVTR LV we obtained ~100% targeting of HSPC at MOI 66 (vs ~40% with VSV-G at MOI 50,750) and ~20% of resting FACS-sorted hematopoietic stem cells at MOI 2, a dose reflective of an in vivo scenario. To measure in vivo access, we first performed intravenous injection of LV in 12-19 wks humanized mice and showed that 1 low dose of BaEVTR LV could transduce 2-4% bone marrow (BM) multipotent progenitors vs no detectable transduction in that population using VSV-G LV. To specifically study BM access to HSPC, we injected LV at D7 after mouse humanization when we established that human cells are localized only in the BM and that HSPC still reflects the donor composition, achieving 2.6% targeting of BM HSPC with one low dose BaEVTR LV. To study access to HSPC in peripheral blood (PB), we infused NBSGW mice with human CD34+ cells immediately followed by LV dosing. We here achieved targeting of 23% BM HSPC with BaEVTR LV at D12, corresponding to 21-23% GFP+ myeloid output in PB over the first 6 weeks after infusion. These mice were later mobilized at 11 wks and injected with LV carrying the RFP gene to measure stability/plasticity of engineered engrafted HSC and susceptibility to multiple transductions. Lastly, we evaluated retargeted fusogen LV engineered to recognize receptors on target cell types via IV injection and showed a striking 100x specificity increase over other broadly tropic LV in targeting a receptor-positive population exclusively localized in the BM, which make up as little as 0.15% of total human cells. Overall, we generated a robust strategy for establishing basal access and achieving efficient specific delivery of genetic payloads to human HSPC.

Keywords: in vivo gene therapy, hematopoietic stem cells, lentiviral vectors

9:00 AM – 9:10 AM

REVERSAL OF POST-HEPATECTOMY LIVER FAILURE USING A BIOARTIFICIAL LIVER SUPPORTING SYSTEM IMPLANTED WITH CLINICAL-GRADE HUMAN INDUCED HEPATOCYTES

Zhang, Ludi[1], Wang, Yifan[2], Zheng, Qiang[2], Sun, Zhen[3], Wang, Chenhua[4], Pan, Guoyu[5], Cai, Xiujun[2] and Hui, Lijian[4]
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Liver resection is the first-line treatment for primary liver cancers, providing the potential for cure. However, concerns about post-hepatectomy liver failure (PHLF), a leading cause of death following extended liver resection, have restricted the population of eligible patients. Here, we engineered a clinical-grade bioartificial liver (BAL) device employing directly reprogrammed human hepatocytes (hiHeps) manufactured and cryopreserved under GMP conditions. In a porcine PHLF model induced by 85% hepatectomy, hiHep-BAL treatment showed a remarkable survival benefit. On the top of the supportive function, hiHep-BAL treatment restored functions, specifically ammonia detoxification, of the remnant liver and facilitated liver regeneration. Notably, an investigator-initiated study in seven patients with extended liver resection demonstrated that hiHep-BAL treatment was well tolerated and associated with improved liver function and liver regeneration, meeting the primary outcome of safety and feasibility. These encouraging results warrant further testing of hiHep-BAL for PHLF, the success of which would broaden the population of patients eligible for liver resection.

Keywords: transdifferentiation, bioartificial liver, liver failure

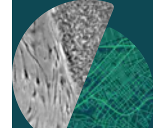
Clinical Trial ID number: NCT 05035108

9:10 AM – 9:20 AM

IN VIVO CRISPR/CAS9 SCREEN IDENTIFIES TNF-NFKB-P53 AXIS LIMITING THE SURVIVAL OF HUMAN PSC-DERIVED POSTMITOTIC DOPAMINE NEURON AT TRANSPLANT

Kim, Taewan and Koo, So-Yeon
Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Development of cell replacement therapy in PD has entered an exciting, new phase with our ongoing clinical trial in 12 patients transplanted using off-the-shelf human pluripotent stem cell (hPSC)-derived dopamine neurons. However, several challenges remain such as i) overcoming extensive cell death following implantation, with < 10% of grafted dopamine neurons surviving, and ii) developing a paradigm enabling postmitotic DA neuron engraftment to further maximize safety. Here, we performed a pooled CRISPR/Cas9 screen to enhance the survival of postmitotic dopamine neurons in vivo. We identified TP53-mediated apoptotic cell death as a major contributor to dopamine neuron



loss and uncovered a causal link of TNFa-NFκB signaling in limiting cell survival. As a translationally applicable strategy to purify postmitotic dopamine neurons, we performed a cell surface marker screen that enabled purification without the need for genetic reporters. Combining cell sorting with adalimumab pre-treatment, a clinically approved and widely used TNFa inhibitor, enabled efficient engraftment of postmitotic dopamine neurons leading to extensive re-innervation and functional recovery in a preclinical PD mouse model. Thus, transient TNFa inhibition presents a clinically relevant strategy to enhance survival and enable the engraftment of postmitotic human PSC-derived dopamine neurons in PD.

Keywords: Cell therapy, Cell Survival, Genetic Screen, Cell purification, Parkinson's disease, Transplantation,

TRACK: CELLULAR IDENTIY (CI)

CELLULAR IDENTITY MECHANISMS AND APPLICATION

8:30 AM – 9:30 AM
Room 257, Meeting Level 2

8:30 AM – 8:40 AM

METABOLIC REWIRING UNDERPINS HUMAN TROPHOBLAST INDUCTION

Zylicz, Jan J.[1], Van Nerum, Karlien[2], Wenzel, Anne[2] and Lavro, Viktoria[2]
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Development is driven by a complex sequence of transcriptional, epigenetic, and metabolic changes. However, these do not operate in isolation as they are functionally coupled to one-another. How such complex regulatory networks coordinate specific cell-state changes remains largely unknown. Here we address this question in the context of the first lineage specification during human development, when blastomeres are allocated towards either the pluripotent or trophectodermal (TE) lineage. By using naïve human embryonic stem cells (hESC) induced towards trophoblast stem cells (TSCs) and blastoids we have uncovered a dramatic metabolic rewiring during TE-fate induction. Metabolic engineering of the hESC-to-TSC induction further revealed that this metabolic asymmetry constitutes a significant bottleneck in the induction of GATA3+ve TSC-like cells. Importantly, a short metabolic pre-treatment of naïve hESCs was sufficient to render them over 7-fold more competent towards the TE-lineage. In line with this finding, metabolically engineered media also promoted blastoid development and cavitation. Metabolism not only affects the way that cells produce and consume energy, but it also has a direct impact on the activity of chromatin modifiers and signaling pathways. Indeed, we find that metabolic pre-treatment of naïve hESC resulted in: partial dissolution of the naïve pluripotency regulatory network; altered global levels of specific active histone modifications but not H3K27me3; the opening of enhancers associated with specific transcription factors and changes to key signalling pathways. Further functional assays confirmed that both signalling and other chromatin mechanisms sense the metabolic state of naïve hESCs and regulate their competence towards TE-lineage. This work highlights the importance of the non-canonical function of metabolism in signaling towards chromatin and regulating cell identity.

Funding Source: This work was supported by grants from Novo Nordisk Fonden (NNF) (NNF21CC0073729), Lundbeckfonden (Lundbeck Foundation) (R345-2020-1497) and Danmarks Frie Forskningsfond (DFF) (0134-00031B, 0169-00031B).

Keywords: blastocyst, metabolism, epigenetics

8:40 AM – 8:50 AM

ESSRB GUIDES NAIVE PLURIPOTENT CELLS THROUGH THE FORMATIVE TRANSCRIPTIONAL PROGRAM

Martello, Graziano[1], Carbognin, Elena[1], Carlini, Valentina[2], Panariello, Francesco[3], Chieregato, Martina[4], Guerzoni, Elena[4], Benvegnù, Davide[4], Perrera, Valentina[1], Malucelli, Cristina[1], Cesana, Marcella[6], Grimaldi, Antonio[4], Mutarelli, Margherita[4], Carissimo, Annamaria[3], Tannenbaum, Eitan[6], Kugler, Hillel[6], Hackett, Jamie[2] and Cacchiarelli, Davide[3]
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During embryonic development, naive pluripotent epiblast cells transit to a formative state. The formative epiblast cells form a polarised epithelium, exhibit distinct transcriptional and epigenetic profiles and acquire competence to differentiate into all somatic and germline lineages. However, we have limited understanding of how the transition to a formative state is molecularly controlled. Here we used murine ESC models to show that ESRRB is both required and sufficient to activate formative genes. Genetic inactivation of Esrrb leads to illegitimate expression of mesendoderm and extraembryonic markers, impaired formative expression and failure to self-organise in 3D. Functionally, this results in impaired ability to generate Formative Stem cells and primordial germ cells in the absence of Esrrb. Computational modelling and genomic analyses revealed that ESRRB occupies key formative genes in naive cells and throughout the formative state. In so doing, ESRRB kickstarts the formative transition, leading to timely and unbiased capacity for multi-lineage differentiation.

Funding Source: G.M.'s laboratory is supported by grants from the Giovanni Armenise–Harvard Foundation, the Telethon Foundation (GJC21157), Microsoft Research and an ERC Starting Grant (MetEpiStem).

Keywords: Pluripotency, Formative, Esrrb

8:50 AM – 9:00 AM

MG01: SINGLE, OFF-THE-SHELF TREATMENT OF CNS PATHOLOGY IN MUCOPOLYSACCHARIDOSES

Douvaras, Panagiotis[1], Buenaventura, Diego[1], Sun, Bruce[1], Lepack, Ashley[1], Baker, Elizabeth[1], Simpson, Elizabeth[2], Ebel, Mark[2], Lallos, Gregory[1], LoSchiavo, Deven[1], Stitt, Nicholas[1], Adams, Nathaniel[2], McAuliffe, Conor[2], Tallman, Elizabeth[2], Fisher, Stephanie[3], Wang, Jing[1], Tomishima, Mark[2], Paladini, Carlos[1], Wilkinson, Dan[2], Soh, Chew-Li[2], Srinivas, Maya[2], Patsch, Christoph[1] and Irion, Stefan[1]
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Lysosomal storage disorders (LSDs) are a group of inherited metabolic diseases, caused by a single gene defect. Lysosomal enzyme deficiency leads to accumulation of toxic, undegraded substrates in a patient's cells, resulting in a progressive degenerative disorder. Mucopolysaccharidoses (MPS) is a subgroup of LSDs where accumulation of glycosaminoglycans (GAGs) impact many organs including the central nervous system (CNS) with neurological regression, developmental delays and mortality typically observed early in life. Current treatments like enzyme replacement therapy or hematopoietic stem cell transplantation are often insufficient to deliver therapeutically relevant levels of the enzyme to the CNS. Introducing allogeneic off-the-shelf donor cells, capable of long-term survival in the CNS while secreting functional lysosomal enzymes offer a potential treatment for several LSDs with a single therapeutic agent. Here we demonstrate that human pluripotent stem cell-derived microglia, termed MG01, are replete with wild-type levels of lysosomal enzymes and correct the enzymatic deficiency of in vitro and in vivo models for two MPS, as representative LSDs. We developed an assay where MG01 were co-cultured with cells lacking alpha-L-iduronidase (IDUA) or beta-glucuronidase (GUSB), mimicking the diseased cells in MPS I or MPS VII, respectively. Functional lysosomal enzymes were secreted by MG01 and were taken up by the diseased cells, which showed reduced levels of intracellular, toxic GAGs. To establish animal proof of concept, we treated transgenic animal models of MPS I and MPS VII with a single, bilateral intracerebroventricular infusion of MG01. We show the presence of grafted cells, enzymatic activity of IDUA or GUSB, and reduction of GAGs in CNS tissues for at least eight months after MG01 transplantation. Finally, MG01 treatment was able to prevent behavioral deficits in both diseased models, providing the exciting opportunity for a one-time cell delivery strategy to treat multiple LSDs with a single therapeutic modality.

Keywords: Cell therapy, iPSC-derived, Microglia

9:00 AM – 9:10 AM

FROM A STEM CELL TO A NEURON: HOW ALTERNATIVE RNA SPLICING CONTROLS CELL FATE DECISIONS

Manuel, Jeru Manoj, Khan, Muhammad, Avino, Mariano and Laurent, Benoit
Biochemistry and Functional Genomics, Universite de Sherbrooke, QC, Canada

Neuronal differentiation is a complex process that integrates signals driving the engagement of stem cells into a neural lineage, and subsequently the maturation of neural progenitors into terminally differentiated neurons. Many studies highlighted the importance of alternative splicing (AS) during neurogenesis as a mechanism critical for cell fate decisions, neuronal migration, axon guidance, and synaptogenesis. Here we report the deep analysis of the gene regulatory network that sustains each transition of human neuronal differentiation. To do so, we used an engineered human induced pluripotent stem (iPS) cell line that can yield a homogeneous population of mature neurons in four days upon inducible expression of NGN1 and NGN2. Paired-end RNA sequencing was performed at three differentiation timepoints: stem cell stage (day 0; D0), progenitor stage (day 2; D2) and mature neurons (day 4; D4). We determined the temporal signature of gene expression, the differential usage of transcripts and the landscape of AS events (including micro-exons) during neuronal differentiation. We identified 2289 genes differentially expressed between D0 to D4 (up n=1055; down n=1234). Interestingly, we discovered a D2-specific transcriptional bursting of a subset of genes. Inhibition of D2-specific gene candidates led to a defect of neuronal differentiation, highlighting the importance of this gene subset for the engagement of progenitors to terminal maturation. We also analyzed AS events at each differentiation stage and identified around 170,000 AS events per stage, and discovered D2-specific AS events that are critical for the progression of neuronal maturation. Pulsing of these events at D2 is necessary for the engagement to terminal differentiation since inhibition of D2-specific candidate isoforms leads to abnormal neuronal maturation. Together, our findings highlight the importance of transient transcriptional and AS events that are pivotal for the advance of neuronal differentiation and underscore the need to investigate their deregulation in neurodevelopmental disorders and neurodegenerative diseases.

Funding Source: JMM is funded by NSERC-CREATE RNA Innovation Post-doctoral fellowship. The project is funded by Banting Research foundation and CIHR.

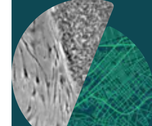
Keywords: alternative RNA splicing, iNGN stem cells, neuronal differentiation

9:10 AM – 9:20 AM

INCEPTOR BINDS AND DIRECTS INSULIN TO LYSOSOMAL DEGRADATION IN STEM CELL-DERIVED PANCREATIC ISLETS

Siehler, Johanna[1], Bilekova, Sara[1], Jain, Chirag[1], Sterr, Michael[1], Malhotra, Chetna[1], Ansarullah, Ansarullah[1], Chapouton, Prisca[1], Kurth, Thomas[2], Burtscher, Ingo[1] and Lickert, Heiko[1]
[1]Institute of Diabetes and Regeneration Research, Helmholtz Center Munich, Neuherberg, Germany, [2]Center for Molecular and Cellular Bioengineering, TU, Dresden, Germany

The main function of pancreatic beta cells is to produce, store, and secrete the glucoregulatory hormone insulin. Insulin degranulation and blunted first-phase insulin secretion are early signs of diabetes. Thus, a thorough understanding of basic mechanisms and druggable targets that regulate insulin homeostasis are urgently needed to prevent diabetes progression. Here, we reveal that the insulin inhibitory receptor (inceptor, encoded by the gene IIR), which was previously described as an insulin signaling desensitizer, acts as an insulin and proinsulin binding receptor regulating insulin turnover in beta cells. Using human induced pluripotent stem cell (iPSC)-derived pancreatic islets, we show that IIR knockout (KO) leads to enhanced stem cell-derived (SC)-beta cell differentiation, maturation, and survival. Moreover, IIR KO SC-beta cells show reduced proinsulin degradation leading to increased (pro)insulin stores and glucose-stimulated insulin secretion. Mechanistically, inceptor interacts with the adaptor protein complex of clathrin-coated vesicles endocytosed from the plasma membrane and nascent secretory granules budding of the trans-Golgi network (TGN) thereby facilitating the transport of insulin and proinsulin to lysosomes. Strikingly, targeting the inceptor:insulin interaction using a therapeutically relevant monoclonal antibody against inceptor increases insulin stores and improves glucose-stimulated insulin secretion of SC-beta



cells. Altogether, our findings identify inceptor as a novel TGN sorting receptor that mediates (pro)insulin degradation and provide evidence that inceptor can be targeted to restore beta cell function of diabetic patients.

Keywords: Insulin, Beta cells, Diabetes

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)

REGENERATION AND DISEASES IN A DISH
8:30 AM – 9:30 AM
Room 253, Meeting Level 2

8:30 AM – 8:40 AM

CARDIAC ORGANOIDS REVEAL CHAMBER-SPECIFIC 3D CHROMATIN STRUCTURE MECHANISMS DYSREGULATED IN CONGENITAL HEART DISEASE

Bertero, Alessandro[1], Becca, Silvia[1], Hahn, Elisa[1], Snijders, Kirsten[1], Ratto, Maria Luisa[1], Balmas, Elisa[1], Calogero, Raffaele[1] and Mendjan, Sasha[2]
[1]Molecular Biotechnology Center "Guido Tarone", Università di Torino, Italy, [2]Austrian Academy of Sciences, Institute of Molecular Biotechnology, Vienna, Austria

Congenital heart disease (CHD) is the most prevalent severe birth defect, affecting ~1 in 100 newborns and ~1.4 million adults in the US. Despite substantial recent progress in early detection and surgical correction, the incidence of CHD continues to increase. Alas, no specific drugs are available for neither children nor adult carriers. CHD is often caused by mutations in key cardiac transcription factors (i.e., GATA4) or chromatin structure regulators (i.e., CTCF). 3D chromatin organization has emerged as an important regulator of gene expression during embryogenesis. Nevertheless, whether altered dynamics of genome architecture are implicated in CHD remains elusive. We deployed a new model of chamber-specific cardiac organoids (cardioids), derived from human induced pluripotent stem cells (hiPSCs), to correlate morphogenetic defects with chromatin structure-function alterations, measured by chromatin conformation capture and single cell genomics. We found that CTCF binding and the resulting intergenic looping poses a repressive barrier to premature upregulation of cardiomyocyte genes that must move from the inactive (B) to active (A) compartment during cardiogenesis. On the other hand, GATA4 acts as a pioneer factor promoting the unwinding of chromatin at the same loci and their B to A transition. The differentiation of pluripotent stem cells into cardiac progenitors and then cardiomyocytes is facilitated by the gradual downregulation of CTCF up to ~50% and requires the progressive transcriptional activation of GATA4. Haploinsufficiency in CTCF or GATA4 biases this finely balanced tug-of-war, leading to early depletion of cardiac progenitors or their delayed specification into cardiomyocytes, respectively. Conversely, cardiac fibroblasts are underrepresented or overabundant in CTCF versus GATA4 haploinsufficient cardioids. These effects are predominant for derivatives of the second heart field (SHF): the right ventricle and the atria. Similar functional alterations in 3D chromatin remodeling may also play a role in other forms of CHD, including those resulting from environmental exposures. Cardioids are not just powerful models to unravel CHD mechanisms, but also represent a scalable platform to test potential novel therapies such as epigenetic modulators of chromatin remodeling.

Funding Source: This work was supported by an Armenise-Harvard Foundation Career Development Award (to A.B.) and an Additional Ventures Single Ventricle Research Fund grant (to A.B. and S.M.).

Keywords: Cardiac organoids, Congenital heart defects, 3D chromatin organization

8:40 AM – 8:50 AM

DURABLE ALVEOLAR ENGRAFTMENT OF PSC-DERIVED LUNG TIP-LIKE CELLS INTO IMMUNOCOMPETENT MICE

Herriges, Michael, Wang, Feiya, Villacorta-Martin, Carlos and Kotton, Darrell
Center for Regenerative Medicine, Boston University, Boston, MA, USA

Recent work suggests that mouse Sox9+ embryonic lung epithelial tip cells cultured in vitro can engraft and differentiate in injured immunocompromised mouse lungs, providing a potential method for cell-based therapy of lung injury. However, the use of embryonic donor cells and immunocompromised recipients severely limits the clinical applicability of this approach. Directed differentiation of pluripotent stem cells (PSCs) offers an alternative source of donor cells which can overcome these limitations. Here we describe an important step toward human PSC-based lung cell therapy with the development of a protocol for the directed differentiation of murine PSCs into distal tip-like cells. The resulting cells express distal tip markers, maintain low levels of mature alveolar markers, and can be expanded in culture, similar to cultured primary tip cells. These mPSC-derived tip-like cells can be transplanted into syngeneic and immunocompetent mouse lungs, where they gave rise to both AT2-like and AT1-like cells that persisted for up to 6 months post transplantation. Furthermore, donor-derived cells demonstrate the lamellar body organelles and facultative progenitor capacity of endogenous AT2 cells. This suggests that donor-derived AT2-like cells are functionally similar to endogenous AT2 cells and representative of true pulmonary engraftment. Together this work provides evidence of successful engraftment of PSC-derived cells into immunocompetent mouse lungs. Further characterization of this system will provide important information for the development of PSC-derived cell therapy of human pulmonary diseases.

Keywords: Lung, Syngeneic Engraftment, ESC-derived

8:50 AM – 9:00 AM

DYSREGULATED EPITHELIAL-MESENCHYMAL CROSSTALK IN THE STEM CELL NICHE DRIVES INTESTINAL POLYP FORMATION

Li, Mei Lan[1], Figetakis, Maria[2], Wang, Minming[2], Jin, Jason[2], McDonald, Elizabeth[2], Smith, Zachary[2] and Sumigray, Kaelyn[2]
[1]Genetics, Yale University, New Haven, CT, USA, [2]Genetics, Yale School of Medicine, New Haven, CT, USA

Epithelial-mesenchymal crosstalk is a crucial mechanism regulating stem cell niches and tissue architecture. Extensive efforts have revealed that heterogeneous fibroblast populations play key roles as niche factors in supporting epithelial stem cells. In the mammalian small intestine, distinct fibroblast populations are spatially compartmentalized, secreting and restricting Wnt signals in proliferative crypts and Bmp signals in differentiated villi. However, we lack understanding of how distinct fibroblast subtypes are organized and regulated to maintain homeostasis. We and others have found that loss of fibroblast Bmp signaling transforms the epithelium into hyperproliferative polyps with

disrupted crypt-villus axes, though the underlying mechanisms are completely unknown. Our inducible Bmp loss-of-function mouse model reveals novel polyp-initiating events that involve ectopic internal tissue fold formation coupled with dramatic fibroblast dysregulation before epithelial hyperproliferation. This initial tissue architectural change separates the epithelium from its underlying stroma and muscle layers, disrupting normal stem cell-niche interactions. Ongoing transcriptomic analyses have uncovered key changes to fibroblast cellular states and functions that support their roles in tissue deformation and epithelial dysregulation. Primary fibroblasts treated with Bmp inhibitor in vitro acquire an activated state, verifying a pathological activation of fibroblast cellular states. Moreover, distinct villus- and crypt-associated fibroblasts mislocalize and accumulate at ectopic tissue folds with increased fibronectin deposition. These relocalization events could potentially disrupt the normal niche signaling gradients essential for stem cell homeostasis, resulting in ectopic crypt fission, misplacement and deformation. Taken together, our data suggest that fibroblasts require Bmp signaling to maintain their cellular specification and compartmentalization to critically regulate epithelial stem cell dynamics and homeostasis. These new findings offer essential principles on fibroblast signaling and stem cell-niche crosstalk, which are crucial for understanding tissue homeostatic regulation and niche-mediated pathogenesis.

Funding Source: ACS Research Scholar Grant, NIH F31DK132866, George Robert Pfeiffer Fellowship, NCI T32 CA193200, Yale School of Medicine

Keywords: epithelial-mesenchymal, niche, polyp

9:00 AM – 9:10 AM

GENERATION OF HUMAN CORTICAL ORGANOIDS WITH STRUCTURED OUTER SUBVENTRICULAR ZONE

Walsh, Ryan[1], Giacomelli, Elisa[1], Rittenhouse, Chelsea[1], Ciceri, Gabriele[1], Galimberti, Maura[2], Wu, Youjun[1], Muller, James[1], Vezzoli, Elena[2], Jungverdorben, Johannes[1], Zhou, Ting[1], Cattaneo, Elena[2], Studer, Lorenz[1] and Baggiolini, Arianna[3]
[1]Developmental Biology, Sloan Kettering Institute, New York, NY, USA, [2]Department of Biosciences, University of Milan, Italy, [3]Institute of Oncology Research, Bellinzona, Switzerland

Outer radial glia (oRG) are human-enriched, cortical progenitor cells that directly support the development of an enlarged outer subventricular zone (oSVZ) and, in turn, the expansion of the neocortex. The in vitro generation of oRG is essential to model and investigate underlying mechanisms of human neocortex development and expansion. By activating the STAT3 pathway with recombinant human LIF, we developed a cortical organoid model from human pluripotent stem cells (hPSCs) which recapitulated the expansion of a progenitor cell population into the oSVZ. Those progenitor cells expressed specific oRG markers such as GFAP, LIFR, HOPX and closely matched human oRG in vivo. Upon LIF treatment, cortical-derived interneurons appeared in culture, and cortical excitatory neurons showed faster maturation with enhanced metabolic and functional activity. Inclusion of hPSC-derived brain vascular pericytes-expressing LIF in cortical organoids partially mimicked the effects of LIF treatment. These data suggest that, increasing the cellular complexity of the cortical microenvironment including cell-types expressing LIF, may result in an organoid platform that recapitulates human cortical development at improved resolution by producing a broader diversity of cell types present in the developing human cortex.

Funding Source: Rubicon NWO

Keywords: Outer radial glia, Cortical organoid, Leukemia inhibitory factor

POSTER TEASERS:

POSTER # 916

ELECTRICAL STIMULATION ENHANCES PLURIPOTENT STEM CELL-DERIVED PHOTORECEPTOR CELL REPLACEMENT THERAPY TO RESTORE VISUAL FUNCTION

O'Hara-Wright, Michelle[1], Smith, Grady, Lim, Benjamin Y., Wong, Emilie, Aryamanesh, Nader, Gonzalez-Cordero, Anai
Children's Medical Research Institute, University of Sydney, Australia

POSTER # 453

CELLULAR AND MOLECULAR MECHANISMS OF ALVEOLAR CELL FATE DIFFERENTIATION AND PATTERNING IN THE DEVELOPING HUMAN LUNG

Lim, Kyungtae[1], He, Peng[2], Sun, Dawei[3], Donovan, Alex[1], Tang, Walfred[1], Pett, Patrick[2], Teichmann, Sarah A.[2], Marioni, John C.[4], Meyer, Kerstin B.[2], Rawlins, Emma L.[1]
[1]University of Cambridge, UK, [2]Wellcome Sanger Institute, Hinxton, UK, [3]Broad Institute, Cambridge, USA, [4]European Bioinformatics Institute, Cambridge, UK

POSTER # 529

CELLULAR BARCODING OF THE LEUKEMIC NICHE REVEALS AN APELIN-MEDIATED CLONAL EXPANSION OF NICHE ENDOTHELIAL AND MESENCHYMAL STROMAL CELLS

Baron, Chloe S.[1], Avagyan, Serine[2], Yang, Song[1], McKenna, Aaron[3], Zon, Leonard[1]
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POSTER # 585

TRANSGENE-FREE DIRECT CONVERSION OF FIBROBLASTS INTO FUNCTIONAL MUSCLE STEM CELLS UTILIZING SYNTHETIC MRNA AND SMALL MOLECULES

Ghosh, Adhideb[1], Qabrati, Xhem[1], Kim, Inseon[1], Bundschuh, Nicola[1], Noé, Falko[1], Palmer, Andrew S.[2], Bar-Nur, Ori[1]
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POSTER # 511

BIOENGINEERED IPSC-DERIVED MODELS OF HUMAN BONE MARROW FOR STUDIES OF INJURY AND DISEASE

Tavakol, Daniel Naveed[1], Graney, Pamela L.[1], He, Siyu[1], Baldassarri, Ilaria[1], Samaritano, Maria[1], Zhuang, Richard[1], Brown, Jessie A.[1], O'Donnell, Aaron[1], Leong, Kam W.[1], Azizi, Elham[1], Palomero, Teresa[1], Ferrando, Adolfo[1], Hirschi, Karen K.[2], Vunjak-Novakovic, Gordana[1]
[1]Columbia University, New York, USA, [2]University of Virginia, Charlottesville, USA

POSTER # 771

CASC3 SUPPRESSION MITIGATES NEURODEGENERATION IN DIVERSE FORMS OF ALS/FTD

Rubin-Sigler, Jasper, Tu, Sharon, Ichida, Justin
University of Southern California, Los Angeles, USA

POSTER # 791

KCNQ2-RELATED GENOTYPE SPECIFIC NETWORK CHARACTERISTICS IDENTIFIED BY HIGH DENSITY MEA RECORDINGS IN IPSC-DERIVED EXCITATORY NEURONS

Dirkx, Nina[1], Kaji, Marcus[1], De Vriendt, Els[2], Asselbergh, Bob[1], Miceli, Francesco[3], Zonnekein, Noortje[2], Taglialatela, Maurizio[3], Weckhuysen, Sarah[1]
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TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)

AGING, EPIGENETICS, AND PROGENITOR CELL REGULATION
8:30 AM – 9:30 AM
Room 254, Meeting Level 2

8:30 AM – 8:40 AM

CHROMATIN REGULATION OF TRANSCRIPTIONAL ENHANCERS AND CELL FATE BY THE SOTOS SYNDROME GENE NSD1

Sun, Zhen[1], Lin, Yuan[2], Islam, Mohammed[2], Koche, Richard[3], Hedehus, Lin[1], Liu, Dingyu[2], Huang, Chang[1], Vierbuchen, Thomas[2] and Helin, Kristian[1]
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Nuclear-receptor-binding SET-domain protein 1 (NSD1), a methyltransferase that catalyzes H3K36me2, is essential for mammalian development and frequently dysregulated in diseases, including a spectrum of cancers and Sotos syndrome, a multisystemic developmental disorder. Despite its function in modulating the chromatin landscape, a direct role of NSD1 in transcriptional regulation remains largely unknown. Using mouse ESCs and directed differentiation, we show that NSD1 and H3K36me2 are enriched at cis-regulatory elements, particularly enhancers, in a cell type-specific manner. We demonstrate that NSD1 enhancer association is conferred by its unique tandem quadruple PHD-PWWP domain, which selectively recognizes the p300-deposited enhancer mark H3K18ac and is a hotspot for Sotos syndrome missense mutations. By combining a chemical genetic approach allowing for acute NSD1 degradation with time-resolved epigenomic and nascent transcriptomic analyses, we demonstrate that NSD1/H3K36me2 plays a critical role in facilitating enhancer-dependent gene transcription by promoting RNA polymerase II pause release. Specifically, NSD1 upholds enhancer activity and promotes productive elongation through PAF1 and SPT5. Notably, our system, which enables high temporal resolution, reveals a decoupling of the rapid reduction in transcription upon NSD1/H3K36me2 loss and slow changes in H3K27me3 and DNA methylation, demonstrating that the primary coactivator role of NSD1 is independent of its functional interplay with PRC2 and DNMT3A/B. Moreover, using embryoid body formation and forebrain organoid differentiation, we show that NSD1 regulates ESC multilineage differentiation through facilitating transcriptional activation of critical developmental programs implicated in Sotos syndrome pathogenesis. Collectively, we have identified NSD1 as an enhancer-acting transcriptional coactivator and provided mechanistic insights into its contribution to cell fate transition and association with a human developmental disorder.

Keywords: chromatin, transcriptional enhancer, cell fate

8:40 AM – 8:50 AM

USING SPATIAL TRANSCRIPTOMICS TO REVEAL FETAL LIVER HEMATOPOIETIC STEM CELL-NICHE INTERACTIONS

Dong, Ruochen[1], Li, Hua[2], Russell, Jonathon[3], Malloy, Seth[4], Mao, Xinjian[1], Yang, Zhe[1], Hall, Kate[5], Petentler, Kaitlyn[5], Scott, Allison[5], McKinney, Cathy[6], Smith, Sarah[7], Wang, Yongfu[5], McKinney, Sean[8], Haug, Jeff[9], Perera, Anoja[10], Unruh, Jay[11], Slaughter, Brain[12], He, Xi[4] and Li, Linheng[4]
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The hematopoietic stem cell (HSC) microenvironment, termed the niche, supports the proliferation, self-renewal, and differentiation abilities of HSCs. The definitive HSCs emerge from the hemogenic endothelium in the aorta-gonad-mesonephros (AGM) region after E10.5, and then migrate to the fetal liver after E12.5 for expansion. In this study, we use cutting-edge spatial transcriptomics , slide-seq, and 10x Genomics Visium Spatial Gene Expression, to investigate the interactions between HSCs and the niche cells in the fetal liver. By using single-cell RNA seq, we first revealed the transcriptomics of HSCs and potential niche cells, including hepatoblasts, endothelial cells, macrophages, megakaryocytes, and mesenchymal stromal cells (MSCs) in E14.5 and E16.5 mouse fetal liver. Interestingly, we found that MSCs and hepatoblasts were characterized by enriched N-cadherin expression. Both slide-seq and 10x Visium showed that the majority of fetal liver HSCs are near N-cadherin-expressing MSCs and endothelial cells in the portal vessel area, indicating a supportive role of N-cadherin-expressing MSCs and endothelial cells in HSC maintenance. Subsequent CellPhoneDB (CPDB) analysis demonstrated that the N-cadherin-expressing MSCs are major niche-signaling senders with an enriched expression of niche factors, such as CXCL12 and KITL, and stemness pathway-related ligands, indicating N-cadherin-expressing MSCs could be the major niche cells in supporting HSCs in the fetal liver. We then generated a N-cadCreER;Cxcl12 f/f strain to conditionally knockout the well-studied niche factors, CXCL12, in N-cadherin-expressing cells. Interestingly, conditional knockout

of Cxcl12 in N-cadherin-expressing cells resulted in an increase in the number of HSCs, along with a depletion of lymphoids, resulting in a myeloid-biased differentiation. Subsequential slide-seq showed that fetal liver HSCs were not enriched near MSCs in portal vessels region due to loss of Cxcl12. Meanwhile, HSCs were enriched near megakaryocytes in distal regions. In summary, we postulated that N-cadherin-expressing cells, especially MSCs, maintain fetal liver HSCs. The knockout of Cxcl12 in N-cadherin-expressing cells leads to the migration of HSCs towards megakaryocytes, which may induce HSC expansion and biased differentiation.

Keywords: Hematopoietic stem cells (HSCs), Niche, Spatial transcriptomics

8:50 AM – 9:00 AM

VEGFA MRNA-LNPS PROMOTE LIVER PROGENITOR CELL DIFFERENTIATION TO HEPATOCYTES AND RESTORE LIVER FUNCTION IN LIVER INJURY MOUSE MODELS

Rizvi, Fatima[1], Diaz-Aragon, Ricardo[2], Florentino, Rodrigo[1], Smith, Anna R.[1], Everton, Elissa[1], Wu, Susan[1], Sarjoo, Arianna[1], Tam, Ying[3], Pardi, Norbert[4], Weissman, Drew[4], Soto-Gutierrez, Alejandro[2] and Gouon-Evans, Valerie[1]
[1]Center for Regenerative Medicine, Boston University, Boston, MA, USA, [2]Department of Pathology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [3]Acuitas Therapeutics, Vancouver, BC, Canada,[4] University of Pennsylvania, Philadelphia, PA, USA

The ability of liver to regenerate via proliferation of mature hepatocytes is dramatically reduced in severe acute or chronic liver injury. In these cases, Biliary epithelial cell (BEC)-derived progenitors, commonly referred to as liver progenitor cells (LPCs), are thought to give rise to de novo hepatocytes, however, this mechanism of regeneration is not very efficient. Our previous work using mouse and human embryonic stem cell (ESC) differentiation system revealed that KDR+ fetal hepatic progenitors are bona fide hepatoblast precursors and that KDR activation is required for hepatic specification of the human ESC-derived KDR+ hepatic progenitors. This led us to hypothesize that LPCs in injured adult livers express KDR and that its ligand VEGFA can promote their conversion to hepatocytes and restore liver function. The hypothesis was tested in the acute liver injury induced with acetaminophen (APAP), and a chronic liver injury model of choline deficient diet supplemented with 0.1% ethionine. Krt19-CreERT2; R26-STOPFl/Fl-tdTomato mice were used to fate trace BECs and Kdr-2A-CreERT2-2A-eYFP, R26LSL tdTomato mice to trace KDR-expressing cells. AAV8-Tbg-p21 viruses were administered to mimic hepatocyte senescence associated with severe acute or chronic human liver diseases. Following injury, VEGFA was delivered twice via IV injection of nucleoside-modified mRNA encapsulated into lipid nanoparticles (mRNA-LNP) to allow expression in liver. Further, human cirrhotic liver tissues were assessed for BEC-to-hepatocyte differentiation and identification of KDR-expressing BECs. Delivery of VEGFA in mice via non-integrative and safe mRNA-LNP induced robust BEC-to-hepatocyte conversion and reversion of steatosis and fibrosis. In human and murine diseased livers, we further identified KDR-expressing BECs associated with KDR-expressing cell-derived hepatocytes. Fate-tracing of KDR-expressing cells also demonstrated emergence of large clusters of de novo hepatocytes being differentiated from KDR-expressing cells in both acute and chronically injured mice treated with VEGFA mRNA LNP. The study reveals novel therapeutic benefits of VEGFA via safe delivery of mRNA-LNP for harnessing BEC-driven repair to potentially treat liver diseases.

Keywords: Liver regeneration, liver progenitor cells, mRNA-LNPs

9:00 AM – 9:10 AM

LIN28A MAINTAINS A SUBSET OF ADULT MUSCLE STEM CELLS IN AN EMBRYONIC-LIKE STATE

Ng, Shyh-Chang
Institute of Stem Cells and Regeneration, IOZ, China

During homeostasis and after injury, adult muscle stem cells (MuSC) activate to mediate muscle regeneration, but much remains unclear regarding MuSCs' heterogeneous capacity for self-renewal and regeneration. Using lineage tracing with tdTomato in mice, we show that Lin28a is expressed in embryonic limb bud muscle progenitors, and that a rare reserve subset of Lin28a+ Pax7- skeletal muscle stem cells (MuSCs) can respond to injury by replenishing some adult Pax7+ MuSCs to drive muscle regeneration. Compared with adult Pax7+ MuSCs, Lin28a+ MuSCs showed enhanced myogenic potency in vitro and in vivo upon transplantation. In terms of their DNA methylation epigenome, according to 5-methylcytosine patterns, adult Lin28a+ MuSCs showed remarkable resemblance to embryonic muscle progenitors. RNA-Seq confirmed that Lin28a+ MuSCs co-expressed higher levels of several embryonic limb bud transcription factors, telomerase components, the p53 inhibitor Mdm4, and lower levels of myogenic differentiation markers, resulting in enhanced self-renewal and stress-response signatures. Mechanistic studies revealed that Lin28a activated the hypoxic stress and unfolded protein responses by optimizing mitochondrial ROS (mtROS), thereby maintaining MuSC self-renewal and regeneration. Conditional ablation and induction of Lin28a+ MuSCs in adult mice showed that these cells are necessary and sufficient for efficient muscle regeneration. Our findings connect the embryonic factor Lin28a to mitochondrial metabolism, mitohormesis, stem cell self-renewal and juvenile regeneration in mice.

Keywords: Juvenile regeneration, Mitochondrial metabolism, Embryonic factors

POSTER TEASERS:

POSTER # 1014

DECIPHERING THE ROLE OF INTERFERON SIGNALING ON THE ACQUISITION AND MAINTENANCE OF EPIGENETIC MEMORY AND ITS IMPACT ON INFLAMMATORY BOWEL DISEASE

Morral Martinez, Clara[1], Qiu, Jingya[1], Karakasheva, Tatiana[2], Zhou, Yusen[2], H. Rhoades, Joshua[3], Uzun, Yasin[4], Li, Ning[3], Tan, Kai[2], Aleynick, Daniel[2], Weinbrom, Sarah[2], Chen, Chia-Hui[2], Fulton, MaryKate[1], Bewtra, Meenakshi[1], Kelsen, Judith R.[2], Soto, Gloria E.[2], Thadi, Anusha[2], Lengner, Christopher J.[3], Hamilton, Kathryn E.[2], Minn, Andy J.[1]
[1]University of Pennsylvania, Philadelphia, USA, [2]Children's Hospital of Philadelphia, USA , [3]University of Pennsylvania School of Veterinary Medicine, Philadelphia, USA , [4]Pennsylvania State University, Philadelphia, USA

POSTER # 1118

THE CONTRIBUTION OF THE GUT MICROBIOME TO BRAIN AGING AND REJUVENATION

Gasperini, Caterina[1], Limone, Francesco[1], Showkat, Nazaf[1], Hakenova, Kristina[2], Holton, Kristina M.[1], Rubin, Lee L.[1]
[1]*Harvard University, Boston, USA,* [2]*Charles University Prague, Czech Republic*

CONCURRENT TRACK SESSIONS

10:00 AM – 11:40 AM

TRACK: CLINICAL APPLICATIONS (CA)

IPS-DERIVED CELLS IN CLINICAL TRIALS

Sponsored by: BlueRock Therapeutics

10:00 AM – 11:40 AM
Room 258, Meeting Level 2

10:05 AM – 10:25 AM

HUMAN PLURIPOTENT STEM CELLS: OVERVIEW OF CLINICAL TRIALS AND STUDIES FOR IMPROVING TRANSFUSION SAFETY

French, Deborah[1], An, Hyun Hyung[2], Pavani, Giulia[3], Gadue, Paul[3] and Chou, Stella T.[3]
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Pluripotent stem cell (PSC) technology has reached a pivotal time with over 100 clinical trials studying PSC derivative cells for a multitude of indications. A brief overview of these clinical trials including products and targeted organ systems will be presented. Presentations in this session will provide an overview of both clinical trials and preclinical studies targeting several organ systems including the eye, brain, kidney, liver, muscle, and pancreas. Our work focuses on red blood cell (RBC) transfusion which is a critical medical therapy for which over 10 million units are transfused per year in the United States alone. Severe blood shortages during the COVID-19 pandemic led to a national crisis. Presently, increased demand due to aging populations, challenges of screening for new infectious agents, and requirements for specific phenotypes of RBCs, has created a global search for alternative sources to public donation. RBC generation from human induced pluripotent stem cells (iPSCs) is an attractive alternative as they have the capacity for unlimited proliferation and can be effectively differentiated into RBCs. As few as 10 human iPSC lines with rare blood protein phenotypes would be sufficient to treat 99% of individuals affected by alloimmunization. Alloantibody production disproportionately affects patients with sickle cell disease (SCD) who are frequently transfused and exhibit high genetic diversity in the Rh blood group system. Alloimmunization to foreign Rh proteins (RhD and RhCE) on donor RBCs remains a challenge for transfusion effectiveness and safety. We used gene editing to generate "designer" iPSCs including type O, Rh null cells since donor Rh null RBCs are exceedingly rare. Type O, Rh null RBCs are attractive as a universal donor cell as they completely lack the most immunogenic membrane proteins, ABO and Rh, rendering them superior to current "universal" donor type O- cells that lack RhD but express other Rh family proteins. By using a differentiation protocol that generates fetal-like progenitors, we produced a renewable source of rare RBCs with unique membrane protein profiles and demonstrate their utility as diagnostic tools for RBC alloantibody identification. These studies lay the groundwork for future commercialization of our "designer" lines in transfusion medicine.

Keywords: Hematopoiesis, RBCs, Transfusion

10:25 AM – 10:35 AM

PHASE 1/2A STUDY OF OPREGEN (HUMAN EMBRYONIC STEM CELLS-DERIVED RETINAL PIGMENT EPITHELIAL CELLS) IN AGE-RELATED MACULAR DEGENERATION PATIENTS WITH GEOGRAPHIC ATROPHY

Reubinoff, Benjamin E.[1], Barak, Adiel[2], Boyer, David[3], Ho, Allen[4], Jaouni, Tareq[5], McDonald, Richard[6], Riemann, Christopher[7], Telander, David[8], Zhang, Miao[9], Gao, Simon[9], Wiley, Henry[9], Chang, Dolly[9], Ben-Shabat, Avi[10], Hogge, Gary[11] and Banin, Eyal[5]
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OpRegen®–a suspension of human embryonic stem cells-derived retinal pigment epithelial (RPE) cells created by directed differentiation–has the potential to counteract RPE cell loss in areas of retinal geographic atrophy (GA) by supporting retinal structure and function. We evaluated the safety and tolerability of OpRegen in a Phase 1/2a clinical study in patients with GA secondary to age-related macular degeneration (NCT02286089). Cohort 1-3 (n=12, Best Corrected Visual Acuity [BCVA] ≤20/200 legally blind) and cohort 4 pts (n=12, BCVA 20/64-20/250 with impaired vision) received up to 200,000 OpRegen cells via subretinal delivery. Safety and efficacy (retinal structure and visual function) were assessed at 1 year. Results are presented as mean ±SD. Overall, OpRegen has been well tolerated in all cohorts; most adverse events (AEs) were mild, and no cases of rejection following OpRegen delivery have been reported. Efficacy analyses were conducted focusing on cohort 4 patients who had less advanced GA. In cohort 4, minimal change in BCVA was observed in the untreated fellow eye at 1 year (+1.3 ±6.4 letters), while most pts showed an improvement or maintenance of baseline BCVA in the OpRegen-treated eye (+7.6 ±8.7 letters). Among 5 patients whose atrophic areas were extensively covered by the subretinal surgical bleb containing OpRegen, there was a greater improvement in BCVA from baseline (+12.8 ±3.8 letters) and evidence of improvement in outer retina structure of RPE and photoreceptor layers as assessed by optical coherence tomography. The reversal of complete and incomplete RPE and outer retinal atrophy (cRORA and iRORA, respectively) at the borders of GA was observed in multiple patients and persisted at the 1-year visit. These data suggest that subretinal delivery of

OpRegen cells in patients with GA appears well tolerated and has the potential to slow, halt, or reverse GA progression.

Funding Source: Genentech, Inc.

Keywords: AGE-RELATED MACULAR DEGENERATION, GEOGRAPHIC ATROPHY, RETINAL PIGMENT EPITHELIAL CELLS

Clinical Trial ID number: NCT02286089

10:35 AM – 10:45 AM

DEVELOPMENT OF NOVEL CELL THERAPEUTIC STRATEGIES FOR AKI AND CKD USING HUMAN IPSC-DERIVED NEPHRON PROGENITOR CELLS

Araoka, Toshikazu[1], Ryosaka, Makoto[1], Toyohara, Kosuke[1], Inui, Chihiro[1], Watanabe, Akira[2] and Osafune, Kenji[1]
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Acute kidney injury (AKI) and chronic kidney disease (CKD) are global problems, and the number of patients requiring dialysis continues to increase worldwide. However, “silver bullet” drugs for AKI and CKD have not been developed. As a new approach to kidney disease, the therapeutic effects of human iPS cell-derived nephron progenitor cells (hiPSC-NPCs) on AKI have been reported but have not yet been clinically applied. In addition, there are no reports of studies using hiPSC-NPCs for CKD, and the therapeutic efficacy is unknown. On the other hand, it has recently been pointed out that the properties of hiPSC-NPCs differ depending on differences in iPS cell lines and batches among experiments. Furthermore, a large number of uniform hiPSC-NPCs are required to realize clinical application of cell therapies for AKI and CKD. Therefore, it is necessary to develop effective expansion cultures for hiPSC-NPCs that maintain therapeutic potential. The aims of this study are to develop an inexpensive mass-production system for hiPSC-NPCs with the same quality and to determine the therapeutic effects on AKI and CKD. We have established a novel expansion culture method (CFY medium) for hiPSC-NPCs that allows for more than 1,000-fold growth in three passages while NPC marker expressions are maintained by screening the low-molecular-weight compounds and growth factors. Expanded hiPSC-NPCs in CFY medium suppressed kidney injury and improved survival rate in cisplatin-induced AKI mice. Furthermore, hiPSC-NPCs inhibited kidney functional decline, kidney interstitial fibrosis, and kidney senescence in aristolochic acid-induced CKD mice. In addition, the contralateral kidneys in AKI and CKD mice transplanted with hiPSC-NPCs were also treated, suggesting that the therapeutic effects of hiPSC-NPCs were due to reno-protective factors. Therefore, we administered conditioned medium (CM) produced by expanded hiPSC-NPCs to cisplatin-induced AKI mice, which prevented kidney functional decline and improved survival rate. Furthermore, we identified some of the reno-protective factors contained in CM. In summary, the expanded hiPSC-NPCs are useful to develop cell therapies for AKI and CKD and will open new avenues in the treatment of kidney diseases.

Keywords: Cell therapies for AKI and CKD, Expanded hiPS cell-derived NPC, Kidney senescence

10:45 AM – 10:55 AM

HOST PRECONDITIONING AND TRANSIENT MITOGEN EXPRESSION VIA MRNA-LNP LEAD TO ROBUST PRIMARY HUMAN HEPATOCYTE ENGRAFTMENT AND TRANSIENT IPSC-DERIVED HEPATOCYTE-LIKE CELL SURVIVAL IN MICE

Smith, Anna R.[1], Rizvi, Fatima[2], Everton, Elissa[2], Adeagbo, Anisah[2], Liu, Hua[2], Tam, Ying[3], Pardi, Norbert[4], Weissman, Drew[4] and Gouon-Evans, Valerie[2]
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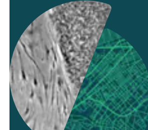
Liver transplantation is the treatment for end stage liver disease, though donor organs are quite scarce. Alternatively, transplantation of healthy liver cells – either primary human hepatocytes (PHH) or induced pluripotent stem cell (iPSC) derived hepatocyte-like cells (HLC) – is a promising approach to restore liver function. PHH transplantation has been validated as safe in human, though major challenges that remain are low efficiency and lack or sustained benefit. HLC transplantation remains entirely preclinical, and factors that limit HLC engraftment in liver disease mouse models include poor survival, proliferation, and maturation of transplanted cells. We hypothesize that stimulating key regenerative pathways in transplanted hepatocytes using hepatocyte growth factor (HGF) and epidermal growth factor (EGF) and preconditioning the host liver with P21 expression to prevent host hepatocyte proliferation will improve survival, proliferation, and engraftment of PHHs and HLCs in an injured mouse liver. We established a safe way to transiently express HGF and EGF specifically in the liver using nonintegrative nucleoside-modified mRNA encapsulated in lipid nanoparticles (mRNA-LNP). We use AAV8-Tbg-P21 to precondition the host mouse liver with long lasting P21 expression specifically in hepatocytes. NSG-PiZ mice serve as our injury model, recapitulating alpha-1 antitrypsin deficiency associated (AATD) liver disease. We find that both preconditioning the host mouse liver with AAV8-Tbg-P21 and the HGF and EGF mRNA-LNP treatments significantly augment transplanted PHH survival and proliferation in vivo in NSG-PiZ mice, evidenced by histological quantification of transplanted cells and human albumin levels in mouse sera in comparison to control. Combined treatment leads to robust repopulation of the mouse liver with functional human cells (~30%) and amelioration of AATD liver disease. Furthermore, HGF and EGF mRNA-LNP transiently improves transplanted iPSC-derived HLC survival in NSG-PiZ mice. Thus, stimulating survival and proliferation in transplanted hepatocytes with HGF and EGF mRNA-LNP and blocking host hepatocyte proliferation with AAV8-Tbg-P21 augments PHH engraftment in the NSG-PiZ mouse, making these highly promising strategies to improve iPSC-derived HLC engraftment.

Funding Source: NIH NIDDK R01DK124361-01A1 NIH NIDDK 1F31DK135378-01 Boston University CTSI TL1 Pre-Doctoral Fellowship in Regenerative Medicine TL1TR001410 March of Dimes Research Grant #6-FY14-530 Alpha 1 Foundation Research Grant #640084

Keywords: hepatocyte cell therapy, mRNA-LNP, liver regeneration



10:55 AM – 11:05 AM

DEVELOPMENT OF AN IPSC-DERIVED THERAPY FOR LIMB-GIRDLE MUSCULAR DYSTROPHY TYPE 2A/R1

Jacob, Sheela
Vita Therapeutics, USA

Limb-girdle muscular dystrophy type 2A/R1 (LGMD2A/R1) is a rare form of muscular dystrophy with around 4000 patients in the US and approximately 80-100 new patients identified every year. LGMD2A/R1 is caused by mutations in the CAPN3 gene, which leads to loss of functional calpain-3 protein, resulting in symmetrical muscle wasting of the proximal limb and girdle muscles. There is currently no approved treatment for LGMD2A/R1. Regenerative therapies derived from induced pluripotent stem cells (iPSCs) may provide a promising approach to regenerate muscle mass associated with muscle wasting. Here we describe the pre-clinical development of an iPSC-based autologous therapy for LGMD2A/R1. A CRISPR-based knock-in strategy was developed to replace the endogenous defective CAPN3 gene with a functional version in LGMD2A/R1 patient-derived iPSCs. Using a chemically defined, step-wise myogenic lineage specification protocol, PAX7-expressing myogenic progenitor cells (MPCs) were then generated; upon myogenic fusion induction, these cells formed functional myotubes that produced CAPN3 mRNA and protein. We then transplanted CAPN3 edited LGMD2A/R1 iPSC derived MPCs into the injured TA muscles of NSG mice and demonstrated donor cell-derived muscle regeneration. Furthermore, a subpopulation of transplanted MPCs seeded in the local muscle stem cell niche area under the basal lamina in mice where they adopt a quiescent state and contribute to regeneration upon additional injury, thus providing evidence of a long-term maintenance and regenerative capability. To facilitate in vivo efficacy studies in an animal model of LGMD2A/R1, we generated an immunodeficient calpain-3 null mouse by back-crossing CAPN3KO mice (JAX: CC041-Capn3em10Lutzy/J) with NSG (JAX: NOD.Cg-Prkdcscid Il2rgtm1Wjl/SzJ) mice. Intramuscular transplantation of CAPN3 edited MPCs into injured muscle of CAPN3KO-NSG mice leads to donor-derived muscle fiber regeneration, supporting the rationale for continued development. Manufacturing of LGMD2A/R1 iPSC-derived MPCs to support IND-studies and first-in-human trials is ongoing with the goal of IND-filing.

Keywords: MPC-Muscle Progenitor Cells, LGMD2A/R1), iPSC derived cell therapy for Cell therapy for Limb-girdle muscular dystrophy type 2A/R1 (LGMD2A/R1); CAPN3 gene correction

11:05 AM – 11:15 AM

A PHASE I/II CLINICAL TRIAL OF HPSC-DERIVED INHIBITORY INTERNEURON CELL THERAPY, NRTX-1001, FOR DRUG-REFRACTORY FOCAL EPILEPSY

Nicholas, Cory R.[1], Blum, David[1], Madrid, Sheri[1], Adler, Andrew[1], Lee, Seonok[1], Feld, Brianna[1], Jung, Ji-Hye[1], Larios, Rose[1], Bershteyn, Marina[1], Zhou, Robin[1], Parekh, Mansi[1], Hampel, Philip[1], Fuentealba, Luis[1], Chen, Chun[2], Palop, Jorge[2], Bulfone, Alessandro[1], Shevchuk, Sergei[1], Banik, Gautam[1] and Priest, Catherine[1]
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GABAergic inhibitory interneuron cell therapy represents a novel therapeutic strategy for the treatment of drug-refractory focal epilepsy and potentially other chronic neurological disorders characterized by local hyperexcitability of neural circuits. We have developed a cell therapy candidate, called NRTX-1001, comprising human pluripotent stem cell (hPSC)-derived post-mitotic GABAergic interneurons of a specific medial ganglionic eminence (MGE) pallial-type identity. NRTX-1001 was cleared for clinical investigation by the FDA in 2021 and is being evaluated for safety and efficacy in an ongoing Phase I/II trial (NCT05135091) for drug-resistant unilateral mesial temporal lobe epilepsy (MTLE). The first patients have been dosed and followed, to date, up to nine months post-administration for adverse events, immune-rejection, seizure frequency and severity, seizure activity by electroencephalogram, and changes in cognition. In addition to this clinical update, we will present unpublished data on the preclinical characterization of NRTX-1001. Single cell RNA sequencing of the interneurons before and after transplantation into rodent models indicates that the human cells appropriately mature into somatostatin and parvalbumin sub-lineages of MGE pallial interneurons. Electrophysiological analysis of the grafted human cells confirms interneuron-specific, fast-spiking action potential firing properties and functional synaptic integration into the rodent brain. Further, NRTX-1001 exhibits compelling disease modifying activity across a broad range of doses in a rodent model of MTLE. Durable focal seizure elimination, reduced temporal lobe sclerotic tissue damage, and increased animal survival were consistently observed in epileptic rodents treated with independently manufactured lots of NRTX-1001. In summary, these clinical and preclinical data highlight the significant progress and promise of human inhibitory interneuron cell therapy for the potential future treatment of chronic focal epilepsy.

Funding Source: California Institute for Regenerative Medicine (CLIN2-13355)

Keywords: MGE GABA inhibitory interneuron cell therapy, Epilepsy seizure cell therapy clinical trial, NRTX-1001 hpsc cortical neuron gmp

Clinical Trial ID number: NCT05135091

11:15 AM – 11:35 AM

PRE-CLINICAL AND CLINICAL TESTING OF STEM CELL DERIVED ISLETS TO TREAT DIABETES

Kieffer, Timothy
Cellular & Physiological Sciences, University of British Columbia, BC, Canada

Diabetes results from insufficient production of insulin from beta cells in pancreatic islets. Islet transplantation can replace the lost beta cells in patients but is limited by the scarcity of available donor organs. Our aim is to differentiate pluripotent stem cells into functional islets that can serve as an unlimited source for transplantation to treat diabetes. We have investigated the therapeutic potential of pancreatic endoderm cells derived from human embryonic stem cells. Several weeks following transplant into diabetic rodents, these cells mature and secrete sufficient human insulin, in a regulated manner, to reverse diabetes. In rats, we observed inconsistent survival of pancreatic endoderm cells implanted subcutaneously in macroencapsulation devices designed to be immunoprotective via use of a cell impermeable layer, but this was rectified by the addition of portals designed to enable direct capillary vascular permeation into the device interior. In contrast both device types supported cell survival, differentiation and function in mice, with more rapid C-peptide release and better glucose tolerance observed using the devices containing portals. Kidney capsule grafts often contained ductal cells and cysts, whereas cells implanted subcutaneously within macroencapsulation devices differentiated predominantly to endocrine cells. As part of a ViaCyte clinical trial, we investigated the safety and efficacy of pancreatic endoderm cells implanted in non-immunoprotective macroencapsulation devices for the treatment of patients with type 1 diabetes and hypoglycemic unawareness. Patients underwent subcutaneous implant of cell products combined with an immunosuppressive

regimen. After implant, patients had increased fasting C-peptide levels, increased glucose-responsive C-peptide levels, and developed mixed meal-stimulated C-peptide secretion. Patients had reduced insulin requirements, increased time in target blood glucose range, and improved hypoglycemic awareness. Explanted grafts contained cells with a mature beta cell phenotype. Collectively, these findings support future investigation into optimizing cell therapies for diabetes.

Keywords: Diabetes, islet, insulin

TRACK: CELLULAR IDENTIY (CI)

MODELING EMBRYONIC CELL FATE SPECIFICATION
10:00 AM – 11:40 AM
Room 257, Meeting Level 2

10:05 AM – 10:25 AM

INTEGRATING IMAGING WITH SINGLE-CELL 'OMICS TO MAP ENDODERM CELL IDENTITIES IN 3D

Hadjantonakis, Anna-Katerina, Gatie, Mohamed, Wershof, Esther, Hess, Joshua, Haviv, Doron, Setty, Manu, Kuo, Ying-Yi, Nowotschin, Sonja and Pe'er, Dana
Developmental Biology, Sloan Kettering Institute for Cancer Research, New York, NY, USA

The gut endoderm is the precursor of the respiratory and digestive tracts and their associated organs, including the lungs, liver and pancreas. By employing a combination of approaches including quantitative imaging, single-cell 'omics and perturbations, we are defining mechanisms driving the development of the gut endoderm in vivo in mouse embryos, and in vitro in mouse and human pluripotent stem cell-based gastruloid models. We are working towards establishing a mechanistic understanding of how the gut endoderm arises, how it subsequently elaborates into a (gut) tube, which later becomes patterned into transcriptionally-distinct domains correlating with future endodermal organs, and whether the developmental origin of individual endodermal cells impacts their identity or behavior during development, homeostasis or disease progression. I will discuss ongoing studies integrating single-cell resolution multiplexed imaging of gene expression within the developing endoderm to spatially annotate single-cell 'omics data to map cell identities in 3D to generate a dynamic atlas of endoderm cell states.

Keywords: endoderm, embryo, mouse

10:25 AM – 10:35 AM

NANOG EXPRESSION DURING NAIVE TO PRIME TRANSITION BIASES LINEAGE SPECIFICATION AT GASTRULATION

Santos, Silvia, Gharibi, Borzo, Inge, Oliver and Strohbuecker, Stephanie
Quantitative Stem Cell Biology Lab, Francis Crick Institute, London, UK

Embryonic stem cells have the ability to undergo multi-axial self-organization and give rise to a spatial pattern of a plethora of fates with precise cell proportions. Heterogeneity in transcription factors expression is thought to drive the very first cell fate specification in the pre-implantation embryo. However, it is unknown how fates with the right cell proportions are specified during gastrulation, in the post-implantation embryo. Using light-sheet imaging of a 3D embryonic organoid model of gastrulation (gastruloids) and mouse embryos we show that lineage specification during gastrulation is initiated very early, during the transition from naïve to primed pluripotency. We find that heterogeneity in Nanog expression at this transition predicts the proportion of cells specified and, importantly, biases pluripotent cells towards notochord, endoderm and gut lineages at the expense of ectoderm and NMPs. Dynamic modulation of Nanog levels with an CRISPR-based inducible system shows that context-dependent rewiring of Nanog regulatory networks is the molecular mechanism underlying these lineage commitment biases. Our findings show that early Nanog levels at primed pluripotency biases cell fate decisions and lineage proportions days later at the gastrula stage and suggests that heterogeneity in transcription factor expression is a recurring control principle in fate specification.

Keywords: Fate-decisions, Embryonic stem cells, Gastruloids

10:35 AM – 10:45 AM

ENDOGENOUS NODAL DICTATES ENDODERM VERSUS MESODERM SPECIFICATION IN GEOMETRICALLY CONSTRAINED HUMAN PLURIPOTENT CELLS

Ortiz Salazar, Miguel Angel and Warmflash, Aryeh
Biosciences, Rice University, Houston, TX, USA

The posterior central nervous system and the paraxial mesoderm arise from bipotent neuromesodermal progenitors (NMPs). This cell population has been the subject of intense study due to their ability to remain competent to generate cells from multiple germ layers during axial elongation. These progenitors are maintained in the tailbud of the embryo by FGF8 and WNT3a. Indeed, NMP-like cells are induced when human embryonic stem cells are exposed to these ligands under standard culture conditions. In contrast, however, when the same protocol is performed in geometrically constrained colonies, an intricate 3D structure emerges, featuring a ball of epiblast disk-like cells (SOX2+, OCT4+, NANOG+, ECAD+) on top of layers of definitive endoderm (DE) (SOX17+, FOXA2+, GATA6+). Surprisingly, when confined colonies are exposed to increasing Wnt doses, signaling levels as measured with live GFP::ß-catenin are elevated, however, these elevated Wnt signals do not induce mesoderm or posteriorize the responding cells. By manipulating signaling pathways, we found that on micropatterns, elevated endogenous NODAL signaling together with the exogenous WNT drives cells to DE. The ability of WNT to induce NMPs and their specialized descendants (CDX1+, CDX2+, and TBX6+ or SOX1+) is restored only when WNT activation is combined with Nodal inhibition. Furthermore, measuring live Nodal dynamics revealed that the first 24 hours of TGF-ß activation are crucial for regulating the decision between endoderm and somitic-mesoderm. Altogether, these findings highlight the role that spatial control and ligand dynamics play in regulating the early fate decisions of pluripotent cells.

Funding Source: Funding sources: CONACYT 41944, NIH R01GM126122 and NSF MCB-2135296.

Keywords: neuromesodermal progenitors, micropatterning hESCs, signaling dynamics

10:45 AM – 10:55 AM

HUMAN AND MARMOSET TROPHOBLAST STEM CELLS RECAPITULATE DIVERGENT MODES OF TROPHOBLAST INVASION AND DIFFER IN SIGNALING REQUIREMENTS.

Siriwardena, Dylan[1], Penfold, Christopher[1], Kohler, Timo[2], Ellermann, Anna[2], Bergmann, Sophie[1], Weberling, Antonia[2], Slatery, Erin[1], Hollfelder, Florian[2] and Boroviak, Thorsten[1]
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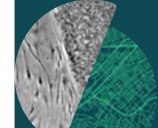

Human embryo implantation and early trophoblast development has remained elusive due to the inaccessibility of early implantation stages in vivo. Non- human primate models are an essential system for comparative evolutionary perspectives and access to early implantation samples. Moreover, diverging implantation strategies between primate species provides an exciting opportunity to study the evolutionary origins and differential regulation of trophoblast invasion. In this study, we identified regulators of in vivo and in vitro pre- and early postimplantation trophoblast development in the Common marmoset. We differentiated marmoset naïve pluripotent stem cells (PSCs) into trophoblast stem cells (TSCs) that exhibit trophoblast-specific transcriptome, differentiation potential and long-term self-renewal. Human TSC culture conditions with WNT and MEK activation failed to support marmoset TSC derivation, instead promoting extraembryonic mesoderm-like fates in the marmoset. MEK, TGFβ, and histone deacetylase inhibitors stabilized a periimplantation trophectoderm-like identity as determined by spatial identity mapping. Identical conditions promoted a TSC fate in human PSCs, however WNT activation was required to prevent spontaneous extravillous trophoblast differentiation. Marmoset TSCs spontaneously gave rise to correctly polarized spheroids in vitro that formed syncytium when implanting in vitro. Interestingly, comparative implantation assays reveal that human and marmoset trophoblast spheroids recapitulate diverging implantation modes between the two species. Our work presents a paradigm to harness the evolutionary divergence in implantation strategies to elucidate human trophoblast development and invasion.

Funding Source: This research is supported by the Wellcome Trust, Centre for Trophoblast Research, and EU Horizon 2020 Marie Skłodowska-Curie Actions.

Keywords: Trophoblast stem cells, Implantation, Non-human primate model

10:55 AM – 11:05 AM

LOSS OF TET HYDROXYMETHYLATION ACTIVITY CAUSES MOUSE EMBRYONIC STEM CELLS DIFFERENTIATION BIAS AND DEVELOPMENTAL DEFECTS

Wang, Mengting, Huang, Yanxin, Wang, Liping, Gao, Shaorong and Chen, Jiayu
School of Life Sciences and Technology, Tongji University, Shanghai, China

Tet family is well known for active DNA demethylation that plays important roles in regulating transcription, epigenome and development. Previous studies used knockdown or knockout models to investigate the function of Tet not only failed to clearly distinguish its enzymatic and non-enzymatic roles, but also involved compensatory effects among Tet family, which makes the functional mechanism of Tet controversial. Here, we successfully generated Tet catalytically inactive (Tetm/m) mice for all Tet members individually. Distinct developmental defects, including infertility, perinatal lethal, gender imbalance and growth retardation were observed in individual Tetm/m mice when compared to those of knockout mice. Besides, Tetm/m mouse embryonic stem cells (mESCs) could be successfully established but Tet1m/m mESCs entered a messy developmental program, showing impaired transcriptome and disorganized differentiation capacity following with enhanced 2C and extraembryonic activation. Unexpectedly, Tet3, which used to be thought inessential for the pluripotency of mESCs due to the low expression level, also greatly influenced the global hydroxymethylation, gene expression and differentiation potential of mESCs. In addition, we demonstrated that mutation-induced methylation and hydroxymethylation configurations lead to global imbalances in epigenetic modifications including disturbed H3K4me3 and H3K27me3 deposition, which were highly associated with their differentiation defects. Therefore, our study provides a new reference for understanding the functional mechanisms of Tet in pluripotency regulation and development.

Keywords: Tet mutant, 5mC, mESC differentiation

11:05 AM – 11:15 AM

THE BRAIN ARISES FROM TWO SEPARATE EMBRYONIC ORIGINS, WITH IMPLICATIONS FOR DEVELOPMENT, DISEASE, AND EVOLUTION

Loh, Kyle M.[1], Dundes, Carolyn[2] and Jokhai, Rayyan[2]
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The brain is often perceived as a single organ generated from a common progenitor population. By contrast, we discover the brain is a composite tissue originating from two independent cellular sources in vivo: the "anterior neural ectoderm" (progenitor to the forebrain and midbrain) and "posterior neural ectoderm" (progenitor to the hindbrain). These two types of lineage-restricted brain progenitor arise early, during gastrulation. We developed methods to differentiate human pluripotent stem cells (hPSCs) into anterior vs. posterior neural ectoderm, and found that they could not interconvert in vitro. The identification of posterior neural ectoderm as the long-sought hindbrain precursor allowed us to differentiate hPSCs into human hindbrain neurons in vitro, which were hitherto inaccessible. Finally, anterior and posterior neural ectoderm exist in primate, mouse, chicken, zebrafish, and acorn worm, suggesting that the dual origins of the brain were deeply conserved across 500 million years of animal evolution. Taken together, we propose that the brain is a composite organ derived from two distinct cellular sources. This new model has broad ramifications for brain development, disease, and evolution.

Keywords: Ectoderm, Neural development, Human pluripotent stem cell

11:15 AM – 11:35 AM

MOLECULAR KNOBS COORDINATING CELL FATE DYNAMICS AND TISSUE MORPHOGENESIS IN THE EARLY MOUSE EMBRYO

Bedzhov, Ivan
Max Planck Institute for Molecular Biomedicine, Münster, Germany

The early embryo gradually adopts various shapes during its developmental progression. As shape and function are intrinsically interconnected, the dynamic changes in the tissue architecture and the cell fate transitions of the early lineages have to be tightly coordinated. On a cellular level, a major driver of embryonic morphogenesis is the establishment of epithelial polarity which takes place at precise developmental time points. This process forms the early cell layers and luminal spaces, increasing the complexity of the developing embryo. The extraembryonic tissues are the first to adopt epithelial morphology during the preimplantation stages, followed by the pluripotent cells of the epiblast immediately after implantation. We found that the developmental timing of epiblast morphogenesis is controlled by the molecular cooperativity of the core pluripotency transcription factors Oct4 and Sox2. Essentially, the pluripotent cells are sustained in an apolar state, enabling proper tissue segregation of the epiblast and the primitive endoderm. After implantation, the cup-shaped epithelial monolayer of the epiblast acts as a canvas upon which the blueprint of the body plan is laid down

by patterning signals. Interestingly, epiblast morphogenesis is a continuous process even when the transient pace of embryonic development is put on hold. We found that during embryo dormancy (diapause) the epiblast forms a radially polarised rosette-like structure. This results in the nuclear accumulation of Yap, which is essential for the long-term maintenance of the epiblast. Thus, the tissue-scale reorganisation of the epiblast is synchronized with the cell fate dynamics during transient embryogenesis and is essential for preserving the developmental capacity of the embryo during diapause.

Keywords: mouse embryo, epiblast, morphogenesis, pluripotency, diapause

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)

MODELING THE MICROENVIRONMENT AND CELL-CELL INTERACTIONS
10:00 AM – 11:40 AM
Room 255, Meeting Level 2

10:05 AM – 10:25 AM

IT TAKES TWO TO REMYELINATE: LESSONS LEARNED FROM A MACROGLIA TISSUE ENGINEERED PLATFORM TO STUDY ASTROCYTE-OLIGODENDROCYTE CROSSTALK

Pêgo, Ana Paula[1], Carvalho, Eva D.[2], Morais, Miguel R.G.[1], Athanasopoulou, Georgia[1] and Rocha, Daniela N.[2]
[1]i3S/INEB/ICBAS - University of Porto, Portugal, [2]i3S/INEB/FEUP - University of Porto, Portugal

The loss of the myelin sheath insulating axons is the hallmark of demyelinating diseases. No effective therapies are currently available to promote remyelination. Several elements contribute to the inadequacy of remyelination, thus understanding the intricacies of the cellular and signalling microenvironment of the remyelination niche will help us to devise better strategies to enhance remyelination. Using a new in vitro rapid myelinating artificial axon system based on engineered microfibres, we investigated how reactive astrocytes influence oligodendrocyte (OL) differentiation and myelination ability. This artificial axon culture system enables the effective uncoupling of molecular cues from the biophysical properties of the axons, allowing the detailed study of the astrocyte-OL crosstalk. Oligodendrocyte precursor cells (OPCs) were cultured on polyester electrospun microfibres (diameter: 0.64±0.10µm) that served as surrogate axons. This platform was then combined with a tissue engineered glial scar model of astrocytes embedded in alginate matrices, in which astrocyte reactive phenotype was acquired using meningeal fibroblast conditioned medium. This behaviour being influenced by the hydrogel network properties being dependent on the activity of the small rhoGTPase RhoA. OPCs were shown to adhere to uncoated engineered microfibres and differentiate into myelinating OL. Reactive astrocytes were found to significantly impair OL differentiation ability, after six and eight days in a co-culture system. Differentiation impairment was seen to be correlated with astrocytic miRNA release through exosomes. We found significantly reduction on the expression of pro-myelinating miRNAs and an increase in anti-myelinating miRNA content between reactive and quiescent astrocytes. Additionally, OPC differentiation inhibition could be reverted by rescuing the activated astrocytic phenotype with ibuprofen, a RhoA inhibitor. Modulating astrocytic function might be an interesting therapeutic avenue for demyelinating diseases. The use of these engineered microfibres as an artificial axon culture system will enable the screening for potential therapeutic agents that promote OL differentiation and myelination while providing valuable insight on the myelination/remyelination processes.

Keywords: demyelinating diseases, oligodendrocyte progenitor cells, astrogliosis

10:25 AM – 10:35 AM

VASCULARIZED HIPSC-DERIVED 3D CARDIAC MICROTISSUE ON CHIP

Arslan, Ulgu, Brescia, Marcella, Meraviglia, Viviana, Nahon, Dennis, van Helden, Ruben, Vila Cuenca, Marc, Stein, Jeroen, van den Hil, Francijna E., van Meer, Berend, Mummery, Christine and Orlova, Valeria
Anatomy and Embryology, Leiden University Medical Centre, Leiden University Medical Centre, Netherlands

Functional vasculature is essential for delivering nutrients, oxygen and cells to the heart and removing waste products. Current 3D organoid and microtissue models often integrate self-organized microvascular-like networks. However, these networks are often not functional and nutrient delivery in these models solely depend on the passive diffusion as they are maintained in static cultures without perfusion. Here, we developed an in vitro vascularized cardiac microtissue model based on human induced pluripotent stem cells (hiPSCs) in a microfluidic organ-on-chip by co-culturing hiPSC-derived, prevascularized, cardiac microtissues (MTs) with vascular cells within a fibrin hydrogel. We showed that vascular networks spontaneously formed in- and around these MTs and that they were lumenized and interconnected through the process called anastomosis. Anastomosis was fluid flow dependent whereby perfusion increased vessel density and thus enhanced formation of the hybrid vessels. Vascularized cardiac MTs showed altered contractile dynamics as a result of enhanced endothelial cell-cardiomyocyte communication and these contractile dynamics were reversed upon inhibition of endothelial cell-derived nitric oxide. Finally, stimulation with interleukin-1β induced production of proinflammatory cytokines and led to consequent changes in contractile parameters only in vascularized cardiac MTs but not in non-vascularized MTs in chips. These results highlight the importance of vascularization in inflammatory response. The platform sets the stage for studies on the role of organ-specific endothelial cell barrier upon delivery of drugs or inflammatory mediators.

Funding Source: European Union's Horizon 2020 research and innovation programme (812954) Netherlands Organ-on-Chip Initiative (024.003.001) Novo Nordisk Foundation Center for Stem Cell Medicine by Novo Nordisk Foundation (NNF21CC0073729).

Keywords: human induced pluripotent stem cells, cardiac microtissue, heart-on-chip

10:35 AM – 10:45 AM

RECONSTRUCTING VASCULARIZED PRIMITIVE GUT TUBE WITH PROPER MESENCHYME IN A DISH

Miao, Yifei[1], Pastrana-Gomez, Victor[2], Tan, Cheng[2], Yu, Zhiyun[2], Iwasawa, Kentaro[3], Pek, Nicole[2], Whitsett, Jeffrey[4], Zorn, Aaron[5], Wells, James[6], Takebe, Takanori[3], Chen, Ya-Wen[7], Kotton, Darrell[8], Guo, Minzhe[4] and Gu, Mingxia[2]
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The proper arrangement of the lateral plate mesoderm (LPM)-derived splanchnic mesoderm (SM) is critical for the development of the embryonic gut tube and its derivatives. The vascular network also co-develops with mesenchyme and epithelial progenitors to support gut tube formation, while reciprocally receiving cues to adopt organ-specific fingerprints. Because this early developmental stage is difficult to capture in the human embryo, we aim to engineer an iPSC-derived organoid system with multiple endodermal and mesodermal lineages to study cell-cell crosstalk in human development and disease. Embryonic bodies are exposed to continuous stimulation of Nodal signaling and pulsatile induction of WNT and BMP4, essentially mimicking the early gastrulation stage. Combining both single-cell RNA-sequencing and histological examinations, we observed the emergence of a mesendoderm-like spheroid composed of both LPM and definitive endoderm. More importantly, we found that BMP not only controls the balance between endoderm and mesoderm in the first three days, but profoundly predisposes the early organoid to the regionalization cues that ultimately determine the gut tube patterning - high BMP treatment from day 1-3 posteriorized the gut tube to generate intestinal and colonic lineages, while low BPM on day 1 anteriorialized the organoid to generate lung lineage. By temporally controlling the WNT, BMP, FGF, and angiogenic signals, these miniature structures further regionalized into different primitive gut tubes surrounded by the FOXF1+ SM intertwined with ample endothelium. These primitive gut tubes were further specified into NKX2.1+ lung/thyroid, CDX2+/GATA4+ small intestinal, or CDX2+/SATB2 colonic progenitors. Notably, the endothelium and mesenchyme co-developing in a lung microenvironment gained lung-specific gene signatures (HPGD+ alveolar endothelium and TBX4+ mesenchyme). This complex organoid model provides a unique system for us to study the developmental defect in Alveolar Capillary Dysplasia (ACD) caused by FOXF1 mutations. Although FOXF1 was highly enriched in endothelial cells, we observed reduced alveolar epithelial cell differentiation in the vascularized alveolar organoids derived from FOXF1 mutant iPSCs, indicating abnormal endothelial-epithelial crosstalk in ACD.

Funding Source: NHLBI PCTC

Keywords: Endothelial Cell, Splanchnic mesoderm, Gut tube

10:45 AM – 10:55 AM

TELOCYTES ARE AN IMPORTANT SOURCE OF WNTS ESSENTIAL FOR HAIR FOLLICLE REGENERATION

Shoshkes Carmel, Michal, Canella, Marco, Nalick, Simcha, Corem, Noa, Gharbi, Amal and Ben-Porath, Ittai
Developmental Biology and Cancer Research, The Hebrew University of Jerusalem, Israel

Stem cells reside within niches determined by local cues which maintain its function in support of tissue homeostasis. It is well established that the Wnt/b-catenin signaling is essential in the control of a variety of stem-cells, including neural, mammary, intestine and skin. Though the need for active Wnt-signaling in the stem-cell compartment has long been determined, the cellular identity of the stem-cell niche, which provides the molecular Wnt ligands essential to induce proliferation is still controversial. We recently identified a subepithelial network of unique mesenchymal cells, expressing the transcription factor, Forkhead Box l1 (Foxl1), called telocytes as an important stem cell niche component essential for intestinal regeneration. In this study, we set to test whether Foxl1 labels telocytes in the skin and whether telocytes are an important hair follicle stem cell (HFSC) niche component. Using careful tissue fixation conditions, whole mount tissue clearing and detailed histology of two independent Foxl1 driven mouse models we revealed a comprehensive 3D network of inter and sub-follicular telocytes along the entire HF concentric layers accompanying stem, progenitor and differentiated cells. We specifically ablated telocytes or Wnt signaling emanating from telocytes at the onset of hair follicle growth and showed that Foxl1+ telocytes are a critical source of Wnt proteins essential for HF regeneration and thus constitute the HFSC niche.

Keywords: stem-cell niche, mesenchyme, regeneration

10:55 AM – 11:05 AM

EMBIGIN IS A FIBRONECTIN RECEPTOR THAT REGULATES THE DIFFERENTIATION AND METABOLISM OF SEBACEOUS PROGENITORS

Sipila, Kalle[1], Rognoni, Emanuel[2], Jokinen, Johanna[3], Vietri Rudan, Matteo[1], Talvi, Salli[3], Kapyla, Jarmo[3], Heino, Jyrki[3] and Watt, Fiona[1]
[1]Centre for Gene Therapy and Regenerative Medicine, King's College London, UK, [2]Blizard Institute, Queen Marry, London, UK, [3]Biochemistry, University of Turku, Finland

The renewal and differentiation of adult stem and progenitor cells are regulated by interactions with their microenvironment. Regardless of recent progression in identifying progenitor cell populations in different anatomical compartments, little is known about the molecular factors specific to distinct stem cell niches. Here, by using skin epithelium as a model system and combining single-cell RNA-seq data, immunofluorescence, and transgenic mice, we show that sebaceous gland cells show high and specific expression of transmembrane receptor embigin (EMB). EMB interacts with monocarboxylate transporter 1 (MCT1) in vivo and the deletion of EMB affects lactate metabolism. In addition, the detailed analysis of sebum shows that while the lipid production is compromised in Emb-/- sebaceous glands, the ratio between different lipid species and the amount of lipids on skin surface is not changed, which indicates higher turnover of sebocytes. Interestingly, sebaceous gland progenitor cells of EMB knockout mouse show faster exit from progenitor cell compartment towards differentiation, which can indicate a reduced interaction with their niche. To study a possible mechanism, we performed a ligand screening that, surprisingly, unveiled that embigin is a direct extracellular matrix receptor: the outer immunoglobulin domain of embigin forms a high affinity interaction with the

N-terminus of fibronectin independently of integrins. Our results demonstrate how embigin couples cell adhesion and metabolism by interacting with monocarboxylate transporter 1 and fibronectin to regulate sebaceous gland progenitor cell function in vivo.

Keywords: Cell adhesion, Lactate metabolism, Sebaceous gland

11:05 AM – 11:15 AM

CO-GRAFT OF DOPAMINE PROGENITORS AND SUPPORTING CELLS TO ENHANCE CELL-BASED THERAPY FOR PARKINSON´S DISEASE

Sozzi, Edoardo, Garcia Garrote, Maria, Mudannayake, Janitha, Nilsson, Fredrik, Åkerblom, Malin, Storm, Petter, Fiorenzano, Alessandro and Parmar, Malin
Experimental Medical Science, Lund University, Lund, Sweden

Parkinson´s Disease (PD) is one of the most common neurodegenerative disorders, characterized by the loss of midbrain dopaminergic (DA) neurons in the substantia nigra, with consequent depletion of DA in the striatum and the rise of motor symptoms. Transplantation of midbrain DA progenitors derived from human pluripotent stem cells is currently being explored in, and developed for, clinical trials, aiming to replace neurons lost in the disease and thereby restore DA neurotransmission in the striatum. It is interesting though, that within these fully functional grafts, only a small proportion of cells are mature DA neurons. The reason for this graft diversification and the role of other cell types in the graft remains to be determined. In this study, we assess potential function and support for the development and maturation of the therapeutic DA neurons by other cell types performing co-grafting experiments. We co-transplanted different cell types, including glial progenitor cells, striatal progenitors, and ventral forebrain (vFB) progenitors together with DA progenitors into the striatum of 6-OHDA lesioned nude rats. Histological analysis has shown that co-grafting of DA and vFB progenitors together results in a higher yield of TH+ neurons and more extensive innervation of the striatum, compared to grafting DA progenitors alone. Single-cell RNA sequencing of the co-grafts revealed a variety of cell types in the graft, including multiple DAergic and interneuron subtypes, astrocytes, and OPCs. We used molecular barcoding to investigate the lineage relationships between cell of origin and neuron subtypes. Overall, this study sheds light on the role of graft composition on DA neuron development and maturation and paves the path for a more refined and effective product for cell replacement therapy for PD.

Keywords: Cell replacement therapy, Parkinson´s Disease, Dopaminergic neuron

11:15 AM – 11:35 AM

GENERATION OF PANCREATIC ISLET ORGANOIDS USING RESIDENT PROCR PROGENITORS

Zeng, Yi Arial[1], Wang, Daisong[1], Yu, Qing Cissy[2] and Song, Wenqian[3]
[1]Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, Shanghai, China, [2]CEMCS, Chinese Academy of Science, Shanghai, China, [3]Shanghai Institute of Biochemistry and Cell Biology, Shanghai, China

Pancreatic Beta cells are the only cells that produce insulin in humans as well as in almost all other vertebrates. However, producing functional β cells in vitro has been a challenging task. In our recent study, we discovered a novel Procr cell population in adult mouse pancreatic islets. These cells lack differentiation markers and exhibit epithelial-to-mesenchymal transition (EMT) characteristics. Through genetic lineage tracing, we found that Procr islet cells undergo clonal expansion and generate all four endocrine cell types during adult homeostasis. When sorted, Procr cells, which represent approximately 1% of islet cells, can form islet-like organoids when cultured at clonal density. These organoids can be exponentially expanded over long periods by serial passaging, and differentiation can be induced at any time point in culture. The differentiated islet organoids are dominated by Beta cells, while alpha, delta and PP cells occur at lower frequencies. The organoids are glucose-responsive and insulin-secreting. When transplanted into diabetic mice, the islet organoids effectively restore normoglycemia. These findings demonstrate that the adult pancreatic islet contains a population of Procr progenitors. We will also describe the relevance of these progenitors in human islets.

Keywords: pancreatic islet, adult stem cell, Procr progenitors, organoid, diabetes

TRACK: NEW TECHNOLOGIES (NT)

SINGLE-CELL MULTI-OMICS AND SPATIAL TRANSCRIPTOMICS

Sponsored by: NanoString Technologies

10:00 AM – 11:40 AM

Room 259, Meeting Level 2

10:05 AM – 10:25 AM

IMAGE-BASED SPATIAL GENOMICS IN HEALTH & DISEASE

Wang, Siyuan
Genetics and Cell Biology, Yale University, New Haven, CT, USA

The three-dimensional (3D) organization of the genome affects many genomic functions. Changes in genome architectures have been associated with normal development, aging, and a wide range of diseases. Despite its critical importance, understanding the spatial organization of genome in single cells, the variation of the organization in diverse cell types in complex mammalian tissue, and the regulatory mechanisms and functions of the organization in different biomedical processes remains a major challenge. To address these questions, we developed image-based 3D genomics and spatial multi-omics techniques termed chromatin tracing and MINA to map 3D genome and multi-ome in single cells and complex mammalian tissues. We are applying these developments to depict multiscale genomic architectures associated with gene expression and other genomic functions in different types of cells and tissues undergoing different biological processes in cancer, aging, and immunology. We are also systematically identifying novel regulators of 3D genome by developing high-content image-based CRISPR screens. These novel regulators may serve as a new class of therapeutic targets to halt or even reverse deleterious 3D genome changes in diseases. In sum, the talk will focus on our efforts on: 1) characterizing the 3D genome with new technology developments, 2) understanding 3D genomic functions in the native tissue context in health and disease, and 3) building the 3D genomic "regulatome" to manipulate the 3D genome.

Keywords: 3D genomics, 4D nucleome, spatial transcriptomics, multi-omics, chromatin folding, high-content screen, CRISPR, cancer, biomarkers

10:25 AM – 10:35 AM

DECIPHERING CELL STATES AND GENEALOGIES OF HUMAN HEMATOPOIESIS WITH SINGLE-CELL MULTI-OMICS

Weng, Chen[1], Yu, Fulong[2], Yang, Dian[3], Liggett, L. Alexander[4], Poeschla, Michael[4], Jones, Matthew[3], Weissman, Jonathan[3] and Sankaran, Vijay[4]
[1]Genomics, Broad Institute/Whitehead Institute, Cambridge, MA, USA, [2]Genetics, Broad Institute, Boston, MA, USA, [3]Genetics, Whitehead Institute, Cambridge, MA, USA, [4]Hematology/Oncology, Boston Children's Hospital, Boston, MA, USA

The human blood system is maintained through the differentiation and massive amplification of a limited number of long-lived hematopoietic stem cells (HSCs). Perturbations to this process underlie a diverse set of diseases, but the clonal contributions to human hematopoiesis and how this changes with age remain incompletely understood. While recent insights have emerged from barcoding studies in model systems, simultaneous detection of cell states and phylogenies from natural barcodes in humans has been challenging, which has limited the ability to explore functional differences between HSC clones. Here, we introduce an improved single-cell lineage tracing system based on deep detection of naturally-occurring mitochondrial DNA (mtDNA) mutations with simultaneous readout of transcriptional states and chromatin accessibility. We use this system to define the clonal architecture of HSCs, and map the physiological state and output of these clones. We uncover functional heterogeneity in HSC clones, which is stable over months and manifests as differences in total HSC output as well as biases toward the production of different mature blood and immune cell types. We also find that the diversity of HSC clones decreases dramatically with age leading to an oligoclonal structure with multiple distinct clonal expansions. Our study thus provides the first clonally-resolved and cell-state aware atlas of human hematopoiesis at single-cell resolution revealing an unappreciated functional diversity of human HSC clones both in young and aged individuals and more broadly paves the way for refined studies of clonal dynamics across a range of tissues in human health and disease.

Keywords: Hematopoietic stem cell, Lineage-tracing, Single cell multiomics

10:35 AM – 10:45 AM

AN APPROACH FOR UNIQUELY BARCODING CELLS IN A 3D STEM CELL NICHE FOR SPATIAL TRANSCRIPTOMIC DATA COLLECTION

Sokol, Jan[1], Wang, Yuting[1], Ding, Ke[1], Ambrosi, Thomas[2], Zhao, Liming[1], Sinha, Rahul[1], Conley, Stephanie[1], Borrelli, Maria[3], Longaker, Michael[1], Weissman, Irving[1], Sahoo, Debashis[4] and Chan, Charles[1]
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In this study, we demonstrate a novel approach to fluorescently label cells in stem cell niches in mouse skeletal tissues. By uniquely labeling each cell in a cell cluster composed of up to 100 cells, we can trace the original spatial locations of cells that have undergone single-cell index FACS sorting followed by single-cell analysis techniques including single-cell RNA-sequencing, ATAC-seq, and CyTOF. This approach utilizes confocal imaging and pre-trained machine-learning models for cellular image-segmentation. We show that it is possible to recover fluorescent barcodes of each cell in a small cell cluster with a high accuracy to be able to estimate its original location in a 3D confocal image. Building a reliable spatial transcriptomic tool at a single-cell resolution is an important milestone for the understanding of disease pathologies because it allows for true actual recording of cell-cell interactions, rather than predicted or inferred spatial relationships. This type of analysis is important for understanding dynamic signaling crosstalk that maintains tissue-specific stem cells like the skeletal stem cell (SSC), and for uncovering underlying mechanisms of stem cell aging, while also revealing signaling cues that lead to maladaptive responses like scarring.

Keywords: spatial transcriptomics, cellular image segmentation, confocal microscopy

10:45 AM – 10:55 AM

DECIPHERING TRANSCRIPTOMIC AND FUNCTIONAL DIFFERENCES IN BONE MARROW-DERIVED STEM CELL PROGRESSION IN AGING AND SPACEFLIGHT MODELS

Kubik, Angela[1], Allen, Noah[1], Pendyala, Meghan[1], Cheng-Campbell, Margareth[2], Song, Ju (Hera) Yeun[1], Joshi, Jasmine[1], Narahari, Harshitha[1], Bai, Yang[1], Juran, Cassandra[3], Almeida, Eduardo[4], Chan, Deva[5] and Blaber, Elizabeth[1]
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The collective interest in human presence and habitation in space has increased over the past decade, making the future of civilian travel beyond low Earth orbit (LEO) possible. This surge in space exploration highlights the need to understand the effects of prolonged exposure to spaceflight factors. Recently, studies have demonstrated that extended exposure to the spaceflight environment resembles that of physiological aging on Earth, through increased oxidative stress, senescence induction, and impaired stem cell-based tissue regeneration. Although phenotypic correlations have been drawn between spaceflight- and age-induced effects, there is little insight into cellular and transcriptomic changes. We therefore aimed to leverage various next generation sequencing techniques (i.e. single cell and spatial transcriptomics), senolytic mouse models, and primary cell culture studies to demarcate the differences and similarities between load and age-related degenerative function. We therefore conducted several studies that interrogated the functional and transcriptomic state of mesenchymal and hematopoietic precursors derived from the bone marrow milieu. Firstly, single cell RNA sequencing (scRNA-seq) data from mice undergoing simulated microgravity, true spaceflight, various loading paradigms, and aging reveal similar shifts in immune progenitor populations after both loss of mechanical signaling and aging, which are compounded in aged mice exposed to true spaceflight. Additionally, the progression of certain hematopoietic progenitor lineages (i.e. B Cells) respond more sensitively to exercise-facilitated loading upon inhibition of senescence-associated molecules, such as those seen to increase with age. Spatial transcriptomics pipelines are being optimized to capture the localization of these transcriptomic effects and, interestingly, we have found that PFA-fixation with accelerated decalcification is able to preserve RNA quality more efficiently than typical RNA preservation methods in joint tissues. Lastly, ex vivo culture of bone marrow-derived stem cells under osteoblastic induction suggest that senescence propagates in aged mice even in

CDKN1a/p21-/- mice. However, mineralization and regenerative potential is enhanced in knockout cultures across all age groups.

Funding Source: This project was supported by the Biomedical Engineering department at Rensselaer Polytechnic Institute (RPI) and NASA Space Biology Grant NNH14ZTT001N 0062 under the advisement of Dr. Elizabeth Blaber

Keywords: Spaceflight, Aging, Senescence

10:55 AM – 11:05 AM

HUMAN MICROGLIAL STATE DYNAMICS IN ALZHEIMER'S DISEASE PROGRESSION

Victor, Matheus Brandao[1], Sun, Na[2], Kellis, Manolis[2] and Tsai, Li-Huei[1]
[1]Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA, USA, [2]Computer Science and Artificial Intelligence, Massachusetts Institute of Technology, Cambridge, MA, USA

In response to changes to the brain microenvironment, microglia undergo vast rearrangements in transcriptional programs to alter its functional repertoire and cellular state. Altered microglial states are thought to mediate neuroinflammation and exacerbate neurodegeneration. Yet, the spectrum of cellular states adopted by microglia in response to aging or disease are poorly understood. This is in large part due to the low numbers of microglia that have been profiled from postmortem human brains, limiting our understanding of the role of these cells in the pathobiology of neurological diseases. Here, using single-nucleus sequencing (snRNA-seq), we report the transcriptomes of 194,000 microglia isolated from 444 human subjects across six brain regions. Of these individuals, 220 displayed varying degrees of Alzheimer's disease (AD) pathology. Our data reveals the molecular signatures of 12 distinct microglial states, including inflammatory and lipid processing states that were present in significantly increased proportions in AD individuals and positively correlated with levels of amyloid plaque and tau tangle burden. Using transcription factor-driven regulatory networks, we inferred master regulators of microglial states and their transitions. Through enrichment analysis of iMGLs profiled by snRNAseq, our work defines the transcriptional state of iPS-derived microglia-like cells (iMGLs) in relation to human microglial states. We demonstrate that forced expression of transcription factor regulators of microglia homeostasis can induce homeostatic features in iMGLs, and that inhibiting the induction of transcription factors predicted to drive inflammatory states with CRISPRi is sufficient to block transcriptional features of LPS-induced inflammation. Additionally we leveraged iMGLs to recapitulate transcriptional programs that governs microglial response to the phagocytosis of amyloid beta fibrils, uncovering a temporal program of inflammatory microglia state transitions that map to snRNA-seq of aged human brains. Collectively, our study provides a roadmap to design microglia state specific therapies aimed at curbing neuroinflammation and halting Alzheimer's disease progression.

Funding Source: HHMI Hanna H. Gray Postdoctoral Fellowship

Keywords: Single-cell, Microglia, Alzheimer's disease

11:05 AM – 11:15 AM

A CONSERVED GENOME-WIDE EPIGENETIC REPRESSIVE SIGNATURE UNDERPINS CELL IDENTITY

Sinniah, Enakshi A.[1], Shen, Sophie[1], Mizikovsky, Dalia[1], Shim, Woo-Jun[1], Zeng, Jian[1], Shah, Sonia[1], Souilmi, Yassine[2], Boden, Mikael[3], Llamas, Bastien[2] and Palpant, Nathan[1]
[1]Institute for Molecular Bioscience, The University of Queensland, Brisbane, Australia, [2]Australian Centre for Ancient DNA, School of Biological Sciences, University of Adelaide, Adelaide, Australia, [3]School of Chemistry and Molecular Biosciences, The University of Queensland, Brisbane, Australia

Cell identity is shaped by the chromatin landscape, which regulates access to the underlying genome and its activity. Yet, identification of genomic elements or loci that control cell identity- particularly in the non-coding genome- remains challenging. Here, we analyze 833 EpiMap epigenomes and map the conserved deposition of repressive H3K27me3 genome-wide across diverse cell types to define a unique chromatin signature that identifies genomic regions involved in cell fate specification. Using single-cell transcriptomic profiling of genetically perturbed human pluripotent stem cells (hPSCs), we test the functional requirement of genome-wide H3K27me3 for the establishment and maintenance of somatic cell identity. We find that these regions enrich for signals of adaptive introgression and are intolerant to genetic variation, suggesting these loci have been selectively retained in humans across millions of years of evolution. Based on this signature, we develop an adaptable framework that incorporates multi-omic data to infer cell identity-defining features of the human genome at single nucleotide resolution. We apply our framework to assess variant pathogenicity in large-scale GWAS data and prioritize both coding and non-coding causal genetic variants linked to complex traits and disease, including ClinVar pathogenic variants, enriched in these conserved regions. Interfaced with accessible chromatin data spanning 733 biosamples, we systematically define and map the cell-type specific activity of 21,947 candidate cis-regulatory elements predicted to regulate cell identity in 291 distinct cell types. We predict not only novel enhancers, but also silencers and bifunctional elements displaying variable activity depending on the cellular context. Lastly, we use our framework to identify and genetically validate RP11-17E9.1 (NKX2-6-AS1), as a novel divergent long non-coding RNA (lncRNA) that promotes NKX2-6 transcription and is functionally required for cardiac specification of hPSCs in vitro. Together, this study demonstrates that a conserved signature of epigenetic repression can be exploited to infer cell type-specific regulatory networks underpinning cell identity across the genome, and can provide mechanistic insight into development, differentiation, and disease.

Funding Source: This work is supported by the Medical Research Future Fund Genomics Health Futures Mission (grant: APP2016033)

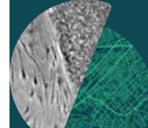
Keywords: Cell Identity, Epigenetics, Computational tool

11:15 PM – 11:35 PM

A SINGLE MOLECULE SEQUENCING PLATFORM-BASED LONG-READ SINGLE-CELL ATAC-SEQ METHOD TO DETECT CHROMATIN ACCESSIBILITY AND GENETIC VARIANTS SIMULTANEOUSLY WITHIN AN INDIVIDUAL CELL

Tang, Fuchou
Peking University, Beijing, China

Single-cell assay for transposase-accessible chromatin using sequencing (scATAC-seq) on the next-generation sequencing



(NGS) platform is a powerful tool to decode chromatin states. However, it is difficult to detect structural variations (SVs) simultaneously with short-read sequencing. We developed scNanoATAC-seq, an scATAC-seq method based on nanopore sequencing platform. The performance of scNanoATAC-seq on revealing chromatin accessibility features was comparable to that of NGS-based scATAC-seq. Using scNanoATAC-seq, we discriminate parental alleles for each peak in GM12878 by genetic polymorphisms flanking the peak, which cannot be achieved by NGS-based scATAC-seq. We found that 1.1% of the peaks were allele-specific in GM12878, mainly enriched on X chromosome. Moreover, we simultaneously identified SVs and copy number variations (CNVs) using scNanoATAC-seq data. Finally, we provided the direct evidences of co-accessibility between neighboring peaks from scNanoATAC-seq, where the chromatin accessibility of two sites in the same single cell was detected simultaneously by a long read. Our method provides a new strategy for research on chromatin state within an individual cell, which detects chromatin accessibility and genetic variants simultaneously within an individual cell. We will also discuss other third generation sequencing (TGS) platform-based single cell epigenome sequencing technologies.

Keywords: single molecule sequencing, thrid-generation sequencing, single cell ATAC-seq, chromatin accessibility, structural variation, co-accessibility

CONCURRENT TRACK SESSIONS

1:30 PM – 3:10 PM

TRACK: ETHICS, POLICY AND STANDARDS (EPS)

ETHICS AND PUBLIC ENGAGEMENT REGARDING THE 14 DAY RULE

1:30 PM – 3:00 PM
Room 253, Meeting Level 2

1:40 PM – 1:55 PM

THE 14 DAY RULE: A SOCIOLOGICAL ASSESSMENT

Franklin, Sarah B.
Sociology, University of Cambridge, UK

The 14 day rule is widely regarded as the 'backbone' of the Human Fertilisation and Embryology legislatation in the UK, and the foundation for much of the social consensus that enabled the 'strict but permissive' framework of regulation. The nature of this consensus, or social contract, is the subject of this brief presentation, which identifies its key sociological components, arguing these must be clearly understood in order for future reformulations of it are to win widespread public trust.

Keywords: HFEA, regulation, sociology, embryo, public trust

1:55 PM – 2:05 PM

CURRENT STATE OF THE SCIENCE

Wang, Hongmei
Institute of Zoology, CAS, China

Researching human embryonic development is an exciting field with significant implications for cell and developmental biology. Early developmental errors can cause negative pregnancy outcomes, such as embryo loss, miscarriage, and birth defects. Despite its importance, human embryonic development, particularly post-implantation development which occurs in the uterine, remains largely unknown. To uncover the mysteries of early embryo development, we developed various culture systems to support ex-uterus embryogenesis in mice, non-human primates, and humans. Our uterus-inspired niche (UN) culture system successfully supported mouse blastocysts until heartbeat formation, laying the foundation for primate embryo cultures. We also successfully cultured human embryos up to day post-fertilization (d.p.f.) 14. We terminated the cultures based on ethical limitations. In 2019, we cultured cynomolgus macaque embryos up to d.p.f. 20, beyond early gastrulation, and recently up to d.p.f. 25, early neurulation. Our in vitro cultured macaque embryos showed morphologic, transcriptional, and epigenetic developmental features similar to their in vivo counterparts. Our future work includes optimizing culture systems with dynamic culture systems, biomaterials, and real-time monitoring, among others, to support mouse and non-human primate embryos' development to organogenesis stages. If the ethical limitation for human embryo culture is lifted, our current culture systems can be applied to human embryos, aiding in exploring crucial human developmental mysteries. Our culture systems and findings will lay the foundation for studying the mechanisms of normal and abnormal developments.

Keywords: primate, early embryonic development, ex uterus embryo culture

2:05 PM – 2:15 PM

ONE SCRO'S ROUTE TO EXTENDING APPROVAL BEYOND 14 DAYS

Wilkerson, Amy
Research Support, The Rockefeller University, New York, USA

This short report on the considerations reviewed, the process of deliberation by, and conditions required by a SCRO in arriving at their approval for in vitro culture of human embryos up to 21 days is provided in hopes that it will be of value to other SCROs in undertaking their own review and in support of the panel and session discussion on ethics and public engagement regarding the 14 day rule.

Keywords: SCRO, embryo, ethics

2:15 PM – 2:20 PM

POTENTIAL USERS PERSPECTIVES ON IN VITRO GAMETOGENESIS RESEARCH AND APPLICATIONS

Le Goff, Anne G., Jeffries Hein, Robbin and Landecker, Hannah
Institute for Society and Genetics, University of California, Los Angeles, CA, USA

The prospect of in vitro gamete generation has recently become more imminent with the recapitulation of male and female gametogenesis in mice, and the completion of key milestones in nonhuman primates. While significant hurdles remain before IVG can produce functional human gametes safe for reproductive use, these steps bring the technology towards a preclinical stage that is relevant to humans. The potential of IVG for reproductive biology, diagnosis of infertility, and assisted reproductive technologies has already been noted by experts in science and bioethics, the media, and commercial interests. However, little is known about the perspectives of potential patients. Here, we report on a qualitative social science study of the perspectives on IVG of stakeholders representing potential users of IVG in the future. We conducted focus groups and interviews with individuals who have lived experiences of infertility and/or belong to the LGBTQ+ community in the US. These two groups who are not fully, or at all, served by current assisted reproductive technologies form the core of anticipated users of IVG and participants in future clinical trials. A majority of participants expressed an extremely high interest for IVG for personal use and in some instances over existing methods, and commended IVG for its potential for increasing reproductive justice for LGBTQ+ people.

However, participants highlighted a host of ethical and social issues, in particular appropriate regulation of research, in particular with respect to the culture of human embryos, safety for pregnant persons and future children, costs and risks of inequity of access, and concern about social acceptance of the technology in broader society. This data highlights the importance of eliciting and studying the perspectives of the public on stem cell technologies involving the use of human gametes and embryos in order to devise a robust ethical framework and garner broad public support for these technologies.

Funding Source: NIH grant #R21HG012248

Keywords: ethics, in vitro gametogenesis, human embryos

2:20 PM – 2:30 PM

PUBLIC ATTITUDES TOWARDS RESEARCH INVOLVING HUMAN EMBRYOS AND THE 14 DAY RULE IN AUSTRALIA

Nicol, Dianne[1], Niemeyer, Simon[2] and Paxton, Rebecca[3]
[1]Faculty of Law, University of Tasmania, Hobart, Australia, [2]Centre for Deliberative Democracy and Global Governance, University of Canberra, Australia, [3]Food Values Research Group, University of Adelaide, Australia

Research has consistently shown a high level of public trust in researchers and public research organisations involved in human genomic and stem cell research in Australia. However, there is evidence that members of the public are much more circumspect and diverse in their opinions when it comes to research involving human embryos. This presentation reports on a group of public engagement exercises undertaken in Australia over the past five years, including surveys, interviews and a citizen deliberation, the Australian Citizens' Jury on Genome Editing (ACJ). Although the primary focus of this research effort was on genome editing more broadly, research involving human embryos was a central feature canvassed in each exercise. Collectively, the findings from this research illustrate that there is a broad diversity of views amongst members of the Australian public regarding genome editing. To some extent, this diversity is correlated with gender, age and nationality. However, it is also correlated with a set of underlying value typologies that are not necessarily linked to these or other demographic characteristics. For example, irrespective of their demographic characteristics, ACJ participants expressed a diverse range of views, from deep concerns about any use of genome editing through to a view that regulation should not impede the rapid clinical adoption of this technology. The view of the majority of citizens' jury participants could perhaps best be described as cautiously optimistic that genome editing could provide a valuable contribution to healthcare in future, provided that it is properly regulated, well researched and delivered equitably. Even so, many participants across a number of value types expressed discomfort with research involving human embryos, and even those who were supportive of research involving human embryos were not convinced that there was good reason to relax the 14 day rule. This suggest that, in Australia at least, any proposal to relax the 14-day rule will require compelling evidence of the need to do so, extensive public engagement and robust models for regulation prior to implementation, if at all. To do otherwise could significantly compromise public trust.

Funding Source: Australian Medical Research Futures Fund Genomics Health Futures Mission

Keywords: Public engagement, Human embryo research, 14 day rule

TRACK: CLINICAL APPLICATIONS (CA)

IN VIVO AND EX VIVO GENE EDITING
1:30 PM – 3:00 PM
Room 258, Meeting Level 2

1:35 PM – 1:55 PM

BRILLIANCE: A PHASE 1/2 SINGLE ASCENDING DOSE STUDY OF EDIT-101, AN IN VIVO CRISPR GENE EDITING THERAPY, IN CEP290-RELATED RETINAL DEGENERATION

Pennesi, Mark E., Pierce, Eric, Aleman, Tomas, Lam, Byron, Jayasundera, K. Thiran, Myers, Rene, Ashimatey, Bright and Mei, Baisong
Casey Eye Institute, Oregon Health and Science University, Portland, OR, USA

Purpose: Mutations in CEP290 cause severe early-onset retinal degeneration. The BRILLIANCE trial evaluates the safety and efficacy of EDIT-101, an adeno-associated virus vector comprising DNA encoding Cas9 expressed under the photoreceptor-specific GRK1 promoter and two specific guide RNAs. Following the subretinal injection of EDIT-101, the guide RNAs target Cas9 to the IVS26 mutation in CEP290, where it excises the IVS26 mutation. Approach: BRILLIANCE is an open-label, Phase 1/2 single ascending dose study. The primary objective is to evaluate the safety and tolerability of EDIT-101. Adult and pediatric patients with homozygous or compound heterozygous c.2991+1655A>G mutation in IVS26 of CEP290, and best-corrected visual acuity (BCVA) of light perception to 0.4 logMAR are eligible. EDIT-101 is administered to the eye with worse visual acuity at three doses: 6.0E+11 vg/ml (low-dose), 1.0E+12 vg/ml (mid-dose), and 3.0E+12 vg/ml (high-dose). Safety endpoints are incidence of dose-limiting toxicities (DLTs), frequency of adverse events (AEs) related to EDIT-101, and the number of procedure-related AEs. The secondary objective is to assess efficacy based on BCVA, light sensitivity, and performance on a visual navigation Results: Fourteen participants in cohorts 1- 4 have received EDIT-101. There have been no reports of DLTs nor ocular serious AEs associated with EDIT-101 to date. Most reported AEs were mild to moderate, of which half were related to the surgical procedures. Multiple participants (8/14 participants) showed improvement on at least one vision assessment endpoint, and 75% of these reported a corresponding improvement on the QoL questionnaire. Three of the 14 participants, including both homozygous patients, were responders as defined by clinically meaningful BCVA improvement supported by two other positive clinical responses. The improvements in vision occurred by 3-6 months and were sustained in participants with longer follow-up. Conclusion: EDIT-101 for the treatment of CEP290-related retinal degeneration is the first clinically investigated in vivo CRISPR gene editing therapy. To date, no DLTs or ocular serious AEs have been associated with EDIT-101. Initial assessments of efficacy demonstrate proof of concept of in vivo photoreceptor gene editing.

Keywords: Gene Editing, In-Vivo, Inherited Retinal Dystrophy

1:55 PM – 2:05 PM

CARDIOMYOCYTE THERAPY WITH ENGINEERED DEOXY-ATP DELIVERY IMPROVES FUNCTION IN CHRONICALLY FAILING HEARTS

Murry, Charles E.[1], Mhatre, Ketaki[2], Mathieu, Julie[2], Martinson, Amy[2], Flint, Galina[2], Reinecke, Hans[2] and Regnier, Michael[2]
[1]University of Washington, Seattle, WA, USA, [2]Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA, USA

Transplanting human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) improves cardiac contractile function in multiple preclinical models when delivered in the acute or sub-acute phases of infarction. Enigmatically, despite engrafting well in chronically infarcted hearts, hPSC-CM have not improved mechanical function in established heart failure. 2'-deoxy-ATP (dATP) is an allosteric activator of cardiac myosins that increases contractility but exists at vanishingly low levels in post-mitotic cardiomyocytes. Engineering hPSC-CMs to overexpress the enzyme that controls dATP production, ribonucleotide reductase (RNR), enhances dATP levels and increases contractility. Moreover, when cocultured with wild type (WT) hPSC-CMs, the RNR-expressing cells transfer dATP to WT cells via gap junctions, increasing contractility in a non-cell-autonomous manner. Here, we hypothesized that transplanting RNR-expressing hPSC-CM into chronically infarcted hearts would deliver dATP throughout the heart via its extensive gap junction network, thereby increasing contractility. Human iPSCs were CRISPR-edited by knocking RNR into the AAVS1 locus under control of a muscle-specific promoter. Athymic rats were infarcted and, 4 weeks later, received grafts of dATP-producing hPSC-CMs, WT controls, or a vehicle injection. The WT and vehicle control groups both showed progressive diminution of fractional shortening over the ensuing 3 months. In sharp contrast, hearts receiving dATP-producing hPSC-CM showed progressive improvement in fractional shortening over 3 months, in parallel with increased dATP levels outside the graft. Rats receiving dATP-producing hPSC-CMs had greater voluntary exercise activity, reduced pulmonary congestion, reduced pathological cardiac hypertrophy, and improved cardiac metabolomic profiles. In summary, transplantation of hPSC-CM engineered to deliver the myosin activator, dATP, markedly improves contractile function in a model of chronic ischemic heart failure, whereas WT cardiomyocytes offered no benefit. This discovery may permit the benefits of hPSC-CM therapy to be extended to the large population of patients with chronic heart failure.

Funding Source: NIH R01 HL128368; NIH R01 HL148081; NIH R01 HL146868

Keywords: Heart Regeneration, Genome Editing, Heart Failure

2:05 PM – 2:15 PM

EPITOPE EDITED HEMATOPOIETIC STEM CELLS ALLOW IMMUNE-BASED IN VIVO SELECTION OF GENOME-ENGINEERED CELLS

Casirati, Gabriele[1], Cosentino, Andrea[1], Mucci, Adele[2], Mahmoud, Mohammed[3], Freschi, Marta[1], Zeng, Jing[2], Brendel, Christian[2], Bauer, Daniel[2] and Genovese, Pietro[2]
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Hematopoietic stem/progenitor cell (HSPC) transplantation (HSCT) offers curative options for patients affected by conditions for which substitution of endogenous hematopoiesis with genetically corrected or healthy donor-derived cells can halt the pathogenic process. Nonetheless, the short and long-term toxicities of genotoxic conditioning remain a substantial barrier to a wider application of HSCT and gene therapy. Whereas monoclonal and toxin-conjugated antibodies (Ab) targeting HSPCs have been proposed as an alternative to chemo/radiotherapy, the mechanism of action and pharmacokinetics of these agents hamper their safe clinical use due to the risk of on-target killing of transplanted HSPCs. Here, we show that precise editing of the targeted epitope in HSPCs can endow hematopoietic lineages with selective resistance to mAbs without affecting stem cell function. This strategy allows improved myeloablation - which can continue after HSCT - and progressive enrichment of gene-modified cells. We have identified amino acid changes in the extracellular domain of KIT (CD117) that abrogate the binding of mAbs without affecting surface expression, ligand affinity, downstream signaling and proliferative response. We exploited adenine base editing (BE) to introduce these mutations with high efficiency (~80%) in CD34+ HSPCs, with preservation of long-term repopulating and multilineage differentiation capacity in primary and secondary recipient mice. To improve HSPC therapies for hemoglobinopathies, such as sickle cell disease, we multiplexed KIT epitope BE and two BCL11A erythroid enhancer motifs. We obtained editing efficiencies comparable to single editing and the erythroid progeny of triple-edited cells showed upregulation of HbF. Mice xeno-transplanted with multiplex BE CD34+ cells showed a 2-fold co-enrichment of both KIT and BCL11A editing in peripheral blood after 2 weeks of Ab administration, confirming the possibility to select gene-modified cells up to therapeutic thresholds. We envision a new paradigm for non-genotoxic conditioning based on transplantation of epitope-engineered HSPCs resistant to immunotherapeutic agents to achieve engraftment and in vivo selection of gene-corrected HSPC with substantial advantages over alternatives in terms of safety and tolerability.

Keywords: non-genotoxic conditioning, epitope engineering, HSCT

2:15 PM – 2:25 PM

CONTROLLING CRISPR-CAS9 GENOME EDITING IN HUMAN CELLS USING A SMALL-MOLECULE INDUCIBLE DEGRADATION STRATEGY

Khajanchi, Namita, Patel, Vrusha and Saha, Krishanu
Biomedical Engineering, University of Wisconsin, Madison, USA

CRISPR/Cas9 has been used to precisely gene edit induced pluripotent stem cells (iPSCs) to create disease models. However, prolonged Cas9 activity has negative consequences such as off-target editing, genotoxicity, immunogenicity, and undesired on-target modifications. Current methods to control the CRISPR/Cas9 system include various small molecules, inhibitors, light and magnetic fields; however, these methods lack high-resolution temporal control over Cas9 activity in vivo and may leave behind residual active Cas9. Recent work has shown that a degron can be controlled by FDA-approved pomalidomide (POM). In this study, we attach degrons to Cas9 and characterize the effectiveness of the degrons in degrading Cas9 and modifying the on- and off-target editing efficiency with POM in both human embryonic stem (H9s) and kidney (HEK293T) cells. We achieved this by transfecting HEK293T and H9s with lentivirus to create Cas9-degron cell lines. Our results demonstrate an overall 50% decrease in Cas9-deg levels with the addition of POM. Withdrawal of POM revealed that Cas9 levels returned within 24 hours, while a single dose of POM continuously degraded Cas9 protein up to 96 hours. On-target editing efficiency of wild-type Cas9 and Cas9-deg was similar, confirming that the

degron units do not hinder Cas9 activity. Furthermore, adding POM to decrease Cas9 levels significantly affected on-target editing efficiency, suggesting that Cas9-deg off-target editing activity will also decrease. To evaluate the impact of POM on off-target editing, we targeted the VEGFA gene in iPSCs and conducted karyotyping to confirm iPSC chromosomal integrity. The results conclude that the small molecule POM reversibly controls Cas9-deg levels, as well as gene editing activity within human cells. In summary, our study highlights the potential of using a degron-engineered Cas9 protein controlled by POM to mitigate the negative consequences of prolonged Cas9 activity and improve the precision of genome editing. The ability to control Cas9 activity with high-resolution temporal control using a safe small molecule inducer that is known to be safe and can pass the blood-brain barrier presents a promising strategy for reversible control of genome editing ex vivo and in vivo in many tissues, including the central nervous system.

Funding Source: NK was supported by an NHGRI training grant to the Genomic Sciences Training Program 5T32HG002760.

Keywords: gene editing, CRISPR/Cas9, small-molecule

2:25 PM – 2:35 PM

HUMAN HYPOIMMUNE PRIMARY PANCREATIC ISLETS EVADE ALLOGENEIC AND AUTOIMMUNE REJECTION WITHOUT IMMUNOSUPPRESSION AND ALLEVIATE DIABETES IN HUMANIZED MICE

Schrepfer, Sonja[1], Hu, Xiaomeng[1], Gattis, Corie[1], Olroyd, Ari[1], Friera, Annabelle[1], White, Kathy[1], Young, Chi[1], Basco, Ron[1], Lamba, Meghan[1], Wells, Frank[1], Ankala, Ramya[1], Dowdle, William[1], Lin, August[1], Egenberger, Kyla[1], Rukstalis, Michael[1], Millman, Jeffrey[1], Connolly, Andrew[2] and Deuse, Tobias[3]
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Transplantation of allogeneic pancreatic donor islets has been shown to restore normal blood glucose and reduce insulin dependence in patients with difficult-to-control insulin-dependent diabetes. However, the systemic immunosuppression (IS) required for procedure prevents this cell replacement therapy from more wide-spread adoption in larger patient populations. Herein we report the hypoimmune engineering of primary human islet cells to an HLA class I and II-negative and CD47-overexpressing phenotype and their reaggregation into human hypoimmune pseudo-islets (HIP p-islets). HIP p-islets showed similar size, cell type composition, and in vitro insulin secretion as unmodified islets (wt p-islets), showing that the engineering itself did not impact the morphology or endocrine function of the organoids. Next, we assessed the survival of p-islets and their cell composition in immunocompetent, diabetic allogeneic humanized SGM3 mice. Wt p-islets were recoverable on the transplant day but were fully rejected at later time points. In contrast, the total number and cell composition of HIP p-islets did not change over time and there was no immune cell infiltrate in or around the HIP p-islet cells as demonstrated by histopathology. Glycemic control was achieved in all recipients of HIP p-islets. For this approach to be relevant in the context of T1D (type 1 diabetes), it is important that a hypoimmune islet graft can evade allo-and auto-immunity without IS. To test this, we created a mouse model (=T1DM mice) humanized with PBMCs from a patient with T1DM. As the beta cells of the patient are destroyed by autoimmunity, we generated iPSCs from the same PBMC pool; one fraction underwent HIP engineering. Both autologous (auto) and HIP auto (HIP) iPSCs were then differentiated into autologous iP-islet cells for subsequent transplantation into T1DM mice. The auto iP-islets vanished quickly over 10 days, confirming the establishment of transferred human autoimmune disease in these T1DM mice. HIP iPSC iP-islets survived in T1DM mice, and their survival was not impacted by the fact that subsequently transplanted auto p-islets were rejected in the same mice. The transplantation of HIP iP-islets where no immunosuppression is required has the potential to lead to wider adoption of this therapy.

Keywords: editing, hypoimmune, islets

THERAPEUTIC GENOME EDITING TO MAKE SAFE EFFECTIVE STEM CELL THERAPIES

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Genome editing is a precise method to change the DNA sequence of the cell. Genome editing by homology directed repair (HDR), previously called gene targeting, enables the insertion of large sequences of DNA into precise genomic locations. Thus, HDR enables the correction of underlying disease causing mutations but also enables using synthetic biology to engineer cells. We have developed a highly active HDR genome editing system for cells using CRISPR ribonucleoprotein (RNP) to make the double-strand break combined with AAV6 to deliver the recombination template (RNP/AAV6). Small molecule enhancers of the process increases the frequency of gene targeting to 50% in hematopoietic stem cells (HSCs) and up to 100% allele targeting frequency in pluripotent cells. In this presentation, I will discuss our continued iterative process in improving the system and our application to treating sickle cell disease, HIV, and Huntington's disease.

Keywords: genome editing, CRISPR/Cas9, AAV6, hematopoietic stem cells, pluripotent cells, sickle cell disease

TRACK: CELLULAR IDENTIY (CI)

EMERGENCE OF THE GERMLINE
1:30 PM – 3:10 PM
Room 257, Meeting Level 2

1:35 PM – 1:55 PM

THE ROLE OF THE RNA-BINDING PROTEIN DEAD END IN MAINTENANCE OF PRIMORDIAL GERM CELL FATE

Raz, Erez
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Germ granules, condensates of phase-separated RNA and protein, are essential for germline development, but how these molecules are organized within the granules and whether such an organization is relevant for germ cell fate is unclear. Combining three-dimensional in vivo structural and functional analyses, we study the dynamic spatial organization of molecules within zebrafish germ granules. We find that the vertebrate-specific Dead end protein is essential for positioning nanos3 RNA at the condensates' periphery, where ribosomes are located. Without Dead end, or when translation is inhibited, nanos3 RNA translocates into granule interiors, far from the ribosomes' location. These findings reveal the molecular mechanisms controlling the spatial organization of RNA within the phase-separated organelle and the importance of sub-granule RNA localization for preserving germ cell totipotency.

Keywords: Zebrafish, Germ Cell, Cell Fate

1:55 PM – 2:05 PM

REGULATION OF ENDOGENOUS RETROVIRUSES BY TRIM28 IS NECESSARY TO LICENSE PRIMORDIAL GERM CELLS FOR GAMETOGENESIS

DiRusso, Jonathan[1], Wang, Allison[2], Robbins, Alexander[2], Xiang, Xinyu[3], Liu, Wanlu[3] and Clark, Amander[2]
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Following specification and epigenetic reprogramming, mammalian Primordial Germ Cells (PGCs) undergo determination, a key lineage restriction event in which the latent pluripotency program is extinguished as the RNA binding protein DAZL is upregulated. Successful determination is thought to be necessary for PGC differentiation into pro-spermatogonia and meiotic germ cells in the embryonic testis and ovary, respectively. These transitions are enigmatic, as the regulatory network that guides determination and licenses the epigenome for gametogenesis is unknown. Given the regulatory roles of Endogenous Retroviruses (ERVs) in early mammalian embryos, including maintenance of pluripotent states, we wondered if ERV regulation may be critical for extinguishing latent pluripotency in PGCs during determination. To test this, we employ a conditional knockout mouse model of TRIM28 in PGCs using TRIM28fl/fl lines bred to Blimp-Cre. TRIM28 is a ubiquitously-expressed epigenetic scaffolding protein that directs establishment of repressive heterochromatin at ERVs. Blimp-Cre is highly efficient in the germline, with recombination efficiencies in PGCs of 100%. Using these tools, we reveal that TRIM28 knockout in PGCs causes derepression of Class II ERV RNAs by E12.5, most notably members of the evolutionarily young IAP family. We also discovered that DAZL expression is heterogeneous in TRIM28 mutant PGCs at E13.5, but all TRIM28 mutant PGCs are DAZL+ by E16.5, despite showing defects in differentiation. Using ATAC-seq at E14.5, we found that TRIM28 mutant PGCs have increased accessibility of ERVs, especially those of the IAP family. Accessible ERVs are enriched for binding motifs active in latent and formative pluripotency. We also found that both sexes have distinct TRIM28-independent ERVs which are silenced in the absence of TRIM28. Collectively, our results support a model in which decommissioning ERVs through chromatin condensation is necessary to license PGCs for gametogenesis.

Funding Source: This work is funded by R01HD058047 to Amander Clark and the UCLA Molecular Biology Institute Whitcome Fellowship to Jonathan DiRusso.

Keywords: PGCs, Transposable elements, mouse models

2:05 PM – 2:15 PM

EXTRACELLULAR MATRIX IS A CRITICAL FACTOR IN THE DIVERGENCE OF THE GERMLINE AND THE AMNIOTIC LINEAGES

Overeem, Arend[1], Chang, Yolanda[1], Moustakas, Ioannis[1], Roelse, Celine[1], van der Schrier, Valérie[1], Mei, Hailiang[2], Freund, Christian[1] and Chuva De Sousa Lopes, Susana[1]
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The human germline is established around week 2-3 of embryonic development, with the emergence of primordial germ cells (PGCs). The origin of human PGCs is still unclear: PGCs may be derived from either the posterior epiblast, the amnion or both. Specification of PGCs depends on bone morphogenic proteins (BMPs), which also induce the formation of the amnion during the same period of development. What determines the separation of the germline from other BMP-induced lineages remains unresolved. The addition of BMP4 to human induced pluripotent stem cells (hiPSCs) cultured as embryoid bodies or micropatterned colonies results in formation of human PGC-like cells (hPGCLCs) but also many non-PGCLC off target cells. Here we report that the extracellular matrix (ECM) is important in hPGCLC versus amniotic fate determination. By adding diluted basement membrane extract (BME overlay) with BMP4, hPGCLCs form with up to 70% efficiency in conventional 2D culture. Single-cell transcriptomics revealed that hPGCLCs differentiated by BME-overlay are highly similar to PGCs from a Carnegie stage 7 human embryo. Furthermore, hPGCLCs, amniotic ectoderm- and amniotic mesoderm-like cells, all seem to arise from a common TFAP2A+ progenitor. Interestingly, without BME overlay, only TFAP2A+/GATA3+ amniotic ectoderm-like cells were formed, but not hPGCLCs. Interrogation of signaling pathways revealed that BME overlay modulated the balance between BMP and Nodal signaling, favoring formation of hPGCLCs by increasing expression of PGC progenitor markers TFAP2A and EOMES. We observed that BME overlay allows the feeder-free maintenance of isolated hPGCLCs and that hPGCLCs cultured without BME do not survive, lose germ cell marker expression, or revert to a SOX17-/POU5F1+ pluripotent state. Current hPGCLC differentiation methods have variable efficiencies and are difficult to scale up. The inability to produce large numbers of hPGCLCs has limited the field to progress in the maturation of hiPSC-derived germ cells. Our results not only revealed an important role for ECM in hPGCLC specification and survival, but we also present a robust and scalable method of generating hPGCLCs which will benefit the field of in vitro gametogenesis in humans.

Funding Source: Funding sources: Dutch Research Council (VICI-2018-91819642), the European Research Council (ERC-CoG-2016-725722 OVOGROWTH), ZonMw (PSIDER-10250022120001) and the Novo Nordisk Foundation Grant (reNEW-NNF21CC0073729).

Keywords: primordial germ cells, In vitro gametogenesis, amniogenesis

2:15 PM – 2:25 PM

ROADMAP TO THE TOTIPOTENT STATE IN VITRO

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Totipotency is the ability to generate any embryonic or extra-embryonic tissue, and in the strictest sense, to form a new individual. The zygote and two cell stage of mouse embryogenesis are totipotent. Recently, cells expressing totipotency markers were observed to emerge spontaneously in mouse pluripotent stem cell cultures. Many groups have identified transcription factors, epigenetic regulators, chromatin remodellers and signalling proteins which promote this transition. However, it remains unclear whether all these inducers generate cells which correspond to those in early embryo. Furthermore, it is not known whether these myriad inducers act through a small set of common pathways, or whether they have unique and diverse mechanisms of action. In order to address this, we identified novel combinations of inducers which increase totipotency-associated marker expression several hundred-fold. This allowed us to cluster totipotent-like cells separately from pluripotent ones, using single-cell RNA sequencing. Crucially, only one cluster was

formed and this clustered with totipotent cells from early mouse embryos, demonstrating the acquisition of a common state. Next, we identified novel markers of this cluster with better sensitivity and specificity than current standard markers. Working with our single cell dataset and confirming the results of previous studies, we observed an increase in the sumoylation and ubiquitination machinery, as well as a shift in eukaryotic initiation factor profile in the totipotent cluster. We also confirmed that cells transiting to totipotency tend to do so in G2/M phase of the cell cycle. Finally, we identified small molecule inhibitors which can induce and prolong this state in vitro, allowing large scale biochemical assays. In conclusion, we uncover new insights into the acquisition of totipotency in vitro, novel markers and a small molecule inhibitor combination which will facilitate large-scale studies of totipotency.

Funding Source: Japan Society for the Promotion of Science Postdoctoral Fellowship

Keywords: Totipotency, Reprogramming, Single-cell RNA sequencing

2:25 PM – 2:35 PM

TRANSGENE DIRECTED INDUCTION OF A STEM CELL-DERIVED EMBRYOID TO MODEL ASPECTS OF HUMAN DEVELOPMENT

Gantner, Carlos[1], Weatherbee, Bailey[1], Daza, Riza[2], Hamazaki, Nobuhiko[2], Iwamoto-Stohl, Lisa[1], Shendure, Jay[2] and Zernicka-Goetz, Magdalena[3]

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The human embryo undergoes morphogenetic transformations following implantation into the uterus, yet our knowledge of this crucial stage is limited by the inability to observe the embryo in vivo. Stem cell-derived models of the embryo are important tools to interrogate developmental events and tissue-tissue crosstalk during these stages. Here, we establish a human post-implantation embryo model comprised of embryonic and extraembryonic tissues. We combine two types of extraembryonic-like cells generated by transcription factor overexpression with wildtype embryonic stem cells and promote their self-organization into structures that mimic aspects of the post-implantation human embryo. These self-organized aggregates contain a pluripotent epiblast-like domain surrounded by hypoblast- and trophoblast-like tissues. We demonstrate that these inducible human embryoids robustly generate several cell types, including amnion, extraembryonic mesenchyme, and primordial germ cell-like cells in response to BMP signaling. This model also allowed us to identify an inhibitory role for SOX17 in the specification of anterior hypoblast-like cells. Modulation of the subpopulations in the hypoblast-like compartment demonstrated that extraembryonic-like cells impact epiblast-like domain differentiation, highlighting functional tissue-tissue crosstalk. In conclusion, we present a modular, tractable, integrated model of the human embryo that will allow us to probe key questions of human post-implantation development, a critical window when significant numbers of pregnancies fail.

Funding Source: This work is supported by The Wellcome Trust, Open Atlas and NOMIS grants (M.Z-G), Allen Discovery Center for Cell Lineage Tracing grants (J.S. and M.Z-G), the Gates Cambridge Trust (B.W.) and Leverhulme Trust (C.G.).

Keywords: Embryoid, Development, Extraembryonic

2:35 PM – 2:45 PM

EMPLOYING TOTIPOTENT CELLS TO RECONSTRUCT MOUSE EMBRYOGENESIS

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Blastoids, a structure similar to blastocysts in morphological and molecular level, can be applied to regeneration research. Using totipotent cells to construct blastoids will extend the information of early development to an earlier stage, and explore clues of regeneration. Totipotent blastomere-like cells (TBLCs) are a novel type of stably cultured mouse totipotent cell line generated by inhibiting spliceosomes. Here, we constructed TBL-blastoids in a new three-dimensional culture system using TBLCs. Morphological and transcriptomic analysis revealed TBL-blastoids contained typical morphology and key cell lineages of blastocysts and had higher degree of consistency in developmental rate and morphology compared to other blastoids. Moreover, TBL-blastoids implanted into uterus, induced decidua and even developed to embryonic tissues, indicating their in vivo developmental potential. The efficiency of generating TBL-blastoids and implantation rate suggest the necessity of TE-like component formation. Meanwhile, TBLCs can differentiate into extraembryonic cell lines directly, which provides an alternative strategy for evaluating totipotency. In conclusion, the induction of TBLCs into blastoids and extraembryonic cells is valuable for promoting regeneration, early embryonic development study and evaluating totipotency.

Keywords: totipotency, blastoids, implantation

2:45 PM – 3:05 PM

MECHANISM AND IN VITRO RECONSTITUTION OF MAMMALIAN GERM-CELL DEVELOPMENT

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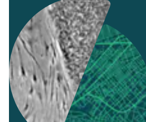
The germ-cell lineage ensures the creation of new individuals, perpetuating/diversifying the genetic and epigenetic information across the generations. We have been investigating the mechanism for germ-cell development, and have shown that mouse embryonic stem cells (mESCs)/induced pluripotent stem cells (miPSCs) are induced into primordial germ cell-like cells (mPGCLCs) with a robust capacity both for spermatogenesis and oogenesis and for contributing to offspring. These works have served as a basis for exploring the mechanism of key events during germ-cell development such as epigenetic reprogramming, sex determination, meiotic entry, and nucleome programming. By investigating the development of cynomolgus monkeys as a primate model, we have defined a developmental coordinate of the spectrum of pluripotency among mice, monkeys, and humans, identified the origin of the primate germ-cell lineage in the amnion, and have elucidated the X-chromosome dosage compensation program in primates. Building upon such knowledge, we have succeeded in inducing human iPSCs (hiPSCs) into human PGCLCs (hPGCLCs) and then into oogonia with appropriate epigenetic reprogramming in xenogeneic reconstituted ovaries. We have also shown that hPGCLCs can be propagated to ~106-fold over a period of 4 months under a defined condition. More recently, we have demonstrated an ex vivo reconstitution of fetal oocyte development in humans and monkeys. These studies have established a foundation for human in vitro



gametogenesis. Here, I present our latest findings regarding the in vitro reconstitution of mammalian germ-cell development.

Keywords: germ cell development, in vitro reconstitution, humans, monkeys

TRACK: NEW TECHNOLOGIES (NT)

LIVE-IMAGING AND SUPER-RESOLUTION MICROSCOPY
1:30 PM – 3:10 PM
Room 259, Meeting Level 2

1:35 PM – 1:55 PM

SUPER-RESOLUTION MICROSCOPY OF SINGLE PROTEINS IN THEIR NANOSCALE STRUCTURAL CONTEXT

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Super-resolution optical microscopy has become a powerful tool to study the nanoscale spatial distribution of molecules of interest in biological cells, tissues and other structures over the last years. Imaging these distributions in the context of other molecules or the general structural context is, however, still challenging. I will present recent developments of novel multiplexed fluorescent probes and pan-Expansion Microscopy sample preparation techniques which tackle this challenge. Our new fluorogenic DNA-PAINT probes enable fast, 3D whole-cell imaging without the need for optical sectioning, adding a versatile tool to the toolbox of single-molecule super-resolution probes. I will further present unpublished work on extending this concept to multiplexed imaging, allowing super-resolution (or conventional) imaging of 10 and more fluorescent labels in the same sample. Furthermore, labeling proteins and other cellular components in bulk in our recent pan-Expansion Microscopy method provides ultrastructural context to the nanoscale organization of proteins, replacing complex correlative light/electron microscopy by an all-optical imaging approach.
Financial Interest Disclosure: J.B. is co-founder of panluminate, a startup company related to Expansion Microscopy.

Keywords: Super-resolution microscopy, single-molecule imaging, 3D correlative microscopy

2:45 PM – 3:05 PM

LABEL-FREE 3D SPATIOTEMPORAL ANALYSIS OF CELLULAR DIFFERENTIATION IN LIVE ORGANOIDS USING LOW-COHERENCE HOLOTOMOGRAPHY

Lee, Sumin[1], Lee, Jaehyeok[1], Kim, Hye-Jin[1] and Park, YongKeun[2]
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The utilization of three-dimensional (3D) visualization plays a critical role in comprehending the physiological functions and cell type diversity of live organoids. However, conventional 3D imaging techniques based on fluorescence markers have limitations with regard to long-term, non-invasive observation of growing organoids as they require exogenous manipulations such as immunostaining, genetic modifications, or fluorophore excitations. Holotomography imaging technology offers a potential solution by providing 3D refractive index (RI) measurements and reconstructions of cell and tissue sections. This technology enables the calculation of dry mass in individual cells and subcellular compartments through the volumetric RI information. In this study, the low-coherence holotomography imaging system was employed, which is suitable for observing multicellular specimens, to examine the morphological features of early-stage murine small intestine organoids. The 3D RI tomograms of live organoids embedded in Matrigel were acquired at hourly intervals for a duration of 120 hours, revealing the early differentiation of small intestine organoids, including the formation of a central cyst structure and crypt-like budding structures. The differentiation of enterocytes, goblet cells, and Paneth cells was distinctly identified through the marker-free observation of subcellular structures such as secretory vesicles and granular structures. Furthermore, the imaging system enabled the observation of cellular dynamics, such as mitotic cell division and the translocation and chromatin condensation of apoptotic cells, by capturing 3D RI tomograms at two-minute intervals. The volume and dry mass of individual organoids were also analyzed, exhibiting fluctuations due to size oscillation and organoid fusion. In conclusion, low-coherence holotomography provides unique capabilities for determining the differentiation qualities of organoids, making it a valuable tool for basic research and therapeutic applications.

Keywords: Labe-free organoid observation for 120 hours, 3D Organoid live imaging, Organoid tracking

2:05 PM – 2:15 PM

REORGANIZING NICHE ARCHITECTURE STILL PRESERVES ORGAN FUNCTION IN THE HAIR FOLLICLE

Wei, Haoyang[1], Du, Shuangshuang[1], Parksong, Jeeun[2], Pasolli, Hilda[3], Regot, Sergi[2], Gonzalez, Lauren[1], Xin, Tianchi[1] and Greco, Valentina[1]
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Stem cells' ability to build and replenish tissues depends on support from their niche. While niche architecture varies across different organs, the functional importance of niche architecture is unclear. During hair follicle growth, multipotent epithelial progenitors build hair via crosstalk with their remodeling fibroblast niche, the dermal papilla, providing a powerful model to functionally interrogate different physical niche architectures. Through intravital imaging, we show that dermal papilla fibroblasts remodel both individually and collectively to form a polarized, structurally robust niche. Polarized TGFβ signaling precedes structural niche polarity, and loss of TGFβ signaling in dermal papilla fibroblasts leads them to progressively lose their stereotypic architecture and instead surround the epithelium. The reorganized niche relocates multipotent progenitors, but nevertheless supports their proliferation and differentiation. However, progenitor differentiation is completed prematurely, resulting in compromised shorter hair production. Overall, our results reveal that niche architecture optimizes organ efficiency, but is not absolutely essential for organ function.

Funding Source: H.W. is supported by China Scholarship Council (CSC) Grant. This work is supported by an HHMI Scholar award (55108527) and NIH grants number R01AR063663, R01AR072668, DP1AG066590 (all to V.G.)

Keywords: stem cell niche architecture, remodeling tissue intravital imaging, skin hair follicle fibroblasts

2:15 PM – 2:25 PM

NUCLEOPORINS REGULATE EPIDERMAL PROGENITOR FATE DECISIONS THROUGH CHANGES IN COMPOSITION AND CHROMATIN BINDING

Neely, Amy[1], Bao, Xiaomin[1], Blummensaadt, Laura[1], Zhang, Hao[2] and Zhang, Yang[3]
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Nucleoporins (NUPs) constitute the nuclear pore complexes (NPCs) that perforate the nuclear membrane and function to transport macromolecules into and out of the nucleus. In addition to their role in transport, NUPs have been shown to regulate genes expression directly through chromatin binding. The roles of NUPs in regulating stem cell fate decisions, between self-renewal versus differentiation, are still poorly characterized. To address this, we leveraged human epidermis as a highly accessible research platform for integrating a variety of approaches. Between the progenitor state and the differentiated states, the majority of NUPs are downregulated, suggesting a potential role of high NUP expression in progenitor maintenance. To address this, we used a three-pronged approach: 1.) we determined if the number or composition of nuclear pores are changing with epidermal differentiation 2.) we investigated if the permeability of the pore was altered with epidermal differentiation and 3.) we clarified the role of NUP98 in directly regulating epidermal homeostasis. First, we leveraged super resolution microscopy to count the number of nuclear pores in undifferentiated and differentiated keratinocytes. Single molecular localization microscopy achieved a resolution of ~20 nm, sufficient for resolving individual nuclear pores for quantification. We found that the number of NPCs is not changing significantly with differentiation. However, we identified that the inner ring nucleoporin known to regulated NPC permeability, NUP93, was significantly decreased with differentiation suggesting that although the number of NPCs are not changing, the composition and possibly the permeability is. Lastly, we found that nucleoporin, NUP98, can freely diffuse inside the nucleoplasm and directly regulate gene expression. NUP98 binds to the promoters of key progenitor maintenance genes such as DNMT1 and UHRF1, and is essential for sustaining the expression of these genes. This chromatin association was dependent upon HDAC activity. Upon HDAC inhibition, NUP98 is relocalized to the nucleolus. Together, these data highlight the diverse roles of NUPs in modulating NPC composition, permeability, as well as direct binding to chromatin, to control progenitor fate decisions between self renewal and differentiation.

Funding Source: National Institutes of Health grant R01 AR075015 American Cancer Society Research Scholar Grant RSG-21-018-01-DDC National Institutes of Health grant R01GM140478 SBDRC Pilot and Feasibility Award Northwestern University

Keywords: Nucleoporins, differentiation, gene regulation

2:25 PM – 2:35 PM

SUPER-RESOLUTION IMAGING UNCOVERS KEY TEMPORAL CHANGES IN CHROMATIN STRUCTURE AND PLURIPOTENT GENE REACTIVATION IN SINGLE REPROGRAMMING CELLS

Martinez-Sarmiento, Jose Angel[1], Cosma, Maria Pia[2] and Lakadamyali, Melike[1]
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Elucidating the mechanism of reprogramming to pluripotency has been hampered by the limitations of current iPSC systems, such as low efficiency and long kinetics, to unravel important molecular processes in cells undergoing a correct reprogramming trajectory. Here, we overcome such limitations by using the highly efficient heterokaryon reprogramming system (fusion between differentiated and pluripotent cells) to dissect the temporal dynamics of key transcriptional and epigenetic events during the early stages of pluripotency conversion at the single-cell level employing super resolution imaging approaches. Using STORM to dissect global chromatin dynamics, we revealed that, immediately after heterokaryon formation the somatic nucleus undergoes a dramatic removal of the repressive histone modification marks H3K9me3 and H3K273me3, but interestingly, not a gain in active H3K4me3 and H3K9ac histone modifications; this early event was followed by a late global chromatin decondensation stage, characterized by decreased nucelosomal density. Next, we applied RNA-FISH and OligoSTORM to visualize the local gene compaction changes and gene expression dynamics of the key pluripotency genes OCT4 and NANOG. We found that OCT4 and NANOG were reactivated at a high efficiency, but with distinct mechanisms and kinetics, where OCT4 undergoes a faster transcriptional reactivation and at higher levels compared with NANOG. Remarkably, OCT4 initial expression is decoupled from the global stage of chromatin decondensation and does not undergo major changes in chromatin decompaction at its local genomic region; in contrast, the late NANOG gene reactivation was preceded by the earlier acquisition of a local open configuration, highlighting that genome structure and function relationship is gene context-dependent

Funding Source: CONACYT scholarship (Becas Doctorado al Extranjero, Mexico) Linda Pechenik Montague Investigator Award (Melike Lakadamyali) 4DN UO1DA052715

Keywords: Reprogramming, Super-Resolution Microscopy, Chromatin

2:35 PM – 2:45 PM

SYNTHETIC GENETIC CIRCUITS TO UNCOVER AND ENFORCE THE OCT4 TRAJECTORIES OF SUCCESSFUL REPROGRAMMING OF HUMAN FIBROBLASTS

Schlaeger, Thorsten[1], Ilia, Katherine[2], Shakiba, Nika[3], Bingham, Trevor[4], Jones, Ross[3], Kaminski, Michael[5], Aravera, Eliezer[2], Bruno, Simone[2], Palacios, Sebastian[2], Weiss, Ron[2], Collins, James[2] and Del Vecchio, Domitilla[6]
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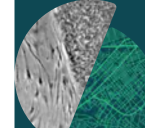
Reprogramming human fibroblasts to induced pluripotent stem cells (iPSCs) is inefficient, with heterogeneity among transcription factor (TF) trajectories driving divergent cell states. Nevertheless, the impact of TF dynamics on reprogramming efficiency remains uncharted. Here, we identify the successful reprogramming trajectories of the core pluripotency TF, OCT4, and design a genetic controller that enforces such trajectories with high precision. By combining a genetic circuit that generates a wide range of OCT4 trajectories with live-cell imaging, we track OCT4 trajectories with clonal resolution and find that a distinct constant OCT4 trajectory is required for colony formation. We then develop a synthetic genetic circuit that yields a tight OCT4 distribution around the identified trajectory and outperforms in terms of



reprogramming efficiency other circuits that less accurately regulate OCT4. Our synthetic biology approach is generalizable for identifying and enforcing TF dynamics for cell fate programming applications.

Funding Source: NIH NIBIB Award Number 5R01EB024591, MIT Amar G Bose Research Grant, and BCH Stem Cell Program

Keywords: Reprogramming, Pluripotency, OCT4

2:45 PM – 3:05 PM

HOW STEM CELL PROGENY INTEGRATE INTO MATURE TISSUE ARCHITECTURE: ULTRASTRUCTURAL INSIGHTS FROM FIB-SEM

O'Brien, Lucy E.[1], Galenza, Anthony[1], Moreno-Roman, Paola[1], Su, Yu-Han[1], Acosta-Alvarez, Lehi[1], Debec, Alain[2], Guichet, Antoine[2], Knapp, Jon-Michael[3], Kizilyaprak, Caroline[4], Humbel, Bruno[4] and Kolotuev, Irina[4]
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Self-renewing tissues face the ongoing task of maintaining physiological function while replacing their cellular building blocks. This challenge is compounded for barrier epithelia, which seal the body interior from the external environment, because the environment-contacting cells must be replaced without losing barrier integrity. Yet in many epithelia, basal stem cells and new progeny lack barrier-forming structures such as a specialized apical membrane and occluding junctions. Their absence raises the question of how new progeny generate and assimilate into an epithelium's mature barrier architecture. To illuminate this process, we leveraged recent advances in Focused Ion Beam-Scanning Electron Microscopy (FIB-SEM) to examine how differentiating cells integrate into the adult Drosophila intestine, an archetypal barrier epithelium. FIB-SEM tomograms revealed the ultrastructure of a surprising choreography between integrating progeny and mature neighbor cells, which create a transient, occluding junction niche that shelters the new cell as it gestates its nascent barrier structures. Once these barrier structures are sufficiently developed, basal-to-apical disassembly of the niche seamlessly assimilates the new cell into the tissue's barrier architecture. Our findings highlight the power of FIB-SEM to reveal otherwise-inaccessible cellular mechanisms that underlie stem cell and tissue biology in vivo.

Keywords: Epithelia, tissue architecture, differentiation

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)

EPIGENETICS AND TISSUE BIOLOGY
1:30 PM – 3:10 PM
Room 254, Meeting Level 2

1:35 PM – 1:55 PM

TRANSCRIPTION-RNA METABOLISM COUPLING CONTROLS ZYGOTIC GENOME ACTIVATION AND TOTIPOTENT REPROGRAMMING

Shen, Xiaohua, Xu, Jingzhao, Hao, Xiaowen, Ma, Shaoqian, Ji, Xiong
School of Medicine, Tsinghua University, Beijing, China

Following fertilization, the zygote must activate gene expression through a process called zygotic genome activation (ZGA) to initiate development. However, the mechanisms governing the transition from noncoding sequences to protein-coding genes during ZGA have remained elusive. We find that the carboxyl-terminal domain (CTD) of polymerase (Pol) II plays a crucial role in facilitating mRNA gene transcription by sensing nascent RNA and connecting transcription with RNA processing. Removal of the CTD disrupts this coupling, resulting in reduced mRNA synthesis and steady-state levels, as well as compromised RNA decay, leading to an increase in intergenic noncoding transcripts. These effects convert the pluripotent program into a two-cell embryonic program, leading to totipotent reprogramming. Reprogrammed cells display two-cell embryo characteristics, including gene signature, epigenetic state, nuclear architecture, and cell cycle consistent with the two-cell stage. These cells can differentiate into embryonic and extraembryonic lineages. Our findings demonstrate the importance of the coupling between polymerases and RNA processing machineries facilitated by the Pol II CTD in activating genes during ZGA, highlighting the interplay between fundamental nuclear processes such as transcription and RNA metabolism in driving early embryonic development.

Keywords: ZGA, totipotent reprogramming, RNA Pol II CTD, transcription, RNA processing and decay

1:55 PM – 2:05 PM

THE MOLECULAR MACHINERY CONTROLLING STEM CELL AND TISSUE PLASTICITY BETWEEN ADULT COLON AND SMALL INTESTINE

Zhou, Qiao Joe[1], Gu, Wei[1], Huang, Xiaofeng[1], Wang, Hua[2], Singh, Pratik[3], Helin, Kristian[2] and Shivdasani, Ramesh[4]
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Cellular plasticity is a crucial mechanism for adult tissues to respond to injuries and repair itself. It must be tightly regulated because undesired plastic events, such as metaplasia, promote dysfunction and tumorigenesis. However, the molecular complexes that safeguard cellular identity and regulate plasticity are poorly understood. By studying the distinct LGR5+ stem cell populations that generate the mucosal linings of the small intestine vs colon, we discovered that the colon-restricted chromatin factor SATB2 is a master regulator of adult colonic stem cell identity and plasticity in mice and humans. Using conditional genetic deletion in mice, single-cell sequencing, epigenetic profiling and human organoid cultures, our data showed that in the absence of SATB2, colonic stem cells are converted into small intestine ileal stem cells and subsequently reconstitute in colon a mucosa that resembles ileum in cell composition, tissue architecture, and physiological functions. Mechanistically, SATB2 restrains intestinal transcription factors (TFs) CDX2 and HNF4A to colon-specific enhancers; in its absence, CDX2 and HNF4A re-localize to primed ileal enhancers in colon and activate small intestinal gene expression and convert colon to ileum. Accordingly, ileal gene activation is abolished in Satb2-/-Hnf4a-/- mutant colon. Using Affinity Purification and Mass Spectrometry, we further uncovered another chromatin factor, MTA2, that partners with SATB2 in plasticity regulation. Mouse knockout and epigenetic studies (ATAC-seq, ChIP-seq) of MTA2 and comparison with SATB2 led to a unified model of tissue plasticity in which permissiveness of plasticity is embedded in the primed enhancers whereas plasticity regulators (such as SATB2 and MTA2) restrain key TFs at tissue-specific enhancers to prevent activation of alternative lineage differentiation; release of these TFs unleashes plasticity. Discovery of this molecular complex has implications for deeper understanding of adult tissue plasticity regulation and

designing novel treatment strategies for Short Bowel Syndrome and Inflammatory Bowel Diseases.

Keywords: intestinal stem cells, plasticity, epigenetics

2:05 PM – 2:15 PM

TRANSCRIPTIONAL REPRESSION UPON S PHASE ENTRY PROTECTS GENOME INTEGRITY IN PLURIPOTENT CELLS

Goekbuget, Deniz[1], Lenshoek, Kayla[1], Boileau, Ryan[1], Bayerl, Jonathan[2], Laird, Diana[2] and Blelloch, Robert[1]
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Coincidence of transcription and replication during S phase of the cell cycle results in replication stress – a source of genome instability. Rapidly dividing cells like pluripotent stem cells are transcriptionally hyperactive and have elevated replication stress yet maintain their genome integrity. The mechanisms underlying this feat are unknown. By studying pluripotent stem cell enriched Forkhead-domain transcriptional repressor FOXD3, we uncover a requirement of transient transcriptional repression upon S phase entry in minimizing replication stress and maintaining genome integrity in pluripotent cells. Acute deletion of FOXD3 results in rapid onset of replication stress, G2/M cell cycle arrest, activation of a 2C-like gene program, genome instability, and P53 dependent apoptosis. At the G1/S transition, FOXD3 binds near the most highly transcribed genes. Acute loss of FOXD3 results in the increased expression of these genes in the immediate S phase followed by delayed cell cycle progression and accumulation of DNA damage markers. Transient Pol II inhibition in S phase rescues the cell cycle progression and replication stress defects in FOXD3 depleted cells. Loss of FOXD3-interacting histone deacetylases HDAC1/2 similarly induces replication stress while transient inhibition of histone acetylation after FOXD3 loss opposes this stress. These results uncover a new role for a transcriptional repressor in the transient inhibition of highly transcribed genes during S phase to enable faithful DNA replication and protect genome integrity of rapidly dividing mouse pluripotent stem cells.

Funding Source: National Institute of General Medical Sciences of the National Institutes of Health grant R01GM125089 (RB) German Research Foundation Research Fellowship GO 2901/1-1 (DG)

Keywords: Pluripotent stem cells, Cell cycle, Transcriptional regulation

2:15 PM – 2:25 PM

TRANSPOSABLE ELEMENTS REGULATE NATURAL KILLER CELL DEVELOPMENT

Najia, Mohamad[1], Jha, Deepak[1], Blainey, Paul[2] and Daley, George[1]
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The hematopoietic system is a paradigm of stem cell biology, yet the role of transposable elements (TEs) remains an underexplored layer of genetic regulation. Accumulating evidence suggests TEs were co-opted as cis-regulatory elements that shape gene regulatory networks. Moreover, TEs are regulated by epigenetic machinery and contribute to local chromatin environments. We hypothesized that TEs impart a regulatory architecture through genetic enhancers and chromatin states to guide human hematopoietic fate decisions. We generated a comprehensive atlas of enhancer-gene regulation using the Activity-by-Contact (ABC) model on all major human hematopoietic cell types amounting to 3.7 million predictions. TEs were enriched in lymphoid ABC enhancers compared to other lineages, harboring lineage-specific TF motifs. TEs were transcriptionally upregulated during lymphoid differentiation, whereas the expression of repressive TE machinery attenuated, implying that epigenetic regulation of TEs is concomitant with lymphoid fate specification. We systematically perturbed genes involved in TE regulation within HSPCs and assessed lymphoid lineage fates. Knockout of the H3K9 methyltransferase EHMT1 resulted in a lineage shift from T to NK cells during in vitro differentiation. Further, knockout of TRIM28, an epigenetic co-repressor with well-documented roles in TE repression, phenocopied EHMT1 loss, supporting the conclusion that TE de-repression mediates the lineage shift. Loss of EHMT1/TRIM28 induced distinct NK progenitor states, identified by single cell RNA/ATAC-Seq, and derepressed TEs harbored NK-relevant TF motifs, suggesting that TE derepression facilitates NK lineage choice. TRIM28 KO NK cells exhibited a proinflammatory state characterized by upregulation of IFN pathway genes, whereas EHMT1 KO NK cells exhibited an enhanced cytotoxic CD16+ phenotype. These data underscore the regulatory contribution of TEs to human hematopoietic lineage decisions and highlight how modulating TEs could be leveraged for NK cell engineering.

Funding Source: NIH RC2 Grant

Keywords: natural killer cells, epigenetics, transposable elements

2:25 PM – 2:35 PM

REPROGRAMMING AND MULTIOME STUDIES UNCOVER A RARE STEM CELL-LIKE POPULATION OF GERMINAL CENTER B-CELLS

Scourzic, Laurianne, Izzo, Franco, Cucereavii, Lucy, Teater, Matt, McNally, Dylan, Chin, Christopher, Polyzos, Alexander, Myers, Robert, Béguelin, Wendy, Stadtfeld, Matthias, Chen, Zhengming, Landau, Dan, Melnick, Ari and Apostolou, Effie
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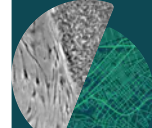
The Germinal Center (GC) B cells, which are derived from antigen-activated mature B cells, constitute the basis of humoral immunity and the cell of origin of most B cell lymphomas. Despite their differentiated nature, GC B cells transiently acquire properties highly reminiscent of stem cells, including high proliferative potential, clonogenicity in vivo, and phenotypic plasticity that enables them to commit to different cell fates (plasma, memory, or recycling). However, the molecular basis of their increased plasticity and its association to lymphomagenesis remain elusive. In this study, we provide molecular and functional evidence for the existence of a stem-like GC subpopulation. Based on bulk transcriptomics and epigenomics data, we found that GC B cells – compared to other mature B cells – show a surprising upregulation of pluripotent stem cell signatures, along with increased chromatin accessibility on stem cell genes and enhancers. To stringently assess their functional plasticity, we employed an inducible OKSM "reprogrammable" mouse stain and showed that – in contrast to other refractory mature B cells – GC B cells manifest a significantly higher amenability to induced pluripotent stem cells. This property relies on a small subpopulation of so-called "recycling" GC B cells (GCREC), which in response to T-follicular helper cells activate mTORC1/Myc anabolic programs and undergo additional rounds of clonal expansion and hypermutation in the GC. Single-cell Multiome analysis further confirmed that GCREC cells exhibit the highest enrichment for pluripotent stem cell signatures and an increased accessibility on stem cell super-enhancers, while simultaneously dampening the B-cell differentiation program. Importantly, B-cell lymphoma patients with high expression of the GC stemness



signature have significantly worse outcomes and reduced overall survival, suggesting a strong association with lymphoma fitness. In agreement, mutations in Histone 1 and Btg1, found in 20-40% of B-cell lymphoma patients, further enhanced GC B-cell reprogramming. Our findings shed light into the mechanisms by which differentiated cells could reactivate stem-like properties and have the potential to transform the way we understand and treat lymphomas.

Keywords: Plasticity, Germinal Center, Reprogramming

2:35 PM – 2:45 PM

PROMOTERS BECOME ACCESSIBLE DURING STEM CELL QUIESCENCE: SLEEPING WITH ONE EYE OPEN?

Malkowska, Anna, Brand, Andrea
NYU Grossman School of Medicine, New York University, NY, USA

Neural stem cells undergo quiescence as development progresses to maintain the stem cell pool in the event of injury, ageing or to support plasticity. In many stem cells, the epigenetic environment influences entrance into proliferation or quiescence. However, dynamic changes in the chromatin landscape of neural stem cells are still poorly characterised. Consequently, the role of epigenetic pathways in inducing quiescence or reactivation, especially in the context of the whole organism, remains an unsolved question. Drosophila is a uniquely suited model to such studies as it combines ease of identification of quiescent neural stem cells in vivo and the ability to perform complex genetic and molecular manipulation. We developed Targeted DamID (TaDa), a genome-wide chromatin-binding technique that provides high specificity and sensitivity on small numbers of cells, without the need for cell isolation, fixation, or immunoprecipitation. TaDa has enabled us to profile the chromatin landscape in neural stem cells in vivo. We performed a systemic analysis of several chromatin-binding proteins and nanobodies that recognise histone modifications throughout neural stem cell development and created a Hidden Markov Model of the chromatin landscape during proliferation, during quiescence, and after reactivation. Our results, validated by conditional loss- and gain-of-function studies, demonstrate a role for both repressive and permissive epigenetic pathways in quiescence regulation. On one hand, the Polycomb complex is crucial for gene repression that is needed to maintain quiescence. On the other hand, and surprisingly, many genomic regions, specifically promoters remain open during quiescence, even at higher levels than during proliferation. To resolve this possible contradiction, we are taking advantage of our recently developed NanoDam approach to identify phosphorylated versions of RNA pol II. Profiling phosphorylated RNA pol II will enable us to assess promoter-proximal pausing, which may allow for more rapid induction of transcription during stem cell reactivation, as shown previously in heat shock-regulated promoters.

Funding Source: Wellcome Trust

Keywords: Quiescence, Chromatin, Development

2:45 PM – 3:05 PM

DEFINING MALADAPTIVE EPITHELIAL PROGRAMS IN INFLAMMATORY DISEASE

Naik, Shruti
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Inflammatory epithelial conditions such as Psoriasis and Inflammatory bowel disease are typified by remitting-relapsing patterns of disease. Importantly, disease often recurs in the same exact tissue area, indicating the presence of a localized disease memory. While cells of the immune system are well known to retain memory, we and others have found that long-lived tissue stem cells can also bear memory in murine models. To extend these findings to human disease we leveraged a primary human skin epithelial organoid system, devoid of all accessory cells, to probe features of inflammatory memory exclusively in epithelium. We first established that epithelial cell organoids retained memory of inflammatory stimuli both at the epigenetic level via chromatin accessibility and functionally by altering sensitivity to secondary stimuli. In addition, we uncovered salient ground truths about how strength and duration of signal influence memory establishment and the remarkable person-to-person variability in encoding memory. Collectively, our data point to a highly individualized view of inflammatory memory in epithelial stem cells.

Keywords: Organoid, inflammation, memory

TRACK: CELLULAR IDENTIY (CI)

PLENARY III: EPIGENETIC REGULATION OF DISTINCT CELL STATES
3:30 PM – 5:10 PM
Ballroom East/West, Level 3

3:50 PM – 4:10 PM

SINGLE MOLECULE DYNAMICS REVEALS EARLY GLOBAL CHROMATIN CHANGES DURING CELLULAR REPROGRAMMING TO PLURIPOTENCY

Zaret, Kenneth S., Zhang, Jingchao and Lerner, Jonathan
Cell and Developmental Biology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA

During the transitions of the mammalian zygote to the 2, 4, and 8 cell stages of the embryo, nuclear chromatin undergoes dramatic changes to enable zygotic genome activation. Linker histones are exchanged, DNA replication rates change, and heterochromatin is first established. During the transitions of somatic cells to pluripotency, as established by Takahashi and Yamanaka (2006, 2007), the transcription factors Oct4, Sox2, Klf4, and c-Myc (OSKM) bind to many diverse sites in the genome, which we have shown largely do not correspond to sites that are essential for expressing pluripotency genes (Soufi et al. 2012). In that context, Oct4, Sox2, and Klf4 act as pioneer transcription factors, mostly targeting intergenic sites that are nucleosomal, whereas c-Myc mostly targets open promoters (Soufi et al. 2015). Roberts/Soufi (2021) have shown that nucleosomal targeting by Oct4 is essential for pluripotency conversion. However, whether and how global chromatin dynamics accompany pluripotency conversion is unknown. Using flourescence recovery after photobleaching (FRAP), Mosherer/Misteli (2006) found that pluripotent cells exhibit "hyperdynamic" chromatin. We have used histone H2B tagged with HALO to map nucleosome dynamics at the single molecule level and observe a marked difference between somatic cells, which exhibit much highly constrained nucleosomes, and embryonic stem cells, which exhibit hyperdynamic features (Lerner et al. 2020). We now have examined multiple stages of the transition of human somatic cells to OSKM-induced, hyperdynamic pluripotency. Using cell surface markers during live cell imaging, we have mapped global H2B molecular dynamics in cells on the path to pluripotency and in cells not on the path to pluripotency. We have discovered that the initial expression of OSKM leads to a dramatic, global change in chromatin dynamics at the onset of reprogramming. These changes are associated with changes in Sox2 genomic residence times during the reprogramming process. I will discuss causes and consequences of the global chromatin change that help explain

how reprogramming to pluripotency occurs and may be involved in diverse other directed cell fate changes.

Keywords: transcription factor, chromatin, reprogramming

4:10 PM – 4:30 PM

XIST RNA AND COT-1 RNAS AS ARCHITECTS OF CHROMOSOME REGULATION

Jeanne B. Lawrence
Departments of Neurology and Pediatrics, University of Massachusetts Chan Medical School, Worcester, MA, USA

Emerging evidence indicates that long non-coding RNAs broadly serve a structural role as platforms for an insoluble RNP scaffold that impacts the large-scale architecture of nuclear chromosome territories. CoT-1 repeat-rich RNAs are abundant in the insoluble scaffold of euchromatin, excluded from heterochromatin, and the removal of this hnRNA causes rapid euchromatin condensation. Using an inducible human XIST iPSC system we examined very early steps in XIST RNA function and find that XIST not only recruits histone modifiers, but quickly and more directly acts to modify non-chromatin elements of territory architecture. We show that sparse transcripts spread and begin impacting architectural elements within hours, whereas chromosome-wide silencing of active coding genes takes days; gene silencing occurs largely after condensation of the large Barr Body which is depleted of CoT-1 RNAs. Insight into this puzzling timing comes from studying a "minigene" comprised of just the tiny A-repeat fragment (4%) of XIST. A-repeat RNA does not spread on the chromosome but quickly silences numerous genes in a local region of high RNA density. Collective results support a model whereby XIST acts early to compact the DNA/RNA territory, thereby facilitating a density-dependent function of the A-repeat RNA required for gene silencing. The human XIST inducible system developed here also has important translational value, as it is designed to silence one of three chromosome 21s in Down syndrome patient-derived stem cells. This unique iPSC system has been used to reveal insights into the poorly studied cell biology of Down syndrome, as briefly highlighted. Finally, identification of the more "deliverable" A-repeat XIST minigenes has potential implications for DS but also many small chromosomal abnormalities. Studies of X-chromosome dosage compensation are fascinating basic biology, but also has untapped relevance to common chromosomal imbalances in people.

Keywords: lncRNA, XIST, chromosome

4:30 PM – 4:50 PM

A GENE REGULATORY NETWORK CLOCK OF HUMAN EPIBLAST DEVELOPMENT

Reik, Wolf[1], Rostovskaya, Maria[2], Coussement, Louis[2], Argelaguet, Ricard[1]
[1]Altos Labs, Cambridge, UK, [2]Epigenetics, Babraham Institute, Cambridge, UK

Pluripotency is the ability of single cells to differentiate to any cell type of the body. In human, the pluripotent epiblast emerges 6 days after fertilisation; however, cell specification occurs only later, with different lineages sequentially segregating from the epiblast in a defined order over the next 2 weeks. How directionality, timing and order of events during this 2 week-long "pluripotency window" are controlled remains unknown. Human pluripotent stem cells (hPSCs) are the in vitro counterpart of the embryonic epiblast. Previously we established an hPSC-based model of the entire window of epiblast development from its emergence to dissolution, which closely follows its transcriptional dynamics and timing in embryos, also called pluripotent state transition. To understand its molecular control, we simultaneously profiled transcriptome and chromatin accessibility in single cells and found that the transition is a stepwise rather than a gradual process. As the transition occurs under fixed culture conditions, this stepwise switch is not extrinsically-induced, but an intrinsic cell decision process. Thus the pluripotent state transition is a self-guided linear endogenous programme driving hPSCs through this stepwise process with precise timing. We reconstructed the dynamic gene regulatory network and quantitatively assessed activating and repressive connections between the main modules of transcription factors (TFs). This resulted in a model based on a cascade of TFs ensuring directionality, precise timing and intrinsic decisions during epiblast development ("transcriptional clock"). Hence we discovered that peri-implantation epiblast progression is an endogenous programme that can occur independently of instructive signals, and propose a model of a transcriptional clock establishing its timing and directionality. We hypothesise that intrinsic transcriptional programmes can commonly contribute to guiding differentiation, which was previously underappreciated.

Keywords: Epiblast, gene regulatory network, epigenetics

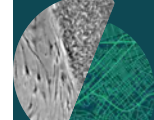
4:50 PM – 5:10 PM

REMOVAL OF FUNCTIONALLY DEFECTIVE HEMATOPOIETIC STEM CELLS RESCUES AGE-RELATED DEFECTS

Zhang, Yi, Wang, Yuting, Zhang, Wenhao
Program in Cellular and Molecular Medicine, HHMI, Boston Children's Hospital, Harvard University, Newton, MA, USA

Aging is a process accompanied by tissue and organ functional decline with social and medical consequences. Previous studies have demonstrated that aged hematopoietic stem cells (HSCs) are functionally compromised, which at least partly contributes to age-related declines of the body health. However, the mechanism underlying defects in aged HSCs is largely unknown. In this study, by performing single-cell RNA-seq, we revealed that the heterogeneity of HSCs is increased during mouse aging. Interestingly, the HSC heterogeneity correlates with CD150 protein levels. Importantly, the CD150low HSCs from old mice maintain their epigenetic and transcriptional features as those in young mice with a better engraftment capacity compared to that of the CD150high HSCs even in the secondary transplantation. Although both CD150low and CD150high HSCs from old mice have a similar capacity in self-renewal, the CD150high HSCs from old mice are compromised in their capacity to generate downstream progenitors and mature lineage-specified cells after transplantation when compared to the CD150low counterpart. Importantly, when the CD150low HSCs were transplanted to old mice, we observed functional improvement in the hematopoietic and other tissues. Our study thus not only reveals aging-related HSC heterogeneity, but also demonstrates it's a contributing factor for aging phenotypes, which can serve as a foundation for the development of rejuvenation approaches.

Keywords: Hematopoietic stem cells (HSC), aging, single cell RNA-seq



TRACK: CLINICAL APPLICATIONS (CA)

CLINICAL NEWS SESSION

IPS CELLS IN CLINICAL TRIALS: OPHTHALMOLOGY
8:00 AM – 9:00 AM
Room 259, Meeting Level 2

8:05 AM – 8:15 AM

RETINAL PIGMENT EPITHELIAL (RPE) STEM CELL-DERIVED RPE PROGENITOR CELL IMPLANTATION FOR DRY AGE-RELATED MACULAR DEGENERATION (DRY AMD)

Stern, Jeffrey[1], Arduini, Brigitte[1], Rao, Rajesh[2], Sareen, Dhruv[3] and Temple, Sally[1]
[1]Neural Stem Cell Institute, Rensselaer, NY, USA, [2]Ophthalmology, University of Michigan Kellogg Eye Center, Ann Arbor, MI, USA, [3]Biomanufacturing Center, Cedars-Sinai Medical Center, West Hollywood, CA, USA

Dry age-related macular degeneration (dry AMD) is a prevalent disease amenable to cell replacement therapy. Relatively few (i.e. 100K) RPE cells are needed to replace those lost during years of disease progression and the results of RPE replacement can be accurately assessed by established measures of vision and retinal structure. We are advancing a resident RPE stem cell (RPESC) to replace the RPE cells that are lost in dry AMD. RPESC isolated from one donor eye are expanded in culture to generate several hundred doses for implantation. Since RPESC are committed to produce RPE progeny (RPESC-RPE), differentiation to produce the RPE cell product is simple and robust. RPESC-RPE are implanted as an intermediate RPE progenitor obtained after 4-weeks of differentiation (RPESC-RPE-4W). This intermediate RPE progenitor stage cell is more effective than mature RPE cells at engraftment and vision rescue. In 2021, we obtained IND allowance for a Phase 1/2a trial of RPESC-RPE-4W implantation. A total of 18 participants are divided into two groups based on 'poor-seeing' 20/200-20/800 and 'better-seeing' 20/70 to 20/100 visual acuities that bracket a moderate extent of AMD-related RPE atrophy. Dose escalation cohorts of 50K, 150K and 250K implanted RPESC-RPE-4W cells are evaluated. Three subjects have been implanted, with preliminary (up to 6-month) results within primary safety endpoints of inflammation, overgrowth, macular sensitivity and visual acuity. Final results will be determined at 1-year post-implantation. Preliminary efficacy assessed as visual acuity show clinical improvements that reflect our preclinical findings. RPESC-RPE-4W implantation and assessment occurred at the Kellogg Eye Center. Clinical grade RPESC-RPE-4W were manufactured at the Cedars-Sinai GMP Biomanufacturing Center. Emmes Corporation monitors trial progress. The positive preliminary findings obtained with RPESC-RPE-4W progenitor cell implantation motivate us to add clinical sites and transition to a cryopreserved cell product. Stem cell-derived RPE cells for replacement therapy hold great promise to restore vision for dry AMD patient benefit.

Funding Source: NIH Regenerative Medicine Innovation Project Luxa Biotechnology

Keywords: Retinal Pigment Epithelial (RPE) cell, Macular degeneration (AMD), Cell replacement therapy

Clinical Trial ID number: NCT04627428

8:15 AM – 8:25 AM

A PHASE I/IIA TRIAL TO TEST SAFETY AND FEASIBILITY OF AN AUTOLOGOUS IPS CELL-DERIVED RETINAL PIGMENT EPITHELIUM PATCH IN AGE-RELATED MACULAR DEGENERATION PATIENTS

Bharti, Kapil and Sharma, Ruchi
National Eye Institute (NEI), National Institutes of Health (NIH), Bethesda, Bethesda, MD, USA

Induced pluripotent stem cells (iPSCs) can provide autologous and allogeneic replacement tissues, potentially for all degenerative diseases. Autologous tissues have the advantage of not requiring immune-suppressive drugs that have deleterious side-effects. The safety and feasibility of autologous iPSC-based therapies hasn't been established. Here, we developed an autologous iPSC-based therapy for age-related macular degeneration (AMD), a blinding eye disease that affects over 30 million people world-wide. AMD is caused by the progressive degeneration of retinal pigment epithelium (RPE), a monolayer tissue that maintains photoreceptor function and survival. We tissue engineered a clinical-grade iPSC-RPE-patch on a biodegradable scaffold using autologous cells from AMD patients. Preclinical investigational new drug (IND)-enabling studies performed on iRPE-patch derived from multiple AMD patients demonstrated reproducible manufacturing, validating our manufacturing process - a key requirement for an autologous phase I trial. Functional validation of clinical-grade iRPE-patches allowed determination of tissue barrier resistance, purity of RPE cells, and RPE cell shape metrics as key critical quality attributes now used as clinical product release criteria. Preclinical animal studies performed in immune-compromised rats confirmed safety of the auto-iRPE-patch and efficacy studies performed in a porcine laser-induced RPE injury model that mimics AMD-like eye conditions demonstrated integration and functionality of RPE patches. A phase I/IIa IND-application for an auto-iRPE-patch to treat AMD was recently cleared by the FDA. This Phase I/IIa clinical trial will test safety, feasibility, and integration of an auto-iRPE-patch in twelve advanced AMD patients. The trial is currently being run as a single site study at the NIH and targets patient enrollment in two cohorts: visual acuity 20/100 and above for the first cohort, and 20/80 and above. One patient was successfully transplanted in August 2022; we plan to transplant additional patients this year.

Funding Source: NEI IRP NIH Common Fund

Keywords: iPS cell therapy, autologous cell therapy, phase I clinical trial

Clinical Trial ID number: NCT04339764

8:25 AM – 8:35 AM

THE NEXT STAGE OF RETINAL REGENERATIVE MEDICINE

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In 2014, we performed the first application of iPS cells: autologous iPS cell-derived retinal pigment epithelium (iPSC-RPE) transplantation. This was followed by transplantation of HLA-matched allogeneic iPSC-RPE cells, and photoreceptor-containing retinal sheets produced from retinal organoids. In these clinical studies, the safety of iPSC-RPE was confirmed. In autologous transplantation, the transplanted sheet maintained its overlying photoreceptor cells and visual acuity for eight years. In HLA-matched allogeneic transplantation, survival of grafted cells were confirmed without systemic immunosuppressive drugs in five cases. Now we begun the next step clinical study, the allogeneic

iPSC-RPE strip transplantation to confirm efficacy. The new clinical study expands the indication to include not only age-related macular degeneration but also RPE insufficiency, which includes all diseases caused by atrophy of the RPE. Disease names are derived from ancient ophthalmologic findings, but sometimes include groups of diseases with different mechanisms. For example, retinitis pigmentosa is a general term for diseases of photoreceptor degeneration often caused by genetic mutations in photoreceptor cells, but it also includes cases of photoreceptor degeneration secondary to genetic mutations in RPE. Thus, while there are cases with the same disease name but different cells to be transplanted, there are also many diseases in which RPE transplantation rescue the visual function even if the disease name is different. From the viewpoint of cell therapy, it is necessary to reorganize the concept of disease names. In preclinical studies of photoreceptor cell transplantation for retinitis pigmentosa, iPS cell-derived 3D retinas were cut into sheets and transplanted under the retina of mouse and monkey models of retinitis pigmentosa, and various tests including immunohistochemistry, electrophysiology, and behavioral analysis were performed to demonstrate the proof of concept (POC) of photoreceptor cell transplantation. Photoreceptor cell transplantation is also the first example of neural network reconstruction in the central nervous system; together with RPE cell sheet therapy, it opens up treatment options for a variety of retinal degenerative diseases.

Funding Source:

Keywords: iPS cells, retina, clinical study

Clinical Trial ID number: jRCTa050200122 jRCTa050200027

8:35 AM – 8:45 AM

LONG-TERM FOLLOW-UP OF SUBJECTS IN A PHASE 1/2A CLINICAL TRIAL OF AN ALLOGENEIC BIOENGINEERED HESC-DERIVED RPE IMPLANT FOR ADVANCED DRY AGE-RELATED MACULAR DEGENERATION

Lebkowski, Jane S.[1], Kashani, Amir[2], Rahhal, Firas[3], Avery, Robert[4], Chan, Clement[5], Chen, Sanford[6], Palejwala, Neal[7], Ingram, April[8], Clegg, Dennis[9], Johnson, Linc[1] and Humayun, Mark[10]

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An open-label phase 1/2a clinical trial assessing the safety and preliminary efficacy of a polarized monolayer of allogeneic human embryonic stem cell-derived RPE cells (CPCB-RPE1) on a biosynthetic substrate was conducted in subjects with geographic atrophy (GA) secondary to dry age-related macular degeneration (AMD). The CPCB-RPE1 implant was delivered to the worst-seeing eye of 15 subjects during outpatient surgery. No attempts were made to HLA match subjects. All subjects received low-dose tacrolimus immunosuppression for 68 days in the peri-implantation period. The median age was 78 years (range 69-85). The treated eyes of all subjects were legally-blind with a baseline best corrected visual acuity (BCVA) of ≤ 20/200. There were no unexpected serious adverse events. Four subjects in cohort 1 had serious ocular adverse events including: retinal hemorrhage, edema, focal retinal detachment, or RPE detachment. This was mitigated in cohort 2 using improved hemostasis during surgery. There was no clinical or serologic evidence of inflammation suggestive of immune response directed towards the donor implant in any subject. At 1 year, a larger proportion of treated eyes experienced >5 letter gain in best corrected visual acuity when compared to the untreated eye (27% vs 7%) and a larger proportion of nonimplanted eyes demonstrated >5 letter loss (53% vs 33%). This trend was maintained as of last follow-up (mean 35.3 months, range 12-54 months) where a larger proportion of treated eyes experienced >5 letter gain when compared to the untreated eye (27% vs 7%) and a larger proportion of nonimplanted eyes demonstrated >5 letter loss (80% vs 47%). One subject died from causes unrelated to the study two years after surgical implantation of CPCB-RPE1. Postmortem histopathology demonstrated the presence of donor mature RPE cells by immunoreactivity for RPE65, Na/K ATPase and Bestrophin. Colocalization of rhodopsin with RPE65 positive donor RPE also suggest the presence of phagosomes within functional donor RPE. In summary, subretinal implantation of the CPCB-RPE1 is feasible and well-tolerated. Sub-retinally implanted, allogeneic, RPE cells survive, express functional markers, and do not elicit clinically detectable intraocular inflammation or serologic immune responses even without long-term immunosuppression.

Funding Source: The Phase 1/2a clinical trial was supported by funding from the California Institute of Regenerative Medicine and from Santen Ventures

Keywords: geographic atrophy, Implant, clinical trial

Clinical Trial ID number: Clinical Trials .gov NCT02590692

8:45 AM – 8:55 AM

UPDATES ON TWO CLINICAL TRIALS USING HUMAN NEURAL PROGENITORS ALONE OR SECRETING GNDF TO TREAT RETINITIS PIGMENTOSA AND ALS

Svendsen, Clive N.[1], Avalos, Pablo[1], Liao, David[2], Lewis, Richard[3] and Mamelak, Adam[4]

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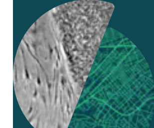
We have developed a clinical-grade human neural progenitor cell (NPC) line from a single human fetal cortical brain sample and expanded under cGMP to create the product CNS10-NPC which is being used for the treatment of Retinitis Pigmentosa (RP). The cell line was also engineered to secrete the powerful growth factor glial cell line-derived neurotrophic factor (GDNF) to create the product CNS10-NPC-GDNF for the treatment of amyotrophic lateral sclerosis (ALS). In extensive pre-clinical studies, we have shown that these NPCs differentiate into astrocytes following transplantation and can protect both photoreceptors and motor neurons. Our first update is from a new trial where we administered a unilateral subretinal injection of CNS10-NPC in subjects with Retinitis Pigmentosa (NCT04284293). Group 1A (n= 3) was treated at a low dose (300,000 total cells) and group 1B (n = 3) at a high dose (1,000,000 cells) all with visual acuity of 20/200 or worse. We have also treated 2 patients in group 2 at the high dose (n = 10) with visual acuity of 20/80 or worse. There have been no serious adverse events to date and using imaging we can see a new layer between the RPE and retina. The trial should be completed end of 2024. We recently published results from a trial transplanting CNS10-NPC-GDNF unilaterally into the spinal cord of 18 subjects with ALS where we showed safety of the approach and survival of the cells and release of GDNF up to 3.5 years after transplantation. A new trial (NCT05306457)



builds on this work by transplanting CNS10-NPC-GDNF unilaterally into the hand knob region of the motor cortex. We have completed treatment of the first group (A), in which 250,000 cells were transplanted into each of 21 sites. Group B will receive an increased dose of 500,000 cells per site. Imaging shows that we are able to target the motor cortex effectively. Finally, we will provide the first evidence that we may be able to replace fetal-derived neural progenitor cells with iPSC derived NPCs for a more scalable and renewable product that would be more practical for commercialization.

Funding Source: Both of these studies were funded by the California Institute for Regenerative Medicine (CIRM) under grant numbers: CLIN2-11620 and CLIN2-12319

Keywords: Neural Progenitor, growth factor, gene therapy

Clinical Trial ID number: NCT04284293 and NCT05306457

TRACK: CLINICAL APPLICATIONS (CA)

NAVIGATING THE REGULATORY HURDLES IN STEM CELL THERAPIES

Sponsored by: Wicell

9:30 AM – 11:10 AM
Room 258, Meeting Level 2

9:35 AM – 9:55 AM

SUSTAINABLE PRODUCTION OF IPSC DERIVED NEUROEPITHELIAL STEM CELLS FOR CLINICAL TRANSLATION OF CELL THERAPY

Falk, Anna
Experimental Medical Science, Lund University, Sweden

Translation of iPSC derived cell therapies from pre-clinical use to clinical use is challenging. Methods, media and technologies developed for experimental pre-clinical science might not be possible to use for producing clinical batches of cell therapy under Good Manufacturing Practice (GMP). Challenges come in several flavours from exchanging the media compounds for defined, xeno-free and GMP validated reagents to work procedure where standardisation is instrumental and quality controls needs to apply to regulatory authorities, additional challenges are the cost for producing clinical batches of iPSC derived cell therapies. Neuroepithelial stem (NES) cells can be captured directly from the developing human brain but can also be derived from pluripotent stem cells. NES cells have an immature identity, are very neurogenic and show good plasticity in directed differentiations. We and others have over the years shown promising results pre-clinically when transplanting NES cell in different spinal cord injuries and stroke. Based on these data we initiated the process of translating the reprogramming, iPSC culture and NES derivation to a clinically relevant GMP process aiming for standardisation, follow regulations and sustainability. To minimise the amount of reagents needed we explored reprogramming and neural induction using microfluidics and decreased reagents 13-fold and the starting number of cells 9-fold. Furthermore, microfluidic reprogramming omitted manual clone isolation and decreased variability in neural induction. Ongoing work for our clinical translation includes exchanging all reagents for GMP reagents, pre-clinically test efficacy of GMP cell therapy doses, investigating where in the process variations are introduced, preparation of clinical batches of cell therapy in GMP clean rooms, identifying gene panels predicting efficacy and potency as well as safety for cell therapy batches while adhering to regulatory authorities. The regulatory hurdles are different in different countries, demonstrating the need for harmonisation and collaboration.

Keywords: iPSC, cell therapy, neural, reprogramming, GMP, regulatory

9:55 AM – 10:05 AM

QUALITY ASSURED PLURIPOTENT STEM CELLS: A JOURNEY FROM BENCH TO BEDSIDE

Mattioli, Elisa[1], Konstantinidou, Chrysoula[2], Lindsay-Hill, Luke[2], Choy, Andrew[2], Zarzoso, Adrian[2], Prince, Judith[2], Warre-Cornish, Katherine[2], Perfect, Leo[2], Wise, Clare[1], Burns, Chris[1] and Carpenter, Lee[1]
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The development of a strict Quality Control strategy is a key aspect for developing safe and consistent cell therapy products. The UKSCB has developed a rigorous QC testing strategy to assure critical qualities of pluripotent stem cell banks. We examined viability percentages post thaw of 21 hESC to discover that this is not representative of the cell line capacity to recover, expand and ultimately differentiate. We measure parameters such as pluripotency through flow cytometry and tri-lineage germ-layer differentiation using qPCR analysis and investigate the effects of processing variables (e.g. cell culture media and use of feeders) using multivariate analysis. Furthermore, 28 clinical grade master cell banks have undergone additional deep characterisation, consisting of whole genome sequencing and deep sequencing of 400+ known oncogenic loci, only one cell line was found with a Tier-1 mutation. We are working to develop a validated assay for the detection of transmissible spongiform encephalopathies (TSEs) suitable for clinical grade cell banks to ensure ultimate safety of the product. All together this in-depth QC strategy provides a full picture of the capabilities of the hESC banks that we hold and how each and everyone may be better suited for a specific purpose. The same knowledge and strict QC approach is then applied to several different research projects including the development of cortical neurons from hESC for the development of a cell-based assay for the tetanus vaccine, through the detection of VAMP-2 cleavage. Expansion of hiPSC and hESCs on an automated cell expansion system, which has proven to be no different from manual cell culture. And lastly development of a PSC and MSC standard where several different cell lines are in the process of being screened to determine the one that provides more consistent results across different laboratories.

Keywords: Embryonic Stem Cells (ESCs), Advanced Therapy Medicinal Products (ATMPs), Quality Control Testing

10:05 AM – 10:15 AM

IDENTIFICATION AND FUNCTIONAL ANALYSIS OF CANCER-RELATED MUTATIONS IN HUMAN PLURIPOTENT STEM CELLS AND THEIR DIFFERENTIATED PROGENIES

Jung, Jonathan, Benvenisty, Nissim, Lezmi, Elyad
The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University, Jerusalem, Israel

Human pluripotent stem cells (hPSCs) are known to acquire genetic aberrations in culture, affecting their growth as well as their tumorigenic potential. We have recently shown using RNA-sequencing, that undifferentiated hPSCs acquire cancer-related point-mutations. Here we have analyzed more than 2,200 published transcriptomes, with our methodology for the identification of cancer-related point-mutations. This dataset covers 146 hPSC lines, originating from 178 studies of in vitro differentiation into cell types of ectodermal, mesodermal and endodermal

lineages. We found that ~25% of the samples, across over 30 different cell-lines, have acquired mutations characteristic of human cancers, during their in vitro propagation, predominantly in TP53, but also in other cancer-related genes. We show that TP53 mutations confer a selective advantage in cultures of both proliferating and differentiating cells, and that they induce aberrant molecular phenotypes related not only to TP53 downstream targets but also to the regulation of cell-fate acquisition. These findings have significant implications on the conclusions derived from studies unknowingly conducted using mutant cells, and on the standards required in the maintenance of cells designated for clinical applications. The initial part of this work was recently published in: Cell Stem Cell (2021) and Nature Protocols (2021).

Keywords: human pluripotent stem cells, cancer-related mutations, differentiation

10:15 AM – 10:25 AM

ADVANCED MATRIX-FREE HUMAN PLURIPOTENT STEM CELL MANUFACTURING BY SEED TRAIN APPROACH AND INTERMEDIATE CRYOPRESERVATION

Ullmann, Kevin[1], Manstein, Felix[2], Triebert, Wiebke[1], Kriedemann, Nils[1], Franke, Annika[1], Teske, Jana[1], Mertens, Mira[1], Lupanow, Victoria[1], Göhring, Gudrun[1], Haase, Alexandra[1], Martin, Ulrich[1] and Zweigerdt, Robert[1]
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Human pluripotent stem cell (hPSCs) derivatives have great potential for advanced drug screening, in vitro disease modelling and regenerative therapies. However, the envisioned routine application of these cells will require robust and economically viable production processes, compatible with industry and regulatory standards. Instrumented stirred tank bioreactors (STBR) are routinely applied for mammalian cell lines cultivation in the biopharmaceutical industry. This platform has also been adapted to the matrix-free suspension culture of hPSCs and recently enabled advanced high density bioprocessing of hPSCs by metabolic control and in silico modelling by our group. In contrast to prior suspension culture processes, which relied on conventional monolayer culture (2D) for process inoculation, we here demonstrate a seed train approach to ensure straightforward process upscaling, further closing the gap between the research state and industry-compliance. Chemical, STBR-controlled dissociation of the matrix-free cell-only hPSC aggregates was established, which crucially supported efficient single cell recovery and process control at each passaging step. This advanced strategy enabled the uninterrupted maintenance of exponential hPSC cell growth for 8 passages (4 days per passage; 32 days in total) in continuous suspension culture (3D). Furthermore, we show the applicability for intermediate high density cryopreservation of suspension-derived hPSCs followed by the direct re-inoculation of 3D suspension culture in STBRs, thereby entirely excluding the requirement of 2D cultivation. Gene expression profiling reveals novel insights into molecular mechanisms associated with continuous hPSC 3D suspension culture compared to conventional 2D controls. Importantly, hPSCs' karyotype stability and differentiation potential was fully maintained after long-term suspension culture. By completely omitting the need for conventional 2D matrix-dependant cultivation of hPSC, the novel culture strategy fosters process automation and facilitates the development of GMP-compliant closed system manufacturing, paving the way for hPS cells expansion and differention at clinically relevant conditions and quantities.

Keywords: human pluripotent stem cells, seed train, stirred tank bioreactor

10:25 AM – 10:35 AM

EPITYPING - ANALYSIS OF EPIGENETIC ABERRATIONS IN HUMAN PLURIPOTENT STEM CELLS UTILIZED FOR MODELING AND CLINICAL APPLICATIONS

Keshet, Gal, Sarel-Gallily, Roni and Benvenisty, Nissim
The Azrieli Center for Stem Cells and Genetic Research, Department of Genetics, The Hebrew University, Jerusalem, Israel

Human pluripotent stem cells (hPSCs) serve as a powerful resource for modeling human development and disease, as well as for regenerative medicine applications. However, when grown in the lab, these cells are known to acquire culture adaptation-related instabilities, thus posing a major challenge for the fidelity of hPSCs as a model system and for their safety for therapeutic purposes. Indeed, these instabilities are not limited to genetic changes, but also include epigenetic aberrations, mainly involving loss of parental imprinting and erosion of X-chromosome inactivation. Nevertheless, epigenetic aberration analysis is rarely performed as a standard procedure in labs using hPSCs. Here, we present EpiTyping: a detailed bioinformatic protocol for detecting such aberrations using RNA sequencing (RNA-seq) data. We describe how to process and analyze RNA-seq samples in a way that allows identifying abnormal bi-allelic expression of genes from about 20 imprinted chromosomal regions, and thus detect loss of imprinting. Furthermore, we show how to differentiate between X-chromosome inactivation, full activation, and aberrant erosion of chromosome X in female hPSCs. Additionally, this pipeline can be easily adapted to perform allelic expression analysis for genes which are not imprinted, and in cells other than hPSCs, thereby contributing to other fields as well. To increase the accessibility of the analysis to the research community, we also developed a free, easy-to-use software which could be utilized by stem cell researchers. We suggest that a regular use of this pipeline can help maintain epigenetically intact hPSC lines suitable for disease modeling and clinical applications.

Keywords: Epigenetics, Genomic imprinting, X-chromosome inactivation

10:35 AM – 10:45 AM

CONSTRUCTION AND EVALUATION OF A CLINICAL GRADE HLA HAPLOBANK OF IPSCS MATCHING APPROXIMATELY FORTY PERCENT OF THE JAPANESE POPULATION

Yoshida, Shinsuke[1], Kato, Tomoaki[1], Sato, Yoshiko[2], Umekage, Masafumi[1], Ichisaka, Tomoko[3], Nomura, Masaki[3], Tsukahara, Masayoshi[1], Takasu, Naoko[3] and Yamanaka, Shinya[2]
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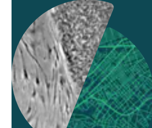
Human induced pluripotent stem cells (iPSCs) are expected to be useful for regenerative medicine for many diseases. Many researchers have tried to generate cells or tissue-like structures, including organoids, which help to ameliorate target diseases. To promote such cell therapies, we established a clinically applicable iPSC haplobank matching as many people as possible in Japan, which is one of the effective strategies considering cost and time. Through cooperation with several organizations, we recruited donors whose human leukocyte antigens (HLAs) are homozygous. The peripheral or umbilical cord blood collected from the donors was used for iPSC production and the produced iPSC lines were then subjected to Quality Control (QC) testing, including genome analyses and sterility, to maximize safety for



clinical use. The reasons to avoid using iPSC lines include the presence of residual episomal vectors or genetic mutations in cancer-related genes. We continued to improve the manufacturing process based on the results of these QC tests, and constructed a clinical-grade haplobank of 27 iPSC lines from 7 donors, in accordance with regulations for clinical use After the first release in 2015, these iPSC lines have been used in more than dozen clinical trials. As of 2023, we have not been notified of any severe adverse events related to transplanted cells, such as rejection or tumorigenicity. Each user of this iPSC haplobank has a plan for follow up for several years and will report outcomes accordingly. The establishment of this haplobank is an important step toward more clinical application of iPSCs in cell therapies. In this presentation, we would like to discuss the qualification for the production method of clinical grade iPS cells.

Funding Source: This study was supported by a research center network for the realization of regenerative medicine of the Japan Agency for Medical Research and Development (AMED) under grant number JP20bm0104001h0108.

Keywords: HLA Haplobank of iPSC, manufacturing, quality control

10:45 AM – 11:05 AM

FDA'S EFFORTS TO HELP FACILITATE THE DEVELOPMENT OF CELLULAR THERAPIES

Marks, Peter
Center for Biologics Evaluation and Research, US Food and Drug Administration, Silver Spring, MD, USA

Cell-based therapeutics are becoming increasingly important therapeutic modalities. Some of these therapies may be targeted to thousands of individuals whereas others only may be targeted to one or a few individuals. Development of these products poses challenges to the scientific community ranging from product characterization and manufacturing to preclinical and clinical development. The Center for Biologics Evaluation and Research at the US Food and Drug Administration (FDA) is responsible for the regulation of cell, tissue, and gene therapies. It also plays an important role in facilitating applied scientific and manufacturing advances in the field. Although notable progress in the development of these products has been made over the past years, and particularly since the passage of the 21st Century Cures Act, there is still much to be done to more rapidly bring these products to benefit individuals in need. FDA is working to apply all available regulatory tools to help facilitate this process, including use of the expedited development programs and a variety of meeting types designed to facilitate early interactions and provide advice on novel product development.

Keywords: cell-based therapeutics, development, regulation

TRACK: CELLULAR IDENTIY (CI)

CELL IDENTITY DURING REGENERATION AND AGING

9:30 AM – 11:10 AM
Room 257, Level 2

9:35 AM – 9:55 AM

ENDOGENOUS RETROVIRUS AS A HALLMARK AND DRIVING FORCE OF CELLULAR SENESCENCE AND TISSUE AGING

Qu, Jing
State Key Laboratory of Stem Cell and Reproductive Biology, Institute of Zoology, CAS, Beijing, China

Endogenous retroviruses (ERVs), which belong to the LTR retrotransposon family, are a relic of ancient retroviral infection of the ancestral germline and are fixed in the genome during evolution. As the “dark matter” of the genome, they comprise about 8% of the human genome and are subjected to stringent epigenetic and cellular surveillance. Of all the human endogenous retroviruses (HERVs), the youngest group, HERVK (HML-2) is able to code all viral proteins and to produce virus-like particles (RVLPs). Some pathological conditions, such as rheumatoid arthritis, neurodegenerative diseases and cancers, are known to trigger the mobilization of HERVK. However, it is still unclear if HERVK becomes reactivated during the aging process or if its mobilization in turn exacerbates age-related degeneration, let alone whether it can be used as a potential target to alleviate aging. In this study, we demonstrate that HERVK is reactivated during aging and that its mobilization contributes to the aging pathologies both endogenously and exogenously. Here, we discovered that endogenous retroviruses expression is increased in organs of aged primates and rodents, and in human tissues and serum from the elderly. In human senescence cells, we find that epigenetic alterations unlock HERVK expression, which leads to the formation of RVLPs. Such HERVK RVLPs are released from senescent cells and capable of conferring a senescence phenotype to young cells. However, neutralizing antibodies or the reverse transcriptase inhibitor blocks HERVK RVLP infection and abrogates the transmissible pro-senescence effect. Importantly, repressing endogenous retroviruses with CRISPR inactivation or Abacavir alleviated tissue aging and, to some extent, organismal aging. These findings indicate that endogenous retrovirus is a hallmark and driving force of cellular senescence and tissue aging.

Keywords: Cellular senescence, tissue aging, endogenous retrovirus, cGAS

9:55 AM – 10:05 AM

COMBINING HUMAN SKELETAL STEM CELL TRACKING IN VIVO WITH FUNCTIONAL AND TRANSCRIPTIONAL ANALYSIS ON THE SINGLE CELL LEVEL TO IDENTIFY NEW THERAPEUTIC TARGETS THAT PRESERVE STEM CELL DIVERSITY

Ambrosi, Thomas H.[1], Chan, Charles[2], Sahoo, Debashis[3], Weissman, Irving[2], Longaker, Michael[2], Sokok, Jan[2], Sinha, Rahul[2], Wang, Yuting[2] and Taheri, Sahar[3]
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With the increasing socioeconomic impact of skeletal disorders resulting from aging and the absence of reliable treatments, innovative approaches are required to prevent bone loss and restore skeletal tissues. Skeletal stem cells (SSCs) show great potential as a new therapeutic option. Despite their promise, progress in the field has been hindered by a lack of understanding regarding the identity and function of homogeneous SSC populations in humans. In this study, we utilized a combination of prospective flow cytometric isolation and SmartSeq2 single cell RNA-sequencing (scRNAseq) to deconstruct the human SSC lineage tree in fetal long bones. Through in vivo tracing of lentivirally barcoded human SSCs in a xenograft mouse model and scRNAseq analysis, we identified unique clonal dynamics of growth plate and periosteal SSCs and specified their localization in situ as well as their underlying functions. Our investigation extended to eight additional skeletal sites, revealing SSC type-specific transcriptomic features that dictate skeletal shape and size. By examining scRNAseq data and performing functional screening of SSCs from over 400 patients ranging from 13 to 96 years old, we found that age-related changes in bone growth and regeneration disorders stem from a pathological shift in the lineage commitment of the SSC pool. Our data suggests that this deviation in hSSC diversity underlies the development of skeletal fragility and nonunions during aging and plays a central role in diseases such as fibrous dysplasia. To address that, we developed an unbiased AI-based Boolean algorithm for scRNA-seq data analysis to uncover gene regulatory networks (GRNs) of parallel functionally tested patient SSCs, identifying new therapeutic targets to reinstate SSC diversity. Indeed, we show that by targeting gene activity in shared GRNs between fetal and dysfunctional patient SSCs using small molecule agonists and inhibitors, we can restore youthful bone-forming capacity in aged stem cells. In summary, our research provides novel insights for developing effective strategies against skeletal aging and disease, addressing an urgent need for improved treatment options.

Keywords: Human Skeletal Stem Cells, Bone Regeneration and Aging, Single Cell in vivo tracking and transcriptomics

10:05 AM – 10:15 AM

NEURONAL FATE INSTABILITY TRIGGERED BY METABOLIC DYSREGULATION OF ALTERNATIVE SPLICING

Traxler, Larissa[1], Herdy, Joseph[2], Stefanoni, Davide[3], D'Alessandro, Angelo[3], Gage, Fred[2] and Mertens, Jerome[4]
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Old age is the most significant risk factor for many diseases, including most neurodegenerative disorders such as Alzheimer's disease (AD). To study the age-dependent pathogenesis of AD, the direct conversion of patient-derived fibroblasts to induced neurons (iNs) has emerged as a useful model system. In contrast to iPSC-based models, iNs retain important molecular features of human aging and other patient-specific disease signatures. Based on iNs of a cohort of sporadic AD patients and age-matched controls, we previously revealed a metabolic switch to aerobic glycolysis in AD iNs, which is similar to the well-described Warburg effect in cancer. We identified an isoform switch of pyruvate kinase M (PKM) to the PKM2 isoform as a trigger of the metabolic switch, and further as a key transcriptional regulator leading to cell fate instability in AD iNs. However, regulation of PKM splicing has not been studied in human neurons, and thus remains largely obscure. MS-based metabolomics and glucose tracing in AD iNs identified a citrate shunt to acetylCoA in otherwise functional mitochondria. Excess acetylCoA in combination with reduced NAD+ levels result in an imbalance of acetylation and de-acetylation reactions. Acetylome analysis confirmed a hyper-acetylated state of AD iNs, which affected several splice factors. Acetylation of splice factors, such as heterogenous nuclear ribonucleoproteins, regulates their stability and their RNA binding pattern, and triggering an isoform switch to PKM2. This ultimately leads to a loss of neuronal fate and maturity, reflected by loss of synapses and neuronal resilience. Inhibition of the citrate shunt reverted the isoform switch in AD iNs in favor of PKM1, re-instating a fully mature and healthy neuronal state. We thus conclude that an AD-specific metabolic switch in neurons regulates alternative splicing, and results in neuronal cell fate instability, and eventually to neurodegeneration.

Funding Source: L'oreal-UNESCO For Women in Science Theodor Körner Fonds BrightFocus Foundation

Keywords: Direct conversion, Alzheimer's disease, Alternative Splicing

10:15 AM – 10:25 AM

HOW DOES AGEING-RELATED STIFFENING OF BRAIN TISSUE MICROENVIRONMENTS AFFECT THE REGENERATIVE CAPACITY OF CNS PROGENITOR CELLS

Buxboim, Amnon[1], Avidan, Nili[1], Fleet, Alex[2], Larrieu, Delphine[2], Ram, Oren[3], Shahak, Hen[1] and Sun, Xue[3]
[1]*Cell and Developmental Biology, Hebrew University of Jerusalem, Israel,* [2]*Pharmacology, Cambridge University, Cambridge, UK,* [3]*Biological Chemistry, Hebrew University of Jerusalem, Israel*

Ageing-related stiffening of neuronal microenvironments in the brain generates potent signals that attenuate the regenerative capacity of oligodendrocyte progenitor cells (OPCs) to proliferate and differentiate. We find that ageing drives substantial remodling of the nuclear lamina in OPCs, in which A-type lamin levels increase and B-type lamin expression decreases. Owing to the ubiquitous role of lamins in anchoring mostly heterochromatic sections at the nuclear envelope known as lamina associated domains (LAD's), we hypothesized that ageing effects are mediated via altered genomic organization and regulation. In this study, we isolate OPCs from neonate and aged rats and study the effects of ageing-related tissue stiffening by designing and optimizing hydrogel-based matrices that mimic the extracellular elasticity and adhesion signals of neonate and aged microenvironments. Indeed, the differences in cellular morphologies and lamina compositions between neonate and aged cells are recapitulated by matrix elasticity. To characterize differences in the structural organization of the nuclear lamina, we combine high-resolution optical and electron microscopies and perform micropipette aspiration based rheology to define the viscoelastic properties of OPC nuclei within intact cells. LAD mapping is performed using optimized CUT&RUN assays that target endogenous lamin-B1, thus avoiding the effects of ectopic expression of nuclear envelope proteins, which is a prerequisite by standard methodologies. Downstream effects on transcriptional regulation are studied via single-cell RNA sequencing (scRNA-seq), thus providing insight into cell-to-cell variations. In summary, our work-in-progress highlights the mechanobiological component

of ageing on progenitor cells of the CNS that can stimulate potential therapeutic strategies.

Funding Source: European Research Council (ERC-StG 678977)

Keywords: Oligodendrocyte precursor cells, Mechanobiology, Regeneration

10:25 AM – 10:35 AM

RETINOIC ACID BREAKDOWN IS REQUIRED FOR POSITIONAL IDENTITY ALONG THE PROXIMODISTAL AXIS OF THE REGENERATING AXOLOTL LIMB

Duerr, Timothy J.[1], Miller, Melissa[1], Voss, Randal[2] and Monaghan, James[1]
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Axolotl salamanders possess the capacity for full limb regeneration following amputation at any location along the proximodistal (PD) axis. This process proceeds through the blastema, a mass of dedifferentiated cells that accumulates on the stump of an amputated limb. Mesenchymal cells within the blastema contain positional information for recognition of their location along the PD axis. This enables the blastema to regenerate an entire arm in proximally amputated limbs or only a hand in distally amputated limbs. Previous studies have implicated retinoic acid (RA) as a determinant of positional identity along the PD axis, where proximally amputated limbs contain high levels of RA signaling and distally amputated limbs contain low levels of RA signaling. It is thought that this difference modulates the expression of cell surface proteins which convey positional identity in mesenchymal cells. However, how this RA gradient is formed along the PD axis is unknown, and a molecular mechanism behind how positional identity is established in a regenerating limb has remained elusive. Here, we show that a gradient of RA signaling is created via the breakdown of RA by the CYP26 family of proteins, namely CYP26B1. We show that Cyp26b1 is more highly expressed in the mesenchyme of distal blastemas than proximal blastemas. Pharmacological inhibition of CYP26 activity in regenerating limbs results in a concentration-dependent proximalization of distal blastemas. We next performed bulk RNAseq on talarozole treated blastemas to uncover transcripts coding for cell surface proteins. In this screen we identified Flrt3, Tenm4, and Lphn2, three RA responsive transmembrane proteins that are differentially expressed in the mesenchyme of proximal and distal blastemas. The expression patterns of these genes mirror the expression of Hoxa13, Hoxa11, and Hoxa9, respectively. Further, genetic ablation of Lphn2 phenocopies Hoxa9 knockout mice, suggesting that Flrt3, Tenm4, and Lphn2 expression could be modulated by classic Hox genes. Collectively, these results point to an RA gradient along the PD axis created by RA breakdown, not de-novo RA synthesis, which leads to expression of transcripts encoding cell surface proteins like Flrt3, Tenm4, and Lphn2 to coordinate PD positional identity in the regenerating limb.

Keywords: Limb regeneration, Retinoic acid, Salamander

10:35 AM – 10:45 AM

INTEGRATED INTRACELLULAR ORGANIZATION AND ITS VARIATIONS IN HUMAN IPS CELLS

Rafelski, Susanne[1], Viana, Matheus[1] and Theriot, Julie[2]
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The Allen Institute for Cell Science aims to understand the principles by which human induced pluripotent stem cells (hiPSCs) establish and maintain robust dynamic localization of cellular structures, and how they transition between states during differentiation and disease. Understanding how a subset of expressed genes dictate cellular phenotype is an enormous challenge due to the large numbers of molecules, their combinatorics, and the plethora of cellular behaviors they determine. We reduced this complexity by focusing on cellular organization, a key readout and driver of cell behavior, at the level of major cellular structures representing distinct organelles and functional machines, and generated the hiPSC Single-Cell Image Dataset (cfe.allencell.org) with over 200,000 live cells in 3D spanning 25 major cellular structures via 25 isogenic human induced pluripotent stem cell (hiPSC) lines from the Allen Cell Collection (allencell.org/cell-catalog). The scale and quality of this dataset permitted the creation of a generalizable analysis frameworkto convert raw image data of cells and their structures into dimensionally reduced, human-interpretable quantitative measurements and to facilitate data exploration. This framework embraces the vast cell-to-cell variability observed within a normal population, facilitates integration of cell-by-cell structural data, and permits quantitative analyses of distinct, separable aspects of organization within and across different cell populations. We found that the integrated intracellular organization of interphase cells was robust to the wide range of cell shape variations in the population, that the average locations of some structures became polarized in cells at the edges of colonies while maintaining the “wiring” of their interactions with other structures, and that, in contrast, structure location changes during early mitotic reorganization were accompanied by changes in their wiring.

Keywords: hiPSC, 3D Live Cell Imaging, Cell organization

10:45 AM – 11:05 AM

CELL REJUVENATION AND DISEASE

Izpisua Belmonte, Juan Carlos
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Aging is characterized by the functional decline of tissues and organs and the increased risk of aging-associated disorders. Different rejuvenating interventions have been proposed to delay aging and the onset of age-associated decline and disease to extend healthspan and lifespan. These interventions include metabolic manipulation, heterochronic parabiosis, pharmaceutical administration and senescent cell ablation. As disease and aging are associated with altered epigenetic mechanisms of gene regulation, such as DNA methylation, histone modification and chromatin remodelling, and non-coding RNAs, the manipulation of these mechanisms might be central to the effectiveness of treating disease as well as age-delaying interventions. I will discuss some of the epigenetic changes that occur during disease and aging and how partial reprogramming by the Yamanaka factors might be a potential avenue to restore cell health and resilience through cellular rejuvenation programming to reverse disease, injury, and the disabilities that can occur throughout life.

Keywords: aging, cell rejuvenation, disease, cell programming, epigenetics

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)

STEM CELLS FOR PERSONALIZED MEDICINE
9:30 AM – 11:10 AM
Room 253, Meeting Level 2

9:35 AM – 9:55 AM

ORGANOID MODELING OF GENE REGULATORY EVENTS DURING FOREBRAIN DEVELOPMENT

Vaccarino, Flora M., Jourdon, Alexandre, Scuderi, Soraya, Mariani, Jessica and Abyzov, Alexej
Child Study Center, Yale University, New Haven, CT, USA

We used induced pluripotent stem cell (iPSC)-derived forebrain organoids to explore the mechanism that govern neural stem cells differentiation into cortical neural lineages in typical development and in families with idiopathic autism spectrum disorder (ASD). We found that organoids were patterned by gradients of morphogens into cellular identities similar to those present in human fetal brains. Cellular composition, cell type specific gene expression and enhancer element activity were evaluated over time across individuals revealing interindividual variation in emergence and differentiation of the main neural lineages of the forebrain. The scale of the dataset allowed an investigation of the sources of variation influencing human neurogenesis in the organoid system over multiple genetic backgrounds. Comparing individuals with idiopathic ASD and their unaffected fathers revealed alterations in genes driving the tempo of cortical excitatory neurogenesis from undifferentiated progenitors. Macrocephalic ASD probands showed an increase in the progenitor pool and an increased proportions of excitatory neurons of the dorsal cortex, whereas normocephalic ASD probands showed a diametrically opposite phenotype. The imbalance in excitatory neuron subtypes was correlated with differential expression of genes driving excitatory neuron differentiation in progenitor cells, as well as differential activity of their linked enhancers and cognate transcription factors. Together, organoids reveal a network of gene-regulatory events that shape divergent cortical development in two intrinsically different subtypes of ASD. These differences could be used as potential stratifying factors in clinical or genetic studies of the disorder. Overall, omics studies in organoid allow to understand heterogeneity of human brain development across individuals and delineate altered trajectories in developmental disorders.

9:55 AM – 10:05 AM

STRAIGHT-IN: A RAPID AND EFFICIENT PLATFORM FOR TARGETED LARGE GENE INSERTIONS IN HUMAN PLURIPOTENT STEM CELLS

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Anatomy & Embryology, Leiden University Medical Center, Leiden, Netherlands

Inserting large DNA payloads (>10 kb) into specific genomic sites or replacing genomic segments in mammalian cells, such as human induced pluripotent stem cells (hiPSCs), still remains technically challenging. Applications ranging from synthetic biology to personalized medicine would greatly benefit from tools that facilitate this process. Here we have merged the strengths of different classes of site-specific recombinases and combined these with CRISPR-Cas9-mediated homologous recombination to develop a platform termed STRAIGHT-IN (Serine and Tyrosine Recombinase Assisted Integration of Genes for High-Throughput INvestigation) for stringent site-specific integration of large DNA payloads or replacement of genomic fragments at least 50 kb in size in hiPSCs. Only one copy of the DNA payload is integrated with full control of where it is targeted in the genome with no cargo size limitation detected to date (>170 kb). The procedure also permits the excision of nearly all the auxiliary DNA sequences which can lead to post-integrative silencing, simply leaving in the genome the desired payload flanked by two minimal scars (< 300 bp). We have demonstrated its applicability by establishing a multi-parameter reporter hiPSC line to assess the excitation-contraction coupling cascade in derivative cardiomyocytes, and simultaneously generating >10 hiPSC lines containing disease variants present in patients with genetic cardiac diseases. In addition, we recently developed an upgraded version of the platform allowing genetically-modified hiPSC lines to be generated with ~100% efficiency and within a two or three-week time period, making the procedure very rapid. Acceptor hiPSC lines with the new landing pad inserted into different safe harbour loci have been generated and validated, and we have created several constitutive and doxycycline-inducible reporter lines to compare expression levels from both genomic regions in a number of differentiated cell types.

Funding Source: Novo Nordisk Foundation grant (NNF21CC0073729)

Keywords: genome editing, disease modelling, synthetic biology

10:05 AM – 10:15 AM

STEM CELL-DERIVED ATRIOVENTRICULAR NODE-LIKE PACEMAKER CELLS FOR APPLICATION AS A BIOLOGICAL PACEMAKER

Lohbihler, Michelle[1], Sarao, Renu[1], Kwan, Maggie[1], Dhahri, Wahiba[1], Mourad, Omar[2], Masse, Stephane[3], Soon, Kayla[2], Backx, Peter[4], Kumaraswamy, Nanthakumar[3], Vasconcelos Nunes, Sara[5], Laflamme, Michael[1] and Protze, Stephanie[1]
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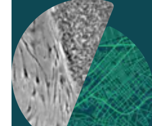
A healthy human heart experiences over three billion beats in a lifetime owing to the remarkable capacity of the pacemaker cells to induce synchronized contractions of the atrial and ventricular chambers. The Sinoatrial Node (SAN) spontaneously generates the electric impulse that propagates through the atria to the Atrioventricular Node (AVN) that establishes and coordinates the connection between the heart chambers. Block of impulse propagation at the AVN causes heart block (AV-block) and can result in significant adverse symptoms including syncope and cardiac death. Due to the poor regenerative capacity of the heart, the current standard of care is lifelong electronic pacemaker (EPM) implantation. 200,000 devices are implanted in North America each year, and although effective, they entail risks. EPMs lack autonomic responsiveness and have a relatively high complication rate (~16%) caused by thoracic trauma and lead infections. Pediatric patients are especially impacted by additional surgeries for EPM lead refitting. Replacing a damaged AVN with a human pluripotent stem cell (hPSC)-derived biological pacemaker (BioPM) is a promising solution to these caveats. Currently, no protocols exist to efficiently differentiate hPSCs into AVN-like pacemaker cells (AVNLPCs) that could act as a conduction bridge in AV-block patients. We generated a NKX2-5eGFP/wtTBX3tdTomato/wt hPSC reporter line to distinguish NKX2-5+TBX3+ (N+T+) AVNLPCs from NKX2-5+TBX3- (N+T-) ventricular-like



cardiomyocytes (VLCMs). Using this cell line, we established an AVNLPC differentiation protocol capable of generating N+T+ cells that express high levels of pacemaker and AVN markers, have typical pacemaker action potentials, and beating rates (65±5bpm) comparable to that of the human AVN. AVNLPCs seeded into engineered heart tissues have slower conduction velocities than VLCM-containing tissues. Importantly, we also showed that AVNLPCs can block the conduction of arrhythmias, closely resembling the conduction properties of the AVN. To assess the conduction properties in vivo, we are currently transplanting AVNLPCs into a guinea pig model. This work will advance the development of a BioPM that has the potential to improve upon the current standard of care for individuals with AV-block, particularly for pediatric patients.

Funding Source: Canada Foundation for Innovation Canadian Institutes of Health Research Ontario Graduate Scholarship

Keywords: Biological Pacemaker, Atrioventricular Node, Cardiac development

10:15 AM – 10:25 AM

REDIRECTING DIFFERENTIATION OF HUMAN STOMACH STEM CELLS TO PRODUCE ISLET-LIKE ORGANOIDS FOR DIABETES TREATMENT

Huang, Xiaofeng (Steve), Gu, Wei, Lan, Ying, Zhang, Jiaoyue and Zhou, Joe

Medicine, Weill Cornell Medicine, New York, NY, USA

Adult stem cells is a major resource that can be harnessed for therapeutic tissue repair. Gut stem cells are accessible by biopsy and expand robustly for many generations in culture. Insulin-producing cells can be induced in mouse gut, but it has not been possible to generate abundant and durable insulin-secreting cells from human gut tissues to evaluate their potential as a cell therapy for diabetes. We established a robust protocol to differentiate cultured human gastric stem cells (hGSCs) into pancreatic islet-like organoids containing gastric insulin-secreting (GINS) cells that resemble pancreatic beta-cells and able to reverse diabetes after transplantation. Primary hGSCs derived from stomach biopsies typically yielded 30-40 colonies that can be amplified to 10^9 cells within 2 months. After sequential activation of NGN3 and PDX1-MAFA, hGSCs transitioned through a SOX4-high endocrine and a GAL-high GINS precursor state before adopting the beta-cell fate at efficiencies approaching 70%. scRNA-seq showed that GINS organoids contained four endocrine cell types that resembled islet alpha-, beta-, delta-, and epsilon-cells. GINS organoids produced from multiple donors rapidly acquired glucose-stimulated insulin secretion (GSIS), 10-12 days post differentiation. GINS cells expressed key genes involved in beta-cell identity, metabolism, ion channel activity, and insulin secretion. To further assess their identity, we applied molecular scorecards of beta-cells (1,034 beta-cell-specific genes) and gastric cells (868 stomach-specific genes) benchmarked from published human scRNA-seq data. GINS cells scored high in beta-cell and low in gastric signature, similar to islet beta-cells. GINS organoids grafted under the renal capsule of immunodeficient mice lived for more than 6 months, contained abundant insulin+ cells, and exhibited GSIS. Transplanting GINS cells into STZ-induced diabetic mice rapidly reversed hyperglycemia and maintained glucose homeostasis for over 100 days until graft removal. No aberrant proliferative cells were detected in over 30 GINS grafts. In summary, this study established a promising approach to procuring autologous human insulin producers for diabetes treatment and further expands the already considerable therapeutic opportunities for gut stem cells.

Funding Source: This work was supported by awards from NIDDK (R01 DK106253, R01 DK13332, R01 DK125817 and UC4DK116280).

Keywords: Human gastric stem cells, Gastric insulin-secreting organoids, Diabetes

10:25 AM – 10:35 AM

REPROGRAMMING-DRIVEN DRUG DISCOVERY IDENTIFIES AN EFFICACIOUS REPURPOSING CANDIDATE FOR LEIGH SYNDROME

Zink, Annika[1], Henke, Marie-Thérèse[2], Wittich, Annika[3], Heiduschka, Sonja[1], Jerred, Caleb[1], Haferkamp, Undine[3], Brunetti, Dario[4], Cecchetto, Giulia[1], Klopstock, Thomas[5], Distelmaier, Felix[1], Carelli, Valerio[6], Pless, Ole[3], Schuelke, Markus[2] and Prigione, Alessandro[1]

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Leigh syndrome (LS) is a severe neurodevelopmental disorder affecting 1/36,000 newborns. It can be caused by mutations in the nuclear DNA (e.g. SURF1) or the mitochondrial DNA (e.g. MT-ATP6). Currently, there is no treatment available for LS patients. We previously demonstrated that neural progenitor cells (NPCs) derived from induced pluripotent stem cells (iPSCs) are an effective model for LS drug discovery. Using NPCs from three LS patients carrying the MT-ATP6 mutation m.9185T>C, we observed hyperpolarized mitochondrial membrane potential (ΔΨm) and aberrant calcium homeostasis. After screening a library of FDA-approved drugs, we discovered that phosphodiesterase type 5 inhibitors (PDE5i) ameliorated the ΔΨm and calcium defects. Here, we aimed to validate PDE5i as potential drugs to be repositioned for LS. Among PDE5i we focused on Sildenafil, due to its favorable safety profile in children, where it is used against pulmonary hypertension. We generated NPCs from nine LS patients carrying different MT-ATP6 mutations (m.9185T>C, m.8993T>G, m.8993T>C, and m.9176T>G) and seven healthy controls. We confirmed that mutant MT-ATP6 NPCs exhibited hyperpolarization of ΔΨm and that Sildenafil normalized it in a dose-dependent manner. No cellular toxicity was observed at the tested dosages. We next generated cortical organoids (COs) from mutant MT-ATP6 iPSCs and control lines. Mutant MT-ATP6 -COs were smaller, with defective neural progenitor organization, and exhibited aberrant calcium homeostasis. Short-term exposure to Sildenafil improved a defective PDE5 pathway in mutant MT-ATP6 COs; investigations into long-term treatment are ongoing. Currently, we are exploring the mechanism-of-action of Sildenafil in NPCs and COs using multi-omics analysis. Based on these encouraging in vitro observations, we initiated individualized compassionate treatments with Sildenafil in five LS patients carrying various MT-ATP6 mutations. All patients are tolerating the drug well and show significant clinical improvement. Taken together, the data suggest a potential use of Sildenafil as a repurposable drug for LS patients with MT-ATP6 defects.

Keywords: Mitochondria, Neurological diseases, Drug discovery

10:35 AM – 10:45 AM

PROOF-OF CONCEPT GENE THERAPY FOR MOST COMMON INHERITED RETINAL DEGENERATIONS USING RETINAL ORGANOIDS

Gonzalez-Cordero, Anai
Stem Cell Medicine, Children's Medical Research Institute, Sydney, Australia

The field of pluripotent stem cells and its derivatives miniaturised organ-like structures, organoids, has evolved rapidly in the past decade. Particularly, eye research has benefitted tremendously by landmark studies showing the potential of pluripotent stem cells to form retinal organoids that mimic the development of the retina. Modulation of culture conditions using biochemical and bioelectric cues promise to improve the maturation of organoids generating differentiation protocols optimised to improve organoids maturation. These studies have enabled modelling of human retinal diseases and testing of new therapies, such as gene therapies, to advance translational research. We hypothesise that improved retinal organoids can generate cells with increased potential and functionality for the testing of therapies, as they can be generated at large scale and adequately model the human disease. Here we present our recent improvements in culturing organoids and the modelling of two of the most common blinding inherited retinal degenerations. Usher2a, a form of retinitis pigmentosa affecting rod photoreceptor cells and Stargardt's disease affecting the cone photoreceptor cells in the human macula. In accordance, organoids mimicked these phenotypic characteristics. Furthermore, a comprehensive molecular characterisation using ScRNA seq demonstrated novel disease biomarkers. Inherited retinal degenerations are untreatable disorders with one FDA approved gene therapy for a specific form of Leber Congenital Amaurosis. Furthermore, standard adeno associated vectors (AAVs) gene therapy augmentation is not an option for Usher2a and Stargardt's diseases as they are caused by mutations in large genes. Here we developed novel proof-of-concept approaches to treat organoids. Gene therapy using dual AAVs systems and gene editing designed for each condition specifically was successfully in rescuing features of disease in vitro. The combination of stem cell technology, its derivative organoids together and state-of-the art gene therapy approaches offer a favourable therapeutic avenue to treat blindness.

Funding Source: NSW Health Luminesce Alliance ID: PPM1 K5116/RD274 Medical Research Future Fund (MRFF) Stem Cell Therapies Mission ID:MRF2008912

Keywords: retinal organoids, AAV gene therapy, inherited retinal degeneration

10:45 AM – 11:05 AM

RECONSTITUTION OF LUNG PROGENITOR COMPARTMENTS IN VIVO BY ENGRAFTMENT OF DIFFERENTIATED PLURIPOTENT STEM CELLS

Kotton, Darrell
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The derivation of lung progenitors as well as differentiated lung epithelia from pluripotent stem cells in culture enables access to a wide variety of cells for basic developmental studies, in vitro disease modeling, and potential therapeutic applications. We have previously utilized these cells as models for modeling genetic lung diseases, developing new cell based therapies, and understanding the mechanisms that regulate cell fate decisions in the developing lung. Here we present transplantation of these engineered cells via airway instillation into immunocompetent, lung-injured mice, successfully achieving durable, functional reconstitution in vivo of the airway and alveolar stem/progenitor compartments as well as the full diversity of their differentiated lung epithelial progeny.

Keywords: lung, regeneration, engraftment

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)

EMERGING MODEL SYSTEMS
9:30 AM – 11:10 AM
Room 254, Meeting Level 2

9:35 AM – 9:55 AM

ENDOGENOUS TENOCYTE ACTIVATION UNDERLIES THE REGENERATIVE CAPACITY OF ADULT ZEBRAFISH TENDON

Galloway, Jenna L., Tsai, Stephanie, Villasenor, Steffany, Shah, Rishita
Center for Regenerative Medicine, Department of Orthopedic Surgery, Harvard Stem Cell Institute, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA

Tendons are essential, frequently injured connective tissues that transmit forces from muscle to bone. Their unique highly ordered, matrix-rich structure is critical for proper function. While adult mammalian tendons heal after acute injuries, endogenous tendon cells, or tenocytes, fail to respond appropriately, resulting in the formation of disorganized fibrovascular scar tissue with impaired function and increased propensity for re-injury. Here, we show that unlike their mammalian counterparts, adult zebrafish tenocytes activate upon injury and fully regenerate the tendon. Using a full tear injury model in the adult zebrafish tendon, we define the hallmark stages and cellular basis of tendon regeneration through multiphoton imaging, lineage tracing, and transmission electron microscopy approaches. Remarkably, we observe that the zebrafish tendon can regenerate and restore normal collagen matrix ultrastructure by 6 months post-injury (mpi). We show that regeneration progresses in three main phases: inflammation within 1 day post-injury (dpi), proliferation and formation of a cellular bridge between the severed tendon ends at 3-5 dpi, and differentiation and matrix remodeling beginning from 5 dpi to 6 mpi. Foremost, we demonstrate that pre-existing scleraxisa (scxa)-expressing tenocytes are the main cellular source of regeneration. Ongoing research is centered on utilizing comparative approaches to identify divergent mechanisms driving tendon regeneration versus fibrosis at single cell resolution. Collectively, our work debuts the zebrafish tendon as one of the only reported adult tendon regenerative models, thereby positioning it as an invaluable comparative system that may be leveraged to elucidate mechanisms required for regeneration that may inspire new treatments in the clinic.

Keywords: tendon, regeneration, zebrafish

9:55 AM – 10:05 AM

ADULT TISSUE-DERIVED THYMIC EPITHELIAL CELL 3D ORGANOIDS RECAPITULATE ITS MORPHOLOGY, HETEROGENEITY, AND FUNCIONALITY

Lim, Sangho[1], Willemsen, Sam[1], van Son, Gijs[2], Eka Yanti, Ni Luh Wisma[1], Poort, Vera[2], Andersson-Rolf, Amanda[1], Korving, Jeroen[1], Begthel, Harry[1], Trabut, Laurianne[2], Clevers, Hans[1]
[1]*Hubrecht Institute, Utrecht, Netherlands,* [2]*Princess Maxima Center for Pediatric Oncology, Utrecht, Netherlands*

The thymus is an essential primary lymphoid organ for T cell development and coordinating entire immune system. In the thymus, thymic epithelial cells (TEC) directly orchestrate T cell development by positive or negative selection. Current studies on TEC regeneration, differentiation, and interaction with thymocytes are limited by insufficient ex vivo modelling of TEC including low expansion capacity. Here, we established long-term expandable 3D TEC organoid, which is Wnt-dependent, from adult thymus tissues. Single-cell analyses demonstrated that the clonal organoids have heterogeneity and differentiation potential towards multipotent progenitor cells. The organoids showed further differentiation to functional medullar- or cortical-TECs by Rank ligand and retinoic acid treatment. We then demonstrated that the TEC organoids can directly produce T cells in vitro, and in vivo after transplantation into athymic nude mice. The TEC organoids could be generated not only from mouse thymus but also from postnatal human thymus tissues. These data provide a novel TEC organoid to study TEC biology and offer a potential strategy for ex vivo T cell development modelling.

Keywords: Thymic epithelial cell, Organoid, T cell maturation

10:05 AM – 10:15 AM

SKELETAL STEM CELL CONTROLS THE CRANIOFACIAL BONE FATES

Takematsu, Eri, Lachmansingh, Rovin, Chan, Charles
Surgery, Stanford University, Palo Alto, CA, USA

Bone is a complex organ comprised of multiple cell types, including skeletal lineage, hematopoietic, and immune cells. These skeletal niche cells communicate with the skeletal stem cells (SSCs), the central hub for bone niche, to maintain homeostasis. The skeletal niche varies depending on the location of the bone; thus, the functional ability of SSCs also diverse in different areas of bones. Our recent study demonstrated that the genetic and functional activity of human fetal SSCs from different parts of bone are diverse, showing a variety of differentiation potentials and self-renewal capacities. While we found the diverse characteristics of SSCs in appendicular bones and vertebrae, we have yet to fully characterize the SSCs in the cranium. In this study, we characterized immunophenotypically isolated SSCs in different cranium areas and found that features of cranial bones might be controlled at the stem cell level. FACS analysis of SSCs and their progenitor cells using previously determined markers demonstrated the significantly higher numbers of progenitor cells in all parts of the cranium compared to the femur in P3 and P5 mice, suggesting that cranial SSC fate may be determined earlier time point than the femur. The functional assay showed that nasal-derived SSCs transplanted in kidney capsules formed cartilage. In contrast, occipital-bone-derived SSCs form cortical bone, demonstrating diverse functional activities of SSCs from different cranium areas. Our microarray data also revealed genes associated with the neural cranium, differentially expressed in different areas of cranial bones. In the presentation, I will further examine the fate of SSCs in situ using SSC reporter mice to show how SSCs in different areas of the cranium contribute to bone/cartilage formation. Overall, this study demonstrated that facial bone characteristics are controlled at the stem cell level, suggesting the importance of a stem-cell centric approach for facial bone regeneration/reconstitution.

Keywords: Skeletal stem cell, Craniofacial bone, Diversity

10:15 AM – 10:25 AM

A ROUNDABOUT RECEPTOR REGULATES APPROPRIATE SPATIAL DIFFERENTIATION OF STEM CELLS IN PLANARIANS

Wang, KuangTse[1], Chen, Yu-Chia[2], Adler, Carolyn[1]
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The goal of regenerative medicine is to restore the function of complex organs, which requires accurate anatomical position and tissue composition. The regulation of cell differentiation is an essential component of replacing individual cell types. Pla-

narians are an excellent system for studying organ regeneration because they can regenerate every organ, due to an abundant population of adult pluripotent stem cells. Upon injuries, these stem cells sense and drive differentiation to replenish missing body parts. However, it is unclear what molecular inputs link missing tissues to the proper spatiotemporal differentiation of stem cells. To address these questions, we focus on the role of stem cells in regenerating the pharynx, a feeding organ composed of neurons, muscle, and epithelial cells. Previous research has shown that the roundabout receptor RoboA, best known for its roles in neural patterning, limits pharynx number and position in planarians. Taking advantage of precise markers for pharynx-specific tissues, we find that RoboA(RNAi) animals induce ectopic pharynx neurons inside the brain, where they otherwise never appear. By perturbing stem cells with RNAi or radiation, we find that the induction of ectopic pharynx neurons relies on stem cells expressing the conserved Forkhead transcription factor FoxA, which are required for normal pharynx regeneration. The dysregulation of these cells outside of their normal anatomical domain suggests that RoboA restricts stem cell activity by suppressing the activation of FoxA-dependent differentiation. Together, our results reveal the coordination of extracellular signaling via the RoboA receptor with the differentiation of stem cells.

Funding Source: National Institutes of Health grant R01GM139933

Keywords: Planarian, Adult stem cells, Cell differentiation

10:25 AM – 10:35 AM

SCALABLE, OPTICALLY-RESPONSIVE HUMAN NEUROMUSCULAR JUNCTION MODEL REVEALS CONVERGENT MECHANISMS OF SYNAPTIC DYSFUNCTION IN FAMILIAL ALS

Miranda, Helen C.[1], Chen, Daniel[1], Freitas Brenha, Bianca[1], Philippidou, Polyxeni[2], Schaffer, Ashleigh[1]
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Neuromuscular junctions (NMJs) are specialized synapses that mediate the communication between motor neurons and skeletal muscles and are essential for movement. The degeneration of this system can lead to symptoms observed in neuromuscular and motor neuron diseases. Studying these synapses and their degeneration has proven challenging. Prior NMJ studies heavily relied upon the use of mouse, chick, or isolated primary human cells; which have demonstrated limited fidelity for disease modeling. To enable the study of NMJ dysfunction and model genetic diseases, we, and others, have developed methods to generate human NMJs from pluripotent stem cells (PSCs), embryonic stem cells and induced pluripotent stem cells. However, published studies have highlighted limitations associated with these complex in vitro NMJ models, including time, variability and limited scalability. Thus, we have developed a faster and more reproducible protocol to efficiently generate human PSC-derived NMJs that are functional, optically responsive and scalable, enabling its use for disease modeling. In this study, we developed a robust PSC-derived motor neurons and skeletal muscle co-culture method, which spontaneously and reproducibly forms human NMJs. To our knowledge, we are the first group to apply a multiwell-multielectrode array (MEA) to quantify the activity of PSC-derived skeletal muscles and to measure the electrophysiological activity of functional human PSC-derived NMJs. We further leveraged our method to morphologically and functionally assess NMJs from the familial amyotrophic lateral sclerosis (fALS) iPSCs, C9orf72 hexanucleotide (G4C2)n repeat expansion (HRE), SOD1A5V, and TDP43G298S. We observed a significant decrease in the numbers and activity of PSC-derived NMJs developed from the different mutant ALS lines compared to their respective controls. Our newly developed method provides a platform for the systematic investigation of NMJs neurodegeneration, embryonic development, homeostasis and diseases, such as motor neuron and neuromuscular disorders. Our faster, reproducible and scalable method is the first suitable for high-throughput screening. We demonstrate that functionally active PSC-derived NMJs can efficiently model specific NMJ dysfunction innate to ALS with high sensitivity.

Funding Source: 1-K01-NS116119-01 and 1-R01-NS121374-01

Keywords: neuromuscular junction, amyotrophic lateral sclerosis, induced pluripotent stem cells

10:35 AM – 10:45 AM

RECONSTITUTION OF HUMAN ADRENOCORTICAL SPECIFICATION AND STEROIDOGENESIS

Mayama, Michinori[1], Cheng, Keren[1], Strauss III, Jerome[2], Sasaki, Kotaro[1]
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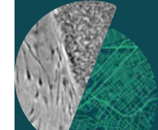
The adrenal cortex and gonads are the two major endocrine hubs that participate in the hormonal regulation of vital aspects of body homeostasis. Accordingly, their developmental aberrancies drive various congenital and adult-onset diseases. Lineage tracing studies in mice reveal that the adrenal cortex and gonads originate from a common progenitor, the adrenogonadal primordium. However, the specification pathways of the adrenal cortex and gonads and their lineage relationship remain poorly understood in humans. Using single cell transcriptomics and histologic profiling, we found that human adrenocortical lineage originates in a temporally and spatially distinct fashion from the gonadal lineage, arising earlier and more anteriorly within the coelomic epithelium. This unique structure that exclusively generates the adrenocortical lineage was named as the adrenogenic coelomic epithelium. The adrenogenic coelomic epithelium subsequently forms adrenal primordium via an epithelial-to-mesenchymal-like transition, which then progresses into the steroidogenic fetal zone (FZ) via both direct route and indirect routes through the definitive zone (DZ). These in vivo study lays the foundation for understanding the molecular pathology of human gonadal and adrenal disorders. Based on these findings in vivo, we have recently developed a first-of-its-kind induction platform of human fetal adrenal organoids from human induced pluripotent stem cells. This stepwise and directed induction generates all major cellular components of human fetal adrenal glands in ACTH-independent manner, including DZ and FZ-like cells and RSPO3-expressing capsule-like cells, as evidenced by histomorphologic, ultrastructural and transcriptomic features. The adrenal organoids produced Δ5 steroids, similar to human fetal adrenal cortex, which was augmented by ACTH/PKA signaling. Finally, we found that NR5A1 promotes survival and steroidogenesis of the human fetal adrenal organoids. The induction platform will serve as a critical foundation for understanding human adrenal development and steroidogenesis and will also serve as a stepping stone for eventual cell replacement therapy for patients with adrenocortical dysfunction.

Keywords: Human adrenal development, Adrenocortical specification, Adrenal organoid



10:45 AM – 11:05 AM

FACILITATORS AND BRAKES ON SUCCESSFUL NEUROREPAIR: A TURQUOISE KILLIFISH PERSPECTIVE

Arckens, Lutgarde, Van houcke, Jolien, Zandecki, Caroline, Mariën, Valerie, Rajagopal, Ayana
Department of Biology, KU Leuven, Belgium

Aging is the main risk factor to develop neurodegenerative diseases as it negatively impacts brain plasticity. The aging mammalian brain displays progressive limited regenerative abilities, and consequently recovery after neuron loss is extremely restricted. Yet, popular research models fail to recapitulate mammalian aging hallmarks or have an impractically long lifespan. In contrast, the African turquoise killifish (N. furzeri) is short-lived and ages extremely fast. We recently described that in young killifish the forebrain heals upon traumatic brain injury (TBI) targeted at the killifish dorsal pallium. On the other hand, the aged killifish seemed to have adopted several aspects of the restricted neurorepair process in mammals, i.e. chronic inflammation and glial scarring. In young killifish, restorative progenitor proliferation was not supported by the radial glia (RG), but by atypical non-glial progenitors (NGP). These NGPs become exhausted with age, while RGs become more proliferative. Single cell RNA-Seq confirmed that most RGs in the young adult killifish telencephalon are quiescent, but a specific RG type becomes proliferative with old age. We discovered four types of RGs, including two spatially distinct astroglia, and two NGP types with both gliogenic and neurogenic potential. Via proteomics analysis, we unveiled pathways underlying the poor neurorepair capacity in the aged killifish. By modulating these pathways via compound administration, we were able to restore youthful progenitor responses, boosting the neuroregenerative capacity in aged killifish. We predict these results will fuel the development of new therapies to install successful neurogeneration in the aged injured or diseased mammalian brain.

Keywords: brain, repair, aging

CONCURRENT TRACK SESSIONS

1:15 PM – 2:55 PM

TRACK: ETHICS, POLICY AND STANDARDS (EPS)

GLOBAL POLICY INITIATIVES
1:15 PM – 2:55 PM
Room 258, Meeting Level 2

1:20 PM – 1:45 PM

CHALLENGES IN DEFINING GLOBALLY RELEVANT GUIDELINES FOR STEM CELL AND HUMAN EMBRYO RESEARCH

Rossant, Janet
The Gairdner Foundation, Canada

Regulatory issues surrounding human embryo and stem cell research continue to require constant vigilance and discussion on the part of scientists, regulators, ethicists, patient groups and other stakeholders. ISSCR can play a special role in these discussions because of its global reach. The ISSCR Stem Cell Guidelines have gained wide recognition as a useful blueprint to help local jurisdictions develop their own specific regulations dependent on local laws and societal norms. However, there are very few completely agreed upon international norms. In attempting to provide overarching global recommendations, we must be careful to be open to diverse cultural viewpoints and be inclusive in our discussions and recommendations going forward.

1:45 PM - 2:00 PM

Gadbois, Ellen
National Institutes of Health, USA

Since FY1996, NIH has been prohibited from funding research involving the creation of human embryos for research purposes or research in which human embryos are destroyed (including for the derivation of human embryonic stem cells). That prohibition is incorporated into the NIH Grants Policy Statement at Section 4.2.5. and the NIH Guidelines for Human Stem Cell Research.

2:00 PM - 2:15 PM

AUSTRALIAN STEM CELL RESEARCHERS PUBLIC ENGAGEMENT: CHALLENGES AND WAYS FORWARD

Lopes McInnes, Edilene[1], Ankeny, Rachel[2], Leach, Joan[3] and Santos, Dan[3]
[1]School of Humanities, The University of Adelaide, [2]History, University of Adelaide, Australia, [3]Australian National Centre for the Public Awareness of Science, Australian National University, Canberra, Australia

This work presents findings from the project “Enabling Openness in Australian stem cell Research (EOAR)”, an interdisciplinary research cluster involving stem cell researchers, bioethicists, and social and legal researchers interested in building trust in stem cell-based research and therapies. Australian embryonic stem cell research history has been marked by reviews that shaped legislation. In 1998, following the media attention and widespread outcry from the cloning of Dolly, the Australian Health Ethics Committee produced a report recommending the prohibition of human cloning and regulation of human embryo research. After that, three reviews were conducted and resulted in the current Australian legislation that prohibits human cloning, allows specific uses for excess human embryos and SCNT under certain circumstances, creation of embryos other than by fertilisation for research purposes under a licence from the Embryo Research Licence Committee. These events have shaped the field of embryonic stem cell research and its public perception. Our research results relate to interviews with 35 stem cell researchers and manufacturers in Australia about their engagement with the public, among other topics. The findings show that, overall, researcher public engagement is ad hoc and related to promoting specific project results to limited groups (mostly patient groups). In the rare instances where there is regular engagement, this is limited to educating the public about specific projects. This can have problematic consequences for re-engaging in a debate about the use of embryonic stem cell research, including the re-examination of the 14-day rule, as the public perception of stem cell research is likely not to have significantly shifted due to the lack of awareness of how the field has moved forward in the recent years. The EOAR project proposes an innovative way forward for this debate. It will involve diverse stakeholders (patients, community organisations, researchers, manufacturers, clinicians, and policy influencers) to identify the main factors necessary to build trust in stem cell research in Australia. The project's next step is to consult with other types of stakeholders by using a mix of engagement strategies.

Funding Source: National Health and Medical Research Council (NHMRC), Medical Research Future Fund (MRFF), Stem Cell Therapies Mission

Keywords: stem cell research, Public engagement, Australia

2:15 PM – 2:55 PM

Polo, Jose
The University of Adelaide, Australia

Embryo models have emerged as invaluable tools for understanding early human development and studying genetic disorders. However, conducting research involving human embryos requires careful navigation of ethical and legal frameworks. This talk aims to explore the challenges and opportunities in adapting to the policies governing embryo models research in Australia. It will delve into the current regulatory landscape, including the National Health and Medical Research Council guidelines, and discuss the considerations researchers face when engaging in this field. Furthermore, the talk will highlight the importance of proactive collaboration between scientists, policymakers, and society to ensure responsible and ethically sound practices in embryo models research.

TRACK: CELLULAR IDENTIY (CI)

GUIDED DIFFERENTIATION OF IPSCS FOR CLINICAL APPLICATIONS

Sponsored by: Stem Cell Network

1:15 PM – 2:55 PM
Room 257, Meeting Level 2

1:20 PM – 1:40 PM

GUIDING IPSC-BASED T CELL DIFFERENTIATION THROUGH POSITIVE SELECTION IN THE ABSENCE OF TCR AND HLA EXPRESSION

Crooks, Gay M., Chang, Patrick, Yoo, Sang Pil
Department of Pathology & Lab Medicine, University of California, Los Angeles, CA, USA

The generation of therapeutic T cells from allogeneic pluripotent stem cells (PSCs) offers several potential benefits over the current use of autologous T cells harvested from the blood. Most obviously, a universal source of PSC-derived T cells could avoid the logistical hurdles and costs associated with creating individual products for each patient. More significantly, the self-renewing capacity of PSCs provides unique advantages over primary cells for complex gene modifications, as master cell banks can be produced from validated clones that possess multiple on-target modifications but lack off-target genotoxicity, thus providing an off-the-shelf source of functionally enhanced and predictable T cell products. However, genetic engineering of PSCs also creates unique biological and manufacturing challenges, as certain modifications in gene expression can disrupt the complex stages of hematopoietic commitment and T cell differentiation required to create mature functional T cells. A particularly important example of this challenge is that expression of both endogenous T cell receptor (TCR) genes and HLA molecules must be absent in the final T cell product to avoid the allogeneic consequences of GVHD and graft rejection respectively. However normal T cell development initiated from uncommitted hematopoietic progenitors in the thymus proceeds through positive selection, a process that requires interaction of the diverse TCR repertoire produced by DNA recombination in T cell precursors, with HLA-peptide complexes that are usually provided by the thymic microenvironment. This presentation will discuss some of the strategies that we have developed to meet the clinical imperative that requires removal of the very genetic machinery that is critical for T cell development and maturation from PSCs.

Keywords: T cells, immunotherapy, iPSCs

1:40 PM – 1:50 PM

TRANSIENT NOTCH ACTIVATION ENABLES CONVERSION OF PSC-DERIVED CARDIOMYOCYTES TOWARD A PURKINJE-LIKE FATE

Dubois, Nicole[1], Dariolli, Rafael[2], Gonzalez, David[1], Moyett, Julia[3] and Sobie, Eric[2]
[1]Cell Development and Regeneration, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Pharmacological Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Medical School, Duke University, Durham, NC, USA

Cardiac Purkinje Fiber (PF) cells coordinate contraction and play a key role in ventricular arrhythmias. While many cardiac cell types can be generated from human pluripotent stem cells (hPSCs), methods to generate PFs are limited, hampering our understanding of conduction system defects. In order to identify pathways involved in PF formation, we analyzed publicly available single-cell RNA sequencing data from E16.5 murine embryonic hearts and performed differential expression and GO/KEGG pathway analysis between PFs and trabecular myocardial cells. This identified several enriched genes, processes, and signaling pathways involved in cardiac conduction, including Notch signaling. To test whether Notch activation could convert hPSC-derived cardiomyocytes (hPSC-CMs) to PFs, we overexpressed Notch in hPSC-CMs using a tamoxifen inducible hPSC line. Following Notch activation, cells took on an elongated morphology and displayed altered electrophysiological properties including increases in conduction velocity, spike slope, and action potential duration (APD), characteristic features of PFs. RNA sequencing demonstrated that Notch-activated cells undergo a transcriptome shift, which included upregulation of key PF marker genes involved in fast conduction such as SCN5A, HCN4 and ID2 and downregulation of genes involved in contractile maturation. GO/KEGG analysis demonstrated an increase in processes regulating heart rate, cardiac conduction, and adrenergic signaling suggesting conversion toward a PF-like fate. We next modified existing in silico models of hPSC-CMs using our transcriptomic data and modeled the effect of several drugs on AP and calcium transient waveforms. Our models predicted that PSC-PFs responded more strongly to dofetilide and amiodarone, while hPSC-CMs were more sensitive to treatment with nifedipine. We validated these findings in vitro, demonstrating that our cell-specific hPSC model can be used to better understand human PF physiology and its relevance to disease.

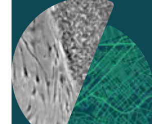
Keywords: purkinje, arrhythmia, Notch,, ventricular conduction system, Computational modeling

1:50 PM – 2:00 PM

IDENTIFICATION OF CELL ADHESION MOLECULE REGULATING ENGRAFTMENT OF HIPSC-DERIVED CARDIOMYOCYTE TRANSPLANTATION

Fujiwara, Yuya[1], Naka, Yuki[2], Noguchi, Mao[3], Tanaka, Aya[3], Sasaki, Masako[2], Nishimoto, Tomoyuki[3], Imahashi, Kenichi[4] and Yoshida, Yoshinori[1]
[1]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan, [2]Center for iPS Cell Research and Application, Kyoto University, Fujisawa City, Japan, [3]iCM Project, Orizuru Theraputics, Inc., Fujisawa City, Japan, [4]Research T-CiRA Discovery and Innovation, Takeda Pharmaceutical Company, Fujisawa City, Japan

A large number of deaths were caused by ischemic heart disease worldwide. Due to the limited proliferation capacity of adult cardiomyocytes, heart transplantation is the only way to treat severe heart failure. Remusculalization using human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CM) is one



of the strategies for repairing an infarcted heart. While many cells were needed to make up for lost cardiomyocytes, the low engraftment rate of hiPSC-CMs is a major issue. In this study, we identified cell adhesion molecules that regulate the engraftment rate of hiPSC-CMs into hearts to overcome this issue. First, we confirmed iPSC-CMs generated by embryoid body (EB) based differentiation method have higher engraftment rate than those using monolayer based differentiation method. Since there was no difference in anoikis sensitivity between hiPSC-CMs generated by these method, we hypothesized there were key cell adhesion molecules regulating cell engraftment. Using RNA-seq analysis, we have identified nine cell adhesion molecule genes (Engraftment-related Genes: EGENs) that showed higher expression in hiPSC-CMs generated by EB based differentiation method. To evaluate engraftment ability in vitro, we developed a cell attachment assay. This assay revealed that knockdown and over-expression of EGEN1 changed the attachment ability of hiPSC-CMs. Moreover we confirmed that EGEN1 localized in cell adhesion region in hiPSC-CMs. Consistent with the results of the cell attachment assay, EGEN1 knockdown hiPSC-CMs reduced engraftment into healthy nude rat hearts. These results suggest that EGEN1 is a key cell adhesion molecule to engraft hiPSC-CMs into the heart.

Keywords: Regenerative medicine, Cardiomyocytes, Cell adhesion molecules

2:00 PM – 2:10 PM

SINGLE-CELL LEVEL COMPARISON OF HUMAN INNER EAR ORGANOIDS WITH THE HUMAN COCHLEA AND VESTIBULAR ORGANS

van der Valk, Wouter[1,2,3], van Beelen, Edward[1], Steinhart, Matthew[3], Nist-Lund, Carl[3], de Groot, John[1], van Benthem, Peter Paul[1], Koehler, Karl[3] and Locher, Heiko[1]
[1]Department of Otorhinolaryngology and Head & Neck Surgery, Leiden University Medical Center, Leiden, Netherlands, [2]Department of Neurobiology, Leiden University, Medical Center, Leiden, Netherlands, [3]Department of Otolaryngology, Boston Children's Hospital, Boston, MA, USA

Genetic disorders affecting the inner ear are common congenital abnormalities that cause hearing loss and balance problems. To accurately model these conditions, tissue culture models of the inner ear should include a combination of both sensory and nonsensory cells. A promising model lies in the multilineage human pluripotent stem cell-derived inner ear organoids. Here, we showed the robustness of the protocol over multiple hiPSC lines and analyzed the cell diversity of these inner ear organoids using single-cell transcriptomics, electron microscopy, and immunohistochemistry. Our findings indicate the presence of on-target inner ear-related periotic mesenchymal cells and off-target cells such as skeletal myocytes, vascular endothelial cells, and ependymal cells. By creating a single-cell transcriptomic atlas of the human fetal and adult inner ear, we discovered that the inner ear organoids contain epithelium with cochlear and vestibular identities similar to the developing human inner ear. Furthermore, the organoids contained immature type I and type II vestibular hair cells. We confirmed the expression of genes and proteins related to sensorineural hearing loss in these putative inner ear cell types. Further analysis of cell-cell communication showed interactions between the endothelial cells and developing sensory epithelium, which could be confirmed using the human fetal inner ear data. This study unified single-cell mapping of human inner ear organoids with human inner ear development, by which we explored the potential of the organoid model in investigating genetic inner ear diseases and the development of the human inner ear.

Funding Source: This work was supported by the Novo Nordisk Foundation (grant NNF21CC0073729), the Hoogenboom-Beckfonds foundation, Erasmus+, ZonMw, and the NIH (grants R01AR075018, R01DC017461, R03DC015624).

Keywords: Human inner ear organoids, Human fetal and adult inner ear, Single-cell

2:10 PM – 2:20 PM

GENERATION OF THYMUS-SEEDING PROGENITOR T CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS BY CHEMICALLY DEFINED ENDOTHELIAL-TO-HEMATOPOIETIC TRANSITION CULTURE

Iriguchi, Shoichi[1], Miyake, Yasuyuki[1], Kassai, Yoshiaki[2] and Kaneko, Shin[1]
[1]Center for iPS Cell Research and Application (CiRA), Kyoto, Japan, [2]T-CiRA Discovery and Innovation, Takeda Pharmaceutical Company, Limited, Fujisawa, Japan

Development of differentiation cultures to generate a large number of functional thymus-seeding progenitor T cells (TSPs) from pluripotent stem cells (PSCs) would enable new therapeutics including accelerated T-cell recovery after hematopoietic stem cell transplantation. Although some groups including our group have reported generation of CD4+CD8+ double-positive (DP) immature thymocytes and mature T cells from PSCs in vitro, successful generation of TSPs from PSCs remains challenging. In this study, we aimed to develop differentiation methods to generate TSPs that were able to home to the thymus and generate mature polyclonal T cells from induced PSCs (iPSCs). Single-cell and bulk RNA sequence analysis revealed that iPSC-derived hematopoietic progenitors after 14 days differentiation and their derivatives cultured additional 14 days in the presence of a NOTCH ligand, delta-like 4 (DLL4), did not express known stem cell-related genes, such as HOXA9, and MEIS1. In addition, single cell transcriptome analysis at earlier differentiation days (Days 7 and 11) where endothelial-to-hematopoietic transition (EHT) occurs identified that hemogenic endothelial cells (HECs) and HPCs at day 7 expressed HOXA genes and NOTCH target genes including HES and GATA3 but lost its expressions by day 11 after differentiation. We thus hypothesized that loss of NOTCH signaling during EHT resulted in the loss of in vivo engraftment activity. Through the optimization of culture conditions, we found that HECs gave rise to CD34HiCD7+/- progenitor T cells expressing HOXA9 and MEIS1 when cultured in the medium containing recombinant human albumin, hematopoietic cytokines and other additives on immobilized DLL4 and retronectin-coated plates. When transplanted to immunodeficient mice, they were able to engraft thymus and differentiated into CD4-single positive (CD4SP) and CD8-single positive (CD8SP) cells via DP cell intermediates 8 weeks after infusion. Matured CD4SP and CD8SP T cells were also present in the blood, liver, and spleen of the recipients. Flowcytometric, single cell-VDJ and RNA sequencing analysis demonstrated that those cells possessed diverse TCR repertoire exhibiting CD62L+CD45RA+CCR7+ naïve phenotype. Collectively, these finding support the notion that we succeed to generate functional TSPs from iPSCs.

Funding Source: This research is supported by a joint collaboration between CiRA and Takeda Pharmaceutical Company Limited.

Keywords: T cells, iPS Cells, Cell Therapy

2:20 PM – 2:30 PM

ENGINEERED STEM CELLS FOR IMMUNE EVASION IN A TYPE 1 DIABETES MODEL

Alonso-Guallart, Paula[1], Pizzato, Hannah[2], Woods, James[1], Ho, Lilian[1], Hazzard, Iyawnna[1], Chukwukere, Uche[1], Zimmer, Matthew[1], Butt, Annie[1], Dale, Nathan[1], Cipriani, Filippo[1], Ahmed, Simi[1], Wesely, Josephine[1], Johannesson, Bjarki[1], Bhattacharya, Deepta[2] and Monsma Jr., Frederick[1]
[1]The New York Stem Cell Foundation Research Institute, New York, NY, USA, [2]Department of Immunobiology, University of Arizona, College of Medicine, Tucson, AZ, USA

Type 1 diabetes (T1D) is an autoimmune disease that affects over 8 million people worldwide. For the last 100 years, insulin administration has been the only treatment available. While cell replacement therapies based on pancreas transplantation or encapsulation of donor islets have been carried out, these approaches present major clinical limitations. Currently, alternative cell replacement therapies are being explored utilizing beta cells from directed differentiation of pluripotent stem cells (PSCs). However, scaling up beta cell production, and prevention of allo-graft rejection and recurring autoimmunity without systemic immunosuppression remain challenging. We have generated a high-throughput, automated platform to differentiate PSCs into pancreatic organoids containing functional beta cells that express NKX6.1 and c-peptide. To address immune rejection, we have genome-edited PSCs to eliminate or overexpress a set of proteins associated with several immunological pathways. To this end, we have previously assessed through in-vivo teratoma assays the optimal combination of factors that could facilitate immune evasion. Modified human PSCs survived in wild type (WT) mice for at least 11 weeks compared to unedited PSCs that were rejected 2-3 weeks after transplantation. Genetically modified PSCs were successfully differentiated into pancreatic organoids expressing beta-cell signature markers at the end of the differentiation. Overexpression of immunomodulatory proteins was maintained throughout the differentiation and the organoids showed functionality in vitro as evidenced by glucose-stimulated insulin secretion tests. When these cells were transplanted subcutaneously into immunodeficient (NSG) mice, human c-peptide secretion was detected in mouse serum, demonstrating in-vivo functionality of the edited beta cells in the absence of immune onslaught. In conclusion, we have generated genome-edited PSCs that survived in WT mice for at least 11 weeks; they also successfully differentiated into pancreatic organoids containing functional beta cells responsive to glucose stimuli in both in-vitro and in-vivo settings. We are currently pursuing studies to evaluate survival of our immune-edited pancreatic organoids in both allo- and auto-immune contexts.

Funding Source: JDRF, Lisa Dean Moseley Foundation

Keywords: Immune evasion, Type 1 diabetes, Pancreatic organoids

2:30 PM – 2:50 PM

Abstract not available at time of printing

Studer, Lorenz
Memorial Sloan Kettering Cancer Center, New York, NY, USA

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)

ADVANCING IN VITRO MODELS
1:15 PM – 2:55 PM
Room 253, Meeting Level 2

1:20 PM – 1:40 PM

DRUG DISCOVERY FOR WOLFRAM SYNDROME USING HESCS-DERIVED SC-BETA CELLS AND CEREBRAL ORGANOIDS

Li, Weida
Tongji University, China

Wolfram Syndrome (WS) is an autosomal recessive genetic disorder, and the main clinical features are manifested by insulin-dependent diabetes mellitus and neurodegeneration. The average life span of WS patients is 30 years and the major cause is WFS1 loss-of-function (LOF). However, there is no effective clinical treatment due to the lack of deep understanding of the pathogenic mechanism, which is limited by scarcity of proper human models. Therefore, we used hESCs-derived SC-β cells and cerebral organoids to model WS and explore therapeutic molecules for this disease. On one hand, with WFS1 deficient SC-β cells, we found that integrated stress response (ISR) with elevated stress granule formation contributes to delayed SC-β cell differentiation and dysfunction. Accordingly, treatment with ISRIB (ISR inhibitor) inhibits the formation of stress granules, mitigates delayed differentiation and dysfunction of SC-β cells, and finally improves glycemic control in vivo in mice with WFS1 specific depletion in islet β cells. On the other hand, we used the WFS1 deficient cerebral organoids to model WS neurodegeneration, and found neural WFS1 deficiency causes neuronal loss, impaired synapse formation and function associated with reduced astrocytes. Our results demonstrated that Riluzole treatment rescues disrupted synapse formation and function by restoring glutamate transporter (EAAT2) expression in WFS1 deficient astrocytes and alleviating glutamate toxicity to neurons. More importantly, Riluzole treatment rescues the depressive-like behavior and spatial memory deficiency in WFS1 neural conditional-knockout mice. Taken together, based on drug discovery with hESCs-derived human tissues, our study sheds light on pathogenesis for WS, and provides potential therapeutic molecules for this life-threatening disease.

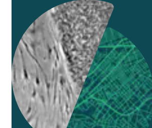
Keywords: SC-β cell, cerebral organoids, wolfram syndrome

1:40 PM – 1:50 PM

IN VITRO GENERATION OF MOUSE EMBRYOGENESIS FOUNDER CELLS

Li, Huanhuan[1], Wu, Jinyi[1], Chang, litao[1], Bates, Lawrence[2], Huang, Jiahui[1], Guan, Wei[1], Stuart, Hannah[2], Guo, Mingyue[1], Huang, Boyan[1], Zhang, Man[1], Min, Mingwei[1], Wu, Guangming[1], Hutchins, Andrew [3]and Silva, José[1]
[1]Basic Research Department, Guangzhou Laboratory, Guangzhou Laboratory, China, [2]University of Cambridge, Wellcome – MRC Cambridge Stem Cell Institute, Cambridge, UK, [3]Department of Biology, Southern University of Science and Technology, Shenzhen, China

Generating cells with molecular features of early embryo cells is an aim with fundamental biological and medical relevance. Here we communicate the in vitro generation of mouse totipotent 8-16 cell-like embryo stage cells via manipulation of signaling pathways. We termed these Embryogenesis Founder Cells (EFCs). EFCs are molecularly distinct from embryonic stem cells



and cluster instead with totipotent 8-16-cell stage embryo cells. Strikingly, EFCs are competent to robustly and reproducibly generate advanced embryo-like structures in vitro, resembling morphologically and molecularly in vivo post-implantation mouse embryos up to E7.75 stages. When introduced into morulae, EFCs contributed to all early embryonic and extraembryonic lineages. In addition, totipotent chimerism was unbiased and the molecular signature of the integrating cells was indistinguishable from control embryo cells. Our findings pave the way to the harnessing of totipotency and to the creation of mouse advanced/post gastrulation in vitro synthetic embryos from one single cell population.

Keywords: Totipotency, Synthetic embryos, In vitro mouse embryo model

1:50 PM – 2:00 PM

GENERATION OF "DON'T EAT ME" RECEPTOR KNOCKOUT MACROPHAGES FOR THE TREATMENT OF SOLID TUMORS

Smith, Portia[1], Sedzro, Divine[1], Emmen, Isla[1], Majumder, Aditi[1], Juang, Terry[2], Ayuso, Jose[2], Beebe, David[2] and Slukvin, Igor[1]
[1]Wisconsin National Primate Research Center, University of Wisconsin, Madison, WI, USA, [2]Department of Biomedical Engineering, University of Wisconsin, Madison, WI, USA

Albeit the remarkable success of treating blood cancers with chimeric antigen receptor (CAR) T cell therapy, solid tumor cancers largely remain resistant to current immunotherapies. Macrophages within the tumor microenvironment (TME) are often polarized into pathogenic tumor-associated macrophages (TAMs), implicated in the inhibition of cytotoxic lymphocytes and blockade of macrophage-driven antitumor functions. Although TAMs are often highly involved in growth and survival of the tumor, macrophages have unique access to the TME, making them an attractive candidate for solid tumor immunotherapy. Many tumors over-express the "don't eat me" receptors CD47 and CD24, recognized by macrophage receptors SIRPa and Siglec10, respectively; these receptors block macrophage-driven phagocytosis of target cells by inhibiting pro-phagocytic signaling within the cell. To overcome this obstacle, we hypothesized knocking out the "don't eat me" receptors SIRPa and Siglec10 in human induced pluripotent stem cells (iPSCs) to generate macrophages would antitumor functions against solid tumor cancers. We have found through CRISPR/Cas9 genetic engineering that SIRPa-knockout (KO) iPSC-Macrophages (iMacs) have significantly increased antibody-dependent phagocytosis and cytotoxicity against SKOV-3 ovarian cancer, MCF7 breast cancer, and WM266-4 melanoma cancer cell lines than WT iMacs in vitro. Additionally, we have produced Siglec10-KO and double SIRPa-Siglec10-KO iPSC lines to generate antitumorigenic iMacs. Against SKOV-3, SIRPa-Siglec10-KO iMacs show significantly higher ADCC and suppression of tumor growth than WT iMacs in vitro. Using an NSG mouse model, luciferase-expressing human SKOV-3 is engrafted in the peritoneal cavity or subcutaneously to recapitulate solid tumor cancer. This model is currently being assessed for the antitumorigenic properties of SIRPa-KO iMacs + anti-HER2 monoclonal antibody. These ongoing in vivo experiments will provide pertinent evidence for the clinical use of "don't eat me" knockout iPSC-derived macrophages. In conclusion, we have found that SIRPa-KO and Siglec10-KO human iPSCs produce functional macrophages with superior capacity for antibody-dependent antitumorigenic activities against solid tumor cancers and have potential for clinical application.

Keywords: solid tumor, immunotherapy, macrophage

2:10 PM – 2:20 PM

AN EPIGENETIC BARRIER SETS THE TIMING OF HUMAN NEURONAL MATURATION

Ciceri, Gabriele[1], Cho, Hyunwoo[2], Kshirsagar, Meghana[2], Baggiolini, Arianna[3], Aromolaran, Kelly[4], Walsh, Ryan[3], Goldstein, Peter[4], Koche, Richard[5], Leslie, Christina[2] and Studer, Lorenz[3]
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The pace of human brain development is highly protracted compared to most other species. The maturation of cortical neurons is particularly slow, extending over months to years to reach adult- like functions. Remarkably, such protracted timing is retained in cortical neurons derived from human pluripotent stem cell (hPSC) during in vitro differentiation or upon transplantation into the murine brain in vivo. Those findings suggest the presence of a cell intrinsic clock that sets the pace of neuronal maturation, though the molecular nature of such a clock has remained elusive. Here, we identify an epigenetic developmental program which sets the timing of human neuronal maturation. First, we developed a human PSC-based approach to synchronize the birth of cortical neurons in vitro which allowed us to define a detailed atlas of progressive morphological, functional, and molecular maturation in human cortical neurons. Interestingly, we observed a slow, temporal unfolding of maturation programs that is limited by the retention of a specific set of epigenetic factors. Loss-of-function studies for several of those factors in cortical neurons enables precocious molecular and physiological maturation. Remarkably, transient inhibition of EZH2, EHMT1/2 or DOT1L, at the progenitor stage primes newly born neurons to rapidly acquire mature properties upon differentiation. Therefore, our findings reveal that the rate at which human neurons mature is set well before neurogenesis through the establishment of an "epigenetic barrier" in progenitor cells. Mechanistically, this barrier acts by holding transcriptional maturation programs in a poised state that gets gradually released during neuronal differentiation to ensure the prolonged timeline characteristic of human cortical neuron maturation.

Keywords: Developmental timing, Neuronal maturation, Epigenetic

2:20 PM – 2:30 PM

USING HUMAN IPSC-DERIVED ORGANOIDS TO MODEL DEMYELINATION, OLIGODENDROCYTE DYSFUNCTION AND MICROGLIAL TOXICITY IN MULTIPLE SCLEROSIS

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Mechanistic understanding of demyelinating diseases like Multiple Sclerosis (MS) is critical for identifying new treatments. However, this remains challenging due to current model sys-

tems being limited in their capacity to recapitulate the complex human myelination processes and this results in lack of available treatments targeting remyelination for MS patients. We therefore aimed to pioneer an organoid model of human demyelination. Using human induced pluripotent stem cells (iPSC), we generated 3D organoids containing neural cell types including microglia and myelinating oligodendrocytes, as well as neurons and astrocytes, which we successfully demyelinated using lysophosphatidylcholine (LPC), a toxin which causes focal demyelination. Briefly, we neuralise, caudalise and ventralise iPSC to generate OLIG2+ precursors and then commence myelin induction (time 0) using a published protocol. After 3 weeks we seed in TdTomato-tagged microglia-like precursor cells. At 11 weeks, we treat organoids with LPC (or vehicle) and then collect organoids for characterisation of: demyelination at 5h, 24h and 1 week, and signs of remyelination at 3 and 6 weeks following LPC. The thymidine analogue EdU was also added post-LPC treatment to track new oligodendrocyte generation. Myelin fragmentation was quantified using the three- dimensional analysis software, IMARIS, whereby we applied a specific surface mask to measure myelin sheath length. Myelin fragmentation was significantly higher at 5 h, 24 h, 7 d and 14 d in LPC treated organoids, compared to vehicle ($p< 0.05$ for all). To assess the microglia response, we analysed the change in microglial soma size and process area using IMARIS and used a novel multiplex immunolabelling technique to further stratify the microglial population. Our preliminary data show robust expression of L-ferritin, CD68, and Iba1 and an increased expression of HLA-DR in LPC treated organoids comparative to vehicle treated control organoids. New oligodendrocyte generation, differentiation and remyelination in these organoids are now being characterised. In conclusion, we have successfully generated a humanised model of demyelination. This system will allow mechanistic insight and a platform for screening drugs that may promote remyelination providing hope for MS patients.

Keywords: Organoids, Multiple Sclerosis, Myelin

2:30 PM – 2:50 PM

MANAGING BRAIN MALIGNANCIES IN 3 DIMENSIONS

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Despite the remarkable efficiency of immune checkpoint modulators against metastatic melanoma, there is a low percentage of responders, and clinical trials report severe immune-mediated side effects and disease relapse. An accumulated body of evidence shows that non-tumor cells within the tumor microenvironment (TME), including tumor vasculature and immune stromal cells, dictate the overall therapeutic efficacy. We synthesized a biodegradable, off-the-shelf, and cost-effective nano-sized polymeric platform that combines a cancer vaccine with the targeted inhibition of molecular and/or cellular immune suppressive players. These precision nano-sized medicines aim to re-educate and harness patient T-cell response against tumors, leading to an immunological memory able to control tumor relapse without any follow-up treatment. The design of these advanced peptides and RNA immunotherapeutics is guided by the identification of lead immune suppressor factors and tumor-specific antigens using novel 3D bio-printed tumor-immune spheroids developed in our lab. Our first nano-immunotherapy candidates sensitized brain malignancies mouse models to immune-checkpoint modulators, dramatically increasing disease-free survival rates. Clinical trials aiming to validate these approaches have recently been initiated.

Keywords: Cancer, 3D-bioprinting, tumor-host interaction, nanomedicine

TRACK: NEW TECHNOLOGIES (NT)

SINGLE-MOLECULE METHODS AND BIOMOLECULAR CONDENSATES
1:15 PM – 2:55 PM
Room 259, Meeting Level 2

1:20 PM – 1:40 PM

STICKY PROTEINS AND MOVING GENOMES: TOWARDS A SINGLE-MOLECULE PERSPECTIVE OF INTRA-NUCLEAR DYNAMICS DURING PLURIPOTENT CELL DIFFERENTIATION

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In the early mammalian embryo, pluripotent cells differentiate into distinct cell lineages through mechanisms that remain poorly understood. To provide molecular insight into this process, we have developed in vitro single-molecule imaging tools that reveal 3D chromatin organisation and mobility but also the chromatin binding kinetics of nuclear proteins. Using these approaches, we reveal the formation of intra-nuclear hubs enriched for enhancers, promoters and nuclear proteins. We also reveal the chromatin binding kinetics of key transcription factors and chromatin regulators required for differentiation and lineage choice – NANOG, SOX2, the remodeller NuRD and the histone methyltransferase MLL2. We describe differences between these proteins and the implications for how they function. Next, we show how NuRD and MLL2 influence 3D chromatin organisation and mobility. We show that they alter the range genes can explore within the nucleus, highlighting an important link between chromatin mobility and differentiation. Using single-cell transcriptomics (scRNAseq) and chromosome conformation capture (Hi-C/Micro-C), we show that chromatin mobility is linked to the length-scale over which enhancers activate transcription of nearby genes and we discuss the implications of this on transcriptional dynamics and lineage choice as pluripotent cells differentiate. Finally, to take these findings to the next level, we are establishing similar technologies within live mouse embryos to ultimately reveal the underlying molecular mechanisms of cell-fate decisions in vivo.

Keywords: pluripotency, single-molecule, condensate

1:40 PM – 1:50 PM

H3K36 METHYLATION REGULATES INTESTINAL CELL FATE

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The small intestine is one of the most important interfaces between our body and the outside world. In mammals, the intestine is lined with a single layer of epithelial cells that serve functions such as nutrient digestion and absorption, barrier function, and immune homeostasis. However, these processes can damage the epithelial layer, requiring continuous renewal to maintain function and integrity. To meet this need, the intestine has evolved a robust stem cell compartment that replenishes all intestinal cell types. Disruption of cell fate programming and differentiation can lead to cancer and other intestinal diseases. Therefore, it is crucial to understand how intestinal stem cells dif-

ferentiate to maintain the proper proportion of specialized cells. In many contexts, epigenetic mechanisms, such as histone modifications, establish and maintain cell identity. However, the epigenetic regulation that specifies intestinal cell identity remains elusive. Here, we examined H3K36 methylation in intestinal cell fate specification and maintenance. We profiled histone modifications via CUT&Tag from purified FACS-sorted populations of intestinal cell types. We found that while enhancer and promoter marks are largely unchanged between stem cells, enterocytes, goblet cells, and Paneth cells, H3K36 methylation differs dramatically between these cell types at genes that are crucial for cell fate. To establish a functional role for H3K36 methylation, we leveraged a dominant-negative lysine-to-methionine mutant that specifically suppresses methylation at H3K36. Combining gene expression, CUT&Tag, and immunofluorescence analyses, we observed that loss of H3K36 methylation disrupts secretory cell maturation. Additionally, we found that suppressing H3K36 methylation enhances fetal-related transcriptional signatures and promotes a regenerative phenotype, suggesting that this modification is necessary to both establish and maintain mature cell fates in the intestine. Our data suggest that H3K36 methylation is an important epigenetic regulator of intestinal cell fate that reinforces expression of lineage specific genes. Understanding this regulatory mechanism in the intestine is a crucial step in realizing the tremendous potential of stem cells and epigenetics for basic science and medicine.

Funding Source: NIH R35GM142884-02S, NIH T32GM008759

Keywords: histone methylation, chromatin, intestinal homeostasis

1:50 PM – 2:00 PM

HIJACKING OF RNA CONDENSATES CORRUPTS CELL IDENTITY AND PROMOTES ONCOGENESIS

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Post-transcriptional mechanisms have emerged as fundamental regulators of progenitor cell identity and their dysregulation promotes malignant transformation. Targeting post-transcriptional mechanisms in cancer is a conceptually novel and potentially highly effective therapeutic approach. Here, we performed genome-wide CRISPR screens in normal and transformed hematopoietic progenitor cells and identified regulators of biomolecular condensates (i.e., P-bodies) as crucial vulnerabilities in myeloid leukemia. Although P-bodies are thought to play important roles in various RNA-related processes, their molecular function and role in cancer is poorly understood. We found that AML cells have elevated numbers of P-bodies compared to normal hematopoietic stem and progenitor cells. We further demonstrate that P-body assembly is crucial for the initiation and maintenance of leukemia. Molecular characterization of purified, intact RNA condensates from human leukemia cells revealed that P-bodies sequester mRNAs encoding key tumor suppressors from the translational machinery. Congruently, P-body dissolution in AML cells liberates mRNAs encoding tumor suppressive chromatin regulators, which re-enter the ribosome pool. Increased translation of these targets impacted leukemic cell self-renewal by profoundly rewiring the DNA methylation landscape and the chromatin architecture of cancer cells. Collectively, our data determine a molecular node between RNA sequestration in P-bodies, genome topology, and oncogenesis that might be exploited in therapeutic settings to treat leukemia and other cancers.

Keywords: RNA condensates, Hematopoiesis, Leukemia

2:00 PM – 2:10 PM

PROTEOMIC CHARACTERIZATION OF CELL TYPE-SPECIFIC EXTRACELLULAR VESICLE MOLECULES FROM HUMAN IPSC-DERIVED NEURONS, ASTROCYTES, MICROGLIA, AND OLIGODENDROCYTES

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Extracellular vesicles (EVs) are known to carry pathogenic molecules in neurodegenerative diseases and have potential utility as biomarker discovery. There is a gap in knowledge about neuronal cell type-specific molecules for distinguishing the cellular origin of EVs that arise from differing cell types within the central nervous system. Here we profiled the proteome of EVs isolated from human induced pluripotent stem cell (hiPSC)-derived neural and glial cells, which include excitatory neurons, astrocytes, microglia, and oligodendrocytes. The specificity of the cell types was validated by immunofluorescence and quantitative gene expression analysis for the selected markers. Proteomic profiling identified potential novel cell type-specific EV proteins for excitatory neurons (ATP1A3, NCAM1), astrocytes (LRP1, ITGA6), microglia (ITGAM, CD300A) and oligodendrocytes (LAMP2, FTH1). Super-resolution microscopy and robust biochemical assessment identified that ATP1A3, a transmembrane Na+, K+-ATPase, is abundantly expressed in EVs isolated from hiPSC -derived neurons, brain tissues, cerebrospinal fluid, and plasma in comparison with the frequently used neuron-derived extracelluar vesicle (NDEV) markers NCAM1 and L1CAM. Synaptic markers and cargo proteins relevant to Alzheimer's disease are greatly enriched in brain-EVs following immunoprecipitation using ATP1A3 when compared to NCAM1 or LICAM. Thus, ATP1A3 may be a better marker to isolate human NDEV for future Neuro-EV research.

Funding Source: This work is funded by Florida Department of Health 22A04 (YY), Alzheimer's Association AARF-22-918114 (YY), Cure Alzheimer's Fund (TI, SI), NIH RF1 AG054199 (TI), R01AG054672, R01 AG066429 (TI), R01 AG067763 (TI), R01 AG072719 (TI).

Keywords: Extracellular vesicles, super-resolution microscopy, proteomics, single molecule imaging

2:10 PM – 2:20 PM

SPATIALLY RESOLVED EPIGENOMIC PROFILING OF SINGLE CELLS IN COMPLEX TISSUES

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The recent development of spatial omics methods has enabled single-cell profiling of the transcriptome and 3D genome organization with high spatial resolution. Expanding the repertoire of spatial omics tools, a spatially resolved single cell epigenomics

method will accelerate understanding of the spatial regulation of cell and tissue functions. Here, we report a method for spatially resolved epigenomic profiling of single cells using in situ tagmentation and transcription followed by multiplexed imaging. We demonstrated the ability to profile histone modifications marking active promoters, putative enhancers, and silent promoters in individual cells, and generated high-resolution spatial atlas of hundreds of active promoters and putative enhancers in embryonic and adult mouse brains. Our results suggested putative promoter-enhancer pairs and enhancer hubs regulating developmentally important genes. We envision this approach will be generally applicable to spatial profiling of epigenetic modifications and DNA-binding proteins, advancing our understanding of how gene expression is spatiotemporally regulated by the epigenome.

Keywords: Spatial Epigenomics, Epigenetics, Imaging

2:20 PM – 2:30 PM

DECODING HOW THE PIONEER FACTOR OCT4 ENGAGES EPIGENETICALLY SILENCED DNA

Tan, Daisylyn Senna Y.[1], Cheung, Shun Lai[1], Gao, Ya[1], Weinbuch, Maike[2], Hu, Haoqing[1], Shi, Liyang[3], Ti, Shih-Chieh[1], Hutchins, Andrew[3], Cojocaru, Vlad[4] and Jauch, Ralf[1]
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Oct4 is master stem cell factor essential to the driving and maintenance of pluripotency. Oct4 is a part of a class of DNA binding transcription factors (TFs) called pioneer TFs that have a unique ability to bind and activate epigenetically silenced genes. During embryonic development, widespread and locus specific methylation reprogramming is required for cell fate changes. CpG methylation was thought to repel TFs from their binding sites which was a key reason why CpG methylation leads to repressive chromatin. However, Oct4 was reported to bind a palindromic DNA element with a methylated CpG core, hereafter called “CpGpal”. Yet, how Oct4 binds to this element and whether this binding modality contributes to its roles in development and pluripotency remains unclear. Here, we performed a comprehensive re-analysis of Oct4 ChIP-seq data across all stages of iPSC generation to reveal the dynamics of Oct4 engagement with CpGpal. Surprisingly, despite global demethylation of the majority of Oct4 bound enhancers, methylation at the CpGpal is largely maintained when cells transit to a pluripotent state. We, then, performed biochemical binding assays, in-vitro liquid-liquid phase separation (LLPS), and structural modeling to decode how Oct4 is binding the methylated CpGpal element. We reveal that Oct4 protein binds to the CpGpal as a homodimer solely driven by the POU homeodomain while the POU-specific domain is likely detached from DNA. Residues at the possible dimerization interface affect pluripotency induction. Collectively, we report a novel binding configuration of Oct4 across cell fate transitions that mediate its regulatory role in the context of methylated DNA.

Funding Source: Hong Kong PhD Fellowship Scheme (HKPFS) of Research Grants Council (RGC), HK

Keywords: Oct4, DNA Methylation, Pioneer Factor

2:30 PM – 2:50 PM

Spatial Multi-Omics Driving the Next Wave of Biomedical Research Revolution

Fan, Rong
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Despite latest breakthroughs in single cell sequencing that revealed cellular heterogeneity, differentiation, and interactions at an unprecedented level, the study of multicellular systems needs to be conducted in the native tissue context defined by spatially resolved molecular profiles to better understand the role of spatial heterogeneity in biological, physiological and pathological processes. In this talk, I will begin with discussing the emergence of a whole new field – “spatial omics”, and then focus mainly on a new technology platform called Deterministic Barcoding in Tissue (DBiT) for spatial omics sequencing developed in our laboratory over the past years. We conceived the concept of “spatial multi-omics” and demonstrated it for the first time by co-mapping whole transcriptome and proteome (~300 proteins) pixel-by-pixel directly on a fixed tissue slide in a way compatible with clinical tissue specimens including FFPE. It has been applied to the study of developing mouse brain, human brain, and human lymphoid tissues associated with normal physiology, disease, or aging. Recently, our research enabled another new field – “spatial epigenomics” – by developing multiple DBiT-based spatial sequencing technologies for mapping chromatin accessibility (spatial-ATAC-seq), histone modification (spatial-CUT&Tag), or further combined with transcriptome or proteins for spatial co-profiling. These new technologies allow us to visualize gene expression regulation mechanisms pixel by pixel directly in mammalian tissues with a near single cell resolution. The rise of NGS-based spatial omics is poised to fuel the next wave of biomedical research revolution. Emerging opportunities and future perspectives will be discussed with regard to clinical biomarker discovery and therapeutic development.

Keywords: Spatial Omics, Neuroscience, Cancer

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)

PHYSICAL PROPERTIES AND REGENERATIVE RESPONSES OF PERTURBED TISSUES

1:15 PM – 2:55 PM
Room 254, Meeting Level 2

1:20 PM – 1:40 PM

THE MECHANICAL LINKS BETWEEN TISSUE MORPHOGENESIS AND PROGENITOR CELL DIFFERENTIATION

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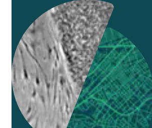
Organogenesis and organ regeneration require both (re)creation of tissue form, a process known as morphogenesis, as well as specification of cell fate, a process known as differentiation. We have developed microfluidic approaches to investigate the mechanical forces and downstream signaling pathways responsible for generating the airways and differentiated cell types of the lung. I will discuss how we combine these experimental techniques with computational models to uncover how physical forces drive lung development, with a specific focus on determining which comes first: tissue form or specification of cell fate. I will also describe efforts to uncover and actuate the different



physical mechanisms used to build the airways in lungs from birds, mammals, and reptiles.

Keywords: Morphodynamics, mechanical stress, Yap, epithelial, mesenchymal

1:40 PM – 1:50 PM

MITOCHONDRIA-RICH EXTRACELLULAR VESICLES FROM PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES RESTORE ENERGY METABOLISM OF ISCHEMIC MYOCARDIUM IN A PRECLINICAL PORCINE MODEL

Ikeda, Gentaro, Bayardo, Nathan, Lyons, Jennifer, Takashima, Hiroyuki, Tzng, Eileen, Ueyama, Tsuyoshi and Yang, Phillip
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Disruption of mitochondrial energy metabolism underlies the pathophysiology of ischemic heart failure. We previously demonstrated that intramyocardial injection of mitochondria-rich extracellular vesicles (M-EVs) from iPSC-derived cardiomyocytes (iCMs) transfer mitochondrial and nonmitochondrial biologics into the recipient cardiomyocytes, stimulating mitochondrial biogenesis and functional capacities in the murine acute myocardial infarction (MI) model. However, the therapeutic potential and underlying mechanism in larger animal models remain to be assessed. Yorkshire pigs were subjected to myocardial ischemia for one hour via balloon occlusion of the left anterior descending artery. M-EVs were isolated from the conditioned medium of human iCMs via differential ultracentrifugation and 1.0 x 10^11 M-EVs were administered to the infarct border zone using a percutaneous catheter delivery system (Biocardia, Inc, CA). Cardiac functions were analyzed by cardiac MRI. Liquid chromatography-tandem mass spectrometry was performed to investigate comprehensive protein profiles of M-EV content and pig heart tissue samples. Flow cytometric and electron microscopic analysis revealed that mitochondria inside M-EVs retained membrane potential and structural integrity. M-EV therapy significantly improved left ventricular (LV) ejection fractions (30.5 vs. 21.2 %, p=0.004) and reduced LV end-diastolic volume (119 vs. 192 mL, p=0.047) at week-4 as compared with PBS control. No difference was observed in the scar size. Proteomics analysis identified a total of 37 significantly enriched proteins in M-EVs, which directly or indirectly interact with a proliferator-activated receptor γ coactivator-1 α (PGC-1α), a master regulator of mitochondrial biogenesis. Integration of proteomes of M-EVs and pig myocardial tissues suggested that M-EV therapy restored dysregulated protein profiles and mitochondrial energy metabolism in the injured myocardium. M-EV-mediated transfer of mitochondria and enriched proteins enhanced cardiac function by restoring energy metabolism in the pig acute MI model. M-EV therapy may represent a novel biologic that directly targets energy metabolism to restore mitochondrial function and cellular bioenergetics.

Funding Source: American Heart Association Career Development Award #933382

Keywords: Extracellular Vesicles, Mitochondria, Induced Pluripotent Stem Cell

1:50 PM – 2:00 PM

MECHANISMS OF ALVEOLAR EPITHELIAL TYPE 2 CELL SELF-RENEWAL IN LUNG INJURY AND REPAIR

Huang, Jessie, Villacorta-Martin, Carlos, Sohal, Ruhi, Alysandratos, Konstantinos-Dionysios and Kotton, Darrell
Center for Regenerative Medicine, Boston University, Boston, MA, USA

Alveolar epithelial type 2 cells (AT2s) are facultative progenitors that are quiescent in the uninjured adult lung, but reenter cell cycle upon injury. While this process is observed in animal models, the mechanisms controlling human AT2 self-renewal are less well-understood. We previously developed a human induced pluripotent stem cell (iPSC)-derived AT2 (iAT2) model, and we hypothesize that iAT2 self-renewal progresses under defined signals recapitulating lung injury/repair. To test this, human iAT2s were derived by directed differentiation of an iPSC line with an SFTPCtdTomato reporter, enabling monitoring of the AT2 program. Self-renewing iAT2s were single-cell passaged every 10-14 days. For comparison, proliferative AT2s were captured in Sftpc-CreERT2;R26-diphtheria toxin A mice, where a dose of tamoxifen ablates ~57% AT2s at 2 days post-injury (dpi). Proliferation kinetics of iAT2s during passaging and mouse AT2s after injury were determined by EdU. Single-cell RNA sequencing was performed on iAT2s and AT2s with RT-qPCR validation. Pairwise comparisons of proliferative vs non-proliferative (i)AT2s were used to identify overlapping differentially expressed genes (DEGs); small molecule inhibitors for DEGs were tested in iAT2s to determine changes in AT2 program and proliferation. We found iAT2s proliferated robustly at the beginning of passage, reducing as they reach confluency. Similarly, mouse AT2s proliferated rapidly at 2 dpi and decreased to baseline by 14 dpi. Transcriptomic data revealed AT2 maturation signatures inversely correlated with cell cycle phase, indicating a cyclical pattern of self-renewal and maturation. The 244 DEGs in proliferative AT2 clusters included E2F family members and chromatin remodeler EZH2. Inhibition of EZH2 in iAT2s resulted in significantly increased proliferation, reduced maturation, and upregulation of transitional cell markers. Our data suggest that (i)AT2 self-renewal involves an initial proliferative, less mature state, followed by return to a less proliferative, more mature state. Combined analysis of human and mouse datasets identified shared upregulated transcripts in proliferating (i)AT2s, and inhibition of EZH2 resulted in increased proliferation and decreased maturation, suggesting that EZH2 may be important in AT2 self-renewal.

Keywords: lung, regeneration, iPSC

2:00 PM – 2:10 PM

HEMATOPOIETIC RECONSTITUTION DYNAMICS OF MOBILIZED- AND BONE MARROW-DERIVED HEMATOPOIETIC STEM CELLS AFTER GENE THERAPY

Scala, Serena[1], Ferrua, Francesca[1], Basso-Ricci, Luca[1], Dionisio, Francesca[1], Omrani, Maryam[1], Quaranta, Pamela[1], Jofra Hernandez, Raisa[1], Del Core, Luca[1], Benedicenti, Fabrizio[1], Monti, Ilaria[1], Giannelli, Stefania[1], Fraschetta, Federico[1], Darin, Silvia[1], Albertazzi, Elena[1], Galimberti, Stefania[2], Montini, Eugenio[1], Calabria, Andrea[1], Cicalese, Maria[1] and Aiuti, Alessandro[1]
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Mobilized peripheral blood (MPB) is increasingly used instead of bone marrow (BM) as source of autologous Hematopoietic Stem/Progenitor cells (HSPC) for transplantation (HSCT) or ex vivo gene therapy (GT), because of higher numbers of HSPC collected and rapid hematopoietic reconstitution. However, there is limited information on the kinetics of hematopoietic reconstitution and the clonality of the graft after GT using these two sources. To dissect the behavior and fate of gene-corrected BM and MPB HSPC subpopulations, we performed an exploratory research analysis evaluating hematopoietic dynamics in the unique model of 13 Wiskott-Aldrich syndrome GT patients who received,

under the same treatment scheme, CD34+ cells derived from either BM or MPB transduced with same vector and in vitro transduction protocol. Despite the two groups were similar in the infused product vector copy number (VCN), CD34+ cell dose and transduction level, deep-phenotyping of CD34+ cell composition before transduction revealed the presence of higher amounts of primitive and myeloid-committed progenitors in MPB compared with BM HSPC. In line with HSCT data, we observed faster neutrophil and platelet recovery in the MPB-GT group, which correlated with the number of myeloid progenitors infused. MPB-GT patients also showed higher percentage of transduced colonies in the BM and increased VCN in myeloid cells with respect to BM-GT. Moreover, through vector integration sites, we measured a higher number of engrafted clones in MPB-GT patients, which correlated with the amount of primitive HSPC contained in MPB HSPC. Importantly, similar myeloid and lymphoid reconstitution and stable gene correction were observed from 1-year post-GT in both groups suggesting that both HSPC sources have similar long-term repopulating properties. In addition, in vitro differentiation and transplantation studies in mice confirmed that primitive HSPC from both sources have comparable engraftment and multilineage differentiation potential. Altogether, our analyses revealed that the differential behavior of the two sources after GT was mainly due to the distinct cell composition rather than functional differences of the infused cell products, providing new frames of references for clinical interpretation of HSPC transplantation outcome.

Keywords: Hematopoietic stem cells, Gene therapy, Clonal tracking

Clinical Trial ID number: NCT01515462

2:10 PM – 2:20 PM

YAP AND TAZ COUPLE OSTEOBLAST PRECURSOR MOBILIZATION TO ANGIOGENESIS AND MECHANOREGULATED BONE DEVELOPMENT

Collins, Joseph[1], Ahmed, Saima[2], Dyment, Nathaniel[3], Gottardi, Riccardo[4], Kim, Jong Hyun[1], Lang, Annemarie[3], Moharrer, Yasaman[5], Nijsure, Madhura[1], Nowlan, Niamh[6], Parisi, Cristian[2], Qin, Ling[3], Szeto, Gregory[7] and Boerckel, Joel[1]

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Endochondral ossification requires coordinated mobilization of osteoblast precursors with blood vessels. In adult bone, vessel adjacent osteoblast precursors respond to and are maintained by mechanical stimuli; however, the mechanisms by which these cells mobilize and respond to mechanical cues during embryonic development are unknown. During development, Osterix (Osx)-expressing immature osteoblast precursors originate in the surrounding intramembranous bone collar and co-invade with specialized blood vessels as pericytes to initiate endochondral bone formation. YAP and TAZ are mechanoresponsive transcriptional regulators with important roles in mobilization, angiogenesis, and osteogenesis. Previously, we found that deletion of YAP and TAZ from Osx-expressing osteoblast precursors and their progeny caused perinatal lethality. Here, we show that embryonic YAP/TAZ signaling couples vessel-associated osteoblast precursor mobilization to angiogenesis in developing long bones. Osterix-conditional YAP/TAZ deletion impaired endochondral ossification in the primary ossification center but not intramembranous osteogenesis in the bone collar. Single-cell RNA sequencing of the embryonic forelimb (>120,000 cells, n=3-4 per genotype, genotypes are WT(floxed), WT(Osx-Cre), YAP/TAZ cKOOsx) revealed YAP/TAZ regulation of the angiogenic chemokine, Cxcl12, in vessel-associated osteoblast precursors. YAP/TAZ signaling spatially coupled osteoblast precursors to blood vessels and regulated vascular morphogenesis through CXCL12, which mediated hypertrophic cartilage remodeling at the chondro-osseous junction. In human cells, mesenchymal stromal cell co-culture promoted 3D vascular network formation, which was impaired by stromal cell YAP/TAZ depletion, but rescued by recombinant CXCL12 treatment. Lastly, YAP and TAZ mediated mechanotransduction for fetal movement-induced in bone morphogenesis. Together, we mechanistically unify osteoblast precursor-blood vessel coordinated mobilization and fetal mechanical cues in a single signaling pathway, via the Hippo pathway effectors, YAP and TAZ. These findings have implications for hereditary and congenital conditions of fetal akinesia and for therapeutic approaches for bone repair and regeneration.

Funding Source: NIH/NIAMS: R01 AR073809, R01 AR074948, P30AR069619, NSF CMMI 1548571, 5T32AR007132, ERC Grant agreement (number 336306), Research Fellowship funded by the Deutsche Forschungsgemeinschaft (DFG; project no.: 440525257

Keywords: Bone development, Single cell RNA sequencing, YAP/TAZ

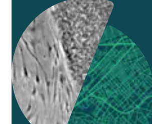
2:20 PM – 2:30 PM

PANETH CELLS AS THE ORIGIN OF INTESTINAL CANCER IN THE CONTEXT OF INFLAMMATION

Verhagen, Mathijs[1], Joosten, Rosalie[1], Schmitt, Mark[2], Sacchetti, Andrea[1], Choi, Jiahn[3], Välimäki, Niko[4], Aaltonen, Lauri[4], Augenlicht, Leonard[3] and Fodde, Riccardo[1]

[1]Pathology, Erasmus Medical Center, Rotterdam, Netherlands, [2]Institute of Pharmacology, University of Marburg, Germany, [3]Department of Cell Biology, Albert Einstein College of Medicine, New York, NY, USA, [4]Department of Medical and Clinical Genetics, University of Helsinki, Finland

Paneth cells (PCs), responsible for the secretion of antimicrobial peptides in the small intestine and for niche support to Lgr5+ crypt-base columnar stem cells (CBCs), have been shown to respond to inflammation by dedifferentiating into stem-like cells in order to sustain a regenerative response. Therefore, PCs may represent the cells-of-origin of intestinal cancer in the context of inflammation. To test this hypothesis, we targeted Apc, Kras, and Tp53 mutations in Paneth cells by Cre-Lox technology and modelled inflammation by dextran sodium sulfate (DSS) administration. PC-specific loss of Apc resulted in multiple small intestinal tumors, whereas Kras or Tp53 mutations did not. Compound Apc and Kras mutations in PCs resulted in a striking increase in tumor multiplicity even in the absence of the inflammatory insult. By combining scRNAseq with lineage tracing to capture the conversion of PCs into bona fide tumor cells, we show that they progress through a "revival stem cell" (RSC) state characterized by high Clusterin (Clu) expression and Yap1 signaling, reminiscent of what has been previously observed upon irradiation of the mouse digestive tract. Accordingly, comparison of PC- and Lgr5-derived murine intestinal tumors revealed differences related to Wnt signaling and inflammatory pathways which match the dichotomy of CBCs and RSCs between human sporadic colon cancers and those arising in the context of inflammatory bowel diseases. Last, we show that western-style dietary habits, known to trigger a low-grade inflammation throughout the intestinal tract, underlie the analogous de-differentiation of



Paneth cells and their acquisition of stem-like features. Taken together, our results show that intestinal cancer arises in the context of inflammation through the dedifferentiation of committed secretory lineages such as Paneth cells and the activation of the RSC state. As such, a true quiescent stem cell identity may be hidden in fully committed and post-mitotic lineages which, upon inflammation, support the regenerative response by re-entering the cell cycle and dedifferentiating into RSCs. The chronic nature of the tissue insult in inflammatory bowel diseases and even in the context of western-style dietary habits is likely to result in the expansion of cell targets for tumor initiation and progression.

Keywords: Paneth cells, dedifferentiation, cell-of-origin

2:30 PM – 2:50 PM

FRIEND OR FOE: SENESCENCE IN THE STEM CELL NICHE

Peng, Tien
Medicine, University of California, San Francisco, CA, USA

Senescence, as the name would imply, is associated with biological aging and the detrimental phenotypes associated with organ decline over time. We have recently demonstrated that senescent cells also have physiologic functions, serving as sentinels in the stem cell niche to sense inflammation and augment normal stem cell repair after tissue injury. Our work would suggest whether senescent cells act as friend or foe depends on the physiologic/pathologic context, and we will highlight how senescent cells' ability to alter the tissue microenvironment can be either adaptive or maladaptive with therapeutic implications.

Keywords: senescence, aging, cancer

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)

PLENARY IV: NICHE REGULATION OF DIFFERENTIATION AND REGENERATION
3:15 PM – 5:15 PM
Ballroom East/West, Level 3

3:20 PM – 3:40 PM

RARE AIRWAY EPITHELIAL CELLS AND NEW MECHANISMS FOR REGENERATION

Rajagopal, Jay
Center for Regenerative Medicine / Harvard Stem Cell Institute, Massachusetts General Hospital and Harvard Stem Cell Institute, MA, USA

We recently identified multiple new cell types and established a new lineage hierarchy that linked these new cells to all the previously known cell types in the murine airway epithelium. We named the first new class of cells "ionocytes" because they resemble cells in frogs and fish that transport ions in response to environmental salinity, and we showed that loss of these rare CFTR-expressing cells led to alterations of airway surface physiology. We named the second new cell type "hillock" cells since they occurred in distinct mounds of stratified cells. Additionally, we identified novel subtypes of chemosensory tuft cells. More recently, we have established that hillocks possess dedicated hillock basal stem cells that exhibit remarkable clonal expansion, resurface a denuded airway, and create a temporary squamous barrier epithelium that then differentiates into a classic airway epithelium with all its component cell types. In this talk, we will discuss the biology of rare cells in the human airway epithelium and discuss the biology of hillocks and their relationship to squamous metaplasia.

Keywords: Epithelial, Airway, lung, hillock, injury, ionocyte, tuft cell, M cell, squamous metaplasia

3:40 PM – 4:00 PM

DEVELOPMENT, REGENERATION, AND REPAIR OF BLOOD VESSELS IN THE HEART

Red-Horse, Kristy
Biology & Institute for Stem Cell Biology and Regenerative Medicine, Stanford University / Howard Hughes Medical Institute, Stanford, CA, USA

Developing organisms create tissues de novo, and the underlying instructions could inform organ regeneration. With this mindset, we study coronary arteries—which bring blood flow to heart muscle—in hopes of eventually treating coronary artery disease, the number one killer worldwide. We have discovered how mouse coronary arteries are built, and reinstated developmental pathways in adults to aid recovery following cardiac injury. Developing organisms create tissues de novo, and the underlying instructions could inform organ regeneration. With this mindset, we study coronary arteries—which bring blood flow to heart muscle—in hopes of eventually treating coronary artery disease, the number one killer worldwide. We have discovered how mouse coronary arteries are built, and reinstated developmental pathways in adults to aid recovery following cardiac injury.

Keywords: Developmental Biology, Cardiovascular Biology, Blood Vessel, Heart, Coronary Arteries

4:00 PM – 4:20 PM

REGULATION OF STEM CELL FATE BY NUCLEAR MECHANOTRANSDUCTION

Wickström, Sara
Max Planck Institute for Molecular Biomedicine, Muenster, Germany

The structure of tissues is tightly linked to their function. During formation of functional organs, large-scale changes in tissue elongation, stretching, compression, folding/buckling, and budding impact the shape, position, packing, and contractility state of cells. Conversely, changes in single cell contractility, shape and position locally alter tissue organization and mechanics. Thus, forces function as important ques that are transmitted to the nucleus to coordinate gene expression programs to control cell states. On the other hand, excessive mechanical stresses have the potential to damage cells and tissues. In my presentation I will discuss our recent research on how cells use the nucleus and the nuclear envelope/chromatin interface to sense mechanical forces and how these mechanosignals are integrated with biochemical inputs to alter cell states and to protect against force-induced damage.

Keywords: mechanotransduction, chromatin, cell fate regulation

4:20 PM – 4:40 PM

CHROMATIN-LEVEL REGULATION OF NEURAL STEM CELL FATE DURING MOUSE NEOCORTICAL DEVELOPMENT

Gotoh, Yukiko
University of Tokyo, Japan

A fundamental question in understanding tissue development is how resident stem cells or multipotent progenitors give rise to the various cell types in appropriate numbers and at the right locations to achieve tissue organization. Neural stem/progenitor cells (NPCs) in the mammalian neocortex initially divide symmet-

rically to increase their pool size (expansion phase). They then start to divide asymmetrically and give rise to neuronal and glial cell types in a region- and developmental stage–dependent manner. In this talk, I will present data regarding the mechanisms underlying the transition from the expansion phase to the neurogenic phase and discuss their potential role in psychiatric diseases such as autism spectrum disorder.

Keywords: neural stem-progenitor cell, neocortical development, mouse, chromatin

4:40 PM – 5:15 PM

ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD LECTURE: UNDERSTANDING INTERCONNECTEDNESS IN LIVER DEVELOPMENT AND DISEASE

Takebe, Takanori[1,2,3]
[1]Cincinnati Children's Hospital Medical Center, OH, USA, [2]Osaka University, Japan and [3]Tokyo Medical and Dental University, Japan

Remarkably divergent cell types form tightly embedded connections in our body. Complete loss of interconnectedness leads to devastating clinical conditions, including lethal organ failure endpoints. For example, biliary atresia (loss of hepato-biliary connection: inter-organ), is the most prevailing cause of irreversible liver failure for which existing cures are currently absent. In hepatology, our lab seeks to understand how the living system creates interconnectedness across strata, how interconnectedness plays a role in orchestrating tissue development and maturation, and how biological alterations in interconnectedness threaten our health. The past three decades of embryology research, together with evolving genetics and genomics toolsets, have revealed a high-resolution developmental roadmap to understanding how lineage specification occurs through intricate transcriptional regulation. With the Zorn/Wells lab, we have revealed how paracrine signals from the neighboring mesenchyme direct embryonic foregut endoderm towards hepato-pancreatic-biliary fate. These developmental studies laid the foundation for designing the in-a-dish principle to synthesize biological tissues. We recently showed that it is possible to induce the entire hepato-biliary-pancreatic (HBP) pattern in vitro from human pluripotent stem cells (hPSCs). The HBP multi-organ model established a functional connection of the bile duct within tissues. In disease modeling, we have developed "en masse phenotyping platform" that allows for large-scale population-scale phenotypic analyses and can help to elucidate the contributions of personalized mechanistic traits to metabolic liver diseases. Here I will summarize our ongoing studies to investigate human liver development and disease through the lens of interconnectedness biology. Our goal is to define personalized mechanisms as a fundamental step toward developing evidence-based, rational solutions for mechanism-directed diagnostic and therapeutic investigation.

Keywords: Organoids, Pluripotent Stem Cells, Liver, Development, Disease

SATURDAY, 17 JUNE

CONCURRENT TRACK SESSIONS

8:15 AM – 9:55 AM

TRACK: CLINICAL APPLICATIONS (CA)

GENE EDITED ALLOGENEIC T CELLS
8:15 AM – 9:55 AM
Room 258, Meeting Level 2

8:20 AM – 8:40 AM

ENGINEERED IPSC AS OFF-THE-SHELF SOURCE OF CAR T CELLS

Themeli, Maria
Hematology, Amsterdam Vrije Universiteit, Amsterdam Medical Center

The technology of induced pluripotent stem cells (iPSC) offers new perspectives for the production of immunotherapeutic cellular products due to two major characteristics. First, iPSCs can be cultured unlimitedly in vitro and be successfully differentiated towards the lymphoid lineage. Having access to constant and continuous production of T lymphocytes offers solution to cell number and doses limitations due to restricted availability or expansion of primary cells. Second, iPSCs can be easily amenable to genetic transformations in vitro and thus, can generate immune effectors, which may eventually be genetically modified to augment their applicability, potency and persistence. While the potential for multiplex gene editing is limited in primary cells, iPSC can theoretically bear unlimited genetic changes. In contrast to primary cells, genetic engineering of iPSCs results in fully modified clonal lines, which could be extensively evaluated resulting in a stable and safe source. The use of CARs endows iPSC-derived T cells with HLA-independent and customizable antigen recognition. Recent data show that timely and calibrated CAR expression can allow the generation of mature adaptive CD8αβ CAR T cells. The major barrier limiting the applicability of allogeneic iPSC-derived products is the HLA-disparity between the effector T cells and the host, which may lead to graft rejection or graft-versus-host (GvH) reaction. Hypoimmunogenic, histocompatible pluripotent stem cell lines can be generated by elimination of HLA class I and II expression. Allogeneic cells, which lack "self" class I HLA molecules can however be rejected by host NK cells. Introduction of HLA-E, HLA-G or of patient-specific HLA-C have been shown to reduce NK mediated rejection of iPSC-derived cells. There are still multiple roadblocks to be overcome to improve the clinical potential of iPSC-derived CAR T, such as: a) the complexity of genetic engineering to generate master-producer iPSC banks; b) the suboptimal function and developmental maturity of iPSC-derived; c) the lack of robust, scalable, and exportable manufacturing protocols for clinical-grade iPSC-derived CAR-T cells; d) the absence of clear regulation for the product quality assessment and release for clinical use

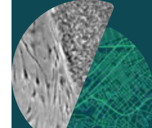
Keywords: iPSC, CAR T, genetic engineering

8:40 AM – 8:50 AM

IPSC-DERIVED HYPOIMMUNOGENIC T CELLS ENRICHED WITH TISSUE RESIDENT MEMORY T CELLS POWERFULLY ATTACK CERVICAL CANCER

Ando, Miki[1], Ishii, Midori[1], Furukawa, Yoshiki[1], Igarashi, Kyomi[2], Kinoshita, Shintaro[1], Azusawa, Yoko[3], Terao, Yasuhisa[4], Ando, Jun[3] and Nakauchi, Hiromitsu[2]
[1]Department of Hematology, Juntendo University School of Medicine, Tokyo, Japan, [2]Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA, [3]Cell Therapy and Transfusion Medicine, Juntendo University School of Medicine, Tokyo, Japan, [4]Obsterics and Gynecology, Juntendo University School of Medicine, Tokyo, Japan

Cervical cancer harbors high-risk human papilloma virus (HPV) oncoproteins in 99% of the cases. Although HPV vaccines ef-



fectively prevent HPV infections, they have no effect on established cancers. As metastatic cervical cancer is highly refractory to chemotherapy and prognosis is extremely poor, especially in young patients, development of an effective cervical cancer treatment is an urgent issue. Functionally rejuvenated HPV-specific CTLs (HPV-rejTs) generated from iPSCs robustly suppress cervical cancer (Honda et al., Molecular Therapy 2020). However, autologous rejT generation is time-consuming, leading to difficulty in treating patients with advanced cancer. Although use of allogenic HPV-rejTs can obviate this, a major obstacle is rejection by the patient immune system. We generated HLA-A24&-E dual-integrated HPV-rejTs after erasing HLA class I antigens. These rejTs not only suppressed recipient immune rejection, but also retained more robust cytotoxicity than the original CTLs. HPV-rejTs did not require peptide pulses and showed stronger cytotoxicity against endogenous antigens, whereas the original CTL clones required peptide pulses for killing. Single-cell RNA sequencing analysis revealed that HPV-rejTs were highly enriched in tissue-resident memory T (Trm) cells and showed high expression of genes associated with cytotoxicity, whereas these genes were expressed at low levels in the original CTLs. Genes associated with immunological synapse were also upregulated in HPV-rejTs. These features may have promoted stronger TCR activation and increased TCR-mediated target cell death. Based on this preclinical study, we have begun production of clinical grade HPV-rejTs and have successfully established a master cell bank of HLA-edited iPSCs at our cell processing center. We are currently generating HPV-rejTs from iPS cells in this master cell bank. With these Trm-enriched HPV-rejTs, we hope to deliver “off-the-shelf” T cell therapy for women who are suffering from cervical cancer in the near future.

Funding Source: These studies were supported by a grant from KAKENHI program (Grant Number 18K07273) and by grants from the Japan Agency for Medical Research and Development (JP19bm0404032 and JP21bk0104117).

Keywords: Trm-enriched hypoimmunogenic HPV-CTLs, single cell RNA-sequencing, CRISPR/Cas9 gene editing

8:50 AM – 9:00 AM

A SCALABLE, BIOREACTOR-BASED PROCESS UTILIZING A SYNTHETIC CYTOKINE RECEPTOR PLATFORM FOR PRODUCING HIGH YIELDS OF IPSC-DERIVED CYTOTOXIC INNATE LYMPHOCYTES AS AN “OFF-THE-SHELF” CANCER THERAPEUTIC

Rowland, Teisha[1], Arnold, Cassidy[2], Jarrell, Dillon[2], O’Hara, Samantha[3], Yingst, Ashley[3], Vereide, David[3], Koning, Ryan[4], Nicolai, Chris[5], Hernandez, Susana[6], Wu, Way[7], Mittelsteadt, Kristen[5], Leung, Wai-Hang[6], Green, Shon[6], Michels, Kathryn[6], Beitz, Laurie[5], Ryu, Byoung[5], Crisman, Ryan[8], Scharenberg, Andrew[9], Garbe, Christopher[10], Larson, Ryan[11] and Salinas, Branden[12]

[1]Engineered Allogeneic Therapies, Umoja Biopharma, Broomfield, CO, USA, [2]iPSC Process Development, Umoja Biopharma, Boulder, CO, USA, [3]Cellular Discovery, Umoja Biopharma, Boulder, CO, USA, , [4]Cellular Discovery, Umoja Biopharma, Seattle, WA, USA, [5]Discovery, Umoja Biopharma, Seattle, WA, USA, [6]In Vivo Modeling, Umoja Biopharma, Seattle, WA, USA, [7]Vector Biology, Umoja Biopharma, Seattle, WA, USA, [8]Technical Operations, Umoja Biopharma, Boulder, CO, USA, [9]CEO, Umoja Biopharma, Seattle, WA, USA, [10]Manufacturing, Umoja Biopharma, Boulder, CO, USA, [11]Immunology, Umoja Biopharma, Seattle, WA, USA, [12]Process Development, Umoja Biopharma, Boulder, CO, USA

While induced pluripotent stem cells (iPSCs) are a renewable, modifiable, and scalable starting material for cancer immunotherapies, current approaches for differentiating iPSCs into therapeutic immune effector cells require complex cytokine regimens and feeder cells to achieve sufficient yields for even early clinical trials. Here, we present a controllable differentiation and expansion process for manufacturing immune effector cells, termed Synthetic Receptor Enabled Differentiation (ShRED), which is xenogeneic- and feeder-free and has reduced cytokine requirements. In ShRED, iPSCs undergo precision gene editing to express a synthetic cytokine receptor, the Rapamycin-Activated Cytokine Receptor (RACR). RACR activation, with FDA-approved small molecule rapamycin, induces signals analogous to JAK/STAT cytokine signaling, promoting differentiation and expansion of highly pure RACR-induced Cytotoxic Innate Lymphoid (iCIL) cells expressing innate activating receptors with unprecedented yields. Using ShRED, we observed >600-fold expansion of hematopoietic progenitors (HPs) (>85% CD43+/CD45+/CD34+/CD38-) and >1 million-fold expansion of the final RACR-iCIL product (>95% CD45+/CD56+/LFA1+) from initial iPSCs. In vivo, RACR engagement in RACR-iCILs promotes engraftment and expansion through pro-survival signals mimicking IL-2/IL-15. Because RACR-iCILs are rapamycin-resistant, whereas the host is sensitive to rapamycin-mediated immunosuppression, host-mediated rejection of RACR-iCILs is inhibited. Functionally, RACR-iCILs demonstrated potent cytotoxicity against multiple solid tumor cell lines, secreting IFNγ and TNFα and outperforming conventionally derived iPSC-NKs. In a preclinical tumor xenograft model, RACR-iCILs demonstrated potent breast adenocarcinoma tumor inhibition in the presence of rapamycin without exogenous cytokines. We are adapting ShRED to a dynamic, scalable, GMP-compatible bioreactor system. Taken together, these data demonstrate the capacity of our process to efficiently generate an effective “off-the-shelf” cancer immunotherapy cell product, improving upon the standard iPSC-based allogeneic manufacturing process by increasing process control and product consistency, while decreasing raw material, complexity, and cost.

Keywords: cancer, immunotherapy, chimeric antigen receptor (CAR)

9:00 AM – 9:10 AM

CLINICAL MANUFACTURING PROCESS FOR ENGINEERED CLONAL IPSC LINES

Bershadsky, Julia[1], Csaszar, Liz[1], Jamieson, Leanne[2], Mann, Jasdeep[3], Ng, Siemon[2], Prochazka, Laura[4], Sahaf, Zahra[4], Sheng, Lifu[2], Titus, Emily[5] and Zeidan, Nabil[4]

[1]Manufacturing Sciences, Notch Therapeutics Inc., Toronto, ON, Canada, [2]Analytical Development and Quality, Notch Therapeutics Inc, Toronto, ON, Canada, [3]Protein and cell engineering, Notch Therapeutics Inc, Seattle, WA, USA, [4]Protein and cell engineering, Notch Therapeutics Inc, Toronto, ON, Canada, [5]Technical operations, Notch Therapeutics Inc, Toronto, ON, Canada

Multiple CAR-T cell therapies have now shown success as cancer immunotherapy. However, current CAR-T products require patient-specific T-cells for the manufacturing of the final drug product, which can be inconsistent due to patient variability and is reliant on complex vein-to-vein logistics. Engineered induced pluripotent stem cells (iPSCs) have the potential to provide consistent, clonal, and functionally enhanced starting cell material for CAR-T cell therapy. One of the challenges in the manufacturing of genetically engineered iPSCs is single cell cloning, specifically, the choice of the optimal culture condition that promotes single cell survival, single cell dispensing technology with confirmation of clonality, and a reliable clonal screening process to support the rapid selection of suitable clones for banking. Here, we present a clinically applicable workflow, and in-process analytics for the generation of genetically engineered iPSC

clonal lines. Before initiating process development, we used risk based assessments to identify raw materials and equipment appropriate for manufacturing. We then developed a workflow for single cell seeding with the VIPS technology, supported with a clonality report for regulatory submission. Next, we optimized the MAD7-based editing conditions for double or triple knock-out iPSC line generation in one round of cloning that achieves > 225 single cell derived clones per campaign. Finally, we established molecular techniques for in-process manufacturing tests for the rapid selection of clones with the desired genetic modifications, genomic stability, and pluripotency. Our analytical testing strategy for iPSC banks has been developed to ensure the banks meet expected regulatory requirements. Our platform can be used for single, double or triple knock-out manufacturing campaigns and is extremely versatile and efficient for supporting additional multiplex engineering processes to generate stable clonal iPSC lines.

Keywords: Engineering iPSC Clonal lines, VIPS technology for single cell seeding, In process analytics for clones selection

9:10 AM – 9:20 AM

DEVELOPMENT OF MASTER IPSCS WITH SWITCHABLE HLA GENES BY MEGABASE-SCALE GENOME ENGINEERING

Aizawa, Yasunori[1], Ohno, Tomoyuki[2], Matsuzawa, Ayumi[2] and Yanashima, Kentaro[2]
[1]School of Life Science and Technology, Tokyo Institute of Technology, Yokohama, Japan, [2]Logomix, Inc., Yokohama, Japan

We have recently developed a genome engineering platform for cells having long and complex genomes such as human cells, called Universal Knock-in System or UKiS. UKiS allows for precise substitution of megabase-scale regions into synthetic genomic sequences of our design in scarless and allele-specific manners in human induced pluripotent stem cells (iPSCs); both alleles of your interest in autosomes can be efficiently modified and any unnecessary sequences such as loxP or markers are not left at the engineered regions. UKiS maximizes the capability of multi-functionalization of human cell for various industrial uses including therapeutic one. We are currently applying this genome engineering platform for generating new types of iPSCs for future allogeneic cell therapy. In this presentation, we introduce two types of master iPSCs that we created to deepen our understanding of HLA-mediated cell-cell interactions between immune and target cells and to develop allogeneic therapeutic cells. The first master cell (HLA-I free master iPSCs) has ~400 kb deletion of all the six HLA class I gene loci and integration of the UKiS donors at both alleles, whereas the second one (All HLA free master iPSCs) has ~1 Mb deletion of all of the six HLA class I and all the 11 HLA class II gene loci and integration of the UKiS donors at both alleles. The UKiS donor alleles can be used as landing pads which can be efficiently replaced with any gene cassettes of your interest. Here, to demonstrate usefulness of our master iPSCs, we created two different iPSC lines from HLA-I free master iPSCs by replacing both UKiS donor alleles with the following gene fragments: 1) anti-CD19 CAR & the entire gene territory of HLA-E*01:01:01 gene containing the signal sequence of HLA-A or 2) the entire gene territories of HLA-A*24:02:01, HLA-B*07:02:01, HLA-C*07:02:01 and HLA-E*01:01:01. In both cases, ~10 kb-long integration of the entire HLA gene territories including promoters and introns was effectively performed, and all the integrated HLA genes were expressed in the endogenous manner because B2M was intact. These master iPSCs are advantageous in investigating the HLA-mediated interaction rules between immune cells and their target cells as well as in developing cell modality for allogeneic cell therapy and regenerative medicine.

Keywords: iPS-based allogeneic cell therapy, Megabase-scale genome engineering, HLA Biology

9:20 AM – 9:40 AM

GENOME EDITING OF T CELLS FOR CANCER IMMUNOTHERAPY

Bonini, Chiara
IRCCS San Raffaele Scientific Institute, Italy

It has been clearly demonstrated that by redirecting T-cell specificity towards selected tumour-associated antigens, T cells can eliminate cancer cells. Early approaches involving ex vivo expansion and reinfusion of tumour-infiltrating lymphocytes has now evolved into gene-transfer based approaches, ie: the insertion of chimeric antigen receptors (CARs) genes. These methods have shown unprecedented clinical results, particularly in B-cell malignancies, but challenges remain to further improve long-term responses in additional haematological malignancies and in solid tumours. For instance, tumor genetic instability and inhibitory mechanisms active in the tumor microenvironment can result in tumor immune evasion. Furthermore, T cell manipulation and expansion may affect the phenotype and overall fitness of the cells. Genome editing adds an extra level of sophistication and opportunities to the field, because, in addition to insertions, genes can be disrupted or substituted, opening up a wide new range of possibilities to manipulate the immune system. We have identified TCRs specific for shared oncogenic antigens and developed genome editing based protocols to completely and permanently redirect T-cell specificity while preserving T-cell fitness. This new opportunity shifted the research focus and raised up novel questions: the main issue is no more how to harvest a sufficient number of tumor-specific T cells from each single patient, but how to isolate design and combine tools to proficiently generate and expand the most fit engineered T cells for each target disease. The selected tools and protocols should ideally allow T cells to infiltrate the tumor mass, to recognize relevant tumor antigens, to survive and resist the immunosuppressive signals present in the tumor microenvironment and to persist as memory cells, to patrol the organism for recurrence. Challenges and opportunities towards the generation of optimal T cell therapy products will be discussed.

Keywords: Cancer Immunotherapy, Adoptive T cell therapy, Genome editing, T cells

THE USE OF STEM CELLS FOR DISEASE MODELING

Sponsored by: bit.bio

8:15 AM – 9:55 AM

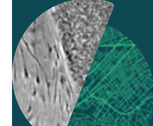
Room 253, Meeting Level 2

8:20 AM – 8:40 AM

RECONSTRUCTING ORGANOTYPIC ENDOTHELIUM AND MESENCHYME FROM IPSCS TO STUDY PULMONARY DISEASES

Gu, Mingxia
CuSTOM Organoid Center, Cincinnati Children's Hospital Medical Center, OH, USA

Different types of human induced pluripotent stem cell (hiPSC) derived organoid models have been established to recreate the architecture and physiology of their in vivo counterparts.



Although it is well recognized that the vasculature co-develops with other cell types during organ formation to provide critical growth factors and improve regional patterning, to date, there is no lung organoid model that contains both organotypic endothelium and alveolar epithelium. Herein, we are developing a novel approach to co-differentiate mesoderm-derived endothelium and mesenchyme with endoderm-derived lung epithelium from hiPSCs, which enables intimate cell-cell communication from the very beginning of lung organogenesis. Excitingly, we found that endothelial cells (ECs) co-developed with distal lung epithelium gained aerocyte (aCap cells) specific gene signatures, providing a promising system to generate and maintain lung-specific ECs in a dish. Leveraging the vascularized lung organoid system, we sought to model a congenital lung disorder called alveolar capillary dysplasia with misalignment of pulmonary veins (ACD/MPV) caused by FOXF1 mutations. ACD/MPV is characterized by capillary malformation and impaired alveologenesis that results in respiratory failure. We found that the development of alveolar capillary network was significantly hampered in organoids derived from hiPSCs harboring FOXF1 mutations compared with controls. This was also accompanied by reduced alveolar epithelial lineages, indicating impaired endothelial-epithelial crosstalk in ACD/MPV. With this new organoid model, we now have a comprehensive platform to understand pulmonary vascular development and related disease mechanisms in humans.

Keywords: lung organoid, endothelial cells, mesenchyme, pulmonary vascular disease

8:40 AM – 8:50 AM

LOSS OF CARDIAC FIBROBLAST BAG3 POTENTIATES TGFBR2 SIGNALING AND FIBROSIS IN DILATED CARDIOMYOPATHY

Wang, Bryan Zicheng[1], Morsink, Margaretha[2], Kim, Seong[3], Luo, Lori[2], Zhang, Xiaokan[4], Soni, Rajesh[5], Lock, Roberta[2], Rao, Jenny[6], Zhuang, Richard[2], Kim, Youngbin[2], Nash, Trevor[7], Gorham, Josh[3], Kim, Yuri[3], Brown, Kemar[8], DeLaughter, Daniel[3], Zhang, Qi[3], McDonough, Barbara[9], Oudit, Gavin[10], Fine, Barry[4], Seidman, Christine[3], Seidman, Jonathan[3] and Vunjak-Novakovic, Gordana[2]

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Loss of function mutations in the co-chaperone protein Bcl2-associated anthanogene 3 (BAG3) are associated with dilated cardiomyopathy (DCM) and reduced sarcomere protein turnover in cardiomyocytes. However, while BAG3 is ubiquitously expressed, its function in other cell types of the heart is unknown. Of particular interest are cardiac fibroblasts (CFs) that maintain the extracellular matrix (ECM), which becomes dysregulated in DCM. Here, we studied the function of BAG3 in iPSC-derived cardiac fibroblasts (CFs) using BAG3 knockout and wild-type human induced pluripotent stem cells (iPSC). By generating engineered heart tissues from a series of cell-type specific knockouts, we determined the contribution of CF BAG3 to engineered heart tissue function. Surprisingly, even if normal CM genotype is maintained, the loss of BAG3 in CFs caused a reduction in contractile force and an increase in collagen deposition, recapitulating the phenotype of DCM. We further modeled BAG3 loss in CFs using culture substrates of varying stiffness. In BAG3-/-CFs cultured on physiologically stiff substrate (8kPa), we observed an increased sensitivity to TGFβ signaling and activation of a fibrogenic response marked by ECM deposition and proliferation. Mechanistically, BAG3 suppresses TGFβ signaling through post-translational regulation of transforming growth factor receptor 2 (TGFBR2). Specifically, BAG3 binds TGFBR2 and mediates its ubiquitination and proteasomal degradation. Loss of BAG3 therefore resulted in increased TGFBR2 levels and downstream SMAD2 signaling. Finally, we performed single-nuclei sequencing of cardiac tissue from three DCM patients harbouring BAG3 truncating variants. We observed an increase in extracellular matrix and fibrotic gene expression in mutant CFs when compared to control samples, validating our observations in-vitro. Together, these results suggest that the cardiac fibrosis observed in BAG3 DCM is a primary effect of BAG3 loss in CFs, rather than a compensatory response to cardiomyocyte death. This suggests that therapeutic interventions targeting cardiomyocytes alone and not fibroblasts may be ineffective. This study highlights the ability of iPSC-based models and tissue engineering to unravel the cell-type specific aspects of cardiac disease.

Funding Source: We gratefully acknowledge funding from the NIH (P41EB027062 and R01HL076485) and the AHA Predoctoral Fellowship (915283).

Keywords: Cardiac, Fibroblasts, BAG3

8:50 AM – 9:00 AM

SINGLE CELL-GUIDED PRENATAL DERIVATION OF PRIMARY EPITHELIAL ORGANOIDS FROM THE HUMAN AMNIOTIC AND TRACHEAL FLUIDS

Gerli, Mattia Francesco Maria[1], Calà, Giuseppe[2], Beesley, Max[3], Sina, Beatrice[3], Tullie, Lucinda[4], Panariello, Francesco[5], Michielin, Federica[3], Sun, Kylin Yunyan[3], Davidson, Joseph[3], Russo, Francesca[6], Jones, Brendan[3], Lee, Dani[3], Savvidis, Savvas[7], Xenakis, Theodoros[3], Simcock, Ian[8], David, Anna[9], O'Callaghan, Christopher[3], Olivo, Alessandro[7], Eaton, Simon[3], Loukogeorgakis, Stavros[3], Cacchiarelli, Davide[5], Deprest, Jan[10], Li, Vivian[11], Giobbe, Giovanni[3] and De Coppi, Paolo[3]

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Despite the current advances in prenatal diagnosis, it is still difficult to predict severity and outcomes of many congenital malformations. New technologies for patient-specific prenatal disease modelling may optimise personalised prediction. We and others have described the presence of mesenchymal stem cells in amniotic fluid (AFSC) that can be reprogrammed into induced pluripotent stem cells (iPSCs), with potential to differentiate in any fetal cell type. However, the extensive manipulations required, and lengthy reprogramming process limits the ability to define individual phenotypes and plan treatments prenatally.

Consequently, it would be advantageous if tissue-specific fetal stem cells could be directly obtained during pregnancy. Using single cell transcriptomic, we drafted an atlas of all the cellular identities present in amniotic fluid (AF), and identified viable epithelial stem/progenitor cells. These cells manifested fetal intestinal, renal and pulmonary origin. With relevance for prenatal disease modelling, we cultured these cells to form clonal epithelial organoids autologous to the fetus and manifesting small intestine, kidney and lung identity and functional properties. Ultimately, to demonstrate validity of our approach for disease modelling, we derived lung organoids from both AF and tracheal fluid (TF) cells of pregnancies affected by Congenital Diaphragmatic Hernia (CDH). These organoids showed differences to non-CDH controls and can recapitulate some pathological features of the disease. The derivation of Amniotic Fluid Organoids (AFO) only requires 4-6 weeks from cells isolation and is compatible with continuation of pregnancy. This strategy allows investigation of fetal epithelial tissues at clinically relevant developmental stages, with a minimally invasive approach. Ultimately, this may enable the development of novel personalised therapeutic tools tailored to the fetus, as well as to predicting the effects of such therapies.

Funding Source: Mattia FM Gerli holds a H2020 Marie Skłowdoska-Curie Fellowship (843265 AmnioticID). Work in our laboratory is supported by the NIHR Great Ormond Street Hospital Biomedical Research Centre.

Keywords: Amniotic Fluid Organoids, Fetal Organoids, Prenatal Disease Modelling

9:00 AM – 9:10 AM

A NOVEL IPSC-DERIVED COLLECTING DUCT CYSTOGENESIS MODEL OF ADPKD FOR DRUG DISCOVERY

Mae, Shin-Ichi[1], Hattanda, Fumihiko[2], Nishio, Saori[2] and Osafune, Kenji[3]
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Autosomal dominant polycystic kidney disease (ADPKD) is caused by mutations in PKD1 or PKD2 and manifests the progressive formation of numerous renal cysts that predominantly arise from collecting ducts (CDs), leading to end-stage renal failure. The detailed mechanism of cystogenesis remain to be elucidated due to the lack of a suitable model that reproduces human CD cystogenesis. Tolvaptan, an antagonist of arginine vasopressin receptor 2 (AVPR2), is clinically used as the only approved drug, but it does not control the disease progression. Therefore, relevant CD cystogenesis models that reproduce human ADPKD pathology are required for elucidating disease mechanisms and discovering therapeutic drugs. In the current study, we succeeded in establishing a long-term expansion culture method for human induced pluripotent stem cell (hiPSC)-derived ureteric bud tip cells (UBTCs), one of the tissue-specific stem cells in embryonic kidneys that give rise to CDs and lower urinary tract epithelia, and found that the expansion culture advances the developmental stage of UBTCs to late branching phase. All CD organoids generated from PKD1 homozygous mutant hiPSCs through these UBTCs spontaneously developed cyst lesions as developmental stage of UBTCs progressed. We also clarified the initiation mechanism of cystogenesis and developed a high-throughput screening (HTS) platform that explores therapeutic drug compounds to suppress cyst enlargement. Finally, we successfully identified retinoic acid receptor (RAR) agonists as novel candidate drugs that significantly suppress cyst enlargement in our in vitro model and further confirmed the therapeutic effects of all-trans retinoic acid (ATRA) on an ADPKD mouse model in vivo. We are currently elucidating the detailed mechanisms by which RAR agonists suppress cyst enlargement and aim to develop novel treatments for ADPKD by drug repurposing. We will further clarify the pathological mechanisms including those underlying the transition from cyst formation to enlargement and eventually develop curative treatments for ADPKD.

Keywords: Human iPS cell, Organoid, Collecting duct

9:10 AM – 9:20 AM

USING HUMAN IPSC-DERIVED NEURONS AS A PLATFORM TO INVESTIGATE SUBTYPE SPECIFIC ALTERATIONS IN NEURODEVELOPMENTAL DISORDERS: OUR PROGRESS ON SSADH DEFICIENCY

Afshar Saber, Wardiya[1], Teaney, Nicole[2], Jumo, Hellen[2], Winden, Kellen[3], McGinty, Gabrielle[2], Ebrahimi-Fakhari, Darius[3], Pearl, Phillip[3] and Sahin, Mustafa[3]
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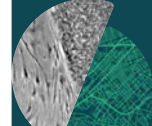
Succinic semialdehyde dehydrogenase (SSADH) deficiency is an autosomal-recessive neurometabolic disorder caused by bi-allelic mutations in the ALDH5A1 gene. It is the most prevalent inherited disorder of GABA metabolism and is characterized by accumulation of two neuromodulators, gamma-aminobutyric acid (GABA) and gamma-hydroxybutyric acid (GHB), in the CNS. Previous studies using rodent models have shown that disruption in GABA signaling can lead to dysregulation of mitochondria numbers, turnover, and function. Over the last 30 years, an expanded understanding of pathophysiology based on the corresponding animal model (Aldh5a1-/- mice) has emerged, but effective pharmacotherapy remains elusive. Alternative models and therapies that address the accumulation of GABA and GHB, and their downstream effects, are needed. In this study, we used fourteen iPSC lines: three patient lines and sex matched parental controls and CRISPR corrected lines each transduced with hNGN2 and hDLX2-hASCL1 respectfully generate excitatory neurons and GABAergic neurons. We show that hiPSCs can differentiate into excitatory neurons and GABAergic neurons regardless of the allelic dosage of ALDH5A1. We found that hiPSC-derived excitatory neurons display altered neurite outgrowth and synaptic development which leads to hyperactivity of the developing excitatory neuronal network. Moreover, we showed that the CRISPR correction ALDH5A1corr/corr shows similar network activity to the parental control ALDH5A1+/- suggesting that hiPSC-derived excitatory neurons network's hyperactivation is linked to the ALDH5A1 mutation. Additionally, we identified neuron subtype-specific metabolic and gene expression changes linked to SSADH deficiency. Furthermore, we showed that similarly to clinical presentation, SSADHD results in increased GABA and GHB levels in hiPSC-derived GABAergic neurons. Furthermore, we developed an imaging platform based on calcium imaging and optogenetics to manipulate the network of neurons formed by hiPSC-derived GABAergic and excitatory neurons in vitro in a high-throughput fashion. Finally, we demonstrated we rescued these phenotypes using ALDH5A1 mRNA demonstrat-



ing the potential of the mRNA-based therapeutics in SSADH deficiency.

Funding Source: IDDRC - SSADH Foundation

Keywords: Neurodevelopmental disorders, GABA, excitatory neurons, neural networks, MEA, calcium imaging and optogenetics

9:20 AM – 9:30 AM

GENERATION OF A DIABETIC IMMUNOPEPTIDOME USING STEM CELL-DERIVED ISLET CELLS

Van Dervort, Alana[1], Klager, Susan[2], Seedhom, Mina[3], Bandyopadhyay, Sushobhana[3], Keskin, Derin[4], Phulphagar, Meera[2], Brehm, Michael[3], Carr, Steve[2] and Melton, Douglas[5]
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Why are beta cells susceptible to immune attack? Endocrine cells are preferentially targeted in organ-specific autoimmunity. In Type 1 diabetes (T1D) insulin-producing beta cells are recognized and destroyed by autoreactive T cells. Self-peptides presented by HLA molecules play a critical role in shaping the specificity of autoreactive T cell recognition. Despite this, the exact autoantigens that trigger this attack are unclear. Likewise, it is unknown whether autoreactive T cells recognize self-peptides presented on other islet cells, such as alpha cells, that are spared from attack. Our understanding of diabetic epitopes, to date, has relied on T cell activation assays and immunopeptidome profiling performed on murine islets or immortalized human beta cells. Furthermore, requirements for high cellular inputs have prevented determination of an immunopeptidome from diabetic patient islets. We took advantage of large-scale in vitro differentiation to generate over one billion stem cell beta and alpha cells from diabetic and healthy patient induced pluripotent stem cell sources. This enabled us to generate the first beta cell and alpha cell immunopeptidome from a diabetic patient donor. Unexpectedly, we observed diabetic autoantigen presentation in both stem cell alpha and beta cells. We also identified known, as well novel epitopes in both the beta cell and alpha immunopeptidome. Finally, using a humanized mouse model of T1D, we identify candidate T1D patient autoreactive TCRs from diabetic stem cell beta cell T cell infiltrate. Together, this represents a proof of principle toward comprehensively defining T1D disease-relevant autoantigens within an individual.

Keywords: type 1 diabetes, HLA immunopeptidome, TCR sequencing, single cell transcriptome, multi-omics

9:30 AM - 9:50 AM

UNEXPECTED ROLES OF EXTRACELLULAR VESICLES IN SARS-COV-2 INFECTION AND TRANSMISSION

Chen, Ya-Wen
Otolaryngology, Cell, Developmental and Regenerative Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

SARS-CoV-2 infection can cause severe lung damage and lethality. The rapid genomic alterations of SARS-CoV-2 have generated highly transmissible variants, and have raised concerns that the virus will evade vaccine-induced immunity. Therefore, there is an urgent need for new therapeutic approaches. Recent studies have identified both the “door” (a receptor called ACE2) and “key” (a protease called TMPRSS2) through which the virus enters host cells. TMPRSS2 was shown to activate the fusion proteins of several respiratory viruses, including human influenza viruses and coronavirus families. Its activity is thus crucial for infectivity and viral spread. While efforts have been focused on developing drugs against the spike protein or the receptor ACE2, TMPRSS2 as an alternative target has not been thoroughly considered. Furthermore, much remains to be learned about the viral transmission inside the lung and why cell types that do not express TMPRSS2 and ACE2 at the mRNA level, such as endothelial cells (ECs) and macrophages, are infected by the virus. Using lung organoid as a model, we found TMPRSS2 present in secreted extracellular vesicles (EVs) along with ACE2 and that EVs significantly enhance the SARS-CoV-2 pseudovirus transduction rate. These data suggest that EVs containing TMPRSS2 and ACE2 potentially interact with SARS-CoV-2 extracellularly and the viruses travel with EVs to recipient cells, providing a potential mechanism for viral transmission in the lungs and to cell types that do not express TMPRSS2 or ACE2, such as ECs and macrophages.

Keywords: lung organoid, SARS-CoV-2, extracellular vesicle

ENGINEERING MODELS OF HUMAN EMBRYOLOGY
8:15 AM – 9:55 AM
Room 259, Meeting Level 2

8:20 AM – 8:40 AM

TROPHOBLAST ORGANOIDS FOR THE STUDY OF MATERNAL-FETAL INTERACTIONS IN HUMAN PREGNANCY

Turco, Margherita
Friedrich Miescher Institute for Biomedical Research, Switzerland

The key to a successful pregnancy is the fascinating yet ill-understood dialogue between the maternal decidua (pregnant lining of the uterus) and fetal placental cells. Major pregnancy disorders are due to the abnormal development and interactions of the placenta with the decidua. However, our understanding of the nature and effect of these interactions in placentation is limited due to the difficulties in studying these early stages of human development. We have established a tissue-derived organoid culture system of the human placenta which recapitulates its morphology, transcriptomic profile and functions providing an invaluable tool to investigate the maternal signals that influence its development and function. By deepening our understanding of the basic biology of the maternal-fetal interactions in human pregnancy, we aim to inform the development of treatments for the preparation of an optimal endometrium to improve implantation and pregnancy outcome.

8:40 AM – 8:50 AM

A HUMAN HEART ORGANOID MODEL RECAPITULATING EARLY CARDIAC DEVELOPMENT TO INVESTIGATE THE MECHANISMS OF MATERNAL DIABETES-INDUCED CONGENITAL HEART DEFECTS

Kostina, Aleksandra[1], Lewis-Israeli, Yonatan[1], Abdelhamid, Mishref[1], Volmert, Brett[1], Wasserman, Aaron[1], Gabalski, Mitchell[1], Huang, Amanda[1], Lankerd, Haley[1], Chen, Kevin[2], Murtaza, Sardar[2], Chan, Christina[1,2], Olomu, Isoken[3] and Aguirre, Aitor[1]
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Congenital heart defects (CHD) constitute the most common birth defect in humans, affecting approximately 1% of all live births. Our knowledge of these disorders is hindered by the inability to model the developing human heart faithfully and an overreliance on animal models which albeit useful, are not always informative. Maternal diabetes (MD) during the first trimester of pregnancy is a substantial risk factor for CHD (~4-10% risk). A key understanding of how MD affects the human fetal heart remains elusive. Here, we aimed to recreate the effects of maternal diabetic conditions on early heart development using human stem cell-derived heart organoids (hHOs). hHOs were generated from pluripotent stem cells by self-assembly under conditions that reflect clinical physiological glucose and insulin levels from both healthy and diabetic mothers. Hyperglycemia and hyperinsulinemia induced significant phenotypic changes in developing hHOs characterized by lower beating frequency, cardiomyocyte hypertrophy, and dysregulated expression of key genes driving early heart formation. scRNA-sequencing revealed a decreased number of cardiomyocytes along with a significant expansion of epicardium in MD-hHOs suggesting a dysfunction in early heart field differentiation and lineage specification. LC-MS metabolomic profiling of MD-hHOs identified an important lipid imbalance in very long chain fatty acids indispensable for cardiogenesis. Further study demonstrated increased oxidative stress predominantly localized to the endoplasmic reticulum and associated with non-canonical IRE1 pathway activation. We found that abnormal IRE1 exoribonuclease activity affected fatty acid desaturase 2 – a key enzyme involved in the biosynthesis of unsaturated fatty acids. Finally, we demonstrated the ability of several therapeutical compounds to diminish IRE1 activity and recover the level of fatty acid desaturase 2 in MD-hHOs, reducing oxidative stress, lowering cardiomyocyte size, and restoration of gene expression. In summary, we created a physiologically relevant human embryonic-like heart platform to model the effects of maternal diabetes on cardiac development, discovered a new molecular mechanism driving pathologic changes in MD-induced CHD, and identified potential avenues for prevention and therapy.

Funding Source: National Heart, Lung, and Blood Institute of the National Institutes of Health under award numbers K01HL135464, R01HL151505, American Heart Association under award number 19IPLOI34660342 and Spectrum-MSU Alliance Foundation

Keywords: Human heart organoids, Congenital Heart Defects, Maternal Diabetes, ER stress, lipid imbalance

8:50 AM – 9:00 AM

GENERATION OF HUMAN BLASTOIDS FROM SINGLE NAÏVE PSCS IN STIRRED-TANK BIOREACTORS UNDER PHYSIOLOGICAL CONDITIONS FOR HIGH-THROUGHPUT SCREENS

Alsolami, Samhan[1], Jin, Yiqing[1], Zhang, Yingzi[1], Pandian, Arun[1], Shakir, Ismail[1], Klein, Shannon[1], Duarte, Carlos[2] and Li, Mo[1]
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Blastoids are a valuable tool to study human early development. Human blastoids can be derived from naïve pluripotent stem cells and consist of all three lineages of the preimplantation blastocyst. Current methods that use static batch culture to generate human blastoids have limitations including (i) low yield, (ii) the need for aggregating cells, which complicates genetic or drug screens, (iii) reproducibility issues due to uncontrolled cellular environment, and (iv) the need for Aggrewell or similar confinements that can exert unnatural geometrical strains on blastoids. Here, we developed a method for large-scale production of human blastoids from single naïve cells in non-geometrically constrained 3D culture in stirred-tank bioreactors that cybernetically maintain physiological pH and O2 with tight tolerance. We showed that blastoids produced using this system are amenable to small molecule screens. Overall, 3D bioreactor blastoids provide a reproducible, scalable, and ethical model of early human development for high-throughput screens.

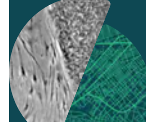
Keywords: Blastoids, Early development, Bioreactors

9:00 AM – 9:10 AM

HUMAN EMBRYO ORGANOIDS AS A MODEL FOR PERI-AND POST-GASTRULATION EMBRYO DEVELOPMENT

Neupane, Jitesh[1], Lubatti, Gabriele[2], Luisa Ruiz Tejada Segura, Mayra[2], Dietmann, Sabine[3], Scialdone, Antonio[2] and Surani, Azim[1]
[1]Wellcome Trust Cancer Research UK Gurdon Institute, University of Cambridge, UK, [2]Institute of Computational Biology, Helmholtz Zentrum München, Neuherberg, Germany, [3]Department of Development Biology, Washington University School of Medicine in St. Louis, MO, USA,

Due to technical challenges and ethical constraints on studying post-implantation human embryo development, most of our insights rely on animal proxies and in vitro models. Pluripotent stem cell-based two-dimensional (2-D) and three-dimensional (3-D) models provide insights into human gastrulation and tissue-specific organogenesis. However, in vitro models of peri-and post-gastrulation embryo development have only been reported in mice thus far. Here, we established a novel self-organising 3-D human embryo organoids (hEOs) model using human embryonic stem cells, which recapitulates crucial features of human post-implantation events, including peri-and post-gastrulation embryo development, within the same system. We show that during 22 days in culture, hEOs reveal the establishment of three germ layers (namely, ectoderm, mesoderm and endoderm) together with the elongation along the rostral-caudal axis, the emergence of primordial germ cell-like cells (PGCLCs) without exogenous bone morphogenetic protein (BMP) supplementation, development of beating heart tube, initiation of gut tube formation and embryonic hematopoiesis in sequential order. Notably, hEOs expressed cardiac troponin type 2 (TNNT2) and myosin heavy chain 2 (MYH2) at protein level, confirming the presence of functional contracting cardiac muscles. Furthermore, hEOs



also expressed RUNX1+ hemogenic endothelial progenitors and CD45+, CD31+cKIT+ hematopoietic cells together with visible de novo patches of red blood cells. Transcriptome analysis at single-cell resolution revealed neuromesodermal progenitors (NMP) contributing to neural tube and spinal cord precursors. A comparison of our dataset with the only available Carnegie stage 7 (CS7) human gastrula revealed a strong alignment with Day (D) 3 hEOs, suggesting the physiological relevance of this model. Our study shows significant advances over prior in vitro models to investigate the events of early post-implantation human embryo development. Our unique model develops beyond the gastrulation stage and will allow the exploration of intractable aspects of post-implantation human embryonic lineages and establish a foundation for advances in reproductive and therapeutic applications.

Funding Source: This work is supported by Wellcome-funded Human Development Biology Initiative (HDBI) (G112785).

Keywords: Human embryonic stem cell-based embryo model, Human embryo organoids, Post-implantation human embryo development

9:10 AM – 9:20 AM

UNDERSTANDING EXTRAEMBRYONIC DEVELOPMENT BY BUILDING HUMAN AMNIOTIC MEMBRANE FROM INDUCED PLURIPOTENT STEM CELLS

Le, Anh Phuong[1], Koehler, Karl[2], Lee, Jiyoon[2], Osorio-Hurtado, Daniel[2], Pourquie, Olivier[3], Serdy, Sara[2] and Kim, Jin[2]
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The amniotic sac protects the developing embryo from physical assaults and regulates fluid exchange between the fetus and the mother. During embryogenesis, the amniotic membrane develops adjacent to the surface ectoderm and is closely associated with extraembryonic mesoderm. The formation of amnion plays an essential role in normal versus abnormal pregnancy, yet the lack of an appropriate model hinders insights into this process in humans. Here we reported a successfully generated amnion sac derived from human induced pluripotent stem cells by subtle modifications to our previous skin organoid protocol. The organoid maintained the unicellular epithelia, transparent membrane, and amnion marker expressions until day 90 while expanding into a gigantic structure – an amnioid. We used a combination of single-cell sequencing, immunostaining, live-cell imaging, and pharmacological perturbation to compare amnioids with hair-bearing skin organoids. Our data reveal potential biochemical and mechanotransduction signaling pathways that may determine cell fate commitment within the surface ectoderm or amniotic membrane. The amnioid cells maintain nuclear YAP localization, pronounced ZO-1 at cell-cell junctions, a large cell area, and prolonged expression of YAP downstream targets and ion channels, suggesting an inter-regulatory role of mechanical pressure, cell proliferation, and cell fate commitment. We also used the skin organoid and the amnioid to uncover potential epithelia-mesenchyme interactions that regulate the mesoderm contribution to epidermis and amnion development. In conclusion, we anticipate that the human amnioid model could be used to gain deeper insights into the logic of surface ectoderm and extraembryonic development and provide an in vitro platform to understand pregnancy problems such as preeclampsia and hydramnios.

Funding Source: National Institute of Arthritis and Musculoskeletal and Skin Diseases (R01 AR075018)

Keywords: organoids, amnion, early development

9:20 AM – 9:30 AM

3D-CULTURED HUMAN BLASTOIDS MODEL LINEAGE SEGREGATION DURING EARLY POST-IMPLANTATION DEVELOPMENT

Karvas, Rowan M.[1], Zemke, Joey[1], Ali, Syed[1], Sane, Eshan[1], Dong, Chen[1], Fischer, Laura[1], Park, Kyoung-mi[1], Upton, Eric[1], Chew, Brian[2], Meyer, Brittany[1], Kelleher, Andrew[3], Spencer, Thomas[3], Dietmann, Sabine[1] and Theunissen, Thorold[1]
[1]Developmental Biology, Washington University in St. Louis, MO, USA, [2]Interdisciplinary Biomedical Graduate Program, University of Pittsburgh, PA, USA, [3]Division of Animal Sciences and Department of Obstetrics, Gynecology, and Women's Health, University of Missouri, Columbia, MO, USA

Since access to human embryos is limited, our understanding of the factors governing blastocyst implantation, trophoblast differentiation, and invasion into the maternal endometrium remains rudimentary. Blastocyst-like structures ("blastoids") generated from naïve human pluripotent stem cells (hPSCs) offer an exciting new approach to model blastocyst formation and implantation. However, the extent to which these structures can recapitulate defining features of human post-implantation development in vitro remains unresolved. Here we report an efficient protocol for generating blastoids from naïve hPSCs derived in 5i/L/A and describe conditions that support human blastoid culture through early post-implantation stages. These conditions include an optimized 3D extracellular matrix and a simplified medium containing estradiol and progesterone that resembles the receptive maternal environment. Single cell transcriptome profiling reveals lineage segregation and an absence of off-target cell types in pre-implantation blastoids, while extended blastoid culture is accompanied by epiblast maturation and rapid expansion and diversification of trophoblast lineages by day 14. 3D-cultured human blastoids undergo lumenogenesis of the epiblast and display robust trophoblast invasion in the presence of human endometrial organoids. Extended blastoid culture for 4 additional days results in the localized activation of gastrulation marker T within the epiblast and the migration of VIM+ extraembryonic mesoderm cells into the trophoblast compartment. We also provide evidence that modulation of WNT signaling alters cell fate decisions in post-implantation blastoids. These results indicate that 3D-cultured human blastoids model lineage segregation during early post-implantation development. Implantation failure is implicated in approximately half of all pregnancy losses and is a major cause of idiopathic infertility. Consequently, our work provides a robust model system to probe a previously inaccessible but critical stage of human development.

Funding Source: Shipley Foundation Program for Innovation in Stem Cell Science, Edward Mallinckrodt, Jr. Foundation

Keywords: Blastoid, Embryonic development, Placenta

9:30 AM - 9:55 AM

UNDERSTANDING MOLECULAR MECHANISMS THAT REGULATE LINEAGE SPECIFICATION IN HUMAN EMBRYOS

Niakan, Kathy
University of Cambridge, UK

During preimplantation development human embryos are comprised of pluripotent embryonic cells, which eventually form the fetus, and extra-embryonic cells, which contribute to the placenta and yolk sac. The central question we address is what are the molecular mechanisms that regulate these early cell fate choices in human embryos. We are using CRISPR/Cas9-mediated genome editing, TRIM-Away protein depletion, dominant negative mutations and small molecules to dissect the function of genes during human embryogenesis. These methods have enabled us to uncover that the first lineage specification event in human embryos is the initiation of a placental program. By integrating signalling insights from human blastocysts we have defined human embryonic stem cell culture conditions that more closely recapitulate the embryonic niche. The molecular basis of these early cell lineage decisions are of fundamental importance and have wide-reaching clinical implications for infertility, miscarriages, developmental disorders and therapeutic applications of stem cells.

Keywords: Human, embryo, development

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)

PHYSIOLOGIC FUNCTION, METABOLISM, AND STEM CELLS
8:15 AM – 9:55 AM
Room 254, Meeting Level 2

8:20 AM – 8:40 AM

EPITHELIAL CA2+ CURRENTS TRIGGERED BY ENTERIC NEURONS HEAL THE GUT

Perrimon, Norbert and Petsakou, Afroditi
Genetics, Harvard University/HHMI, Boston, MA, USA

An unresolved question in regenerative biology is how tissues transition to homeostasis after injury. Answering this question is vital for unmasking the etiology of various chronic disorders like inflammatory bowel diseases and cancer. We addressed this using the Drosophila gut, a powerful regenerative model and made the striking observation that recovery after injury depends on the highly conserved cholinergic pathway. Specifically, reduction of nAchRs (nicotinic Acetylcholine Receptors) in ECs (enterocytes, the main cell type of the Drosophila gut) after injury maintains the intestinal epithelium in an over-inflammatory and over-proliferative state rendering it unable to recover, whereas increase of nAchRs in ECs expedited recovery restoring the epithelium to a state identical to controls. In addition, we identified a small population of cholinergic enteric neurons, referred as ARCENs (Anti-inflammatory Recovery specific Cholinergic Enteric Neurons), that are required for nAchRs in ECs to advance gut recovery. Further, we found that activation of nAchRs in ECs, that are innervated by ARCENs, initiates Ca2+ currents that spread across the tissue by epithelial gap junctions promoting ion balance, epithelial maturation and reducing inflammation. Altogether, we discovered that cholinergic neuro-epithelial communication triggers epithelial gap junctions to spread Ca2+ currents that heal the gut after damage.

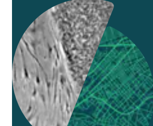
Keywords: Enteric neurons, Ca2+ , nicotinic receptors, regeneration

8:40 AM – 8:50 AM

PREVENTION OF ENGRAFTMENT ARRHYTHMIA FOLLOWING CARDIAC REMUSCULARIZATION WITH GENE-EDITED HUMAN PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

Marchiano, Silvia[1], Nakamura, Kenta[2], Reinecke, Hans[1], Neidig, Lauren[3], Kadota, Shin[4], Lai, Michael[5], Perbellini, Filippo[5], Yang, Xiulan[1], Klaiman, Jordan[1], Blakely, Lesley[1], Karbassi, Elaheh[1], Fenix, Aidan[1], Jayabalu, Anu[5], Kalucki, Faith[5], Futakuchi-Tsuchida, Akiko[5], Pabon, Lil[5], Knollmann, Bjorn[6], Kattman, Steven[5], Thies, R. Scott[5], Sniadecki, Nathan[7], MacLellan, W. Robb[2], Bertero, Alessandro[8] and Murry, Charles[1]
[1]Department of Laboratory Medicine and Pathology, Institute for Stem Cell & Regenerative Medicine at the University of Washington, Seattle, WA, USA, [2]Department of Cardiology, University of Washington, Seattle, WA, USA, [3]Department of Comparative Medicine, University of Washington, Seattle, WA, USA, [4]Department of Regenerative Science and Medicine, University of Japan, Shinshu, Japan, [5]Sana Biotechnology, Seattle, WA, USA, [6]Department of Clinical Pharmacology, Venderbilt University, Nashville, TN, USA, [7]Department of Bioengineering, University of Washington, Seattle, WA, USA, [8]Department of Molecular Biotechnology and Health Sciences, University of Torino, Italy

Transitory but serious ventricular arrhythmias arising after transplanting human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) pose a major challenge in the translation of this technology into the clinic. We named this phenomenon engraftment arrhythmia (EA), and physiological evidence implicates pacemaker-like activity of immature hPSC-CMs in its pathogenesis. Indeed, hPSC-CMs are characterized by automaticity, i.e., the ability to spontaneous depolarize and fire action potentials. To identify ion channels responsible for hPSC-CMs automaticity, we performed bulk RNAseq of hPSC-CMs transplanted in vivo and isolated samples at different time points. We used CRISPR-Cas9 technology to sequentially remove HCN4 (funny current), CACNA1H (T-type Ca2+ current), SLC8A1 (NCX1, Na+-Ca2+ exchanger), and overexpressed KCNJ2 (inward-rectifying potassium current). After characterizing the cell lines in vitro, we proceeded by transplanting 150xe6 cells into healthy pig hearts, and we monitored the heart rate with telemetry system up to 7 weeks after injection. Single, double and even triply edited hPSC-CMs not only exhibited different degrees of automaticity in vitro but also caused EA once transplanted in vivo. Only the combination of the four edits led to hPSC-CMs that, like adult ventricular CMs, are quiescent-yet-excitable. Importantly, these quadruply edited cardiomyocytes engrafted without causing EA ($N = 3$; $p < 0.001$ compared to $N = 7$ WT controls which exhibited weeks of sustained ventricular tachycardia, VT). We then performed a dose-escalation study, transplanting 500xe6 cells into uninjured animals ($N = 2$). In WT animals, this dose showed 100% EA penetrance and 67% mortality. In contrast, animals receiving the quadruple-edited hPSC-CMs exhibited only a brief, self-terminating episode of sustain VT lasting less than one day and returning to sinus rhythm until the 3 months endpoint. Ex vivo live cardiac slices demonstrated that these grafts are viable and electromechanically integrated, beating in synchrony with the host. This study demonstrates that the intrinsic pacemaker-like activity of hPSC-CMs is one of the major causes of EA after hPSC-CMs transplantation. Approaches that target automaticity should



increase the safety profile of hPSC-CM therapy in humans for cardiac regeneration.

Funding Source: UW Heart Regeneration Program, Washington Research Foundation, Mike and Lynn Garvey, a sponsored research agreement from Sana Biotechnology and funding from NIH, Leducq Fondation and Bruce-Laughlin and ISCRM fellowships.

Keywords: engraftment arrhythmia, cardiac regeneration, hPSC-CMs electrophysiology

8:50 AM – 9:00 AM

KLF4 MAINTAINS HAIR FOLLICLE STEM CELL QUIESCENCE

Millar, Sarah E.[1], Zhu, Xuming[1], Moran, Deborah[2], Szigety, Katherine[2] and Xu, Mingang[1]
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The transcription factor KLF4 is essential for embryonic development of the epidermal barrier, but its functions in postnatal skin are poorly understood. KLF4 is expressed in adult suprabasal epidermis and in hair follicles, where it localizes to quiescent bulge stem cells and is absent from proliferating cells. Inducible pan-epidermal Klf4 deletion in postnatal mice caused epidermal hyperproliferation, trans-epidermal water loss, inflammation, and premature entry of hair follicles into the anagen growth phase. The latter phenotype was recapitulated by inducible hair follicle stem cell (HFSC)-specific Klf4 deletion, demonstrating that it was caused by intrinsic loss of Klf4 in HFSCs. To identify candidate targets and partners of KLF4 in HFSCs we carried out multiome single cell RNA-seq and ATAC-seq on control and Klf4-deleted hair follicles and CUT&RUN for KLF4 in telogen hair follicle cells. Compared with controls, Klf4-deleted HFSCs displayed decreased expression of the secreted HFSC quiescence regulator Fgf18 and the cell cycle inhibitor p21, and upregulation of Vdr, which is known to promote anagen onset. We identified multiple sites of altered chromatin accessibility at each of these loci in Klf4 mutants, and KLF4 directly localized to a subset of these. For all these genes, chromatin co-accessibility scores predicted direct interactions of KLF4 with loci containing binding motifs for one or more transcriptional regulators of HFSC quiescence, including FOXC1, FOXP1, RUNX1, NFATC1, TCF3/4 and SOX9. In line with this, proximity ligation assays revealed that KLF4 lies within 40nm of LHX2 and NFATC1 in HFSC nuclei. Together, these data identify KLF4 as a key regulator of HFSC quiescence, and suggest that it performs this function by interacting with multiple other transcription factors to directly activate quiescence genes and repress pro-proliferation genes.

Funding Source: NIAMS/NIH: R01AR076428 NIAMS/NIH: RO1AR063146

Keywords: KLF4, Hair follicle, Stem cell quiescence

9:00 AM – 9:10 AM

MELANOCYTE STEM CELLS ARE MAINTAINED BY DE-DIFFERENTIATION IN A DYNAMIC NICHE.

Sun, Qi[1], Lee, Wendy[2], Hu, Hai[2], Ogawa, Tatsuya[2], De Leon, Sophie[2], Katehis, Ioanna[2], Lim, Chae Ho[2], Takeo, Makoto[2], Cammer, Michael[3], Taketo, Makoto[4], Gay, Denise[2], Millar, Sarah[5] and Ito, Mayumi[2]
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The melanocyte stem cell (McSC) system fails earlier than other adult stem cell populations, for unknown reasons, leading to hair graying in most humans and mice. Current dogma states that McSCs are reserved in an undifferentiated state in the hair follicle (HF) niche, physically segregated from differentiated progeny that migrate away following cues of regenerative stimuli. Instead, we show that most McSCs toggle between transit-amplifying (TA) and stem cell states for both self-renewal and generation of mature progeny, a mechanism fundamentally distinct from those of other self-renewing systems. Live imaging and single-cell RNA sequencing revealed that McSCs are mobile, translocating between HF stem and TA compartments where they reversibly enter distinct differentiation states governed by local microenvironmental cues. Long term lineage tracing demonstrated that the McSC system is maintained by reverted McSCs, rather than reserved stem cells inherently exempt from reversible changes. During aging, there is accumulation of stranded McSCs which do not contribute to the regeneration of melanocyte progeny. These results identify a novel model whereby de-differentiation is integral to homeostatic stem cell maintenance and suggest that modulating McSC mobility may represent a new approach for preventing hair graying.

Keywords: Melanocyte stem cell, Intravital imaging, De-differentiation

9:10 AM – 9:20 AM

RHOJ CONTROLS EMT ASSOCIATED RESISTANCE TO CHEMOTHERAPY

Debaugnies, Maud[1], Rodriguez-Acebes, Sara[2], Blondeau, Jeremy[1], Parent, Marie-Astrid[1], Zocco, Manuel[1], Song, Yura[1], Moers, Virginie[1], Latil, Mathilde[1], Dubois, Christine[1], Coulonval, Katia[3], Impens, Francis[4], Van Haver, Delphi[4], Dufour, Sara[4], Uemura, Akiyoshi[5], Sotiropoulou, Panagiota[1], Méndez, Juan[2] and Blanpain, Cédric[1]
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The resistance of cancer cells to therapy is responsible for the death of most cancer patients. Epithelial-to-mesenchymal transition (EMT) has been associated with resistance to therapy in different cancer cells. However, the mechanisms by which EMT mediates resistance to therapy remain poorly understood. Here, using a mouse model of skin squamous cell carcinoma (SCC)

undergoing spontaneous EMT during tumorigenesis, we found that EMT tumor cells were highly resistant to a wide range of anti-cancer therapy both in-vivo and in-vitro. Using gain and loss of function in vitro and in vivo, we uncovered that RhoJ, a small GTPase preferentially expressed in EMT cancer cells, controls resistance to therapy. Using genome-wide transcriptomic and proteomic profiling, we found that RhoJ regulates EMT associated resistance to chemotherapy by enhancing the response to replicative stress and activating the DNA damage response, allowing tumor cells to rapidly repair DNA lesions induced by chemotherapy. RhoJ interacts with proteins regulating nuclear actin and inhibition of actin polymerization sensitizes EMT tumor cells to chemotherapy induced cell death in a Rhoj dependent manner. Altogether, our study uncovers the role and the mechanisms by which RhoJ acts as a key regulator of EMT associated resistance to chemotherapy.

Keywords: Cancer Therapy, Tumour heterogeneity, Cancer therapeutic resistance

9:20 AM – 9:30 AM

CHOLINE METABOLISM MODULATION REDUCES HEMATOPOIETIC CLONAL DOMINANCE

Gheller, Brandon John-Forde[1], Avagyan, Serine[2], Gopakumar, Jayakrishnan[3], Jaiswal, Siddhartha[4] and Zon, Leonard[5]
[1]Cornell University, Ithaca, NY, USA, [2]Allergy, Immunology, and BMT, Department of Pediatrics, University of California, San Francisco, CA, USA, [3]School of Medicine, Stanford University, Palo Alto, CA, USA, [4]Pathology, Stanford University, Palo Alto, CA, USA, [5]Stem Cell Program, Boston Children's Hospital, Boston, MA, USA

Hematopoietic stem and progenitor cells (HSPCs) accumulate genetic mutations with age that can increase the competitive potential of individual clones causing clonal hematopoiesis (CH). CH predisposes individuals to hematological malignancy, but no therapies exist. We examined if metabolic changes in mutant HSPCs in CH underlie clonal expansion. Our lab created the TWISTR method which combines mosaic mutagenesis of CH-driving genes and HSPC color barcoding allowing for isolation of dominant HSPCs in the zebrafish. Using TWISTR, we isolated wildtype (WT) and dominant asxl1- or ezh2-mutant HSPCs and performed untargeted metabolomics. Of 90 metabolites detected, only seven were significantly different between dominant and non-dominant HSPC clones. Specifically, two catabolic products of choline were decreased in dominant clones – acetylcholine (FC -0.42, $p< 0.01$) and betaine (FC -0.68, $p< 0.01$). This finding was confirmed using a validated, standard containing, choline metabolite profiling assay in an independent asxl1-¬mutant CH experiment. We hypothesized that levels of betaine and acetylcholine were decreased in dominant clones to facilitate phospholipid synthesis leading to aberrant DNA methylation, histone modifications, or cell membranes. To test this hypothesis, we treated zebrafish with large asxl1-mutant clones (>10% variant allele frequency [VAF] in blood) with an inhibitor of the first enzyme in choline-phospholipid metabolism Chka (RSM932A), for 5 days followed by monthly blood collection. At 2 months post-treatment, RSM932A treatment decreased asxl1 VAF by 49.95 ± 38.46% whereas vehicle control treatment increased 42.61 ± 85.80% ($p< 0.01$). The Chka inhibitor did not affect lineage output nor clonal output in WT zebrafish. To determine cell-type specificity of CHKA inhibition, human CD34+ HSPCs with and without ASXL1 mutations were treated with RSM932A during a 14-day culture. Treatment reduced the total number of ASXL1-mutant HSPCs compared to vehicle control ($p< 0.0001$). In sum, our data demonstrate that clonally dominant HSPCs exhibit perturbed choline metabolism and that pharmacological inhibition of Chka in vivo in zebrafish and in human HSPCs in vitro abates clonal dominance. To date this is the first identification of a targetable metabolic liability in CH-causing HSPCs.

Keywords: Clonal Hematopoiesis, Metabolism, Hematopoietic Stem and Progenitor Cell

9:30 AM – 9:50 AM

TIME TO WAKE UP: REGULATION OF NEURAL STEM CELL QUIESCENCE

Brand, Andrea H.
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Neural stem cells (NSCs) can generate new neurons in the brain in response to a range of stimuli, including exercise, nutrition and injury. In this way, stem cells meet the needs of the organism during growth and in response to damage. A key control point is the decision between stem cell quiescence and proliferation. Drosophila NSCs enter quiescence in late embryogenesis and reactivate post-embryonically in response to nutrition. We found that feeding induces the expression of insulin-like peptides within the brain itself and that insulin signalling is essential for the stem cells to exit quiescence and resume proliferation. Most quiescent stem cells are thought to arrest in G0, however, we discovered that quiescent NSCs (qNSCs) in Drosophila are arrested in either G2 or G0. G2/G0 heterogeneity directs NSC behaviour: G2 qNSCs reactivate much more rapidly than G0 qNSCs. We showed that the pseudokinase Tribbles (Trbl) induces NSCs to enter G2 quiescence by promoting degradation of String/Cdc25 and maintains quiescence by inhibiting Akt activation. Insulin signalling overrides Akt repression and silences trbl transcription, allowing NSCs to exit quiescence. The mechanisms controlling NSC reactivation may be conserved in vertebrates, where insulin signalling also promotes NSC proliferation. We have developed powerful methods for whole genome profiling in specific cell- and tissue-types in vivo: Targeted DamID (TaDa), RNA-DamID and NanoDam enabling selective profiling of transcription and chromatin binding in small numbers of cells in intact organisms. We are assessing genome-wide protein and RNA binding in quiescent and reactivated neural stem cells, investigating the genome-wide transcriptional and epigenetic changes in NSCs as they progress from quiescence to proliferation. Understanding the signals that instruct stem cells to produce new neurons at will raises the prospect of future therapies for brain repair after damage or neurodegenerative disease.

Keywords: Neural Stem Cell, Quiescence, Targeted DamID

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)

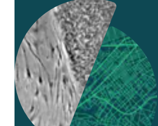
PLENARY V: NEXT GENERATION IN VITRO MODELS
10:00 AM – 11:25 AM
Ballroom East/West, Level 3

10:05 AM – 10:25 AM

VASCULARISED MODELS FOR NEUROLOGICAL DISEASE USING PLURIPOTENT CELLS

Kamm, Roger D., Pavlou, Georgios, Jorfi, Mehdi, Ko, Clare, Spitz, Sarah, Choi, Se Hoon and Wang, Xun
Biological Engineering, Massachusetts Institute of Technology, Cambridge, MA, USA

Neurological diseases affect approximately 50 million Americans each year, and with our aging population, this number will continue to grow. Despite two recently FDA-approved treatments, their success is limited, and new therapies are desperately needed.



One increasingly valuable approach to address this need lies in the use of microphysiological models of the neurovascular system both to screen for new drugs and to test modes of delivery across the blood-brain barrier (BBB) into the brain. A model will be presented comprised of two compartments, one for the vascular network grown by natural self-assembly, and another for neurons. The system includes 4 cell types: endothelial cells, pericytes, astrocytes, and neurons, all human derived. Model systems are generated from either primary cells or using iPS cells from healthy or diseased patients and characterized in terms of vascular permeability, morphology and expression of brain-specific markers. Here we demonstrate one application of the model, cerebral amyloid angiopathy, a condition resulting from accumulation of amyloid beta (Aβ) plaques at the vasculature during the early stages of Alzheimer's disease. Two neuronal cell types are compared, one from healthy ES-derived neurons and another from the same cells but modified to overexpress various isoforms of Aβ. Results show that within one week, high Aβ levels are observed in the Alzheimer's disease cells and within one month, dense Aβ plaques are observed within the endothelial cells. BBB integrity is also found to be impaired.

Keywords: Microphysiological systems, neurovascular model, Alzheimer's disease

10:25 AM – 10:45 AM

USING GASTRULOIDS AND EXTENDED MODELS TO EXPLORE PRINCIPLES OF HUMAN DEVELOPMENT

Moris, Naomi
The Francis Crick Institute, London, UK

The mammalian embryo develops through coordinated cell fate decisions that enable emerging spatiotemporal and morphogenetic complexity. While much insight into this process has been gained through studying model organisms, including mouse embryos, equivalent experiments are technically and ethically challenging in the human embryonic context. Instead, we use gastruloids: 3-dimensional aggregates of pluripotent stem cells that undergo multilineage differentiation to all three germ layers, polarise their gene expression and exhibit axial organisation that recapitulates many of the features of gastrulation and early organogenesis. By closely examining the dynamics and coordination of cell fate decisions and spatial gene expression organisation, we hope to better understand the regulatory logic behind early developmental events, particularly those that are human-specific. Likewise, by carefully manipulating the environment in which these gastruloids are grown, we can bias the structures towards particular lineages and morphological structures of interest. Doing so allows us to explore many of the principles of early development, and provides an opportunity to probe the mechanisms of biomedically-relevant conditions, such as congenital abnormalities.

Keywords: gastruloid, models, somites

10:45 AM – 11:05 AM

IMAGING AND QUANTITATIVE ANALYSIS OF SYNCHRONIZED HES7 OSCILLATIONS IN THE MOUSE SEGMENTATION CLOCK

Kageyama, Ryoichiro
RIKEN Center for Brain Science, Wako, Japan

Somites are periodically formed by segmentation of the anterior parts of the presomitic mesoderm (PSM). In the mouse embryo, this periodicity is controlled by the segmentation clock gene Hes7, which exhibits wave-like oscillatory expression in the PSM. Despite intensive studies, the exact mechanism of such synchronous oscillatory dynamics of Hes7 expression still remains to be analyzed. Detailed analysis of the segmentation clock has been hampered because it requires the use of live embryos, and establishment of an in vitro culture system would facilitate such analyses. Here, we established a simple and efficient method to generate PSM-like tissues from mouse ES cells that carry Hes7-Achilles reporter. In these ES cell-derived tissues, Hes7 expression oscillates like traveling waves, and the posterior-anterior axis is self-organized. This method is applicable to CRISPR-Cas9-mediated gene modification and chemical-library screening and will facilitate the analysis of the molecular nature of the segmentation clock.

Keywords: segmentation clock, Hes7 oscillation, presomitic mesoderm

11:05 AM – 11:25 AM

COMBINING STEM CELL AND DEVICE ENGINEERING FOR IN VITRO MODELS OF HUMAN PHYSIOLOGY.

Herland, Anna, Voulgaris, Dimitrios, Matthiesen, Isabelle, Nikolakopoulou, Polixeni, Rogal, Julia, Enrico, Alessandro and Winkler, Thomas
Department of Protein Science, KTH Royal Institute of Technology, Solna, Sweden

Mammalian cell in vitro studies have a poor translation to human in vivo processes and treatment outcomes. The low resemblance between classical cell culture—a monolayer, static culture of cell lines and the dynamic, three-dimensional, and multicellular in vivo environment explains this gap. However, the demand to accurately model human physiology and pathophysiology has risen with the insights into inter-species differences and the development of human-specific treatments. Engineered human microfluidic Organ-on-Chip models have emerged as a promising new pre-clinical technology to meet this demand. In Organ-on-Chips, cells are cultured in connected microcompartments with perfusion. We are developing these systems from three perspectives: first, to increase human physiological relevance through stem cell engineering and relevant three-dimensional microenvironment; second, to incorporate non-disruptive real-time monitoring of cells; and third, to make them user-friendly and cost-effective. Our specific focus is the neurovascular unit (NVU), the restrictive barrier that lines the capillaries in the brain and spinal cord. Our NVU-on-Chip models are populated with human pluripotent stem cell-derived vascular and neural cells. We have developed a new material, off-stochiometry-thiolene epoxy (OSTE), that allows a one-step fabrication process to integrate real-time barrier monitoring electrodes in the chip. The chip and perfusion system have been tailored to study barrier penetration of small drugs and biopharmaceuticals, as well as cellular interactions and inflammatory responses in real time. Organoids and other self-assembled multicellular structures have a high degree of resemblance with human tissue but typically lack perfusable vascular structures. To enable studies of vascular organoid interactions as well as physiological drug exposure of organoids, we have developed a femtosecond laser patterning method termed cavitation molding. Cavitation molding allows us to pattern 10-20 µm wide lumens in ECM gels in the direct vicinity of an organoid without impairing its viability. These lumens were populated with endothelial cells, forming a defined vascular network around the organoid.

Keywords: neurovasculature, Organ-on-Chip, blood-brain barrier

TRACK: CLINICAL APPLICATIONS (CA)

PLENARY VI: CLINICAL APPLICATION OF GENE THERAPY AND GENE EDITING

Sponsored by: ElevateBio

1:00 PM – 2:40 PM

Ballroom East/West, Level 3

1:05 PM – 1:25 PM

HEMATOPOIETIC STEM CELL GENE THERAPY FOR INBORN ERRORS OF METABOLISM AND IMMUNITY

Aiuti, Alessandro

San Raffaele Hospital, Milano, Italy

Genetic engineering of hematopoietic stem cells has advanced from early stage clinical trials, providing evidence for substantial and durable benefits, to the first approved gene therapy products for genetic diseases. Here I will focus on the progress and challenges of in clinical development, market approval and accessibility of gene therapy for rare genetic diseases focusing on primary immune deficiencies and n metabolic disorders.

Keywords: hematopoietic stem cells, gene therapy, genetic disease

1:25 PM – 1:45 PM

EFFICACY AND SAFETY OF A SINGLE DOSE OF EXAGAMGLOGENE AUTOTEMCEL FOR TRANSFUSION-DEPENDENT Β-THALASSEMIA AND SEVERE SICKLE CELL DISEASE

Corbacioglu, Selim, de la Fuente, Josu, Locatelli, Franco, Frangoul, Haydar, Wall, Donna, Cappellini, Maria Domenica, de Montalembert, Mariane, Kattamis, Antonis, Lobitz, Stephan, Rondelli, Damiano, Sheth, Sujit, Steinberg, Martin, Walters, Marc C., Bobruff, Yael, Simard, Christopher, Song, Yang, Zhang, Lanju, Sharma, Anjali, Imren, Suzan, Hobbs, Bill and Grupp, Stephan

Department of Pediatric Hematology, Oncology and Stem Cell Transplantation, University Hospital Regensburg, Germany

Exa-cel is a cell therapy designed to reactivate fetal hemoglobin (HbF) via non-viral, ex vivo CRISPR/Cas9 gene-editing in autologous CD34+ HSPCs. Two pivotal trials showed an increased HbF and total Hb sufficiently to RBC transfusions in patients (pts) with transfusion-dependent β-thalassemia (TDT) and vaso-occlusive crises (VOCs) in sickle cell disease (SCD). We report efficacy and safety data from the first 75 pts dosed with exa-cel. Following busulfan myeloablation and exa-cel infusion, pts (12-35y) are monitored for engraftment, total Hb, HbF, BCL11A edited alleles, transfusions, VOCs (SCD only), and adverse events (AEs). Data presented as mean (min-max) unless noted. 44 pts with TDT (age 21.3 [12-35]) and 31 pts with SCD (age 22.5 [12-34]) were infused with exa-cel (follow-up 12.3 mo and 9.6 mo, respectively). In the 2-yr period before screening, pts with TDT received 36.0 (15.0-71.0) units RBC/yr and pts with SCD had 3.9 (2.0-9.5) severe VOCs/yr. 42 of 44 pts with TDT stopped RBC transfusions (duration 0.8-36.2 mo); 2 pts had not stopped transfusions but had 75% and 89% reductions in transfusion volume. By Month 3, increases in HbF and mean total Hb levels (>9 g/dL) were achieved, with mean total Hb levels increasing to >11 g/dL thereafter. In all pts with SCD (n=31) VOCs arrested (duration 2.0-32.3 mo). Mean proportion of HbF was ~40% at Month 4 and stable thereafter, with mean total Hb levels >11 g/dL. No pts with SCD had SAEs considered related to exa-cel. There were no deaths, discontinuations, or malignancies. Exa-cel infusion led to elimination of transfusions in almost all patients with TDT and elimination of VOCs in all patients with SCD, with associated clinically meaningful increases in HbF and total Hb that were maintained over time. Proportions of CRISPR/Cas9-edited BCL11A alleles remained stable after more than 1 year, indicating long-term HSCs were successfully edited. Safety profile was generally consistent with busulfan myeloablation and autologous transplant. These results indicate exa-cel has the potential to be the first CRISPR/Cas9-based therapy to provide a one-time functional cure for TDT and severe SCD.

Keywords: Hemoglobinopathies, sickle cell disease, gene editing, CRISPR/Cas9

1:45 PM – 2:05 PM

CLINICAL ADVANCES IN CRISPR-BASED GENOME EDITING FOR TREATMENT OF PATIENTS WITH SEVERE ILLNESS

Sepp-Lorenzino, Laura

Research and Early Development, Intellia Therapeutics, Cambridge, MA, USA

At Intellia, we are deploying a deep toolbox, including novel editing and delivery solutions, to harness the immense power of CRISPR-based technologies for in vivo and ex vivo therapeutic applications The in vivo programs use our proprietary lipid nanoparticle (LNP) platform for IV infusion to deliver the gene editing machinery to hepatocytes in a transient manner. NTLA-2001 is an investigational CRISPR-based therapy with the potential to be the first single-dose treatment for ATTR amyloidosis. NTLA-2001 is being evaluated in a Phase 1, two-part, open-label study in adults with hereditary transthyretin amyloidosis with polyneuropathy (ATTRv-PN) or transthyretin amyloidosis with cardiomyopathy (ATTR-CM). Clinical data from both study arms will be discussed demonstrating that NTLA-2001 led to deep, consistent, and durable TTR reductions and was generally well tolerated. NTLA-2002 is an investigational drug candidate for hereditary angioedema (HAE), designed to knock out the KLKB1 gene in the liver with the potential to permanently reduce total plasma kallikrein protein and activity, a key mediator of the disease. NTLA-2002 is being evaluated in a Phase 1/2 study in adults with Type I or Type II HAE. Clinical data including safety, kallikrein reduction and HAE attack rate data will be discussed. With our ex vivo efforts, we are advancing a unique and proprietary allogeneic technology, which leverages our LNP-based cell engineering platform. Our novel approach is designed to overcome rejection by host T and NK cells, a key limitation to the durability of current allogeneic investigational therapies. Data will be presented demonstrating in vitro and in vivo performance and differentiation from other allogeneic strategies and showcase its application to TCR-T and CAR-T therapies.

Keywords: Liver, CRISPR, LNP

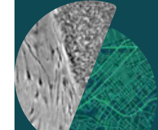
2:15 PM – 2:40 PM

JOHN MCNEISH MEMORIAL LECTURE: GENOME-EDITED CAR T CELLS

Sadelain, Michel

Immunology, Memorial Sloan-Kettering Cancer Center, New York, NY, USA

Chimeric antigen receptors (CARs) are synthetic receptors for antigen that instruct immune effector cells to target and lyse tumor cells. CAR T cells targeting CD19 represent a novel paradigm for cancer immunotherapy and were the first gene therapy products to be approved by the US Food and Drug Administration. The CAR cDNA is typically transduced in patient T cells using gamma-retroviral or lentiviral vectors. The advent of efficient genome editing broadens the scope of CAR T cell engineering. Thus, by adverting semi-random vector integration and targeting the CAR cDNA to a defined location such as the TRAC locus, transcriptional



regulation of CAR expression can be optimized to delay functional exhaustion and provide superior potency of CAR T cells. By preventing premature CAR expression during lymphopoiesis, regulation of CAR expression at the TRAC locus ameliorates the quality of CAR T cells generated from T cell-derived induced pluripotent stem cells (TiPS). We have searched for extragenic genomic safe harbors (GSHs) that may serve as dependable chromosomal locations for the targeted integration and sustained expression of foreign DNA in human T cells. We established 8 criteria to identify such sites, including GSH6, which we found to rival the TRAC locus for ensuring stable and efficient CAR expression in human primary T cells. Genome editing enables additional means to regulate the differentiation and functional persistence of CAR T cells. The disruption of TET2, a methylcytosine dioxygenase, increases overall T cell potency in the short term but also exposes to the risk of unabated CAR T cell proliferation, pointing to the promise and potential pitfalls of epigenetic programming to prolong T cell fate. Disruption of the H3K9 histone methyltransferase SUV39h1 also augments T cell potency but without apparent risk of hyper-proliferation, further supporting the promise of epigenetic programming to enhance cell therapy products.

Keywords: Immunotherapy, genetic engineering

PLENARY VII: AWARDS AND KEYNOTE SESSION

Sponsored by: T-CiRA Joint Program

3:15 PM – 5:25 PM

Ballroom East/West, Level 3

3:35 PM – 4:10 PM

SSCR MOMENTUM AWARD LECTURE: MECHANISMS REGULATING TUMOR TRANSITION STATES

Blanpain, Cédric

Université Libre de Bruxelles, Belgium

Within a tumor, cancer cells exist in different states that are associated with distinct tumor functions, including proliferation, differentiation, invasion, metastasis, and resistance to anti-cancer therapy. The identification of the gene regulatory networks underpinning each state is essential for better understanding functional tumor heterogeneity and revealing tumor vulnerabilities. In cancer, epithelial-to-mesenchymal transition (EMT) is associated with tumour stemness, metastasis and resistance to therapy. I will present evidence that EMT is not a binary process, but rather encompassed multiple tumour subpopulations associated with different EMT states. Although all EMT subpopulations presented similar tumour-propagating cell capacity, they displayed differences in cellular plasticity, invasiveness, and metastatic potential. I will show how specific oncogenic mutations promote hybrid EMT states with increased stemness and metastatic potential. I will present new data uncovering the mechanisms by which EMT is associated with increased resistance to chemotherapy. Finally, I will discuss how new pharmacological intervention that target EMT can be used to sensitize cancer cells to chemotherapy.

Keywords: Cancer, EMT, therapy

4:10 PM – 4:45 PM

ISSCR ACHIEVEMENT AWARD LECTURE: STEM CELL QUIESCENCE, EVOLUTIONARY TRADE-OFFS, AND TISSUE REGENERATIVE POTENTIAL

Rando, Thomas

Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Biology, University of California Los Angeles, CA, USA

Quiescence is a defining feature of many somatic stem cells for most of their existence. While such cells are primed to respond to environmental cues to engage is tissue maintenance or repair, they persist in a non-dividing (but not postmitotic) state for days, months, or years, depending on the organism and tissue in which they reside. Studies from our lab and others have begun to redefine the quiescent state from one of true dormancy to one of active regulation and dynamism. It is now clear that, despite low metabolic activity, there are key transcriptional and post-transcriptional networks actively maintaining cellular quiescence, and disruption of even single network nodes can release quiescent stem cells into the cell cycle. There are also dynamic homeostatic mechanism that respond to environmental cues that shift quiescent stem cells among different states of quiescence, some promoting cellular resilience (e.g., "Deep Quiescence") and others priming cells to enter the cell cycle (e.g., "G-Alert"). These reflect ancient, evolutionarily conserved mechanisms that allocate resources between survival and reproduction and that can be observed in species from microbes to mammals. I will present recent data from our laboratory that explore the molecular mechanisms that underlie the regulation of quiescence, focusing on how they impact stemness and stem cell potency, and how they are disrupted during the aging process. I will also address how these mechanisms respond to interventions (e.g., genetic, pharmacologic, systemic/biologic, lifestyle) that have the potential to restore youthful characteristics to aged quiescent stem cells.

Keywords: Quiescence, regeneration, aging

4:45 PM – 5:20 PM

KEYNOTE ADDRESS: GERM CELLS ILLUMINATE THE BIOLOGY OF HIGHLY POTENT STEM CELLS

Spradling, Allan

Carnegie Institution for Science, Baltimore, MD, USA

Highly potent animal stem cells (HPSCs) utilize fundamental biological processes that underlie much of biomedical science, but also display properties like open chromatin, unusual organelle behavior and atypical metabolism that remain poorly understood. Drosophila female germline stem cells (GSCs) are models that maintain species immortality, while GSC daughters, like mammalian primordial germ cells (PGCs), develop into nurse cells and oocytes within germline cysts. Developing GSCs parallel early embryo development by 1) forming heterochromatin in a transient syncytial state, 2) repressing individual genes and Polycomb domains, and 3) upregulating membrane transport and mitochondrial metabolism toward Myc-dependent growth. Thus, each animal generation involves two similar but distinct stem cell epigenetic cycles: a maternal germline cycle, followed by the better known zygotic cycle that together produce sophisticated but short-lived somatic cells and fully revitalized, immortal gametes. Our evolutionary studies trace pleuripotency to the neoblast-like progenitors of basal animals such as hydra and planaria. We propose that pleuripotent states have been shaped by the massive challenge of resisting transposable element (TE) activity over evolutionary time scales, an endless war memorialized in animal genomes. The unusual cell biological properties of GSCs and other HPSCs are candidate long term TE-resistance mechanisms. The HPSC state necessitates a special transition to the somatic, heterochromatin-based system for differentiation. A better understanding of HPSC properties and of the dual stem cell cycles supporting each animal generation have the potential to improve stem cell lines.

Keywords: Germline, pleuripotency, differentiation

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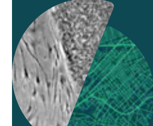

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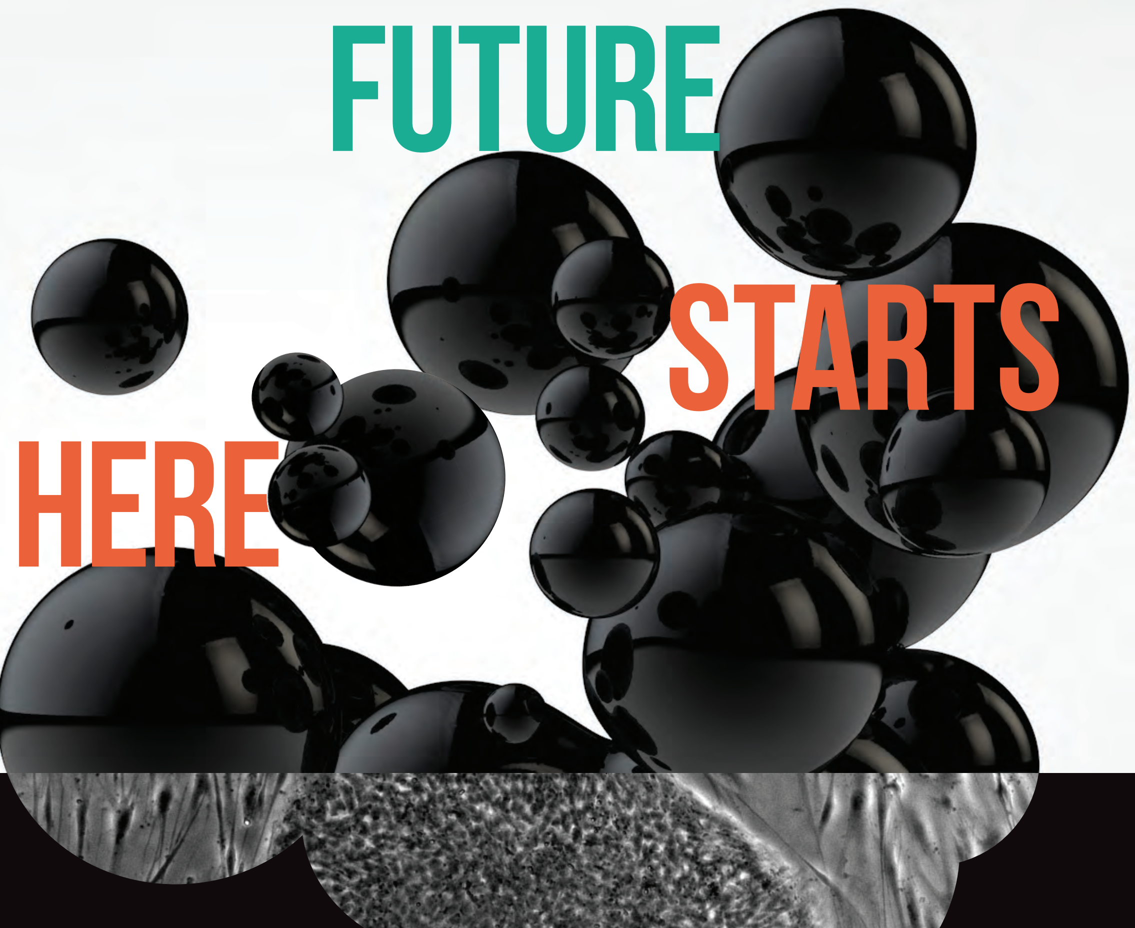

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