

ISSCR 2018

ANNUAL MEETING

**MELBOURNE
AUSTRALIA**

20-23 JUNE

ISSCR2018.ORG

THE
GLOBAL
STEM CELL
EVENT

**PROGRAM
GUIDE**

ENVISION & ENGAGE

Co-sponsored by:



INTERNATIONAL SOCIETY
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MESSAGE OF WELCOME FROM THE MINISTER FOR HEALTH AND AMBULANCE SERVICES



It gives me great pleasure to welcome you to Melbourne for the Annual Meeting of the International Society for Stem Cell Research 2018.

Victoria is a leading location for the generation of new ideas and development of stem cell research and regenerative medicine. We are proud to be home to some of the best and brightest medical minds who are leading the way in revolutionary discoveries that will save lives.

From better treatments for blood cancers, or understanding how the brain and heart grow and heal, to making cells in the lab to study and treat disease, Australian researchers are global leaders in advancing stem cell medicine for a healthier future.

Stem cell science has been a great strength within Australian biomedical research for many decades. The Victorian Government has long recognised this potential and provided support to ensure this sector meets its potential. Through a \$153 million joint venture, the Victorian Government and Monash University have established the Australian Regenerative Medicine Institute. Today the Australian Regenerative Medicine Institute is one of the largest regenerative medicine and stem cell research hubs in the world.

The Annual Meeting of the International Society for Stem Cell Research brings together world leading experts to discuss recent findings and progress that is driving the development of stem cell treatments and cures for disease. For our world-renowned researchers, closer ties with international researchers mean more opportunities to partner with the best in the world and collaborate on medical breakthroughs that will change lives here and abroad.

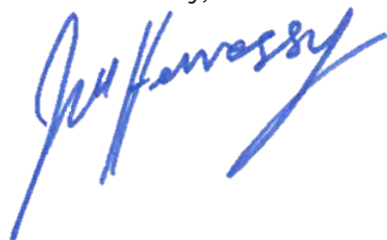
I encourage you all to use this event as an opportunity to share ideas and strengthen international relationships in stem cell research.

As you take part in this important event, I hope you have the chance to enjoy some of what our great state has to offer.

Melbourne is a city celebrated for its food, shopping, sports, arts, culture and year round festivities, and, within a stone's throw of the city we have spectacular coastlines, wildlife reserves, wineries, temperate rainforests, surf beaches, mountains and historic townships.

Please enjoy your time here in our wonderful state, and I wish you the very best for a very productive meeting.

Yours sincerely,



Hon Jill Hennessey MP
Minister for Health
Minister for Ambulance Services
State Government of Victoria



INTERNATIONAL SOCIETY
FOR STEM CELL RESEARCH

Dear Colleagues,

On behalf of the International Society for Stem Cell Research (ISSCR), we warmly welcome you to the 2018 Annual Meeting in beautiful Melbourne, Australia. A global hub of innovation in science and biotech with a rich stem cell history, Melbourne is an ideal location to host the largest meeting of stem cell scientists in the world. It is also a terrific city, with extensive dining options and a vibrant night life; we hope you will take some time to visit and see some of the surrounding natural beauty while you're here.

This year, we are pleased to offer a scientific program that showcases the incredible breadth of stem cell research and its potential to transform human health. An excellent lineup of speakers will cover topics from the most basic elements of stem cell biology to translational work that is moving toward the clinic and the evolving technologies propelling this research forward.

Several sessions will focus on clinical advances, including Plenary VII: Moving to the Clinic: Gene and Stem Cell Therapies, two "Road to the Clinic" concurrent sessions, and pre-meeting clinical education on Emerging Clinical and Cellular Technologies. In addition, Focus Sessions and Innovation Showcases will highlight innovative companies and products, and the latest tools and technologies will be on display at the Exhibit Hall, a vibrant hub of meeting activities.

ISSCR 2018 presents many opportunities to learn about new areas of research and new approaches to stem cell science, expand your network of colleagues and friends, and build new collaborations that can help your research progress. We hope this meeting will inspire you with new ideas and foster a broader appreciation of the field and its exciting potential. Thank you for your continued support of the ISSCR, and your important work that is increasing our understanding of development and disease and advancing the field of regenerative medicine.

Sincerely,

A handwritten signature in blue ink, appearing to read "Hans Clevers", with a long horizontal flourish extending to the right.

Hans Clevers
ISSCR President

A handwritten signature in blue ink, appearing to read "Melissa Little", with a long horizontal flourish extending to the right.

Melissa Little
Program Chair



Friends and Colleagues,

The Australasian Society for Stem Cell Research extends our warmest welcome to our overseas and local delegates attending the 16th Annual Meeting of the International Society for Stem Cell Research (ISSCR) here in Melbourne, Australia.

This year marks 20 years since Professor James Thomson's seminal publication describing the isolation of human embryonic stem cells, a discovery that not only kicked off a whole new area of research, but also sparked the imagination of both scientists and the public at large. Since that event, the science has moved faster than any of us could have imagined, with new therapies entering the early stages of clinical trials, providing hope for many.

From the outset, Australia has been at the forefront of developing and applying stem cell technology and continues to play its part in the revolution that this technology represents. In the 1960s working at the Walter and Eliza Hall Institute here in Melbourne, Professor Don Metcalf developed the now standard approaches for culturing blood progenitors in agar. This discovery enabled the identification of G-CSF, MCSF, GM-CSF, and IL-3, key colony stimulating factors regulating hematopoietic progenitor populations. Professor Perry Bartlett, working at the same Institute, identified the presence of neural stem cells in the postnatal brain in 2001. Professor Alan Trounson, a pioneer in *in vitro* fertilization, was involved in the derivation of some of the earliest human embryonic stem cell lines (2000), working with Professor Martin Pera and Benyamin Reubinoff. Professor Jane Visvader (2006) identified mammary epithelial stem cells capable of recreating the entire breast ductal system when transplanted to a new fat pad, while Professor Paul Simmons described STRO1 as a marker of mesenchymal stromal cells (1991). With such an historical backdrop, this year's conference is sure to be both informative and memorable.

This is the second time Australia has hosted the ISSCR. Indeed, our society was initiated at the 2007 ISSCR meeting in Cairns in order to support stem cell research and researchers within the region and convey to the public the outcomes of that research. While ASSCR welcomes you as the sponsor of this year's event, we do so on behalf of many Australian companies, research institutes and universities that collectively provided funding for the event. We particularly acknowledge the support of CSL Pty Ltd, Stem Cells Australia, and Mesoblast, as well as all other bid co-sponsors from across the country.

We are certain you are going to enjoy the conference, the wonderful city of Melbourne, and most of all, the wonderful science being presented throughout the meeting. We also hope that you will be able to find time during or around the meeting to visit some of Australia's stem cell researchers, and some of our unique wildlife, in their native environment.

Sincerely yours,

Professor Melissa Little
President, ASSCR

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**Cells
Tissues
Organs**

Meet our new editors at ISSCR & claim your free 1-year subscription

Friday 22nd June, Meet-Up Hub, 18:00 – 20:00



“My team and I will work tirelessly to publish findings with potential implications for health and disease in humans. At such an early stage in the scientific process, we will keep a very open mind and be continually supportive of our authors.”

Christoph Viebahn (University of Göttingen)
Co-Editor, Developmental Biology



“We want Cells Tissues Organs to become a major platform for stem cell-based research findings that challenge our pre-existing notions of animal development and help shed novel mechanistic insight into multicellular organization.”

Guojun Sheng (Kumamoto University)
Co-Editor, Stem Cells

Meet **Ryan Gilbert**, our co-editor responsible for Tissue Engineering, at BMES, Atlanta, October 2018.

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VENUE MAPS

Exhibit and Poster Hall Enter through Doors 6 & 7



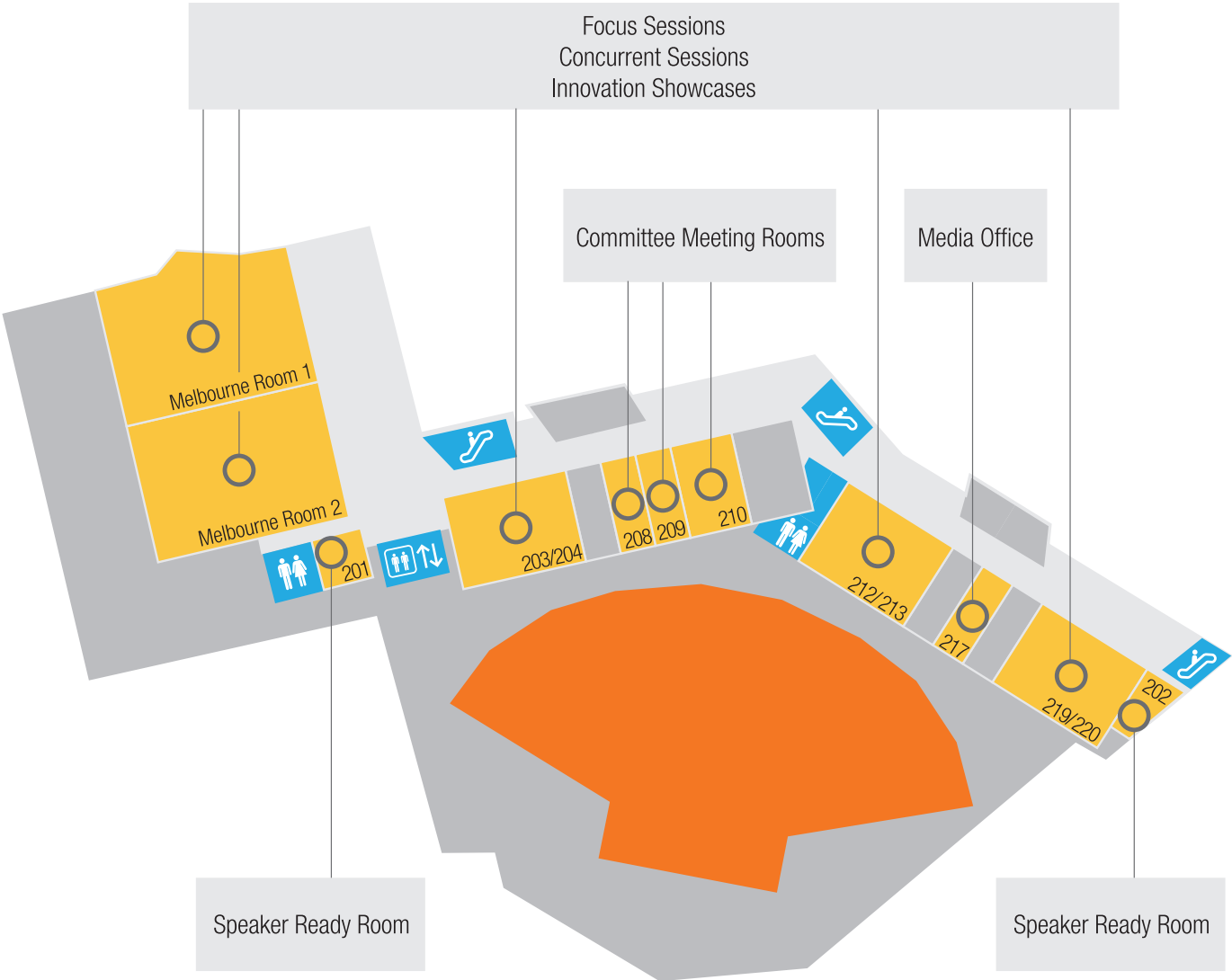
VENUE MAPS

Level One



VENUE MAPS

Level Two



GENERAL INFORMATION

REGISTRATION AND BADGE PICKUP

Pick up your attendee name badge in the registration area in the Melbourne Convention and Exhibition Centre (MCEC), Main Foyer during posted hours. Bring your confirmation email for faster badge retrieval at the Self Check-in kiosks. 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, 19 JUNE 14:00 – 18:00

WEDNESDAY, 20 JUNE 06:30 – 20:30

THURSDAY, 21 JUNE 07:30 – 18:30

FRIDAY, 22 JUNE 07:30 – 18:30

SATURDAY, 23 JUNE 08:00 – 18:30

For hotel matters, please visit the housing assistance desk in the registration area WEDNESDAY and SATURDAY during registration hours.

ATTENDEE ORIENTATION

Curious to find out how to best navigate through ISSCR 2018? Join us at the MCEC, Main Foyer for our Attendee Orientation where ISSCR staff and experienced ISSCR members will explain the annual meeting's highlights and facilitate attendee introductions before the meeting kicks off. There will be two scheduled Attendee Orientations:

TUESDAY, 19 JUNE 15:00 – 16:30

WEDNESDAY, 20 JUNE 07:45 – 08:45

INTERNET ACCESS

Enjoy complimentary Wi-Fi throughout the MCEC thanks to our sponsor STEMCELL Technologies.

To connect to the Wi-Fi:

Network/SSID: ISSCR2018

Password STEMCELLS1

MOBILE APP

Have the ISSCR 2018 schedule in the palm of your hand. Download the free ISSCR 2018 Mobile App from the Apple Store or Google Play to your smartphone and/or tablet device to have immediate access to many features in support of your annual meeting program experience:

- Browse or search for scientific content, presenters, exhibitors or events
- Reach out to fellow attendees onsite using the My Scanned Contacts networking feature
- Check the locations of sessions and exhibitors under the maps icon
- Receive important real-time communications from the ISSCR
- Build a personalized schedule
- Bookmark exhibitors
- Rate the sessions you attend and comment on them, too
- Stay in-the-know and join in on social media with #ISSCR2018 and #GlobalStem-CellEvent

Downloading the mobile app is easy! Simply scan this QR code:



or go to the App Store or Google Play and search for "ISSCR." The ISSCR 2018 mobile app runs on all Android devices with android 4.4.2 and above. For iPhone or iPad the app runs iOS 8.0 or higher.

RECORDINGS PROHIBITED

Still photography, video and/or audio taping of the sessions, presentations and posters at the ISSCR 2018 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.

SPEAKER READY ROOM

Speakers must review their presentations in either one of the two Speaker Ready Rooms (Conference Organiser 201 and Conference Organiser 202 on Level 2) during the following times:

TUESDAY, 19 JUNE 14:00 – 18:00
WEDNESDAY, 20 JUNE 07:30 – 19:00
THURSDAY, 21 JUNE 07:00 – 19:00
FRIDAY, 22 JUNE 07:00 – 19:00
SATURDAY, 23 JUNE 08:00 – 16:30

MEDIA OFFICE

Credentialed members of the media may use work stations and wireless internet, during posted hours in the Media Office (Room 217, Level 2). Please visit the Media Office for media panel details.

WEDNESDAY, 20 JUNE 11:00 – 16:00
THURSDAY, 21 JUNE 07:00 – 16:00
FRIDAY, 22 JUNE 07:00 – 16:00
SATURDAY, 23 JUNE 09:00 – 16:30

THINGS YOU SHOULD KNOW

For your convenience, the Melbourne Convention Centre Customer Service Desk is available to assist with cloak room and business center needs. The Customer Service Desk does not accept exhibitor freight.

Cloak Room

WEDNESDAY, 20 JUNE 07:00 – 20:45
THURSDAY, 21 JUNE 07:00 – 20:30
FRIDAY, 22 JUNE 07:00 – 20:30
SATURDAY, 23 JUNE 07:30 – 19:00

Business Center

WEDNESDAY, 20 JUNE 08:00 – 19:00
THURSDAY, 21 JUNE 08:00 – 19:00
FRIDAY, 22 JUNE 08:00 – 19:00
SATURDAY, 23 JUNE 08:00 – 19:00

Mothers' Room

Located past the Melbourne Convention Cen-

tre Customer Service Desk, no need to check-in with customer service representative.

WEDNESDAY, 20 JUNE 08:00 – 19:00
THURSDAY, 21 JUNE 08:00 – 19:00
FRIDAY, 22 JUNE 08:00 – 19:00
SATURDAY, 23 JUNE 08:00 – 19:00

Food Court

Located in the rear of the Exhibit Hall.

Hours of Operation:

THURSDAY-SATURDAY 11:00 – 15:00

Cafés

Attendees can purchase snacks and beverages at either the Shed Café (located in the Exhibition Centre concourse) or the Plenary Café (located in the Main foyer by Plenary hall).

Hours of operation are:

WEDNESDAY, 20 JUNE 07:00 – 16:00
THURSDAY, 21 JUNE 07:00 – 16:00
FRIDAY, 22 JUNE 07:00 – 16:00
SATURDAY, 23 JUNE 08:00 – 16:00

The South Wharf and the Direct Factory Outlets (DFO) also have a variety of restaurant options available and conveniently located next to the Melbourne Convention Centre.

<https://www.dfo.com.au/south-wharf/dine/>

Smoking

Smoking is prohibited in the MCEC.

Lost and Found

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

Automatic Teller Machines (ATMs)

There are three ATMs, located in:

- One by the Melbourne Convention Centre Customer Service Desk
- Two are located on the concourse of the exhibition centre

Meeting Rooms

Sign up for first-come, first-served ISSCR ad hoc meetings in MCEC, Level 2, Rooms 208, 209 and 210. Sign-up sheets are posted outside each room listing available time slots

GENERAL INFORMATION

for each day. Informal seating areas are also available in ISSCR Central, Meet-Up Hubs, and ISSCR Lounge in the Exhibit & Poster Hall.

Parking and Valet

Self-parking is available 24 hour/7 days a week. The entrance and exit is via Normaby Road.

Monday - Friday: \$17.00 AUD (early bird daily rate)

0.0 - 1.0 hrs	\$14.00
1.0 - 2.0 hrs	\$28.00
2.0 - 3.0 hrs	\$42.00
3.0 + hrs	\$56.00

Parking website: https://www.wilsonparking.com.au/park/3197_Melbourne-Exhibition-Centre-Car-Park_16-Normanby-Road-Southbank

Valet service is not available.

Please note attendees are responsible for paying their own parking garage and valet fees.

Messages

The most effective way to reach out to fellow attendees is through the ISSCR 2018 mobile app. Read more on page 12.

Melbourne Convention Bureau Desk

Please be sure to stop by the Melbourne Convention Bureau desk for information about the city, places to visit and dine. The desk is located next to ISSCR Registration in the Main Foyer of the Melbourne Convention Centre.

Hours:

TUESDAY, 19 JUNE 14:00 - 17:00

WEDNESDAY, 20 JUNE 09:00 - 16:00

THURSDAY, 21 JUNE 09:00 - 16:00

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Susie Kaye Nilsson
Trista E. North
M. Cristina Nostro
Michael O'Connor
Il-Hoan Oh
Steve K.W. Oh
Yohei Okada
Hideyuki Okano
Bradley B. Olwin
Lezanne Ooi
Valeria Orlova
Pierre Osteil
Dmitry Ovchinnikov
Nathan Palpant
Athanasia D. Panopoulos
Eirini Papapetrou
In-Hyun Park
Sergiu P. Pasca
Robert Passier
Alice Pebay
Duanqing Pei
Martin F. Pera
Kathrin Plath
Jose Maria Polo
Enzo Porrello
Colin William Pouton
Louise Purton
April Pyle
Li Qian
Jing Qu
Alireza Rezanian

Stanley R. Riddell
Yuval Rinkevich
Anne Rios
Isabelle Riviere
Pamela G. Robey
Janet Rossant
Filip Roudnický
Alessandra Sacco
Krishanu Saha
Mitinori Saitou
Luca Sala
Max R. Salick
Maïke Sander
Toshiro Sato
Kazunobu Sawamoto
Thorsten Schlaeger
Mark Shackleton
Qin Shen
Michael M. Shen
Robert A.J. Signer
Jose Silva
Douglas Sipp
Julie Beth Sneddon
Hongjun Song
Deepak Srivastava
Lincon Stamp
Ed Stanley
Christopher Michael Sturgeon
Jeremy Sugarman
Qiang Sun
Kazutoshi Takahashi
Takanori Takebe
Clare Tanner
Michael Teitell

Derk ten Berge
Emily Titus
Alan O. Trounson
Ray Jui-Fang Tsai
Leigh Turner
Achia Urbach
Ludovic Vallier
Nicole Van Bergen
Pierre Vanderhaeghen
Louis Vermeulen
Jane E. Visvader
Gordana Vunjak-Novakovic
Amy Wagers
Jianlong Wang
Claudia Waskow
Stephanie Watson
Christine Anne Wells
Sara Wickstroem
Ernst Wolvetang
Justin Wong
Joseph C. Wu
Yasuhiro Yamada
Pengyi Yang
George Cheng Yeoh
Omer Yilmaz
Zhengqin Yin
Kaylene Young
Peter W. Zandstra
Yi Ariel Zeng
Kang Zhang
Hao Zhu
Leonard I. Zon
Thomas P. Zwaka
Robert Zweigerdt

JOIN US ON WEDNESDAY, 20 JUNE FOR THE 2018 ISSCR AWARDS PRESENTATIONS

ISSCR AWARD FOR INNOVATION

The ISSCR Award for Innovation recognizes original thinking and groundbreaking research pertaining to stem cells or regenerative medicine that opens new avenues of exploration toward the understanding or treatment of human disease or affliction.



The 2018 ISSCR Award for Innovation will be presented to Michele De Luca, MD, and Graziella Pellegrini, PhD, Center for Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy during the Presidential Symposium on Wednesday, 20 June. De Luca and Pellegrini are recognized for their leadership in the field of corneal regeneration and skin replacement therapies and their pioneering work in translating epithelial stem cell research into the clinic.

Dr. Pellegrini will present her research in Plenary I, Presidential Symposium, on Wednesday, 20 June, 13:00-15:15. Dr. De Luca will speak in Plenary V, Stem Cell Based Disease Modeling, on Friday, 22 June, 16:00-17:55.

ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR



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

The 2018 ISSCR Dr. Susan Lim Award for Outstanding Young Investigator will be presented to Shuibing Chen, PhD, Associate Professor, Department of Surgery and Department of Biochemistry, Weill Cornell Medical College of Cornell University, U.S. in recognition of her innovative chemical approaches in pluripotent stem cell research, with major contributions in drug screening techniques, and in human disease modeling, genetic testing, and organoid development.

Dr. Chen will present her research in Plenary IV, New Technologies in Stem Cell Engineering, on Friday 22 June, 09:00-11:15.

ISSCR TOBIAS AWARD LECTURE



The ISSCR Tobias Award Lecture is supported by the Tobias Foundation, and recognizes original and promising basic hematology research and direct translational or clinical research related to cell therapy in hematological disorders.

The 2018 ISSCR Tobias Award Lecture will be presented by Connie J. Eaves, PhD, FRS, Distinguished Scientist, Terry Fox Laboratory, BC Cancer Agency, Canada, an internationally recognized leader and authority on stem cells of the blood-forming system and how their properties change over time and by type.

Dr. Eaves will present her research in Plenary I, on Wednesday 20 June, 13:00-15:10.

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.

The 2018 ISSCR Public Service award will be presented to Megan Munsie, PhD, Head of Education, Ethics, Law & Community Awareness Unit, Stem Cells Australia, The University of Melbourne, Australia. Dr. Munsie is a stem cell scientist who has made a significant contribution for many years in outreach to the public and advocacy to policy makers around issues associated with stem cell science and its translation to the clinic.

The award will be presented in Plenary II on Wednesday 20 June, 16:00-18:00.

2018 TRAVEL AWARDS

CONGRATULATIONS TO THE 2018 TRAVEL AWARD WINNERS

2018 ISSCR ZHONGMEI CHEN YONG TRAVEL AWARDS FOR SCIENTIFIC EXCELLENCE

Supported by Chen Yong and the Zhongmei Group, the ISSCR Zhongmei Chen Yong Travel Awards recognize scientific excellence and economic need for trainees who submit abstracts and present at the ISSCR Annual Meeting.

Ana Antonic
Yishai Avior
Arshad Ayyaz
Anushree Balachandran
Ori Bar-Nur
Lawrence E. Bates
Scott Bell
Mimi R. Borrelli
Germán Dario Camargo Ortega
Benjamin Cao
Hsiao-Min Chang
Xi Chen
Alexander Combes
Alison Conquest
Guizhong Cui
Isabelle R. de Luzy
Matthew Decker
Antonia A. Dominguez
Thomas A. Forbes
Leticia Fracaro
Helder T. Freitas
Eriko Fukui
Mahshid Ghasemi Esfidvajani
Henry J. González-Torres
Ani Grigoryan
Christopher L. Grigsby
Markus Grosch
Lin Guo
Lorna J. Hale
John M. Hallett

Michael Hicks
Yuichiro Higuchi
Beatrice Ho
Ilkyun Im
Takuji Ito
Woong Bi Jang
Genevieve Kerr
Jong-Wan Kim
Mirae Kim
Cody Kime
Sam Kimmey
Anja S. Knaupp
Yong Hui Koh
Kai Kretschmar
Santhosh V Kumar
Konomi Kuwabara
Ying-Wei Lan
Dongjun Lee
Hye Jeong Lee
Jin-Woo Lee
Julien M.D. Legrand
Ana Rita Leitoguinho
Jingjing Li
Weiping Li
Kif Liakath-Ali
Hong Kiat Lim
Dawn S. Lin
Vanessa Lundin
Junichi Matsuo
Farideh Moeinvaziri

Sakthi Devi Moorthy
Ali Motazdian
Sara Nolbrant
Takenori Ogura
Adam O'Neill
Sarita Panula
Udit Parekh
Michelle Percharde
Mordecai Peretz
Sara Pijuan-Galito
Ido Sagi
Lakshmi Sandhow
Munirah Santosa
Hyun-Soo Shin
Kazushige Shiraishi
Rupendra Shrestha
John P. Soleas
Nana Takenaka
Sharon Tan
Junichi Tanaka
Ana P. Terrasso
Takafumi Toyohara
Uri Weissbein
You Wu
Jiejia Xu
Kiryu K. Yap
Lamuk Zaveri
Ludi Zhang
Haibo Zhou

2018 ISSCR TRAVEL AWARDS SUPPORTED BY THE AUSTRALASIAN SOCIETY FOR STEM CELL RESEARCH (ASSCR)



With additional support from:

*Australian Regenerative Medicine Institute
Children's Medical Research Institute
Commonwealth Scientific and Industrial Research Organisation (CSIRO)
MIMR-PHI- The Ritchie Centre
Monash University
Monash University, Department of Obstetrics and Gynaecology
Murdoch Children's Research Institute
St. Vincent's Centre for Applied Medical Research
University of Western Australia*

Hyunjun Ahn
Yaser Atlasi
Serine Avagyan
Anna E. Baccei
Jun Chen
Kathryn C. Davidson
Jeffrey C. Davis
Laura De Rosa
Yvanka De Soysa
Florijn Dekkers
Melanie Domingues
Thomas Duncan
Ahmed Fahmy
Hananeh Fonoudi
Victoire Fort
Rodrigo A. Grandy
Elliott J. Hagedorn

Deirdre B. Hoban
Jennifer A. Hollywood
Claire C. Homan
Seon In Hwang
Thierry Jarde
Manabu Kasamoto
Yuko Kokubu
Geoffrey Lee
Cuicui Liu
Xiaodong Liu
Vikas Malik
Cameron L. McKnight
Louise Menendez
Jana M. Mitchell
Natasha Hui Jin Ng
Raphaella Pires Ferreira
Wu Qian

Hudia Rizwan
Tolulope O. Rosanwo
Edwige Roy
Jayesh Salvi
Colinda Scheele
Jian Shu
Charvi Syal
Luyi Tian
Mark van den Hurk
Jorik M. van Rijn
Celia Vandestadt
Yaofeng Wang
Samantha Yammine
Atilgan Yilmaz
Lei Zhou
Xuan Zhou
Jan Jakub Zyllicz

MERIT AWARD WINNERS 2018

CONGRATULATIONS TO THE ISSCR ABSTRACT MERIT AWARD RECIPIENTS

The ISSCR recognizes outstanding abstracts with the ISSCR Merit Abstract Awards. These awards are given to ISSCR trainee members who have submitted distinguished abstracts, as judged by the ISSCR 2018 abstract reviewers.

Yaser Atlasi
Scott Bell
Mimi Borrelli
German Camargo Ortega
Xi Chen
Jun Chen
Laura De Rosa
Yvanka De Soysa
Florijn Dekkers
Melanie Domingues
Ahmed Fahmy
Rodrigo Grandy
Elliott Hagedorn
Michael Hicks
Takuji Ito
Woong Bi Jang
Manabu Kasamoto

Cody Kime
Yuko Kokubu
Choon-Soo Lee
Cuicui Liu
Vikas Malik
Jana Mitchell
Takenori Ogura
John Ouyang
Wu Qian
Jayesh Salvi
Colinda Scheele
Charvi Syal
Jorik van Rijn
Yaofeng Wang
Atilgan Yilmaz
Jan Zylicz

WEDNESDAY, 20 JUNE, PLENARY I

Note that due to a schedule change, Dr. Belmonte will present on Saturday, 23 June, Plenary VI

BEN SCHERES, PHD, WAGENINGEN UNIVERSITY RESEARCH, NETHERLANDS



Dr. Scheres has defined anatomically, experimentally and genetically the root stem cell organization in Arabidopsis, a model system he has developed as appropriate for multidisciplinary dissection of developmental mechanisms. His group was the first to show that the stem cell niche concept was applicable to the plant kingdom. He identified transcription factors defining a dose-dependent combinatorial stem cell identity specification mechanism and has shown that the Retinoblastoma pathway controls stem cell differentiation-allowing comparisons of stem cell maintenance mechanisms across plant and animal kingdom. The group is strongly engaged in computational modeling and mathematical analysis of pattern formation mechanisms.

ELLY TANAKA, PHD, INSTITUTE OF MOLECULAR PATHOLOGY, AUSTRIA



Dr. Tanaka received her AB at Harvard, her PhD at UCSF and post-doctoral work at University College London. She became group leader at the Max Planck Institute of Molecular Cell Biology and Genetics Dresden then Professor at the TU Dresden and since 2016 Senior scientist at the Institute for Molecular Pathology, Vienna. She has developed molecular genetics in the axolotl to identify the stem cells for limb and spinal cord regeneration, identified molecular pathways that control progenitor cell expansion, and patterning.

GRAZIELLA PELLEGRINI, PHD, UNIVERSITY OF MODENA AND REGGIO EMILIA, ITALY



Dr. Pellegrini is a Professor of Biology at the University of Modena and Reggio Emilia. She is Coordinator of Cell Therapy at the Center for Regenerative Medicine “Stefano Ferrari”, and R&D Director and co-founder of Holostem Terapie Avanzate. She has relevant experience on epithelial stem cells, melanocytes for pigmentation disorders, oral mucosa, urethra, phase I gene therapy of epidermolysis bullosa, cell therapy by cultured human epidermis, of ocular surface from 1995, for treatment of limbal stem cell deficiency blindness; translation of cell therapy under ATMP European rules. Dr. Pellegrini is a co-recipient of the 2018 ISSCR Innovation Award with Dr. Michele De Luca.

JUAN CARLOS IZPISUA BELMONTE, PHD, SALK INSTITUTE FOR BIOLOGICAL STUDIES, U.S.



Dr. Belmonte's research interest lies in a better understanding of the fundamental genetic and cellular principles that govern embryonic development, tissue and organ homeostasis, regeneration and aging. His laboratory is contributing to these research fields by developing novel genetic and epigenetic technologies as well as cell and tissue reprogramming approaches both in vitro and in vivo.

Due to a scheduling change, this presentation will be given on Saturday, 23 June.

ANNE MCLAREN MEMORIAL LECTURE

WEDNESDAY, 20 JUNE, PLENARY II

PATRICK P.L. TAM, PHD, *CHILDREN'S MEDICAL RESEARCH INSTITUTE, AUSTRALIA*



Dr. Tam is Head of Embryology Unit at the Children's Medical Research Institute and Professor in Sydney Medical School. He undertakes a systems-based investigation of the functional attributes of gene regulatory network in the context of the cellular and molecular mechanisms that underpin the organization of the basic body plan of the early embryo. The findings provide an in-depth knowledge of lineage differentiation during early embryogenesis, which laid the foundation for directing the first steps of differentiation of stem cells into clinically useful cell types. Patrick Tam is the President's Medalist of the ANZSDB and Fellow of the Australian Academy of Science, Australian Academy of Health and Medical Sciences, Royal Society of Biology and Royal Society of London.

ERNEST MCCULLOCH MEMORIAL LECTURE

THURSDAY, 21 JUNE, PLENARY III

DOUGLAS A. MELTON, PHD, *HARVARD UNIVERSITY AND HARVARD STEM CELL INSTITUTE, U.S.*



Dr. Melton is the Xander University Professor at Harvard and an HHMI Investigator. He is also Co-director of the Harvard Stem Cell Institute. Research in the Melton laboratory focuses on the developmental biology of the pancreas and diabetes. The lab aims to make human islet cells for diabetics and find ways to thwart immune rejection so that patients no longer require blood checks and insulin injections.

PATIENT ADVOCATE ADDRESS

FRIDAY, 22 JUNE, PLENARY V

DANIEL FELLER



Mr. Feller is a Melbourne businessman and father of three to Tess, Alice and Harry. Harry Feller (age six) has inherited recessive genes from his mother (Hollie) and father and was born with Usher Syndrome type 1F. Daniel and Hollie have set up Genetic Cures Australia www.geneticcures.com.au as an awareness building and fundraising site which has garnered support worldwide in 18 months. He is determined to see a cure for Harry and a cure for dozens of inherited genetic conditions the world over. Positive and determined, he feels that we are approaching the final mile for ground-breaking research results into genetic cures for so many conditions with treatments increasingly available today that were only thought of less than a decade ago.

JOHN MCNEISH MEMORIAL LECTURE

SATURDAY, 23 JUNE, PLENARY VII

KATHERINE HIGH, MD, *SPARK THERAPEUTICS, U.S.*



Dr. High is currently President and Head of R&D at Spark Therapeutics, a publicly traded biotech company focused on discovering, developing, and delivering life-altering transformation for those patients and families affected by genetic disease. Prior to joining Spark, Dr. High was the William Bennett Professor of Pediatrics at the Perelman School of Medicine of the University of Pennsylvania, and an Investigator of the Howard Hughes Medical Institute. She is a past president of the American Society of Gene and Cell Therapy.

KEYNOTE ADDRESS

SATURDAY, 23 JUNE, PLENARY VII

JENNIFER DOUDNA, PHD, *UNIVERSITY OF CALIFORNIA, BERKELEY AND HHMI, U.S.*



As a professor of Chemistry and Molecular and Cell Biology at UC Berkeley, Dr. Doudna's research focuses on RNA-mediated gene regulation and genome editing. Doudna is an Investigator with the Howard Hughes Medical Institute and a recipient of multiple research awards. She is the co-author with Sam Sternberg of "A Crack in Creation", a personal account of the advent of CRISPR gene editing technology and the societal and ethical implications of genome editing.

SCHEDULE AT A GLANCE

MONDAY, 18 JUNE	
15:00 - 16:30	Public Symposium - Deakin Edge, Federation Square

TUESDAY, 19 JUNE	
10:00 - 16:30	Pre-Meeting Education: Clinical Advances in Stem Cell Research - WEHI
15:00 - 16:30	Attendee Orientation

WEDNESDAY, 20 JUNE	
07:45 - 08:45	Attendee Orientation
09:00 - 12:00	Focus Sessions
11:30 - 12:45	Early Career Group Leader Luncheon
13:00 - 15:15	Plenary I: Presidential Symposium
15:15 - 16:00	Refreshment Break
15:15 - 18:30	Poster Set Up
15:15 - 20:30	Exhibit Hall Open
16:00 - 18:00	Plenary II: Recapitulating Development from Stem Cells
18:00 - 20:30	Opening Reception
18:30 - 20:30	Poster Session I
21:00 - 24:00	Junior Investigator Social Night - Munich Brauhaus

THURSDAY, 21 JUNE	
08:00 - 08:30	Innovation Showcases
08:15 - 09:00	Morning Coffee
09:00 - 11:10	Plenary III: Systems Biology of Heterogeneity
11:00 - 20:00	Exhibit Hall Open
11:10 - 13:15	Lunch Break
11:15 - 13:15	Poster Set Up
11:30 - 12:30	Innovation Showcases
11:30 - 13:00	Meet the Experts Luncheon
12:15 - 13:00	Meet-up Hubs
13:15 - 15:15	Concurrent Sessions IA - E
15:15 - 16:00	Meet-up Hubs
15:15 - 16:00	Refreshment Break
16:00 - 18:00	Concurrent Sessions IIA - E
18:00 - 20:00	Poster Session II and Reception

SCHEDULE AT A GLANCE

FRIDAY, 22 JUNE	
08:00 - 08:30	Innovation Showcases
08:15 - 09:00	Morning Coffee
09:00 - 11:15	Plenary IV: New Technologies in Stem Cell Engineering
11:00 - 20:00	Exhibit Hall Open
11:15 - 13:15	Lunch Break
11:15 - 13:15	Poster Set Up
11:30 - 12:30	Innovation Showcases
11:30 - 13:00	Meet the Experts Luncheon
12:15 - 13:00	Meet-up Hubs
13:15 - 15:15	Concurrent Sessions IIIA - F
15:15 - 16:00	Meet-up Hubs
15:15 - 16:00	Refreshment Break
16:00 - 17:55	Plenary V: Stem Cell Based Disease Modeling
18:00 - 20:00	Poster Session III and Reception

SATURDAY, 23 JUNE	
08:15 - 09:00	Morning Coffee
09:00 - 11:10	Plenary VI: Cancer Stem Cells
11:00 - 16:00	Exhibit Hall Open
11:10 - 13:15	Lunch Break
11:30 - 13:00	Junior Investigator Career Panel Luncheon
12:15 - 13:00	Meet-up Hubs
13:15 - 15:15	Concurrent Sessions IVA - E
15:15 - 16:00	Refreshment Break
15:15 - 16:00	Meet-up Hubs
16:00 - 18:15	Plenary VII: Moving to the Clinic: Gene and Stem Cell Therapies

THE ISSCR JOB BOARD:

CONNECTING EMPLOYERS AND CANDIDATES BEYOND THE ISSCR ANNUAL MEETING



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ISSCR  INTERNATIONAL SOCIETY
FOR STEM CELL RESEARCH

THE STEM CELL PROGRAM AT BOSTON CHILDREN'S HOSPITAL IS PROUD TO SPONSOR THE ISSCR 2018 ANNUAL MEETING.

ISSCR 2018
ANNUAL MEETING
MELBOURNE AUSTRALIA
20-23 JUNE
ISSCR2018.ORG

The Stem Cell Program at Boston Children's Hospital brings together premier scientists and physicians from many backgrounds and specialties to form one of the top international stem cell research units. Their work in stem cells and cancer has led to novel therapies for patients throughout the world.

Visit stemcell.childrenshospital.org to learn more about our mission: to explore, understand, and translate the promise of stem cells into effective clinical therapies and treatments.

ISSCR



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**Los Angeles
Convention Center**

**26–29 June
2019**

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ISSCR CENTRAL

Network with your fellow attendees at ISSCR Central, the hub of the Exhibit and Poster Hall! In this lounge, you can:

- Relax and charge your electronic devices
- Sign up to ensure you're receiving the latest ISSCR news and information
- Learn more about your ISSCR membership benefits

MEET-UP HUBS

Check the mobile app for the most up-to-date listings

THURSDAY, 21 JUNE

15:15-16:00

German Stem Cell Network

As a fixture at the ISSCR annual meetings the German Stem Cell Network (GSCN) would like to invite German scientists as well as interested researchers to stop by the Meet-up Hub. Information on what is new in the GSCN will be provided and we would like to discuss your needs and wishes too.

15:15-16:00

Industry Scientists Networking

The ISSCR Industry Committee invites Industry Scientists to stop by the Meet-up Hub for networking and to solicit your feedback on areas of interest.

FRIDAY, 22 JUNE

15:15-16:00

Meet the Editors of *Stem Cell Reports*

Do you have a paper nearly ready for submission? Are you looking to find more information about the ISSCR's official journal, *Stem Cell Reports*? Come and meet the editors to discuss your work, our recently published issues, and any topics of interest around open-access, scientific publishing. Hear more about what the journal, now heading into its sixth year, means for the ISSCR.

15:15-16:00

International Policy Issues

The ISSCR Policy Committee invites meeting attendees to stop by the Meet-up Hub to discuss policy and regulatory issues of concern that impact your research.

18:00-20:00

Karger Publishers

The new Editors of *Cells Tissues Organs* warmly invite you to come and claim a free 1-year subscription to the journal. In particular, they look forward to meeting (and forming long-term relationships with) researchers attempting to bridge our understanding between developmental biology, stem cells, and tissue engineering.

SATURDAY, 23 JUNE

15:15-16:00

Volunteer Opportunities at ISSCR

Interested in learning more about volunteer opportunities? ISSCR outreach and communications staff will be available to answer your questions.

JOB MATCH

This innovative opportunity connects academic and industry employers with scientists looking for their next position.

Annual meeting attendees can opt in to Job Match at any time, at no additional fee. Browse the online Job Match Directory for job match profiles that meet your interests. Employers can view details of potential candidates and view CVs and poster information. Job seekers can view open position details.

Contact your favorites to make appointments to meet in person during the annual meeting. Select a location from a variety of on-site meeting places in the MCEC. The Job Match Lounge and ISSCR Central will be open in the Exhibit Hall during Exhibit Hall hours, or you can meet at a job seeker's poster. Visit www.isscr2018.org/jobmatch for additional details.

NETWORKING & EVENTS

EARLY-CAREER GROUP LEADER LUNCHEON

A SUCCESSFUL LAB LAUNCH: THE TERRIFYING PROCESS OF STARTING YOUR OWN GROUP

WEDNESDAY, 20 JUNE 11:30-12:45

MCEC, Level 1, Room 110

Becoming a group leader presents many challenges not directly related to your scientific knowledge or training. Time management, project selection, balancing research with administrative responsibilities, recruiting effectively, and juggling professional relationships inside and outside the lab are among the many challenges group leaders encounter.

Take advantage of this unique opportunity to participate in small group discussions with members of the ISSCR Board of Directors and the ISSCR Junior Investigators Committee to discuss these issues and more.

This is a ticketed event that requires pre-registration. A nominal fee applies.

JUNIOR INVESTIGATOR NETWORKING SOCIAL NIGHT

WEDNESDAY, 20 JUNE, 21:00 - MIDNIGHT

Start your ISSCR 2018 experience by meeting, mingling, dancing and socializing with fellow young investigators from around the world during the meeting's first night.

Venue

Munich Brauhaus Melbourne, 45 S Wharf Promenade (located next to the MCEC)

What to Expect

21:00 - 22:30 Networking "Meet & Mingle"
(light snacks will be provided)

22:30 - 22:40 Thank you from the ISSCR Junior
Investigators Committee

22:40 - 24:00 DJ Spins & JIs Dance

ISSCR annual meeting badge and photo ID required for entry. Must be age 21 or older to attend.

MEET THE EXPERTS LUNCHEONS

THURSDAY, 21 JUNE AND FRIDAY, 22 JUNE, 11:30-13:00

MCEC, Level 1, Room 110

Friday's Meet the Experts is sponsored by Boston Children's Hospital, Harvard Stem Cell Institute, and Massachusetts General Hospital.

Junior Investigators are invited to meet with leaders over lunch to discuss research techniques and topics, career paths and more. These relaxed networking luncheons allow ISSCR trainee members to actively discuss topics of common interest with peers and leaders in our community.

This is a ticketed event that requires pre-registration. A nominal fee applies.

CAREER PANEL LUNCHEON

Navigating Scientific Career Paths in Academia and Industry

SATURDAY, 23 JUNE, 11:30-13:00

MCEC, Level 1, Room 110

Junior Investigators are invited to join the ISSCR Junior Investigators Committee and a panel of experts for an in-depth discussion in a casual lunch setting.

For many of us, choosing the right career path can be daunting. Even after setting career goals, it may not be clear how to reach them. Join us for this luncheon where scientists from various disciplines will share their experiences and advice on how they have successfully navigated their career paths. Attendees and speakers will engage in panel discussion to provide real-life advice on tackling the challenges of finding, and reaching, the career path best suited for you.

MODERATOR

Yvanka de Soysa

J. David Gladstone Institutes and UCSF, U.S.

Member, ISSCR Junior Investigators Committee

PANELISTS

Nick Barker, PhD
Institute of Medical Biology, Singapore

Sheila Chari, PhD
Cell Press/Elsevier, U.S.

Elizabeth Finkel, PhD
COSMOS Magazine, Australia

Karin Innes, BSc, PhD, Dip (IPP)
FB Rice, Australia

Stefan Irion, MD
BlueRock Therapeutics, U.S.

This is a ticketed event that requires pre-registration. A nominal fee applies.

FOCUS SESSIONS

Wednesday, 20 June 09:00 – 12:00

TOOLS FOR BASIC AND APPLIED RESEARCH

Room 105, Level 1

Organized by Stem Cell COREdinates, Presented by STEMCELL Technologies and Thermo Fisher Scientific

Stem Cell COREdinates is a consortium of human pluripotent stem cell-focused core facilities that have joined forces to share experiences, expertise with protocols and reagents, and to establish “best practices.” Our Focus session will be divided into two parts.

AGENDA:

1. Selected presentations from Stem Cell COREdinates members

Session Chair: Tenneille Ludwig, Wicell

09:05 NAVIGATING THE PATH TO THE CLINIC: AVOIDING RESEARCH ROADBLOCKS

Tenneille Ludwig, Wicell

09:15 PARALLEL DERIVATION OF ISOGENIC HUMAN PRIMED AND NAIVE INDUCED PLURIPOTENT STEM

Laurent David, University of Nantes

09:30 OPTIMIZATION OF CRISPR-CAS9 GENOME EDITING IN HUMAN PLURIPOTENT STEM CELLS

Andrew Gaffney, STEMCELL Technologies

09:45 NFI GENES IN NEURAL STEM CELLS

Richard Gronostajski, State University of New York at Buffalo

10:00 DEVELOPING IPSC-BASED MODEL SYSTEMS OF THE HUMAN BRAIN AT THE ST. JUDE DNB STEM CELL CORE

Anjana Nityanandam, St. Jude Children’s Research Hospital

10:15 DISEASE MODELLING WITH HUMAN PLURIPOTENT STEM CELLS, FROM SMALL TO LARGE SCALE CULTURES

Damián Hernández, the University of Melbourne

10:30 CRISPR/CAS9: EMBRACING THE 3 STAGES OF A (R)EVOLUTION

Dmitry Ovchinnikov, University of Queensland

10:45 EDITING AND VALIDATING INDUCED PLURIPOTENT STEM CELLS - HOW TO ENSURE THE QUALITY OF YOUR EDITED CELL LINE

Jennifer Moore, RUCDR

2. Presentations from International Stem Cell Organizations: ISCBI, GAI, hPSCreg, ISCI.

Session Chair: TBD

11:00 PRESENTATION FROM THE INTERNATIONAL STEM CELL BANKING INITIATIVE (ISCBI)

Glyn Stacey, ISCBI

11:15 PRESENTATION FROM THE GLOBAL ALLIANCE FOR IPSC THERAPIES (GAI)

Stephen Sullivan, GAI

11:30 Presentation from the Human Pluripotent Stem Cell Registry (hPSCreg)

Rosario Isasi, hPSCreg

11:45 Presentation from the International Stem Cell Initiative (ISCI)

Nissim Benvenisty, ISCI

12:00 CLOSE

PLANNING, PROFILING AND PARTNERING: TRANSLATING A STEM CELL THERAPY FROM THE UNIVERSITY LAB TO THE PATIENT

Room 106, Level 1

Organized by the ISSCR Industry Committee

With stem cell science rapidly moving from the laboratory towards the patient, there is a growing interest in the translational pathway. This is especially true for academics who are increasingly looking to capitalize on discoveries or those curious about a career in industry. Drawing on experts from industry and academics, this program will highlight key aspects of the process for developing and testing a cell therapy including creating a target product profile, understanding the analytics and standards in addition to building relationships with industry to bring therapies to the clinic.

MODERATOR

Robert Deans, PhD

BlueRock Therapeutics

Member, ISSCR Industry Committee

AGENDA:

09:00 WELCOME AND OPENING REMARKS

Robert Deans, PhD

09:05 WHAT IS A TARGET PRODUCT PROFILE (TPP): TPP 1010

Thorsten Gorba, MSc, PhD, QuintilesIMS

09:25 CASE STUDY FOR TPP - FATE THERAPEUTICS

Bob Valamehr, PhD, MBA, Fate Therapeutics

09:35 INDUSTRY CASE STUDY FOR TPP

09:45 AN OVERVIEW OF ANALYTICS

10:00 COMPATIBILITY AND TESTING

10:20 COFFEE BREAK

10:35 STANDARDS FOR CELL THERAPY PRODUCTS

Robert Deans, PhD and Kim Bure, Akron Biotechnology

10:55 PANEL DISCUSSION

11:20 MODELING THE ACADEMIC-INDUSTRY PARTNERSHIP

Malin Parmar, PhD, Lund University, Akitsu Hotta, PhD, Center for iPS Cell Research & Application (CiRA),
Kyoto University

12:00 CLOSE

USING PLURIPOTENT STEM CELLS TO TREAT DISEASES OF THE NERVOUS SYSTEM

Room 212/213, Level 2

Organized by BlueRock Therapeutics

In just little over a decade, induced pluripotent stem cells (iPSCs) have changed modern medicine. Based on lessons learned from model systems, hundreds of labs around the world are now using human cells to study human disease and to develop therapies - a truly exiting paradigm shift! Remarkably, scientists, physicians, entrepreneurs and the biopharmaceutical industry were quick to embrace this technology and today iPSCs are being used to understand human pathology, to discover new therapeutic agents or serve as the basis of the therapy itself.

Diseases of the central nervous system (CNS) are of particular interest in a society that becomes older and older and where few disease-modifying therapies exist. In this focus session, we will showcase how pluripotent stem cells are being used to advance our treatment options for CNS disease. Our panel of speakers will conclude in a moderated panel discussion with time for the audience to ask questions.

AGENDA:

09:00 WELCOME AND INTRODUCTION

Stefan Irion, Sr. Dir. CNS Program, BlueRock Therapeutics

09:05 CELL THERAPY FOR NEURONAL DISEASE - OPPORTUNITIES AND CHALLENGES

Emile Nuwaysir, CEO, BlueRock Therapeutics

09:20 TOWARDS A PLURIPOTENT STEM CELL BASED THERAPY FOR PARKINSON'S DISEASE

Lorenz Studer, Director, Center for Stem Cell Biology, Memorial Sloan Kettering Cancer Center

09:50 DEVELOPING PATIENT-SPECIFIC STEM CELL MODELS TO INFORM NEW EPILEPSY THERAPIES

Evangelos Kiskinis, Assistant Professor in Neurology, Northwestern University

10:20 GLIAL PROGENITOR CELL-BASED TREATMENT OF MYELIN DISEASE

Steven Alan Goldman, Professor and Co-Director, Center for Translational Neuromedicine, University of Copenhagen and University of Rochester, Member, Clinical Translation Committee

10:50 PLURIPOTENT STEM CELL-DERIVED OPCS PROVIDE A PLATFORM FOR DISCOVERY OF MYELIN THERAPEUTICS

Paul Tesar, Associate Professor, Case Western Reserve University

11:20 PANEL DISCUSSION

12:00 CLOSE

SETTING ETHICAL STANDARDS: DRIVING CLINICAL TRANSLATION AND COUNTERING PREDATORY MARKETING

Room 219/220, Level 2

Organized by the ISSCR Ethics Committee

In this focus session, panelists will discuss ethical and legal issues raised by the continued growth of businesses marketing unproven uses of stem cells, and how academia, medicine, and industry can contribute to the establishment and enforcement of appropriate standards of moral conduct and regulatory policies. We will seek to balance examinations of the illicit industry and the fragmented global regulatory landscape with positive examples of standards-setting work being done by the ISSCR Clinical Translation Committee and successes in stem cell therapeutic development within a regulated framework. Additional focus will be placed on understanding and addressing patients' perspectives and concerns and the role of medical professionals and medical ethics in confronting misleading claims about stem cells.

MODERATOR

Jeremy Sugarman, MD, MPH, MA
*Johns Hopkins University
Member, ISSCR Ethics Committee and ISSCR
Public Policy Committee*

AGENDA:

09:00 WELCOME AND OPENING REMARKS

Jeremy Sugarman, MD, MPH, MA

09:05 OVERVIEW OF ETHICAL ISSUES IN STEM CELL DIRECT-TO-CONSUMER "THERAPIES"

Douglas Sipp, Riken Center for Developmental Biology, Member, ISSCR Ethics Committee, ISSCR Public Policy Committee, and ISSCR Membership Committee

09:25 PATIENT PERSPECTIVES AND ENGAGEMENT

Claire Tanner, PhD, University of Melbourne

09:45 Q&A FOR SESSION 1

09:50 OVERVIEW OF THE LEGAL/POLICY LANDSCAPE

Tamra Lysaght, PhD, National Univ of Singapore Centre for Biomedical Ethics

10:10 DEVELOPING REGULATED STEM CELL PRODUCTS

Graziella Pellegrini, PhD, University of Modena and Reggio Emilia

10:30 Q&A FOR SESSION 2

10:35 COFFEE BREAK

10:45 ROLE OF THE CLINICIAN AND PROFESSIONAL ETHICS

Ian Kerridge, University of Sydney

11:05 OVERVIEW OF THE ISSCR'S CLINICAL TRANSLATION COMMITTEE'S WORK

Roger Barker, PhD, MRCP, University of Cambridge, Director, ISSCR Board of Directors Chair, ISSCR Clinical Translation Committee

11:25 Q&A FOR SESSION 3

11:35 MODERATED DISCUSSION

Jeremy Sugarman, MD, MPH, MA

12:00 CLOSE

Molecular mechanisms of developmental and regenerative biology

11 – 13 November 2018 | Singapore

ORGANIZERS

Ray Dunn
Institute of Medical Biology, SG

Ian Chambers
MRC Centre for Regenerative Medicine, UK

Gerald Udolph
Stem Cell Society Singapore, SG

CO-ORGANIZERS

Huck Hui Ng
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Hans Schöler
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Patrick Tam
Children's Medical Research Institute, AU

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SPEAKERS

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Christa Buecker
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Elly Tanaka
Research Institute of Molecular Pathology, AT

Maria Elena Torres-Padilla
Helmholtz Zentrum München, DE

Val Wilson
MRC Centre for Regenerative Medicine, UK

REGISTRATION

Application deadline

31 August 2018

Abstract submission deadline

31 July 2018

Student/postdoc 500 SGD

Academic 650 SGD

Industry 1200 SGD

meetings.embo.org/event/18-devandregeneration



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20-22 FEBRUARY / 2019

Stem Cells & Organoids in Development and Disease

KEYNOTE
SPEAKERS

Hans Clevers
Hubrecht Institute, Netherlands

Jürgen Knoblich
Institute of Molecular Biotechnology
(IMBA), Austria

Research using organoids is pushing the boundaries of stem cell science. Join your global colleagues for three days of in-depth scientific presentations and discussions exploring this ground breaking technique.

Abstract Submission and Early Registration
open 15 August 2018.

TUESDAY, 19 JUNE

- 10:00 – 16:30 **PRE-MEETING EDUCATION: CLINICAL ADVANCES IN STEM CELL RESEARCH**
Off-site: Walter and Eliza Hall Institute of Medical Research
Advance registration required
- 14:00 – 18:00 **REGISTRATION OPEN** Main Foyer, Ground Level
- 15:00 – 16:30 **ATTENDEE ORIENTATION** Main Foyer, Ground Level

WEDNESDAY, 20 JUNE

- 06:30 – 20:30 **REGISTRATION OPEN** Main Foyer, Ground Level
- 07:45 – 08:45 **ATTENDEE ORIENTATION** Main Foyer, Ground Level
- 08:15 – 09:00 **MORNING COFFEE**

FOCUS SESSIONS *(see page 35 for session details)*

- 09:00 – 12:00 **PLANNING, PROFILING AND PARTNERING:
TRANSLATING A STEM CELL THERAPY FROM THE
UNIVERSITY LAB TO THE PATIENT** Room 106, Level 1
Organized by The ISSCR Industry Committee
- 09:00 – 12:00 **SETTING ETHICAL STANDARDS: DRIVING CLINICAL
TRANSLATION AND COUNTERING PREDATORY
MARKETING** Room 219/220, Level 2
Organized by The ISSCR Ethics Committee
- 09:00 – 12:00 **TOOLS FOR BASIC AND APPLIED RESEARCH** Room 105, Level 1
*Organized by Stem Cell COREdicates
Supported by STEMCELL Technologies and Thermo
Fisher Scientific*
- 09:00 – 12:00 **USING PLURIPOTENT STEM CELLS TO TREAT
DISEASES OF THE NERVOUS SYSTEM** Room 212/213, Level 2
Organized by BlueRock Therapeutics
- 11:30 – 12:45 **EARLY-CAREER GROUP LEADER LUNCHEON** Room 110, Level 1
Advance registration required

- 13:00 – 15:15 **PLENARY I: PRESIDENTIAL SYMPOSIUM** Plenary Room, Ground Level
Sponsored by Fate Therapeutics
Chair: Hans C. Clevers
Hubrecht Institute, Netherlands

- 13:00 – 13:07 **WELCOME TO COUNTRY**

PROGRAM SCHEDULE

WEDNESDAY, 20 JUNE (*continued*)

13:07 - 13:10	OPENING REMARKS: THE HONOURABLE LINDA DESSAU AC, GOVERNOR OF VICTORIA	
13:10 - 13:15	ISSCR PRESIDENT'S ADDRESS: HANS C. CLEVERS	
13:15 - 13:20	RECOGNITION OF THE ISSCR ZHONGMEI CHEN YONG TRAVEL AWARDS FOR SCIENTIFIC EXCELLENCE	
13:20 - 13:25	ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR PRESENTATION TO SHUIBING CHEN	
13:25 - 13:30	ISSCR INNOVATION AWARD PRESENTATION TO MICHELE DE LUCA AND GRAZIELLA PELLEGRINI	
13:30 - 13:55	Ben Scheres <i>Wageningen University and Research, Netherlands</i> INTEGRATED CONTROL OF STEM CELL ACTIVITY IN PLANTS	
13:55 - 14:20	Elly Tanaka <i>Institute of Molecular Pathology, Austria</i> COORDINATING TISSUES DURING AXOLOTL LIMB REGENERATION	
14:20 - 14:45	Graziella Pellegrini <i>University of Modena and Reggio Emilia, Italy</i> EPITHELIAL STEM CELLS AND REGENERATIVE MEDICINE	
14:45 - 14:50	THE ISSCR TOBIAS AWARD PRESENTATION TO CONNIE J. EAVES	
14:50 - 15:10	Connie J. Eaves <i>Terry Fox Laboratory, BC Cancer Agency, Canada</i> THE ISSCR TOBIAS AWARD LECTURE: A PROSPECTIVE ANALYSIS OF HUMAN LEUKEMOGENESIS	
15:15 - 16:00	REFRESHMENT BREAK	Exhibit Hall
15:15 - 20:30	EXHIBIT HALL OPEN	Exhibit Hall

WEDNESDAY, 20 JUNE *(continued)*

16:00 – 18:00	<p>PLENARY II: RECAPITULATING DEVELOPMENT FROM STEM CELLS</p> <p>Chair: Haifan Lin <i>Yale University School of Medicine, U.S.</i></p>	Plenary Room, Ground Level
16:00 – 16:05	<p>ISSCR PUBLIC SERVICE AWARD PRESENTATION TO MEGAN MUNSIE</p>	
16:05 – 16:30	<p>Mitinori Saitou <i>Kyoto University, Japan</i></p> <p>MECHANISM AND RECONSTITUTION IN VITRO OF GERM CELL DEVELOPMENT IN MICE, MONKEYS, AND HUMANS</p>	
16:30 – 16:55	<p>Anne Grapin-Botton <i>DanStem, University of Copenhagen, Denmark</i></p> <p>PANCREAS ORGANOID TO DECONSTRUCT NORMAL AND PERTURBED DEVELOPMENTAL MECHANISMS IN MOUSE AND HUMAN</p>	
16:55 – 17:20	<p>Shahin Rafii <i>Cornell Medical College and Angiocrine Bioscience, U.S.</i></p> <p>VASCULAR NICHE ANGIOCRINE SIGNALS DICTATE ORGANOTYPIC STEM CELL REGENERATION</p>	
17:20 – 17:30	<p>POSTER TEASERS</p>	
17:30 – 17:55	<p>Patrick Tam <i>Children's Medical Research Institute, Australia</i></p> <p>THE ANNE MCLAREN MEMORIAL LECTURE: DEVELOPMENTAL TRAJECTORY OF THE MOUSE EPIBLAST DEFINES THE DEVELOPMENTAL CORRELATE OF EMBRYO-DERIVED PLURIPOTENT STEM CELLS</p>	
18:00 – 20:30	<p>OPENING RECEPTION <i>Sponsored by WiCell</i></p>	Exhibit Hall
18:30 – 20:30	<p>POSTER SESSION I <i>Sponsored By Wicell</i></p> <p>ODD numbered posters present from 18:30 – 19:30 EVEN numbered posters present from 19:30 – 20:30</p>	Exhibit Hall
21:00 – 24:00	<p>JUNIOR INVESTIGATOR SOCIAL NIGHT <i>Junior Investigator event; advance registration required</i></p>	Munich Brauhaus 45 S Wharf Promenade

PROGRAM SCHEDULE

THURSDAY, 21 JUNE

07:30 - 18:30	REGISTRATION OPEN	Main Foyer, Ground Level
INNOVATION SHOWCASES		
08:00 - 08:30	UNION BIOMETRICA ANALYSIS, IMAGING, AND HANDLING OF CELLS AND CELL CLUSTERS IN STEM CELL RESEARCH Rock Pulak <i>Union Biometrica, Inc., U.S.</i>	Room 219/220, Level 2
08:00 - 08:30	THERMO FISHER SCIENTIFIC GMP RAW MATERIALS FOR CELL AND GENE THERAPY MANUFACTURING Kasey Kime Eric Roos <i>Thermo Fisher Scientific, U.S.</i>	Room 212/213, Level 2
08:00 - 08:30	APPLIED STEMCELL HUMAN iPSC-BASED DISEASE MODELING and DRUG SCREENING Xianmin Zeng <i>Applied StemCell Inc., U.S.</i>	Room 105, Level 1
08:00 - 08:30	NOVOHEART MYHEART PLATFORM: UNVEILING NOVOHEART'S NEXT-GENERATION DRUG DISCOVERY TOOLS INCLUDING 3D BIOENGINEERED HUMAN HEART-IN-A- JAR Kevin D. Costa <i>Novoheart, Canada</i>	Room 106, Level 1
08:00 - 08:30	MAXWELL BIOSYSTEMS NOVEL FUNCTIONAL ANALYSIS TECHNIQUES FOR ACCURATE PHENOTYPE CHARACTERIZATION OF HUMAN iPSC-DERIVED NEURONS Michele Fiscella <i>MaxWell Biosystems / ETH Zurich, Switzerland</i>	Room 203/204, Level 2
08:15 - 09:00	MORNING COFFEE <i>Sponsored by PLOS ONE</i>	Main Foyer, Ground Level

THURSDAY, 21 JUNE (*continued*)

- 09:00 – 11:10 **PLENARY III: SYSTEMS BIOLOGY OF HETEROGENEITY** Plenary Room, Ground Level
Chair: Janet Rossant
Gairdner Foundation, Canada
- 09:00 – 09:15 **ISSCR BUSINESS MEETING**
- 09:15 – 09:40 **François Guillemot**
The Francis Crick Institute, U.K.
 STEM CELL HETEROGENEITY IN THE ADULT HIPPOCAMPUS
- 09:40 – 10:05 **Fredrik Lanner**
Karolinska Institute, Sweden
 SINGLE CELL ANALYSIS OF HUMAN PREIMPLANTATION EMBRYOS AND PLURIPOTENT CELLS
- 10:05 – 10:30 **Merav Socolovsky**
University of Massachusetts Medical School, U.S.
 THE HEMATOPOIETIC AND ERYTHROID HIERARCHIES THROUGH THE LENS OF SINGLE CELL TRANSCRIPTOMICS
- 10:30 – 10:40 **POSTER TEASERS**
- 10:40 – 11:05 **Douglas A. Melton**
Harvard University and Harvard Stem Cell Institute, U.S.
 ERNEST MCCULLOCH MEMORIAL LECTURE: MAKING ISLET CELLS FOR DIABETICS
- 11:00 – 20:00 **EXHIBIT HALL OPEN** Exhibit Hall
- 11:10 – 13:15 **LUNCH BREAK**
- 11:30 – 13:00 **MEET THE EXPERTS LUNCHEON** Room 110, Level 1
Junior Investigator event; advance registration required

THURSDAY, 21 JUNE (*continued*)

INNOVATION SHOWCASES

- 11:30 – 12:30 **BIOLAMINA** Room 105, Level 1
CTG BIOLAMININ™ 521 – A BIOLOGICALLY RELEVANT CULTURE MATRIX, ENABLING PRE-CLINICAL RESEARCH PROTOCOLS TO BE TRANSLATED FOR CLINICAL TRIALS
Kristian Tryggvason
BioLamina, Sweden
Malin Parmar
Lund University, Sweden
Fredrik Lanner
Karolinska Institute, and Karolinska University, Sweden
- 11:30 – 12:30 **THERMO FISHER SCIENTIFIC** Room 212/213, Level 2
FROM BENCH TO BEDSIDE: GENERATION OF IPSCS FOR CELL THERAPY AND DISEASE MODELING APPLICATIONS
Kapil Bharti
National Eye Institute, U.S.
David Piper
Thermo Fisher Scientific, U.S.
- 11:30 – 12:30 **CDI** Room 106, Level 1
NOVEL APPLICATIONS OF HUMAN IPSC-DERIVED NEURONS: FROM HIGH-THROUGHPUT SCREENING TO PATCH-SEQ ANALYSIS
Anne Bang
Sanford Burnham Prebys Medical Discovery Institute, U.S.
Cedric Bardy
South Australian Health and Medical Research Institute (SAHMRI), Australia
- 11:30 – 12:30 **ALLEN INSTITUTE FOR CELL SCIENCE** Melbourne Room 1, Level 2
PROVIDING STEM CELL and GENE EDITING RESOURCES TO EMPOWER YOUR RESEARCH
Ruwanthi Gunawardane
Allen Institute for Cell Science U.S.

THURSDAY, 21 JUNE (*continued*)

11:30 - 12:30	<p>NIKON QUANTIFYING NEURODEGENERATION USING LIVE CELL IMAGING</p> <p>Lee L. Rubin <i>Harvard University and the Harvard Stem Cell Institute, U.S.</i></p>	Room 219/220, Level 2
11:30 - 12:30	<p>BIO-TECHNE UNFOLDING ORGANOID: A NEW PLATFORM FOR GENERATING ACCESSIBLE 3-D EPITHELIAL ORGAN TISSUE</p> <p>Scott Schachtele Fabrizio Rinaldi <i>Bio-Techne, U.S.</i></p>	Melbourne Room 2, Level 2
11:30 - 12:30	<p>STEMCELL TECHNOLOGIES GI TRACT ORGANOID: USING ADVANCED TISSUE MODELS TO INTERROGATE ABSORPTION AND REGULATION</p> <p>Heather A. McCauley Ryan K. Conder <i>STEMCELL Technologies Inc., Canada</i></p>	Room 203/204, Level 2
12:15 - 13:00	MEET-UP HUBS (<i>see page 33 for session details</i>)	Exhibit Hall

PROGRAM SCHEDULE

THURSDAY, 21 JUNE (*continued*)

13:15 – 15:15	CONCURRENT IA: MECHANISMS OF REPROGRAMMING 1: TO PLURIPOTENCY Chair: Hans R. Schöler <i>Max Planck Institute for Molecular Biomedicine, Germany</i>	Melbourne Room 1, Level 2
13:15 – 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 – 13:45	Hossein Baharvand <i>Royan Institute, Iran</i> ACQUISITION OF NAÏVE PLURIPOTENCY IN MICE AND MEN BY MODULATING TGF-BETA SIGNALING PATHWAY: TWO SIDES OF THE SAME COIN?	
13:45 – 14:00	Kyoji Horie <i>Nara Medical University, Japan</i> IDENTIFYING HETEROGENEITY OF GROUND STATE PLURIPOTENCY IN MOUSE EMBRYONIC STEM CELLS	
14:00 – 14:15	Amander Clark <i>University of California, Los Angeles, U.S.</i> TFAP2C REGULATES TRANSCRIPTION IN HUMAN NAIVE PLURIPOTENCY BY OPENING ENHANCERS	
14:15 – 14:30	Vincent Pasque <i>KU Leuven - University of Leuven, Belgium</i> EPIGENETIC AND GENETIC EFFECTS OF GENDER ON REPROGRAMMING TO IPS CELLS AND PLURIPOTENCY	
14:30 – 14:45	Jian Shu <i>Broad Institute/Whitehead Institute, MA, U.S.</i> RECONSTRUCTION OF CELLULAR REPROGRAMMING LANDSCAPES AND TRAJECTORIES BY ANALYSIS OF LARGE-SCALE SINGLE-CELL GENE EXPRESSION	
14:45 – 15:10	Xiaohua Shen <i>Tsinghua University, China</i> NOVEL FUNCTIONS OF RNA-BINDING PROTEINS IN TRANSCRIPTION REGULATION AND STEM CELL PLURIPOTENCY	

THURSDAY, 21 JUNE (*continued*)

13:15 – 15:15	<p>CONCURRENT IB: DISEASE MODELING</p> <p>Chair: Martin F. Pera <i>The Jackson Laboratory, U.S.</i></p>	Melbourne Room 2, Level 2
13:15 – 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 – 13:45	<p>Xiao Yang <i>State Key Laboratory of Proteomics, Beijing Institute of Lifeomics, China</i></p> <p>MOUSE MODELS OF GASTRIC CANCERS</p>	
13:45 – 14:00	<p>Jana Mitchell <i>Harvard University, U.S.</i></p> <p>GENETIC NEUROSCIENCE: HOW HUMAN GENES AND ALLELES SHAPE NEURONAL PHENOTYPES</p>	
14:00 – 14:15	<p>Ernst Wolvetang <i>The University of Queensland, Australia</i></p> <p>NUTRACEUTICAL RESCUE OF PATHOLOGICAL CHANGES IN iPSC-DERIVED NEURAL CELL TYPES FROM A CHILDHOOD LEUKODYSTROPHY CAUSED BY MUTATIONS IN ASPARTATE TRNA SYNTHETASE (DARS)</p>	
14:15 – 14:30	<p>Louise Menendez <i>University of Southern California, U.S.</i></p> <p>USING INDUCED SENSORY HAIR CELLS FOR HIGH THROUGHPUT SCREENING TO IDENTIFY OTOPROTECTANTS</p>	
14:30 – 14:45	<p>Tolulope Rosanwo <i>Boston Children's Hospital, U.S.</i></p> <p>ENUCLEATION IN INDUCED RED BLOOD CELLS: A PLATFORM FOR AUTOLOGOUS CELL THERAPY AND IN VITRO MODELING OF SICKLE CELL ANEMIA</p>	
14:45 – 15:00	<p>Ana P. Terrasso <i>Instituto de Biologia Experimental e Tecnológica (iBET), Portugal and Instituto de Tecnologia Química e Biológica António Xavier, Universidade Nova de Lisboa, Portugal</i></p> <p>iPSC-DERIVED NEUROSPHEROIDS RECAPITULATE DEVELOPMENT AND PATHOLOGICAL SIGNATURES OF HUMAN BRAIN MICROENVIRONMENT</p>	

PROGRAM SCHEDULE

THURSDAY, 21 JUNE (*continued*)

13:15 – 15:15	CONCURRENT IC: CARDIAC DEVELOPMENT AND DISEASE Chair: Charles E. Murry <i>Institute for Stem Cell and Regenerative Medicine, University of Washington, U.S.</i>	Room 219/220, Level 2
13:15 – 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 – 13:45	Christine L. Mummery <i>Leiden University Medical Center, Netherlands</i> CARDIAC MICROTISSUES FROM HPSC IN MODELLING CARDIOVASCULAR DISEASE	
13:45 – 14:00	Takafumi Toyohara <i>Beth Israel Deaconess Medical Center, U.S.</i> PATIENT DERIVED-IPS CELLS IDENTIFY A NOVEL PROTECTIVE FACTOR AGAINST ATHEROSCLEROSIS	
14:00 – 14:15	Kai Kretzschmar <i>Hubrecht Institute, Netherlands</i> PROFILING PROLIFERATIVE CELLS AND THEIR PROGENY IN DAMAGED MURINE HEARTS	
14:15 – 14:30	Nadia Rosenthal <i>The Jackson Laboratory, U.S.</i> NEW STRATEGIES FOR ACCELERATING CARDIAC REGENERATION	
14:30 – 14:45	Nathan Palpant <i>The University of Queensland, Australia</i> THE TRANSCRIPTIONAL LANDSCAPE OF CARDIAC DIFFERENTIATION AT SINGLE CELL RESOLUTION	
14:45 – 15:10	Deepak Srivastava <i>Gladstone Institutes, U.S.</i> CARDIAC DEVELOPMENT: BASIS FOR DISEASE AND REGENERATION	

THURSDAY, 21 JUNE (*continued*)

13:15 – 15:15	<p>CONCURRENT ID: EPITHELIAL STEM CELLS</p> <p>Chair: Nick Barker <i>Institute of Medical Biology, Singapore</i></p>	Room 212/213, Level 2
13:15 – 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 – 13:45	<p>Valerie Horsley <i>Yale University, U.S.</i></p> <p>LET'S TALK ABOUT STROMA: ADIPOCYTES AND FIBROBLASTS IN TISSUE REGENERATION AND REMODELING</p>	
13:45 – 14:00	<p>Ya-Chieh Hsu <i>Harvard University Department of Stem Cell and Regenerative Biology, U.S.</i></p> <p>BEYOND GOOSEBUMPS: INTERACTIONS BETWEEN THE HAIR FOLLICLE, THE ARRECTOR PILI MUSCLE, AND THE SYMPATHETIC NERVE DURING DEVELOPMENT AND HAIR FOLLICLE REGENERATION</p>	
14:00 – 14:15	<p>Kif Liakath-Ali <i>King's College London, U.K.</i></p> <p>AN EVOLUTIONARILY CONSERVED RIBOSOME-RESCUE PATHWAY MAINTAINS MOUSE EPIDERMAL STEM CELL HOMEOSTASIS</p>	
14:15 – 14:30	<p>Thierry Jarde <i>Monash University, Australia</i></p> <p>ACTIVATION OF NEUREGULIN1/ERBB SIGNALLING PROMOTES INTESTINAL STEM CELL PROLIFERATION AND IMPROVES TISSUE REGENERATION FOLLOWING DAMAGE</p>	
14:30 – 14:45	<p>Arshad Ayyaz <i>Lunenfeld-Tanenbaum Research Institute, Canada</i></p> <p>ELUCIDATING THE RADIATION RESISTANCE MECHANISMS IN THE REGENERATIVE MOUSE INTESTINE USING SINGLE CELL RNA SEQUENCING</p>	
14:45 – 15:10	<p>Sara Wickström <i>Max Planck Institute for Biology of Ageing, Germany</i></p> <p>REGULATION OF EPIDERMAL STEM CELL FATE BY NICHE-DERIVED SIGNALS AND FORCES</p>	

PROGRAM SCHEDULE

THURSDAY, 21 JUNE (*continued*)

13:15 – 15:15	<p>CONCURRENT IE: HOMEOSTASIS, METABOLISM AND AGING</p> <p>Chair: Sean J. Morrison <i>Children's Research Institute at UT Southwestern, U.S.</i></p>	Room 203/204, Level 2
13:15 – 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 – 13:45	<p>Andrea Brand <i>University of Cambridge, U.K.</i></p> <p>AWAKENING STEM CELLS IN THE BRAIN</p>	
13:45 – 14:00	<p>Charvi Syal <i>Ottawa Hospital Research Institute, Canada</i></p> <p>EPIGENETIC REGULATION OF LIPID METABOLISM IN NEURAL STEM CELL FATE DECISION</p>	
14:00 – 14:15	<p>Stephen Dalton <i>University of Georgia, U.S.</i></p> <p>CONTROL OF PLURIPOTENT STEM CELL FATE DECISIONS BY METABOLIC FLUX</p>	
14:15 – 14:30	<p>Dong-Wook Kim <i>Yonsei University College of Medicine, Korea</i></p> <p>SIRT1 ENHANCES THE SURVIVAL OF HUMAN EMBRYONIC STEM CELLS BY PROMOTING DNA REPAIR</p>	
14:30 – 14:45	<p>Christian Nefzger <i>Monash University, Australia</i></p> <p>FUNCTIONAL REJUVENATION OF AGED INTESTINAL STEM CELLS BY METABOLIC INTERVENTION AND DIRECT REPROGRAMMING</p>	
14:45 – 15:10	<p>Pekka Katajisto <i>University of Helsinki, Finland, and Karolinska Institutet, Sweden</i></p> <p>METABOLIC DETERMINATION OF CELL FATE THROUGH SELECTIVE INHERITANCE OF MITOCHONDRIA</p>	
15:15 – 16:00	<p>MEET-UP HUBS (<i>see page 33 for session details</i>)</p> <p>MEET-UP: INDUSTRY SCIENTISTS NETWORKING</p> <p>MEET-UP: GERMAN STEM CELL NETWORK</p>	<p>Exhibit Hall</p> <p>Meet-Up Hub #1</p> <p>Meet-Up Hub #2</p>
15:15 – 16:00	<p>REFRESHMENT BREAK</p>	<p>Exhibit Hall</p>

THURSDAY, 21 JUNE (*continued*)

16:00 – 18:00	<p>CONCURRENT IIA: GENE EDITING</p> <p>Chair: Angelo Lombardo <i>San Raffaele Telethon Institute for Gene Therapy, Italy</i> <i>Sponsored by The Allen Institute for Cell Science</i></p>	Melbourne Room 1, Level 2
16:00 – 16:05	<p>TOPIC OVERVIEW BY CHAIR</p>	
16:05 – 16:30	<p>Haoyi Wang <i>Institute of Zoology, Chinese Academy of Sciences, China</i> GENE EDITING: OPTIMIZATION AND APPLICATION IN PRIMARY CELLS</p>	
16:30 – 16:45	<p>Ruwanthi Gunawardane <i>Allen Institute for Cell Science, U.S.</i> ENDOGENOUS GENE TAGGING WITH CRISPR/CAS9 TO ILLUMINATE CELL ORGANIZATION AND DYNAMICS</p>	
16:45 – 17:00	<p>Markus Grompe <i>Oregon Health and Science University, U.S.</i> SELF-CLEAVING GUIDE RNAs FOR SELECTIVE EXPANSION OF PRECISELY GENE EDITED HEPATOCYTES IN VIVO</p>	
17:00 – 17:15	<p>Haibo Zhou <i>Institute of Neuroscience, China</i> IN VIVO SIMULTANEOUS TRANSCRIPTIONAL ACTIVATION OF MULTIPLE GENES IN THE BRAIN USING CRISPR-DCAS9-ACTIVATOR TRANSGENIC MICE</p>	
17:15 – 17:30	<p>Rodica Stan <i>City of Hope, U.S.</i> FIRST-IN-HUMAN STUDY OF FEASIBILITY, SAFETY AND ENGRAFTMENT OF ZINC FINGER NUCLEASE CCR5-MODIFIED CD34+ HEMATOPOIETIC STEM/PROGENITOR CELLS IN HIV-1 (R5) INFECTED SUBJECTS</p>	
17:30 – 17:55	<p>Danwei Huangfu <i>Memorial Sloan Kettering Cancer Center, U.S.</i> HUMAN DEVELOPMENT AND DISEASE THROUGH THE LENS OF PLURIPOTENT STEM CELLS</p>	

PROGRAM SCHEDULE

THURSDAY, 21 JUNE (*continued*)

16:00 – 18:00	CONCURRENT IIB: NEURAL DEVELOPMENT Chair: Marianne E. Bronner <i>California Institute of Technology, U.S.</i>	Melbourne Room 2, Level 2
16:00 – 16:05	TOPIC OVERVIEW BY CHAIR	
16:05 – 16:30	Yukiko Gotoh <i>University of Tokyo, Japan</i> REGULATION OF NEURAL STEM/PROGENITOR CELL FATE DURING NEOCORTICAL DEVELOPMENT	
16:30 – 16:45	Germán D. Camargo Ortega <i>Helmholtz Zentrum Muenchen and University of Munich, Germany</i> AKNA, A NEW CENTROSOMAL PROTEIN REGULATES EMT-LIKE FEATURES OF NEUROGENESIS BY MICROTUBULE ORGANIZATION	
16:45 – 17:00	Jan Kaslin <i>Australian Regenerative Medicine Institute, Australia</i> MAKE DO AND MAKE NEW: HOW ZEBRAFISH RAPIDLY REGENERATES SPINAL CORD INJURY	
17:00 – 17:15	Yechiel Elkabetz <i>Max Planck Institute for Molecular Genetics, Germany</i> NEW INSIGHTS ON HUMAN CORTICAL DEVELOPMENT AND MICROCEPHALY USING SINGLE ORGANOID AND SINGLE CELL RNASEQ	
17:15 – 17:30	Hongyan Wang <i>Duke-NUS Medical School, Singapore</i> AN INTRINSIC MECHANISM CONTROLS REACTIVATION OF NEURAL STEM CELLS BY SPINDLE MATRIX PROTEINS	
17:30 – 17:55	Pierre Vanderhaeghen <i>University Brussels UEB, Belgium</i> USING PLURIPOTENT STEM CELLS TO DECIPHER HUMAN-SPECIFIC MECHANISMS OF BRAIN DEVELOPMENT	

THURSDAY, 21 JUNE (*continued*)

16:00 – 18:00	<p>CONCURRENT IIC: ROAD TO THE CLINIC 1</p> <p>Chair: Roger E. Barker <i>University of Cambridge, U.K.</i></p>	Room 219/220, Level 2
16:00 – 16:05	<p>TOPIC OVERVIEW BY CHAIR</p>	
16:05 – 16:30	<p>Xiuyan Wang <i>Memorial Sloan Kettering Cancer Center, U.S.</i></p> <p>CAR T CELL THERAPY: THE CD19 PARADIGM AND BEYOND</p>	
16:30 – 16:45	<p>Charles E. Murry <i>Institute for Stem Cell and Regenerative Medicine, University of Washington, U.S.</i></p> <p>HUMAN ESC-CARDIOMYOCYTES RESTORE FUNCTION IN INFARCTED NON-HUMAN PRIMATE HEARTS</p>	
16:45 – 17:00	<p>John Hallett <i>University of Edinburgh, U.K.</i></p> <p>THE ADULT HUMAN EPCAM+CD24+CD133+ CHOLANGIOCYTE AS A BIPOTENTIAL HUMAN HEPATIC PROGENITOR AND TRANSPLANTABLE REGENERATIVE THERAPY FOR BILIARY DISEASE.</p>	
17:00 – 17:15	<p>Isabelle de Luzy <i>Florey Institute of Neuroscience and Mental Health, Australia</i></p> <p>ISOLATION AND TRANSPLANTATION OF HUMAN PLURIPOTENT STEM CELL-DERIVED MIDBRAIN DOPAMINERGIC PROGENITORS INTO PARKINSONIAN RATS</p>	
17:15 – 17:30	<p>Karl Johe <i>Neuralstem, Inc., U.S.</i></p> <p>INTRACEREBRAL TRANSPLANTATION OF NEURAL STEM CELL LINE, NSI-566, IN CHRONIC ISCHEMIC STROKE PATIENTS FOR TREATMENT OF PARALYSIS</p>	
17:30 – 17:55	<p>Paul Simmons <i>Mesoblast Ltd., Australia</i></p> <p>A PIPELINE OF INNOVATIVE CELLULAR MEDICINES FOR CURRENTLY INTRACTABLE, ADVANCED-STAGE DISEASES</p>	

PROGRAM SCHEDULE

THURSDAY, 21 JUNE (*continued*)

16:00 – 18:00	CONCURRENT IID: TISSUE ENGINEERING Chair: Mattias Lutolf <i>École Polytechnique Fédérale de Lausanne (EPFL), Switzerland</i> <i>Sponsored by eLife Sciences</i>	Room 212/213, Level 2
16:00 – 16:05	TOPIC OVERVIEW BY CHAIR	
16:05 – 16:30	Matthias Lutolf <i>École Polytechnique Fédérale de Lausanne (EPFL), Switzerland</i> ORGANOID DEVELOPMENT BY DESIGN	
16:30 – 16:45	Xufeng Xue <i>University of Michigan, U.S.</i> MECHANICS-GUIDED DEVELOPMENTAL PATTERNING OF NEUROECTODERM TISSUE FROM HUMAN PLURIPOTENT STEM CELLS	
16:45 – 17:00	Francesco Saverio Tedesco <i>University College London, U.K.</i> THREE-DIMENSIONAL IPSC-DERIVED HUMAN ARTIFICIAL SKELETAL MUSCLES MODEL MUSCULAR DYSTROPHIES AND ENABLE MULTILINEAGE TISSUE ENGINEERING	
17:00 – 17:15	Kiryu Yap <i>O'Brien Institute, Department of St Vincent's Institute, and University of Melbourne Department of Surgery at St Vincent's Hospital Melbourne, Australia</i> BIO-ENGINEERING TRANSPLANTABLE HUMAN VASCULARISED LIVER ORGANOIDS	
17:15 – 17:30	Jessica Butts <i>Gladstone Institutes, U.S.</i> CO-EMERGENCE OF MULTIPLE RESPIRATORY HINDBRAIN POPULATIONS FROM HUMAN PLURIPOTENT STEM CELLS	
17:30 – 17:55	Gordana Vunjak-Novakovic <i>Columbia University, U.S.</i> ENGINEERING HUMAN TISSUES FOR REGENERATIVE MEDICINE AND STUDY OF DISEASE	

THURSDAY, 21 JUNE (*continued*)

- 16:00 – 18:00 **CONCURRENT IIE: MUSCLE STEM CELLS** Room 203/204, Level 2
Chair: Peter Currie
Australian Regenerative Medicine Institute, Australia
- 16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**
- 16:05 – 16:30 **Shahragim Tajbakhsh**
Pasteur Institute, France
 INTRINSIC AND EXTRINSIC REGULATION OF THE MUSCLE STEM CELL NICHE
- 16:30 – 16:45 **Michael Hicks**
University of California, Los Angeles, U.S.
 ERBB3 AND NGFR MARK A DISTINCT SKELETAL MUSCLE PROGENITOR CELL IN HUMAN DEVELOPMENT AND HPSCS
- 16:45 – 17:00 **Dhanushika Ratnayake**
Australian Regenerative Medicine Institute, Australia
 STEM CELL-MACROPHAGE INTERACTIONS REGULATE VERTEBRATE MUSCLE REGENERATION: INSIGHTS FROM ZEBRAFISH
- 17:00 – 17:15 **Haibin Xi**
University of California, Los Angeles, U.S.
 DEFINING HUMAN IN VIVO SKELETAL MUSCLE DEVELOPMENT AND IN VITRO PLURIPOTENT STEM CELL MYOGENESIS AT SINGLE CELL RESOLUTION
- 17:15 – 17:30 **Liwei Xie**
Guangdong Institute of Microbiology, China
 BAMBI-MEDIATED SIGNALING PATHWAY IS INVOLVED IN IN SATELLITE CELLS QUIESCENCE AND ACTIVATION
- 17:30 – 17:55 **Amy Wagers**
Harvard University, U.S.
 IN VIVO GENE EDITING IN MUSCLES AND MUSCLE STEM CELLS
- 18:00 – 20:00 **POSTER SESSION II AND RECEPTION** Exhibit Hall
Sponsored by Ontario Institute for Regenerative Medicine (OIRM)
 ODD numbered posters present from 18:00 – 19:00
 EVEN numbered posters present from 19:00 – 20:00

PROGRAM SCHEDULE

FRIDAY, 22 JUNE

07:30 – 18:30 **REGISTRATION OPEN** Main Foyer, Ground Level

INNOVATION SHOWCASES

08:00 – 08:30 **STEMBIOSYS** Room 219/220, Level 2

THERE IS NO PLACE LIKE HOME! CELL DERIVED
MATRICES THE NEXT EVOLUTION IN CELL CULTURE

Sy Griffey

StemBioSys Inc, U.S.

08:15 – 09:00 **MORNING COFFEE** Main Foyer, Ground Level

09:00 – 11:15 **PLENARY IV: NEW TECHNOLOGIES IN STEM CELL
ENGINEERING** Plenary Room, Ground
Level

Chair: Konrad Hochedlinger

*Massachusetts General Hospital and
Harvard University, U.S.*

09:00 – 09:25 **Fred H. Gage**
Salk Institutes for Biological Studies, U.S.
IN VIVO BRAIN ORGANOID MODEL OF VASCULARIZED AND FUNCTIONAL PSC-
DERIVED HUMAN BRAIN ORGANIDS

09:25 – 09:50 **Angelo Lombardo**
San Raffaele Telethon Institute for Gene Therapy, Italy
EXPLOITING TARGETED (EPI)GENOME EDITING FOR THERAPEUTIC
APPLICATIONS

09:50 – 10:15 **Jennifer Phillips-Cremins**
Perelman School of Medicine University of Pennsylvania, U.S.
3D EPIGENOME RECONFIGURATION IN BRAIN DEVELOPMENT AND
NEURODEGENERATIVE DISEASE

10:15 – 10:40 **Alexander van Oudenaarden**
*Hubrecht Institute-KNAW and University Medical
Center, Netherlands*
WHOLE-ORGANISM CLONE-TRACING USING SINGLE-
CELL SEQUENCING

10:40 – 10:45 **POSTER TEASERS**

10:45 – 11:10 **Shuibing Chen**
Weill Cornell Medical College, U.S.
ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR
LECTURE: CONTROL HUMAN PLURIPOTENT STEM CELL FATE USING CHEMICAL
APPROACHES

FRIDAY, 22 JUNE (*continued*)

11:00 – 20:00	EXHIBIT HALL OPEN	Exhibit Hall
11:15 – 13:15	LUNCH BREAK	
11:30 – 13:00	MEET THE EXPERTS LUNCHEON <i>Junior Investigator event; advance registration required</i> <i>Sponsored by: Stem Cell Program at Boston Children's Hospital, Harvard Stem Cell Institute, and Massachusetts General Hospital Center for Regenerative Medicine</i>	Room 110, Level 1

INNOVATION SHOWCASES

11:30 – 12:30	STEMCELL TECHNOLOGIES HUMAN PLURIPOTENT STEM CELL QUALITY: ESSENTIAL CONSIDERATIONS FOR GENE EDITING, CLONING, MAINTENANCE AND DISEASE MODELING Adam Hirst Vivian Lee <i>STEMCELL Technologies Inc., Canada</i>	Room 203/204, Level 2
11:30 – 12:30	IRVINE SCIENTIFIC IMPORTANCE OF USING SERUM-FREE MEDIA IN THE CELL THERAPY FIELD Vanda S. Lopes <i>Irvine Scientific, U.S.</i>	Melbourne Room 2, Level 2
11:30 – 12:30	LONZA AND GUEST FROM SEMMA THERAPEUTICS INDUSTRIALIZATION OF CELL AND GENE THERAPY MANUFACTURING- FROM CONCEPT TO PATIENTS Thomas Fellner <i>Lonza Walkersville, Inc., U.S.</i> Julie Carson <i>Semma Therapeutics, U.S.</i>	Room 106, Level 1

PROGRAM SCHEDULE

FRIDAY, 22 JUNE (*continued*)

11:30 - 12:30	BIOLOGICAL INDUSTRIES THE PROMISE OF INDUCED PLURIPOTENT STEM CELLS: BASIC RESEARCH AND CLINICAL GRADE MANUFACTURING Micha Drukker <i>Helmholtz Center Munich, Germany</i> Achia Urbach <i>Bar Ilan University, Israel</i> David Fiorentini <i>Biological Industries, Israel</i>	Room 212/213, Level 2
11:30 - 12:30	MILTENYI TOWARDS A THERAPY FOR PARKINSON'S DISEASE: LATEST RESEARCH HIGHLIGHTS AND CONCEPTS FOR MANUFACTURING OF ATMPs Malin Parmar <i>Lund University, Sweden</i> Sebastian Knöbel <i>Miltenyi Biotec GmbH, Germany</i>	Room 219/220, Level 2
11:30 - 12:30	THERMO FISHER SCIENTIFIC VALIDATING ANTIBODIES TO DISTINGUISH BETWEEN NAIVE AND PRIMED HPSCS Andrew Laslett <i>CSIRO Manufacturing, Australia</i>	Room 105, Level 1
11:30 - 12:30	MINERVA BIOTECHNOLOGIES THE IMPACT OF VARIOUS STEM CELL GROWTH MEDIA ON LINEAGE DETERMINATION Cynthia Bamdad <i>Minerva Biotechnologies, U.S.</i>	Melbourne Room 1, Level 2
12:15 - 13:00	MEET-UP: EARLY-CAREER RESEARCHERS DOWN UNDER, HUB #1 (<i>see page 33 for session details</i>)	Exhibit Hall

FRIDAY, 22 JUNE (*continued*)

13:15 – 15:15	<p>CONCURRENT IIIA: ORGANOIDS IN MODELING DISEASE AND DEVELOPMENT <i>Sponsored by Decibel Therapeutics</i></p> <p>Chair: Arnold R. Kriegstein <i>University of California, San Francisco, U.S.</i></p>	Melbourne Room 1, Level 2
13:15 – 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 – 13:45	<p>Jeffrey Beekman <i>University Medical Center Utrecht, Netherlands</i></p> <p>INTESTINAL ORGANOIDS FOR CYSTIC FIBROSIS MODELING</p>	
13:45 – 14:00	<p>Jianping Fu <i>University of Michigan, U.S.</i></p> <p>PROGRAMMABLE MICROFLUIDIC SYNTHESIS OF SYNTHETIC HUMAN EMBRYO-LIKE ENTITIES</p>	
14:00 – 14:15	<p>Max Salick <i>Novartis Institutes for Biomedical Research, U.S.</i></p> <p>SINGLE CELL TRANSCRIPTOMICS OF GENE-EDITED HUMAN CEREBRAL ORGANOIDS REVEALS NEURON-SPECIFIC PATTERNING DEFECTS AND A TREATMENT-RESPONSIVE GLIAL INFLAMMATORY SIGNATURE IN TUBEROUS SCLEROSIS</p>	
14:15 – 14:30	<p>Alexander Combes <i>University of Melbourne, Australia</i></p> <p>HIGH THROUGHPUT SINGLE CELL RNA-SEQ OF DEVELOPING MOUSE KIDNEY AND HUMAN KIDNEY ORGANOIDS REVEALS A ROADMAP FOR RECREATING THE KIDNEY</p>	
14:30 – 14:45	<p>Jorik van Rijn <i>UMC Utrecht, Netherlands</i></p> <p>HUMAN INTESTINAL ORGANOIDS AS A MODEL FOR INTESTINAL FAILURE AND ABERRANT LIPID METABOLISM IN PATIENTS WITH DGAT1 DEFICIENCY</p>	
14:45 – 15:10	<p>Alysson Muotri <i>University of California, San Diego, U.S.</i></p> <p>BRAIN ORGANOIDS AS A MODEL SYSTEM FOR NEURODEVELOPMENT AND EVOLUTIONARY STUDIES</p>	

FRIDAY, 22 JUNE (*continued*)

13:15 – 15:15	CONCURRENT IIIB: NERVOUS SYSTEM DISEASE Chair: Steven A. Goldman <i>University of Copenhagen, Denmark and University of Rochester, U.S.</i>	Melbourne Room 2, Level 2
13:15 – 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 – 13:45	Ricardo Dolmetsch <i>Novartis Institutes for BioMedical Research, Inc., U.S.</i> USING STEM CELLS FOR DRUG DISCOVERY IN NEUROSCIENCE	
13:45 – 14:00	Julian Heng <i>Curtin University, Australia</i> FINDING YOUR PLACE: CONTROL OF CELL MIGRATION DURING FETAL BRAIN DEVELOPMENT AND NEURONAL MIGRATION DISORDER IN HUMANS	
14:00 – 14:15	Moa Stenudd <i>Karolinska Institutet, Sweden</i> SPINAL CORD EPENDYMAL CELLS ARE FUNCTIONALLY HETEROGENOUS AND CONTAIN A SMALL SUBPOPULATION OF NEURAL STEM CELLS	
14:15 – 14:30	Scott Bell <i>McGill University, Canada</i> MUTATIONS IN ACTL6B CAUSE AUTISM AND EPILEPSY AND LEAD TO LOSS OF DENDRITES IN HUMAN NEURONS.	
14:30 – 14:45	Deirdre Hoban <i>Lund University, Sweden</i> TRANSPLANTATION OF HUMAN EMBRYONIC STEM CELL DERIVED DOPAMINERGIC NEURONS IN AN ACCELERATED ALPHA-SYNUCLEIN RAT MODEL OF PARKINSON'S DISEASE	
14:45 – 15:10	Clare Parish <i>The Florey Institute of Neuroscience and Mental Health, Australia</i> GDNF ENHANCES THE FUNCTIONAL INTEGRATION OF HUMAN PLURIPOTENT STEM CELL-DERIVED DOPAMINE GRAFTS IN A RAT MODEL OF PARKINSON'S DISEASE	

FRIDAY, 22 JUNE (*continued*)

13:15 - 15:15	<p>CONCURRENT IIIC: MECHANISMS OF REPROGRAMMING 2: TRANSDIFFERENTIATION BETWEEN LINEAGES</p> <p>Chair: Deepak Srivastava <i>Gladstone Institutes, U.S.</i></p>	Room 219/220, Level 2
13:15 - 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 - 13:45	<p>Hynek Wichterle <i>Columbia University, U.S.</i></p> <p>CELL-TYPE- AND STAGE-SPECIFIC CONSTELLATIONS OF ENHANCERS CONTROL COMPLEX GENE EXPRESSION PROGRAMS IN THE NERVOUS SYSTEM</p>	
13:45 - 14:00	<p>Joseph Chen <i>Monash University, Australia</i></p> <p>USING A PREDICTIVE COMPUTATIONAL ALGORITHM TO ESTABLISH A UNIVERSAL TRANSCRIPTION FACTOR ENHANCED DIFFERENTIATION FRAMEWORK</p>	
14:00 - 14:15	<p>Ori Bar-Nur <i>Harvard University, U.S.</i></p> <p>DIRECT REPROGRAMMING OF MOUSE FIBROBLASTS INTO FUNCTIONAL SKELETAL MUSCLE PROGENITORS</p>	
14:15 - 14:30	<p>Evan Appleton <i>Harvard Medical School, U.S.</i></p> <p>A SOFTWARE TOOL FOR DESIGNING TRANS-DIFFERENTIATION EXPERIMENTS WITH COMBINATIONS OF TRANSCRIPTION FACTORS</p>	
14:30 - 14:45	<p>Joanne Lacey <i>University of Sheffield, U.K.</i></p> <p>MITOCHONDRIAL DYNAMICS DETERMINES HUMAN EMBRYONIC STEM CELL FATES</p>	
14:45 - 15:00	<p>Kimberley Babos <i>University of Southern California, U.S.</i></p> <p>HYPERTRANSCRIPTION DRIVES CELLULAR REPROGRAMMING</p>	

PROGRAM SCHEDULE

FRIDAY, 22 JUNE (*continued*)

13:15 – 15:15	CONCURRENT IIID: HEMATOPOIESIS Chair: Leonard I. Zon <i>Boston Children's Hospital, U.S.</i>	Room 212/213 Level 2
13:15 – 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 – 13:45	Andrew Elefanty <i>Murdoch Children's Research Institute, Australia</i> MODELING NORMAL AND MALIGNANT HAEMATOPOIESIS USING HUMAN PLURIPOTENT STEM CELLS	
13:45 – 14:00	Vanessa Lundin <i>Boston Children's Hospital and Dana-Farber Cancer Institute, U.S.</i> YAP REGULATES HEMATOPOIETIC STEM CELL FORMATION IN RESPONSE TO THE BIOPHYSICAL FORCES OF BLOOD FLOW	
14:00 – 14:15	Lei Ding <i>Columbia University Medical Center, U.S.</i> LIVER-DERIVED SYSTEMIC THROMBOPOIETIN IS REQUIRED FOR BONE MARROW HEMATOPOIETIC STEM CELL MAINTENANCE	
14:15 – 14:30	Kathryn Potts <i>Albert Einstein College of Medicine, U.S.</i> THE SPLICEOSOMAL COMPONENT SF3B1 IS ESSENTIAL FOR ZEBRAFISH HEMATOPOIETIC STEM CELL FORMATION THROUGH REGULATION OF THE JAK/STAT SIGNALING PATHWAY	
14:30 – 14:45	Luena Papa <i>Icahn School of Medicine at Mount Sinai, U.S.</i> ROS SUPPRESSION THROUGH P53 ACTIVITY AND A REMODELED MITOCHONDRIAL NETWORK DETERMINES THE FATE OF FUNCTIONAL HUMAN HEMATOPOIETIC STEM CELLS DURING EX-VIVO EXPANSION	
14:45 – 15:00	Stephen Ting <i>Monash University, Australia</i> CONSTITUTIVE DELETION OF AP2A2 RESULTS IN FETAL LIVER HAEMATOPOIETIC EXHAUSTION DUE TO LOSS OF HSC QUIESCENCE AND PERTURBED ASYMMETRICAL:SYMMETRICAL HSC FATE.	

FRIDAY, 22 JUNE (*continued*)

13:15 - 15:15	<p>CONCURRENT IIIIE: STEM CELLS IN ORGAN DEVELOPMENT AND MAINTENANCE</p> <p>Chair: Elly Tanaka <i>Institute of Molecular Pathology, Austria</i></p>	Room 203/204, Level 2
13:15 - 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 - 13:45	<p>Shosei Yoshida <i>National Institute for Basic Biology, Japan</i></p> <p>SPERM STEM CELLS: THEIR CONTEXT-DEPENDENT BEHAVIOR</p>	
13:45 - 14:00	<p>Jayesh Salvi <i>Stanford University, U.S.</i></p> <p>ATR MEDIATED REPLICATION-STASIS CONTROLS MUSCLE STEM CELL QUIESCENCE</p>	
14:00 - 14:15	<p>Colinda Scheele <i>Netherlands Cancer Institute, Netherlands</i></p> <p>IDENTITY AND DYNAMICS OF MOUSE MAMMARY STEM CELLS DURING BRANCHING MORPHOGENESIS</p>	
14:15 - 14:30	<p>Yoji Kojima <i>Center for iPS Cell Research and Application, Japan</i></p> <p>EVOLUTIONARILY DISTINCTIVE MECHANISMS OF HUMAN GERM CELL LINEAGE SPECIFICATION</p>	
14:30 - 14:45	<p>Wolfram Goessling <i>Brigham and Women's Hospital/Harvard Medical School, U.S.</i></p> <p>ESTROGEN REGULATES HEPATOBILIARY FATE DECISIONS DURING VERTEBRATE DEVELOPMENT</p>	
14:45 - 15:10	<p>Peter Currie <i>Australian Regenerative Medicine Institute, Australia</i></p> <p>THE ROLE OF DISTINCT POPULATIONS OF MUSCLE STEM CELLS DURING REGENERATION AND ORGAN GROWTH</p>	

PROGRAM SCHEDULE

FRIDAY, 22 JUNE (*continued*)

13:15 – 14:55	<p>CONCURRENT IIIF: ETHICS AND REGULATORY CONSIDERATIONS</p> <p>Chairs: Megan Munsie <i>University of Melbourne, Australia</i></p> <p>Jeremy Sugarman <i>Johns Hopkins University, U.S.</i></p>	Room 106, Level 1
13:15 – 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 – 13:35	<p>Claire Tanner <i>The University of Melbourne, Australia</i></p> <p>“YOU MUST CLICK THE BUTTON AND DONATE”: ONLINE CROWDSOURCING TO FUND UNPROVEN STEM CELL TREATMENTS</p>	
13:35 – 13:50	<p>Saad Fahd <i>The University of Melbourne, Australia</i></p> <p>THE VIEWS AND PRACTICES OF AUSTRALIAN DOCTORS ON THE MANAGEMENT OF PEOPLE’S PURSUIT OF UNPROVEN STEM CELL-BASED INTERVENTIONS</p>	
13:50 – 14:05	<p>Tereza Hendl <i>The University of Sydney and The University of Melbourne, Australia</i></p> <p>STEM CELL REGISTRIES: SCIENCE OR SCIENTISM?</p>	
14:05 – 14:20	<p>Zubin Master <i>Mayo Clinic, U.S.</i></p> <p>WHAT DO WE KNOW ABOUT PROVIDERS OFFERING UNPROVEN STEM CELL INTERVENTIONS?</p>	
14:20 – 14:35	<p>Kirstin Matthews <i>Rice University, U.S.</i></p> <p>RECONSIDERING THE 14-DAY RULE: CONTRASTING DIFFERENT PATHWAYS FOR HUMAN EMBRYO RESEARCH LIMITATIONS</p>	
14:35 – 14:50	<p>Rosario Isasi <i>University of Miami, U.S.</i></p> <p>THE EUROPEAN HUMAN PLURIPOTENT STEM CELL REGISTRY (HPSCREG): ESTABLISHING A FRAMEWORK FOR ATTESTING ETHICAL AND LEGAL PROVENANCE OF HPSC LINES</p>	
15:15 – 16:00	<p>MEET-UP HUBS (<i>see page 33 for session details</i>)</p>	Exhibit Hall
	<p>MEET-UP: MEET THE EDITORS OF <i>STEM CELL REPORTS</i></p>	Meet-up Hub #1
	<p>MEET-UP: INTERNATIONAL POLICY ISSUES</p>	Meet-up Hub #2
15:15 – 16:00	<p>REFRESHMENT BREAK</p>	Exhibit Hall

FRIDAY, 22 JUNE (*continued*)

- 16:00 – 17:55 **PLENARY V: STEM CELL BASED DISEASE MODELING** Plenary Room, Ground Level
Sponsored by Burroughs Wellcome Fund
Chair: Melissa H. Little
Murdoch Children's Research Institute, Australia
- 16:00 – 16:25 **Steven A. Goldman**
University of Copenhagen, Denmark and University of Rochester Medical Center, U.S.
 HUMANIZED PATIENT-SPECIFIC GLIAL CHIMERIC MICE FOR MODELING NEUROLOGICAL AND NEUROPSYCHIATRIC DISEASE
- 16:25 – 16:50 **Qiang Sun**
Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, China
 CLONING OF MACAQUE MONKEYS BY SOMATIC CELL NUCLEAR TRANSFER
- 16:50 – 17:15 **Joseph Wu**
Stanford University School of Medicine, U.S.
 STEM CELLS AND CARDIOVASCULAR GENOMICS FOR PRECISION MEDICINE
- 17:15 – 17:25 **Daniel Feller**
 PATIENT ADVOCATE ADDRESS
- 17:25 – 17:50 **Michele De Luca**
Centre for Regenerative Medicine, University of Modena and Reggio Emilia, Italy
 THE ISSCR AWARD FOR INNOVATION LECTURE: LIFE-SAVING REGENERATION OF THE ENTIRE HUMAN EPIDERMIS BY TRANSGENIC STEM CELLS
- 18:00 – 20:00 **POSTER SESSION III AND RECEPTION** Exhibit Hall
Sponsored by Karger Publishers
 ODD numbered posters present from 18:00 – 19:00
 EVEN numbered posters present from 19:00 – 20:00
- 18:00 – 20:00 **MEET-UP: MEET THE EDITORS OF CELL TISSUES ORGANS** Meet-up Hub #1

PROGRAM SCHEDULE

SATURDAY, 23 JUNE

08:00 – 18:30	REGISTRATION OPEN	Main Foyer, Ground Level
08:15 – 09:00	MORNING COFFEE	Main Foyer, Ground Level
09:00 – 11:10	PLENARY VI: CANCER STEM CELLS Chair: Urban Lendahl <i>Karolinska Institute, Sweden</i>	Plenary Room, Ground Level
09:00 – 09:25	Allison Bardin <i>Institut Curie, France</i> GENETIC AND EPIGENETIC DEREGLATION OF ADULT STEM CELLS	
09:25 – 09:50	Tannishtha Reya <i>University of California San Diego School of Medicine, U.S.</i> STEM CELL SIGNALS IN CANCER HETEROGENEITY AND THERAPY RESISTANCE	
09:50 – 10:15	Nick Barker <i>Institute of Medical Biology, Singapore</i> LGR5+ STEM CELLS IN EPITHELIAL MAINTENANCE, REPAIR AND CANCER OF THE MOUSE STOMACH	
10:15 – 10:40	Jane Visvader <i>Walter and Eliza Hall Institute of Medical Research, Australia</i> GETTING ABREAST OF THE MAMMARY EPITHELIAL DIFFERENTIATION HIERARCHY	
10:40 – 11:05	Juan Carlos Izpisua Belmonte <i>Salk Institute for Biological Studies, U.S.</i> ORGAN REGENERATION AND ANTI-AGING STRATEGIES	
11:00 – 16:00	EXHIBIT HALL OPEN	Exhibit Hall
11:10 – 13:15	LUNCH BREAK	
11:30 – 13:00	JUNIOR INVESTIGATOR CAREER PANEL <i>Junior Investigator event; advance registration required</i>	Room 110, Level 1
12:15 – 13:00	MEET-UP HUBS (see page 33 for session details)	Exhibit Hall

SATURDAY, 23 JUNE *(continued)*

13:15 – 15:15	CONCURRENT IVA: ROAD TO THE CLINIC II Chair: Paul Simmons <i>Mesoblast Ltd., Australia</i>	Melbourne Room 1, Level 2
13:15 – 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 – 13:45	Peter Coffey <i>University College London, U.K.</i> THE LONDON PROJECT TO CURE BLINDNESS AT 10 YEARS, HAVE WE FOUND A CURE?	
13:45 – 14:00	Dan S. Kaufman <i>University of California, San Diego, U.S.</i> USE OF HUMAN INDUCED PLURIPOTENT STEM CELLS TO PRODUCE CYTOKINE AUTONOMOUS, CHIMERIC ANTIGEN-DIRECTED NATURAL KILLER CELLS WITH IMPROVED ANTI-TUMOR ACTIVITY	
14:00 – 14:15	Kapil Bharti <i>National Eye Institute, U.S.</i> INDUCED PLURIPOTENT STEM CELL DERIVED 3D ENGINEERED EYE TISSUES TO RESTORE BLINDING EYE DISEASES	
14:15 – 14:30	Miki Ando <i>Juntendo University School of Medicine, Japan</i> THE PRECLINICAL STUDY OF IPSC-DERIVED CTL THERAPY FOR EBV-ASSOCIATED LYMPHOMA	
14:30 – 14:45	Claudio Monetti <i>panCELLa, Canada</i> A SOLUTION FOR CELL THERAPY SAFETY	
14:45 – 15:10	Tracy Grikscheit <i>The Saban Research Institute at Children's Hospital Los Angeles, U.S.</i> RESTORING ENTERIC NERVOUS SYSTEM FUNCTION AND ALTERING THE GASTROINTESTINAL TRANSCRIPTOME WITH IMPLANTED NEURAL CREST CELLS DERIVED FROM HPSC	

PROGRAM SCHEDULE

SATURDAY, 23 JUNE (*continued*)

13:15 – 15:15	CONCURRENT IVB: EPIGENETICS AND GENETIC REGULATORY NETWORKS Chair: Marius Wernig <i>Stanford University, U.S.</i>	Melbourne Room 2, Level 2
13:15 – 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 – 13:45	Lin He <i>University of California, Berkeley, U.S.</i> EXPANDED CELL FATE POTENTIAL IN EMBRYONIC STEM CELLS	
13:45 – 14:00	Elizabeth Mason <i>The University of Melbourne, Australia</i> MODELLING TRANSCRIPTIONAL VARIABILITY IN SINGLE CELL RNA-SEQ DATA DURING HUMAN EMBRYOGENESIS CAPTURES CHANGES IN THE REGULATION OF CRITICAL DEVELOPMENTAL GENES	
14:00 – 14:15	Michelle Percharde <i>University of California San Francisco (UCSF), U.S.</i> THE RETROTRANSPOSON LINE1 REGULATES EARLY EMBRYONIC IDENTITY	
14:15 – 14:30	Jan Zyllicz <i>Institut Curie / University of Cambridge, France</i> FUNCTIONAL HIERARCHY OF CHROMATIN CHANGES DURING X-CHROMOSOME INACTIVATION IN MOUSE EMBRYONIC STEM CELLS	
14:30 – 14:45	Yaser Atlasi <i>Radboud University, Netherlands</i> EPIGENETIC REPROGRAMMING OF THE 3D CHROMATIN LANDSCAPE IN GROUND STATE PLURIPOTENCY	
14:45 – 15:00	Ani Grigoryan <i>Molecular Medicine, Germany</i> LAMINA/C REGULATES EPIGENETIC AND CHROMATIN ARCHITECTURE CHANGES UPON AGING OF HEMATOPOIETIC STEM CELL	

SATURDAY, 23 JUNE (*continued*)

13:15 – 15:15	<p>CONCURRENT IVC: TECHNOLOGY FRONTIERS</p> <p>Chair: Chair: Nissim Benvenisty <i>Hebrew University, Israel</i> Sponsored by AAAS/Science</p>	Room 219/220, Level 2
13:15 – 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 – 13:45	<p>Anne Rios <i>Princess Maxima Centrum, Netherlands</i> INVESTIGATING THE CELLULAR DYNAMICS OF ORGANS DEVELOPMENT AND CANCER USING 3D IMAGING</p>	
13:45 – 14:00	<p>Anna Baccei <i>Yale University, U.S.</i> A FLUORESCENT REPORTER OF CELL CYCLE SPEED</p>	
14:00 – 14:15	<p>Hirohide Saito <i>Kyoto University, Japan</i> RNA SWITCH TECHNOLOGIES TO PURIFY AND PROGRAM TARGET CELL TYPES</p>	
14:15 – 14:30	<p>Antonia Dominguez <i>Stanford University, U.S.</i> ENHANCED CRISPR BY THE USE OF BOTH TRANSCRIPTIONAL AND EPIGENETIC ACTIVATORS</p>	
14:30 – 14:45	<p>Wen Bo Wang <i>Cellular Dynamics International (CDI), U.S.</i> DEVELOPING ALLOGENEIC IMMUNOTHERAPY WITH iPSC DERIVED CYTOTOXIC T AND NK CELLS</p>	
14:45 – 15:00	<p>Ajamete Kaykas <i>Novartis Institutes for BioMedical Research U.S.</i> GENOME-SCALE CRISPR SCREENING IDENTIFIES NOVEL HUMAN PLURIPOTENT GENE NETWORKS</p>	

PROGRAM SCHEDULE

SATURDAY, 23 JUNE (*continued*)

13:15 – 15:15	CONCURRENT IVD: STEM CELLS AND CANCER Chair: Jane Visvader <i>Walter and Eliza Hall Institute of Medical Research, Australia</i>	Room 212/213, Level 2
13:15 – 13:20	TOPIC OVERVIEW BY CHAIR	
13:20 – 13:45	Stephanie Ma <i>University of Hong Kong, Hong Kong</i> EXPLOITING STEMNESS AS A CANCER CELL VULNERABILITY USING HEPATOCELLULAR CARCINOMA AS A MODEL SYSTEM	
13:45 – 14:00	Reilly Kidwell <i>Moore's Cancer Center, University of California San Diego, U.S.</i> INHIBITION OF ROR1 STEM CELL SIGNALING BY CIRMTUZUMAB IN CHRONIC LYMPHOCYTIC LEUKEMIA: PHASE 1 CLINICAL TRIAL RESULTS.	
14:00 – 14:15	Florijn Dekkers <i>Hubrecht Institute for Developmental Biology and Stem Cell Research, Netherlands</i> MODELLING BREAST CANCER USING CRISPR-CAS9-MEDIATED ENGINEERING OF HUMAN BREAST ORGANIDS	
14:15 – 14:30	Edwige Roy <i>The University of Queensland, Australia</i> REGIONAL VARIATION IN PROLIFERATIVE ACTIVITY OF INTERFOLLICULAR EPIDERMAL PROGENITORS EPIDERMAL AFFECTS SUSCEPTIBILITY TO ULTRAVIOLET INDUCED CARCINOGENESIS	
14:30 – 14:45	Johnny Kim <i>Max Planck Institute for Heart and Lung Research, Germany</i> TARGETED INACTIVATION OF ONCOGENIC DRIVERS ORIGINATING FROM ADULT STEM CELLS	
14:45 – 15:10	Toshiro Sato <i>Keio University, Japan</i> DISEASE MODELING OF GASTROINTESTINAL CANCERS USING ORGANIDS	

SATURDAY, 23 JUNE (*continued*)

13:15 – 15:15	<p>CONCURRENT IVE: STEM CELL NICHES</p> <p>Chair: Sara Wickström <i>Max Planck Institute for Biology of Ageing, Germany</i></p>	Room 203/204, Level 2
13:15 – 13:20	<p>TOPIC OVERVIEW BY CHAIR</p>	
13:20 – 13:45	<p>Margaret Fuller <i>Stanford University School of Medicine, U.S.</i></p> <p>DIFFERENTIATION AND SURVIVAL IN THE DROSOPHILA MALE GERM LINE ADULT CELL LINEAGE REQUIRE APICAL POLARITY AND JUNCTIONAL COMPONENTS IN SURROUNDING SOMATIC SUPPORT CELLS</p>	
13:45 – 14:00	<p>Elliott Hagedorn <i>Boston Children's Hospital, U.S.</i></p> <p>REPROGRAMMING ECTOPIC VASCULAR BLOOD STEM CELL NICHES IN VIVO</p>	
14:00 – 14:15	<p>Jean-Philippe Hugnot <i>INSERM, France</i></p> <p>MOLECULAR CHARACTERIZATION OF THE HUMAN AND MOUSE ADULT SPINAL CORD STEM CELL NICHES REVEAL A CONSERVED DORSAL-VENTRAL REGIONALISATION AND MSX1+ DORMANT NEURAL STEM CELLS</p>	
14:15 – 14:30	<p>Lakshmi Sandhow <i>Karolinska Institutet, Sweden</i></p> <p>SUPPRESSIVE ROLE OF BONE MARROW MESENCHYMAL STEM CELL DURING ACUTE MYELOID LEUKEMIA DEVELOPMENT IN MICE</p>	
14:30 – 14:45	<p>Melanie Domingues <i>CSIRO, Australia</i></p> <p>IDENTIFICATION OF BONE MARROW ENDOTHELIAL STEM CELLS PROMOTING HEMATOPOIETIC RECONSTITUTION POTENTIAL.</p>	
14:45 – 15:10	<p>Yi Arial Zeng <i>Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, China</i></p> <p>PROTEIN C RECEPTOR IN REGULATING MAMMARY STEM CELLS AND BREAST CANCER</p>	
15:15 – 16:00	<p>MEET-UP HUBS (<i>see page 33 for session details</i>)</p> <p>MEET-UP: VOLUNTEER OPPORTUNITIES AT THE ISSCR</p>	<p>Exhibit Hall</p> <p>Meet-Up Hub #1</p>
15:15 – 16:00	<p>REFRESHMENT BREAK</p>	<p>Exhibit Hall</p>

PROGRAM SCHEDULE

SATURDAY, 23 JUNE (*continued*)

16:00 – 18:15	PLENARY VII: MOVING TO THE CLINIC: GENE AND STEM CELL THERAPIES Chair: Sally Temple <i>Neural Stem Cell Institute, U.S</i>	Plenary Room, Ground Level
16:00 – 16:05	PRESIDENT-ELECT ADDRESS: DOUGLAS A. MELTON	
16:05 – 16:30	Michael Laflamme <i>Toronto General Hospital Research Institute, University Health Network, Canada</i> HEART REGENERATION WITH HUMAN PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES	
16:30 – 16:55	Stanley Riddell <i>University of Washington, U.S.</i> STRATEGIES TO IMPROVE THE EFFICACY OF CAR T CELLS IN HEMATOLOGIC MALIGNANCIES AND SOLID TUMORS	
16:55 – 17:20	Katherine High <i>Spark Therapeutics, U.S.</i> THE JOHN MCNEISH MEMORIAL LECTURE: CLINICAL INVESTIGATION OF GENE TRANSFER FOR GENETIC DISEASE: RESTORING SIGHT, MAKING BLOOD CLOT	
17:20 – 18:00	Jennifer Doudna <i>University of California, Berkeley and HHMI, U.S.</i> KEYNOTE ADDRESS: CRISPR-CAS SYSTEMS AND THE FUTURE OF GENE EDITING	
18:00 – 18:10	POSTER AWARD ANNOUNCEMENTS AND CLOSING REMARKS	

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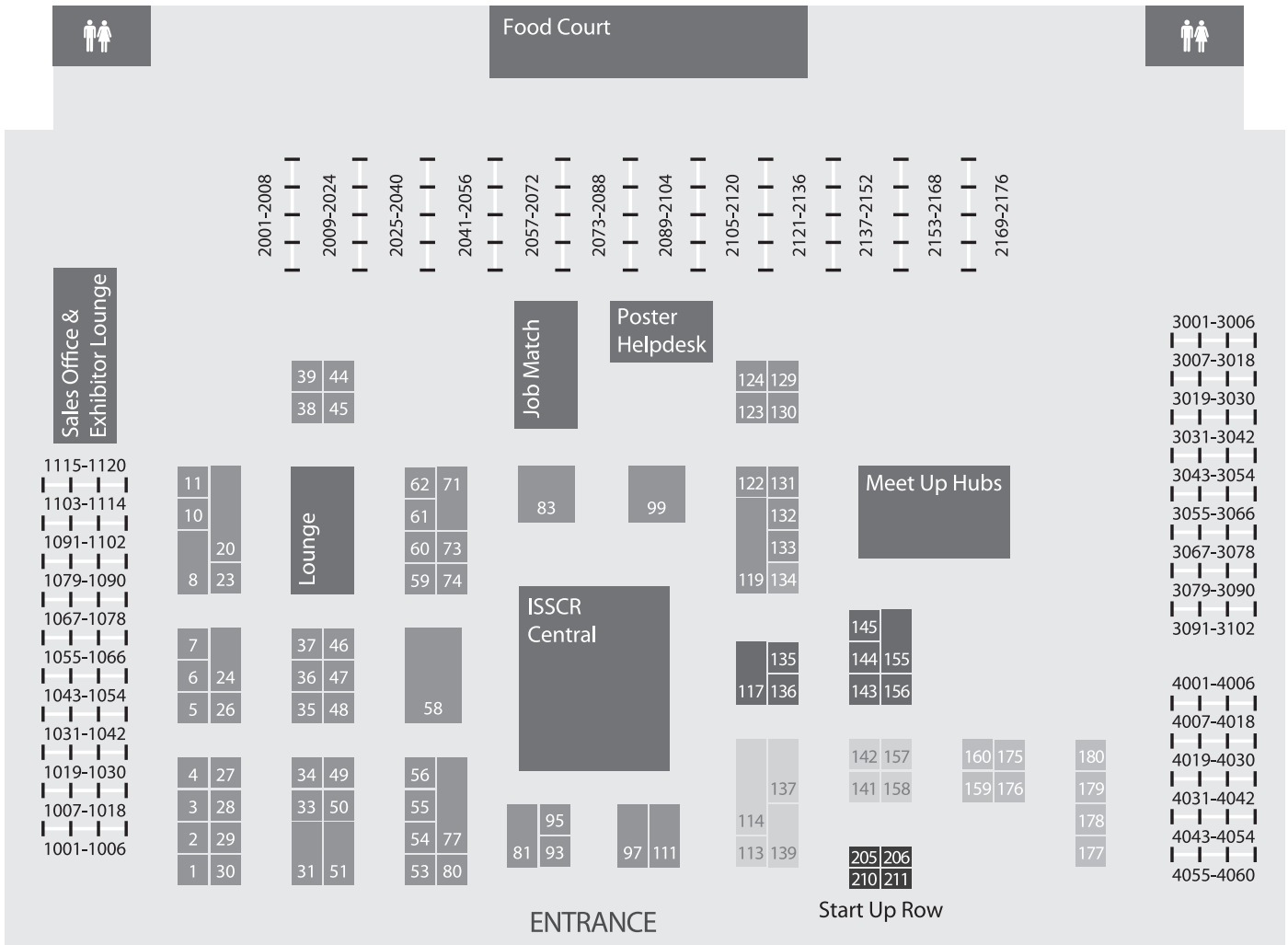


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Australia
www.asscr.org

The Australasian Society for Stem Cell Research was established in 2007 to build an active stem cell research community in Australia and New Zealand, encourage scientific exchange within the region and communicate to the general public information relating to scientific and medical advances and ethical challenges in the broad field of stem cell research. ASSCR is the co-sponsor of ISSCR 2018.

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Novoheart is a global stem cell biotechnology company pioneering an array of next-generation human heart tissue prototypes. Through its MyHeart Platform of bio-engineered 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.

NUCLEUS BIOLOGICS - STAND 205

10929 Technology Place
San Diego, CA 92127
United States
+1 858-251-2010
www.nucleusbiologics.com

Nucleus Biologics, a San Diego-based supplier of premium cell culture products, is redesigning the supply chain by partnering with the source for greater transparency and superior quality. Our premier product is an exceptionally low-viral load, Australian-based fetal bovine serum that is consistent, traceable to an exclusive source, characterized, and provides stable pricing. Our newest product is a xeno-free serum replacement, Physiologix™ XF, for human cells.

ON-CHIP BIOTECHNOLOGIES, CO., LTD. - STAND 11

203, Venture Port, 2-24-16 Naka-cho
Koganei-shi
Tokyo 184-0012
Japan
+81 4-2385-0461
www.on-chipbio.com/

On-chip Biotechnologies is the manufacturer of the world's first microfluidic chip-based flow cytometer and cell sorter. The cell sorter, "On-chip Sort", has an exchangeable and disposable microfluidic cartilage as its core. This innovative technology allows for damage-free cell and large cell cluster (e.g. spheroids) recovery in sterile condition which is not attainable with conventional sorters.

ONTARIO INSTITUTE FOR REGENERATIVE MEDICINE

MaRS Centre, West Tower
661 University Ave
Suite 1002
Toronto, Ontario
M5G 1M1, Canada

The Ontario Institute for Regenerative Medicine (OIRM) was launched in 2014 with a vision to revolutionize the treatment of degenerative diseases and make Ontario a global leader in the development of stem cell-based products and therapies. OIRM has more than 200 research programs at universities and institutions and was realized with investment from Ontario's Ministry of Research, Innovation and Science.



EXHIBITOR/SPONSORS

PAKAIR CARGO SPECIALISTS PTY LTD -

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Pakair Cargo Specialists provide fully integrated Time Critical and Temperature sensitive Courier and Cargo solutions worldwide. From BioMedical samples to Controlled substances, or Hi-Tech parts & film rushes to Food samples, Pakair is the quality choice to ensure swift delivery, specific to your independent needs. We are flexible enough to meet your needs and pro-active enough to keep on your job from start to finish.

PEPROTECH, INC. - STAND 114

5 Crescent Avenue
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PeproTech creates the building blocks of your life science research by manufacturing high-quality products that advance scientific discovery and human health. Since 1988, PeproTech has grown into a global enterprise manufacturing an extensive line of Recombinant Human, Murine and Rat Cytokines, Animal-Free Recombinant Cytokines, Monoclonal Antibodies, Affinity Purified Polyclonal Antibodies, Affinity Purified Biotinylated Polyclonal Antibodies, ELISA Development Kits, Cell Culture Media Products and GMP Cytokines.

PLOS ONE

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PROTEINTECH GROUP INC. - STAND 160

5400 Pearl Street
Suite 300
Rosemont, IL 60018
United States
+1 312-455-8498
www.ptglab.com

Proteintech Group's mission is to fulfill the Human EST fusion protein Project and Proteomic Antibody Project. We've produced over 14,000 antibodies with unparalleled high quality against 14,000 different human proteins, approximately 1/3 of the human genome. All antibodies are validated by WB and IHC on primary tissues and cell lysates. Our worldwide locations in US, China, Europe, and Japan have every single antibody in stock next day delivery.

REPROCELL COMPANY - STAND 74

KDX Shin-yokohama 381 Bldg. 9F
3-8-11, Shin-yokohama, Kohoku-ku
Yokohama 222-0033
Japan
+81 4-5475-3887
www.reprocell.com

The first stem cell company founded in Japan (2003), REPROCELL has expanded through global acquisitions to offer the entire workflow of stem cell products and services including a comprehensive human tissue biobank, cutting-edge reprogramming technologies and iPSC-derived cell types. REPROCELL's pre-clinical contract research organization is also an experienced partner uniquely positioned to provide custom assays services using live human tissue or 3D tissue models.

RORZE LIFESCIENCE INC - STAND 123

1-9-8 Matsushiro
Tsukuba
305-0035, Japan

Rorze LifeScience providing lab-automation and cell culture automation systems to meet your application

SARTORIUS STEDIM BIOTECH - STAND 8

York Way
Royston SG8 5WY
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+44 1763-227200
www.sartorius.com

We deliver and implement rapid and cost-effective Bio-manufacturing solutions from early phase development through scale-up to commercial manufacturing. Benefit from the most comprehensive bioprocess technology portfolio coupled with our expertise in Single-use bioprocess engineering. Our global bioprocess teams are available to discuss your process development and manufacturing requirements.

EXHIBITOR/SPONSORS

SCHOOL OF LIFE SCIENCE AND TECHNOLOGY, SHANGHAITECH UNIVERSITY - STAND 135

No. 393 Middle Huaxia Road
L Building
Shanghai 201210
China
+86 21-20685017
slst.shanghaitech.edu.cn/eng/

SLST aims to develop into a world-class, research-oriented school in life science and technology, drawing strength not only from its outstanding full-time faculty but also from two affiliated world-class biomedical research institutes at ShanghaiTech (including three laboratories led by Nobel laureates) as well as from select faculty members jointly appointed with institutes of Chinese Academy of Sciences in Shanghai who conduct world-class research.

THE STATE GOVERNMENT OF VICTORIA, AUSTRALIA - STAND 155

Victoria boasts a vibrant biotechnology commercial sector, key research and development infrastructure and internationally recognised researchers. Together with a supportive government, and a growing list of international research partnerships, Victoria is a premier location for innovative medical product development including regenerative medicine.

SINO BIOLOGICAL INC. - STAND 31

No. 31 Kechuang 7th Street
Beijing 100176
China
+86 10-58628223
www.sinobiological.com

Sino Biological Inc. is a world leading biological reagents manufacturer located in Beijing, offering premium quality reagents, Proteins (6000+), Antibodies (9000+), Genes (20000+) and ELISA Kits, all of which are produced in-house and cover a broad range of life science research and drug development. It also provides one-stop services for protein and antibody discovery, research, development, production and commercialization.

STEM CELL PROGRAM AT BOSTON CHILDREN'S HOSPITAL

300 Longwood Ave., BCH 3144
Boston, MA 02115
617-919-2068

The Stem Cell Program at Boston Children's Hospital brings together premier scientists and physicians from many backgrounds and specialties to form one of the top stem cell research units in the world. Their work in stem cells and cancer has led to novel therapies for patients throughout the world.

STEM GENOMICS - STAND 95

Institute for Regenerative Medicine & Biotherapies
80 avenue Augustin Fliche
Montpellier 34295
France
+33 642112424
www.stemgenomics.com

Stem Genomics provides a new test to assess genetic integrity of stem cells. This innovative test is carried out on the supernatant collected from cell culture and shipped at room temperature. It is rapid, sensitive, conclusive and cost effective, allowing routine testing of pluripotent stem cells in culture.

STEMBIOSYS INC. - STAND 37

3463 Magic Drive, Ste. 110
San Antonio, TX 78229
United States
+1 210-877-9323
www.stembiosys.com

StemBioSys® has developed The Next Evolution in Stem Cell Research™ through our novel High Performance Micro Environment (HPME®) technology. Our patented HPME® products create a natural, protein based environment that allows a variety of stem cells to replicate more rapidly and with greater preservation of stem cell potency and potential. This product has also enabled us to provide various cell lines with unique characteristics.



EXHIBITOR/SPONSORS

STEMCELL TECHNOLOGIES INC - STAND 77

1618 Station St
Vancouver, BC V6A1B6
Canada
+1 604-675-7575
www.stemcell.com



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 - STAND 80

1 Discovery Drive
Rensselaer, NY 12144
United States
+1 518-621-0848
www.stemcultures.com

StemCultures manufactures StemBeads, Controlled Release Growth Factors. StemBeads are the discovery of Dr. Sally Temple and NSCI. StemBeads are a patented Micro-Encapsulation Technology that controls protein levels in culture such as FGF2, EGF, and Activin-A. More specifically, the technology has improved stability of growth factors while avoiding manipulation of proteins. Better regulation of endogenous growth factors demonstrates significant benefits in cell culture performance and consistency.

STEMEXPRESS, LLC - STAND 29

1743 Creekside Drive
200
Folsom, CA 95630
United States
+1 530-303-3822
www.stemexpress.com

StemExpress provides leading biomedical researchers around the world human hematological samples at life-changing speed. Our nationwide procurement network and state-of-the-art collection centers ensure StemExpress can reliably obtain the highest quality and most varied source material, including Leukopaks, peripheral and maternal blood, and bone marrow. Isolated cell lines are purified less than 24 hours from procurement, guaranteeing the purity, viability, and quality you need.

SURROZEN

240 E. Grand Ave
2nd Floor
South San Francisco, CA
94080, U.S.A.



Surrozen is an innovative biopharmaceutical startup founded by world-leading scientists from Stanford University and funded by The Column Group, a leading biotech venture capital firm in the San Francisco Bay Area.

The company is focused on harnessing the Wnt pathway to identify novel therapeutics for regenerative medicine, leveraging breakthrough insights from our founders in protein engineering, stem cell dynamics, and fundamental Wnt biology.

TAKEDA PHARMACEUTICAL COMPANY LIMITED - STAND 180

1-1, Doshomachi 4-chome, Chuo-ku
Osaka 5408645
Japan
+81 6-6204-2111
www.takeda.com



Takeda is a global, research and development-driven pharmaceutical company committed to bringing better health and a brighter future to patients by translating science into life-changing medicines. Takeda focuses its R&D efforts on oncology, gastroenterology and central nervous system therapeutic areas plus vaccines. Takeda conducts R&D both internally and with partners to stay at the leading edge of innovation.

THERMO FISHER SCIENTIFIC - STAND 58

5781 Van Allen Way
Carlsbad, CA
92008, U.S.A.
www.thermofisher.com

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.

EXHIBITOR/SPONSORS

TRENDBIO - STAND 130

Phone: 1300 720 574
Email: info@trendbio.com.au
www.trendbio.com.au

TrendBio is a leading supplier of specialised instrumentation for the Life Sciences. We are proudly supporting ISSCR 2018 and will showcase the following products; Holographic Live Cell Imaging, Maestro MEA Platform, Wes, the Fully automated Western Blotting System, ELISA, hands-free, single or multi-analyte with no cross-reactivity, Animal Imaging - Optical, CT, Optoacoustic, PET/SPECT

UNION BIOMETRICA, INC. - STAND 48

84 October Hill Rd.
Holliston, MA 01746
United States
+1 508-893-3115
www.unionbio.com

Union Biometrica Large Particle Flow Cytometers automate the analysis and sorting of objects that are too big / fragile for traditional cytometers. Examples include large cells / cell clusters, cells in/on beads and small model organisms. COPAS and BioSorter models cover the full 10-1500um range of particle sizes. A special rotating horizontal sample chamber is available for introducing fragile samples.

WICELL - STAND 81

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Madison, WI
53719, U.S.A.
+1 (888) 204-1782
www.wicell.org

Celebrating 20 years of human pluripotent stem cell research. Stop by our booth #81 to join in the celebration and for your chance to win WiCell gear.

About WiCell:

As a recognized world leader in pluripotent stem cell banking, distribution, and characterization services, WiCell provides the stem cell community with high quality cell lines as well as accurate and reliable characterization testing.

Products and Services offered:

- Stem Cells (1200+ ES, iPS, disease model and controls, modified and GMP compliant cell banks)
- Cell Banking and Distribution Services for researchers and companies generating cell lines
- Characterization Testing (G-banded karyotyping, SKY, FISH, SNP microarray, and Identity testing via STR)
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WILEY - STAND 144

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+65 6643-8000
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Wiley, a global company, helps people and organizations develop the skills and knowledge they need to succeed. Our online scientific, technical, medical, and scholarly journals, combined with our digital learning, assessment and certification solutions help universities, societies, businesses, governments, and individuals increase the academic and professional impact of their work.

ZHEJIANG HOPSTEM BIOENGINEERING

COMPANY LIMITED - STAND 133

3F,Build#16,Chitic Sci&Tech Park,No.260, 6th Street, Xia-sha, Hangzhou, Zhejiang, China
Hangzhou 310018
China
+86 571-88197776
www.hopstem.com

Zhejiang Huode (Hopstem) Bioengineering Ltd Co is founded by neuroscience and stem cell scientists from Johns Hopkins University on January 2017 in Hangzhou. Hopstem has world leading advantages in human iP-SCs/ESCs neural differentiation, gene editing, cell banking and cell engineering. Hopstem aims to use the most cutting edge technologies to promote the diagnoses, research and therapies of neurological and other disorder



INNOVATION SHOWCASES

THURSDAY, 21 JUNE

APPLIED STEMCELL

Room 105, Level 1

8:00 – 8:30

HUMAN IPSC-BASED DISEASE MODELING & DRUG SCREENING

Xianmin Zeng, *Scientific Advisory Board, Applied Stem Cell, Inc. United States*

Human induced pluripotent stem cell (iPSC) technology offers the benefits of a cell line coupled with the advantage of using human primary cells. We have developed a large panel of iPSC lines including isogenic and reporter lines for disease modeling and drug discovery. I will discuss the utility of these cells for modeling neurodegenerative disorders including Parkinson's disease and Alzheimer's disease, as well as neurotoxicity and neuroprotective assays with iPSC-derived neurons, glia and their co-culture.

NOVOHEART

Room 106, Level 1

8:00 – 8:30

MYHEART™ PLATFORM: UNVEILING NOVOHEART'S NEXT-GENERATION DRUG DISCOVERY TOOLS INCLUDING 3D BIOENGINEERED HUMAN HEART-IN-A-JAR

Kevin D. Costa, *CSO, Novoheart, United States*

Drug development is a notoriously lengthy, expensive and inefficient process, with cardiotoxicity being a frequent cause for failure. Conventional non-human cell and animal models are poorly predictive of human responses, leading to false negative and positive results that compromise overall success rates. Novoheart's MyHeart™ Platform aims to revolutionize this process, offering a hierarchy of bioartificial human pluripotent stem cell-derived heart tissue constructs designed as screening tools for predicting cardiotoxicity as well as drug efficacy. This includes our human ventricular Cardiac Anisotropic Sheet (hvCAS) assay for electrophysiology, our human ventricular Cardiac Tissue Strip (hvCTS) assay for contractility, and our unique human ventricular Cardiac Organoid Chamber (hvCOC, or "human heart-in-a-jar") assay, the only macroscopic human cardiac model on the market capable of pumping fluid, with unprecedented biofidelity mimicking the native human heart. We will also introduce the new MyHeart™ Platform 2.0, which delivers additional value in terms of throughput, sensitivity and accuracy, with hardware and software innovations

including machine learning for smart drug classification, markedly enhancing Novoheart's capabilities for next-generation drug discovery.

THERMO FISHER SCIENTIFIC

Room 212/213, Level 2

8:00 – 8:30

GMP RAW MATERIALS FOR CELL AND GENE THERAPY MANUFACTURING

Kasey Kime, *Regulatory Affairs, Clinical and Compliance Manager, Thermo Fisher Scientific, United States*

Eric Roos, *Strategic Alliance Manager, Cell Therapy, Thermo Fisher Scientific, United States*

Have you ever wondered what to consider when you are selecting raw materials for your cell therapy clinical research? This presentation will cover regulatory requirements for cGMP raw materials and the importance of regulatory documentation and support to enable successful clinical translation. As you move through clinical trials toward commercialization you'll need solutions that can scale with you to meet the clinical need. The second part of this session, will address aspects you should consider now such as scalability, consistency of supply and commercial use rights to help clear your path to commercial manufacturing in the future.

UNION BIOMETRICA

Room 219/220, Level 2

8:00 – 8:30

AUTOMATION FOR ANALYSIS, IMAGING, AND HANDLING OF CELLS AND CELL CLUSTERS IN STEM CELL RESEARCH

Rock Pulak, *Director of Life Science Technologies, Union Biometrica, Inc., Holliston*

Cells growing in clusters communicate with each other and behave differently than cells grown as monolayers or in suspension. These interactions are likely to be important for proper function. Union Biometrica Large Particle Flow Cytometers automate the analysis, sorting, and dispensing of objects too big or too fragile for traditional cytometers, some of which are studied by stem cell researchers. Sample types include embryoid bodies, neurospheres and other spheroids, and organoids. Flow cytometry data, Profiles and brightfield images of the sample constituents are collected for analysis and used to make sorting decisions. This technology provides automation for the analysis and handling of these sample types in multiwell plate format and increases

reproducibility by removing some of the day-to-day variability that can be introduced between researchers and by the same researcher from one day to the next.

MAXWELL BIOSYSTEMS

Room 203/204, Level 2

8:00 – 8:30

NOVEL FUNCTIONAL ANALYSIS TECHNIQUES FOR ACCURATE PHENOTYPE CHARACTERIZATION OF HUMAN iPSC- DERIVED NEURONS

Michele Fiscella, PHD – *MaxWell Biosystems / ETH Zurich*

iPSC technology enabled in vitro studies with human neurons for investigating disease mechanisms and for finding treatments.

We will present techniques to dissect the functional phenotype of A53T α -synuclein dopaminergic neurons, modeling Parkinson's disease. We will discuss how the electrical activity of whole cell networks can be monitored label-free and long-term, at high spatio-temporal resolution. By observing cell networks across multiple days, the capability of iPSC-derived neurons to form synaptic connections can be analyzed. In addition, we will show how the activity of single neurons can be isolated and studied, together with subcellular details, such as the propagation of action potentials along single axons.

Our methods are powered by a high-throughput electrophysiology platform using high-resolution microelectrode array (MEA) technology. The platform allows access to individual cells simultaneously through 26'400 electrodes. With this platform, we found differences in physiological activity between the A53T α -synuclein cell line and the isogenic control cell line. Phenotype differences were detected at different scales, ranging from network connectivity to subcellular structures as axons.

ALLEN INSTITUTE FOR CELL SCIENCE

Melbourne Room 1, Level 2

11:30 – 12:30

PROVIDING STEM CELL & GENE EDITING RESOURCES TO EMPOWER YOUR RESEARCH

Ruwanthi Gunawardane, *Allen Institute for Cell Science, Seattle, U.S.*

Allen Institute for Cell Science; providing stem cell & gene editing resources to empower your research.

We will share details about our legacy collection of endogenous, fluorescently-tagged hiPS cell lines highlighting key structures within the cell. You will hear how these lines were generated, including gene editing strategies, the plasmids used to generate them and the substantial quality controls performed before making these cells and plasmids publicly available. We will share details about our efforts to differentiate these lines to cardiomyocytes, featuring images from some of our newer 'cardio-specific' lines. We will touch briefly on the other resources available on our website (www.allencell.org), including our large, high replicate 3D image data sets showing the subcellular localization of each of our tagged structures, our microscopy pipeline workflow and 3D segmentations. We will also discuss machine learning and label-free approaches to build integrated and predictive models of cell organization, and will wrap up the presentation with a guided tour through our website to familiarize you with where all these resources can be found.

BIOLAMINA

Room 105, Level 1

11:30 – 12:30

CTG BIOLAMININ™ 521 – A BIOLOGICALLY RELEVANT CULTURE MATRIX, ENABLING PRE-CLINICAL RESEARCH PROTOCOLS TO BE TRANSLATED FOR CLINICAL TRIALS

Kristian Tryggvason, *CEO, BioLamina, Sweden*

Malin Parmar, *Professor, Lund University, Sweden*

Fredrik Lanner, *Karolinska Institute and Karolinska University Hospital, Sweden*

As a complement to our portfolio of defined and xeno-free laminin stem cell substrates, we now offer a

cell therapy grade (CTG) Biolaminin 521 cell culture substrate For Research Use or Non-commercial Manufacturing of Cell, Gene, or Tissue-Based Products. Biolaminin 521 CTG (CT521) has been developed and manufactured to allow customers to qualify the material for use in the manufacturing of cells for clinical research. USP Chapter 1043: Ancillary materials for cell, gene and tissue-engineered products has been considered in the design of the product. The product is animal origin component free and has supporting documentation, such as Certificate of Analysis, Animal Origin Free Statement and Bill of Material provided with every lot to support regulatory filings. CT521 is a full-length, human, recombinant laminin 521 substrate, the only one of its kind on the market, providing an optimal environment for feeder-free culture of human PSCs, MSCs and most anchorage-dependent progenitor cell types. With this new clinical grade product, scientists are supported throughout their cell therapy development process - from concept to commercialized therapy. It recreates a biologically relevant milieu in vitro, promoting high survival and robust expansion of hPSCs, and subsequent cell lineage specification. The cells grow in a homogeneous monolayer, easy to monitor. The substrate is flexible and compliant with any cell culture medium. It allows an operator-independent culture maintenance and reliable, standardized protocols which can easily be adapted to automation platforms.

CDI

Room 106, Level 1

11:30 - 12:30

NOVEL APPLICATIONS OF HUMAN IPSC-DERIVED NEURONS: FROM HIGH- THROUGHPUT SCREENING TO PATCH-SEQ ANALYSIS

Anne Bang, *Director, Cell Biology, Sanford Burnham Prebys Medical Discovery Institute*

Cedric Bardy, *Assistant Professor - South Australian Health and Medical Research Institute (SAHMRI Mind & Brain)*

Dr. Anne Bang will discuss the use of hiPSC-derived neurons, including iCell® GABANeurons and iCell DopaNeurons, in high-throughput assays for phenotypic analyses and drug screening. She will describe the development of a suite of foundational assays in higher throughput formats to monitor neuronal morphology, mitochondrial function, and electrophysiology, and address the challenges of balancing higher throughput with relevance. Dr. Cedric Bardy will discuss patch-seq characterization of hiPSC-derived neurons with electrophysiology, morphologi-

cal analysis and single-cell RNAseq. The integration of single-cell electrophysiology, morphology and transcriptomics analysis of live human neural cells enables a bridging of human neurophysiology with gene expression. This novel approach allows the identification of neurons in specific functional states and can compensate for variations among cell lines.

STEMCELL TECHNOLOGIES

Room 203/204, Level 2

11:30 - 12:30

GI TRACT ORGANOID: USING ADVANCED TISSUE MODELS TO INTERROGATE ABSORPTION AND REGULATION

Heather A. McCauley and Ryan K. Conder, *STEM-CELL Technologies Inc., Vancouver, Canada*

Organoid cultures have redefined the type of biological data that can be obtained using in vitro models. These techniques enable researchers to maintain and manipulate cells that recapitulate many of the intra- and intercellular characteristics of their specific tissue-of-interest, including disease phenotypes. We have developed specialized, robust organoid culture kits that reduce the variability in these systems and make organoids a more accessible research tool. Enteroendocrine cells (EECs) are gastrointestinal nutrient-sensing cells that secrete hormones in response to nutrient ingestion. While EECs only comprise 1-2% of the intestinal epithelium, they are essential regulators of nutrient absorption. The mechanisms underlying how EECs control this process, however, are poorly understood. Using CRISPR/Cas9, we introduced a specific mutation in human pluripotent stem cells to generate human intestinal organoids lacking EECs. This organoid model system allowed us to investigate how EECs couple an epithelial-neurohormonal signal with nutrient and ion transport to regulate nutrient absorption. Generation of EEC-free intestinal organoids also provided insight on the potential role for ECCs in regulating intestinal cell differentiation

THERMO FISHER SCIENTIFIC

Room 212/213, Level 2

11:30 - 12:30

FROM BENCH TO BEDSIDE: GENERATION OF iPSCS FOR CELL THERAPY AND DISEASE MODELING APPLICATIONS

Kapil Bharti, *Earl Stadtman Tenure-Track Investigator, National Eye Institute; Adjunct Group Leader, National Center for Advancing Translational Sciences, National Institutes of Health*

David Piper, *Director, Research and Development, Thermo Fisher Scientific*

Today, iPSC are most prominently used in disease modeling and the most promising iPSC application of tomorrow is the emerging area of iPSC-derived cell therapies. In this session, Dr. Kapil Bharti will discuss his journey to the clinic and Dr. David Piper will review new methods to facilitate disease modeling. Dr. Kapil Bharti will discuss the preparation of a phase I clinical trial using iPS cell derived ocular tissue to treat age-related macular degeneration (AMD). Combining efforts in developmental biology and tissue engineering, Dr. Bharti will review the development of a clinical-grade iPS cell derived RPE-patch on a biodegradable scaffold for potential transplantation of an autologous iPS cell therapy. Dr. David Piper will review the use of iPSCs to create diseased and disease-corrected lines for potential use in screening and for clinical research. In his talk he will delve into methods developed to overcome current bottlenecks in delivery, identification, selection and subsequent clonal outgrowth. These optimizations facilitate consistent and reliable gene knock-out and knock-in to create engineered iPSC lines resulting in isogenic disease model cell lines that can be differentiated into the cell type of interest for downstream applications.

NIKON

Room 219/220, Level 2

11:30 - 12:30

QUANTIFYING NEURODEGENERATION USING LIVE CELL IMAGING

Lee L. Rubin, *Professor and Director of Translational Medicine Harvard University and the Harvard Stem Cell Institute, Boston, U.S.*

Live cell imaging of specialized cell types derived from stem cells holds much promise as a new approach to drug discovery and personalized medicine. In a long-term collaboration with Nikon Corporation, we have been using the BioStation CT to

characterize disease-relevant neuronal subtypes, including motor neurons, dopaminergic neurons, and cortical neurons made from pluripotent cells engineered to express cell-type specific fluorescent reporters. These studies utilize live-cell imaging analysis to determine the cellular changes that underlie neurodegenerative diseases and to design and perform new types of drug screens. Measurements of neuronal properties, such as soma size and neurite growth, can be paired with single cell tracking for prolonged time courses (up to weeks). These studies have revealed some of the earliest morphological changes that foretell impending death. Further, we have identified properties of degenerating neurons that determine whether or not they can be rescued. These types of analyses provide the basis for a physiologically relevant human neuron-based approach to finding new treatments for neurodegenerative diseases.

BIO-TECHNE

Room: Melbourne Room 2, Level 2

11:30 - 12:30

UNFOLDING ORGANOID: A NEW PLATFORM FOR GENERATING ACCESSIBLE 3-D EPITHELIAL ORGAN TISSUE

Scott Schachtele and Fabrizio Rinaldi, *Bio-Techne, Minneapolis, U.S.*

Three dimensional (3-D) cell culture models are quickly being adopted for toxicology, drug discovery, and disease modeling. These models, including organoids, experience difficulties with variability, tissue viability, and experimental accessibility. Overcoming these obstacles is paramount for the logistical incorporation of 3-D tissues into high throughput toxicity and disease modeling workflows. In this showcase we introduce MimEX™ Tissue Model Systems, a new technology for the generation of sustainable and accessible 3-D human organ tissue. Using MimEX GI, a gastrointestinal model system, we demonstrate the principle and benefits of the technology, including methods for the efficient isolation, expansion, and differentiation of adult human "ground-state" stem cells from the gastrointestinal epithelium. The second part of the showcase focuses on the flexibility of MimEX Tissue Model Systems, including demonstrating how the technology can be used to generate 3-D models of other epithelial-derived organ tissues. In addition, we show that adult epithelial stem cells can be isolated from pathogenic tissue and will differentiate back into the diseased tissue in vitro, yielding a new method for modeling human disease.

FRIDAY, 22 JUNE

STEMBIOSYS

Room 219/220, Level 2

8:00 – 8:30

THERE IS NO PLACE LIKE HOME! CELL DERIVED MATRICES THE NEXT EVOLUTION IN CELL CULTURE

Sy Griffey, *StemBioSys Inc.*

In standard cell culture procedures, cells are first extracted from their native tissue and then placed in a foreign environment (polystyrene, collagen coated dish, etc). Cells react to this by altering their gene expression to construct a provisional matrix or differentiate based on the signals (or lack thereof) from this new environment.

StemBioSys has developed technologies and methods to produce a natural cell culture substrate that will revolutionize cell culture methods. The CELLvo™ Matrix is a cell-constructed extracellular matrix that provides cells with a natural microenvironment and substrate for attachment and growth. Cells grown on an intact cell derived ECM proliferate more quickly, maintain a phenotype more consistent with that expressed while in their native environment and are more responsive than cells grown on other substrates. We will discuss our matrix technology as well as several important potential applications in tissue engineering and regenerative medicine.

THERMO FISHER SCIENTIFIC

Room 105, Level 1

11:30 – 12:30

VALIDATING ANTIBODIES TO DISTINGUISH BETWEEN NAIVE AND PRIMED HPSCS

Andrew Laslett, *CSIRO Manufacturing, Clayton, Victoria, Australia*

This session will discuss the validation and characterisation of a panel of new monoclonal antibodies to defined cell surface proteins found on human pluripotent stem cells. This panel of antibodies is useful for the detection and enrichment of human pluripotent stem cells and can be used to distinguish between naive and primed human pluripotent stem cells. Additionally, the session will cover the Thermo Fisher Scientific Antibody Validation Initiative and using data show the value of using well-validated monoclonal antibodies.

LONZA AND GUEST FROM SEMMA THERAPEUTICS

Room 106, Level 1

11:30 – 12:30

INDUSTRIALIZATION OF CELL & GENE THERAPY MANUFACTURING- FROM CONCEPT TO PATIENTS

Thomas Fellner, *Head of Cell & Gene Therapy, Lonza Pharma & Biotech*

Julie Carson, *Principal Scientist, Semma Therapeutics*

The cell and gene therapy market has experienced an immense growth driven by the recent landmark approvals of therapies such as Novartis' Kymriah, Kite/Gilead's Yescarta and Spark's Luxturna. A pipeline filled with promising pre-clinical and clinical candidates provides confidence that the cell and gene therapy field is becoming a key player in the pharmaceutical world. While the products are showing remarkable therapeutic efficacy, there is an emerging need for flexible and robust manufacturing platforms capable of both scaling up and scaling out, while maintaining control over the cell processing parameters to achieve consistent product of highest quality and safety. Further production of these therapies at a large scale will be key to bringing these therapies to patients globally. Production costs of cell and gene therapies remain another obstacle the field has been facing; this is mostly driven by manual processing, manufacturing footprint requirements and expensive raw materials and testing. Automation represents itself as a potential solution for at least some of these challenges and therefore driving commercial viability of these therapies. During this session we will outline the specific challenges development and manufacturing of these ground breaking therapies are facing and how innovative platforms may help overcome some of the issues faced by the industry.

STEMCELL TECHNOLOGIES

Room 203/204, Level 2

11:30 – 12:30

HUMAN PLURIPOTENT STEM CELL QUALITY: ESSENTIAL CONSIDERATIONS FOR GENE EDITING, CLONING, MAINTENANCE AND DISEASE MODELING

Adam Hirst and Vivian Lee, *STEMCELL Technologies Inc., Vancouver, Canada*

Human pluripotent stem cells (hPSCs) hold tremendous promise for a wide range of applications, in-

cluding regenerative medicine, disease modeling, drug discovery and toxicology. Recently, there has been a dramatic increase in the generation of genome-edited hPSC lines due to widespread use of the CRISPR-Cas9 technology. As a result, researchers are becoming more aware of the critical importance of cell quality for generating robust and relevant data. This seminar will focus on how to maintain and assess high-quality hPSC cultures throughout the various stages of your research with an emphasis on five critical quality control aspects: genomic integrity, pluripotency, gene and marker expression, the epigenetic landscape and culture morphology. Speakers will also discuss the ArciTect™ family of products for ribonucleoprotein-based CRISPR-Cas9 genome editing, providing you with a rapid, flexible and precise protocol to modify the hPSC genome for various applications. Finally, methods to model neurological disease with cerebral organoids derived from high-quality hPSCs will be discussed.

MINERVA BIOTECHNOLOGIES

Melbourne Room 1, Level 2

11:30 – 12:30

THE IMPACT OF VARIOUS STEM CELL GROWTH MEDIA ON LINEAGE DETERMINATION

Cynthia Bamdad, *CEO of Minerva Biotechnologies*

Minerva and end-users will present studies using AlphaSTEM® System, which uses a serum-free single growth factor (NME7AB) media, an antibody adhesion surface and a synthetic peptide that breaks the pluripotency interaction and induces differentiation, thus eliminating risk of teratoma.

Side-by-side comparisons of AlphaSTEM® to mTeSR and E8 for differentiation of iPSCs to hepatocytes, neural progenitors, MSCs and cardiomyocytes will be presented. Comparisons will include ease of use, yield and quality of the differentiated cells. A discussion of the effect of stem cell media on manufacturability, scale-up, and cost of stem cell derived therapeutics will follow.

Lunch and discount coupons provided.

BIOLOGICAL INDUSTRIES

Room 212/213, Level 2

11:30 – 12:30

THE PROMISE OF INDUCED PLURIPOTENT STEM CELLS: BASIC RESEARCH AND CLINICAL GRADE MANUFACTURING

Micha Drukker, *Leader of the junior research group Human Pluripotent Stem Cell Lineage-Choice Research and the Human Induced Pluripotent Stem Cell Unit at the Institute of Stem Cell Research, Helmholtz Zentrum München*

Achia Urbach, *Institute of Nanotechnology and Advanced Materials, Bar-Ilan University*

David Fiorentini, *VP of Scientific Affairs, Biological Industries*

Pluripotent Stem cells research has generated tremendous excitement, and holds promise for the treatment of many uncured diseases. Early stage clinical trials using differentiated induced pluripotent stem cells (iPS) show great potential in cell-based therapeutics. Bridging the gap between research models and clinical applications is the utmost goal to ensure clinically relevant stem cell products. The first part of this innovation showcase will present a research work on SNF5, which is one of the core subunits of the SWI/SNF chromatin-remodeling complex. Mutations in this protein might have significant effects on the epigenetic state of human embryonic stem cells and on their phenotype and precise levels of SNF5 are required in order to preserve the pluripotent state of the cells. The second part will focus on the manufacturing of clinical grade human iPS under cGMP conditions as a critical part of the translation from research to clinical therapeutics. The innovation showcase will address the challenges of the generation, expansion and storage of iPS cells, including tissue biopsies, xeno-free culture procedures and raw materials, testing and cryopreservation.

MILTENYI

Room 219/220, Level 2

11:30 - 12:30

TOWARDS A THERAPY FOR PARKINSON'S DISEASE: LATEST RESEARCH HIGHLIGHTS AND CONCEPTS FOR MANUFACTURING OF ATMPs

Malin Parmar, *Senior Project Manager R&D Stem Cells, Miltenyi*

Sebastian Knöbel, *Biotec GmbH, Bergisch Gladbach*

Cell therapy for Parkinson's disease (PD) based on pluripotent stem cell (PSC) derived products is approaching clinical trials. Malin Parmar will give an update on latest developments on her road to the clinic aiming at the first in man study for PD in Europe using ES derived dopaminergic progenitors. This will include GMP manufacturing and cryopreservation of the cells, as well as a discussion of the key pre-clinical in vivo assays for safety and efficacy. Sebastian Knöbel will highlight recent developments towards an automated manufacturing platform for ATMPs, the CliniMACS Prodigy. A closed system Tubing Set and software package adapted for adherent cells together with high quality QC and cell culture reagents constitute major advances for development and scaling of cell manufacturing processes for a variety of applications. Besides PSCs expansion and DA differentiation, MSC isolation from bone marrow plus subsequent cultivation will be presented. Finally, cells sorting using the GMP compliant cell sorter MACSQuant Tyto will be discussed in the context of ATMPs.

IRVINE SCIENTIFIC

Room: Melbourne Room 2, Level 2

11:30 - 12:30

IMPORTANCE OF USING SERUM-FREE MEDIA IN THE CELL THERAPY FIELD

Vanda S. Lopes, *Senior Scientist, Irvine Scientific*

Cell therapy is a growing area that focuses on the application of cells as the therapeutic product, and where cell culture is the manufacturing process. Currently the main challenges in this approach reside in the generation of enough cell numbers, with consistent clinical quality. While this may seem rather straightforward, cell culture is a process that involves a large number of interlinked variables, such as cell quality and culture media. In an attempt to move towards a consistent manufacturing process, the removal of undefined components is critical. In here we will address the importance of using serum-free media in the development of cell therapy. We will also introduce some alternative products for the culture of several cell types (HSC, T Cell and NK cells) that can help in addressing some of the challenges in translational cell applications.



MELBOURNE TAKES BIOTECH TO A NEW LEVEL

Melbourne is Australia's leading location for cell therapies and regenerative medicine, with academic and industry sectors actively partnering to deliver innovative health treatments for the world. It is recognised for its high-quality, streamlined clinical development pathway, research expertise and a supportive government. Melbourne continues to grow its international research partnerships to deliver new regenerative medical products and services.

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STEM CELL REPORTS

EDITOR-IN-CHIEF

Christine Mummery, PhD,
Leiden University Medical Center

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INTERNATIONAL SOCIETY
FOR STEM CELL RESEARCH



WEDNESDAY, 20 JUNE, 13:00 – 15:15

PLENARY I: PRESIDENTIAL SYMPOSIUM

Plenary Room, Ground Level

Sponsored by Fate Therapeutics

13:30 – 13:55

INTEGRATED CONTROL OF STEM CELL ACTIVITY IN PLANTS

Scheres, Ben, Chakraborty, Bandan, Mulder, Bela, ten Tusscher, Kirsten and Mahonen, Ari-Pekka

Wageningen University and Research, Wageningen, Netherlands

Plants grow continuously throughout their life cycle and 'behave' by adaptation of developmental programs to the environment. Growth is fuelled by somatic stem cells that reside in stem cell niches. The specification of stem cell niches is dynamic and depends on signals, of which the indolic small molecule auxin is the most important, that are positioned by continuous interactions among many cells. The same signals regulate rapid responses of growth to the environment. We have investigated how signal accumulation leads to the activation of a small suite of transcription factors that together maintain the multipotent state, and how a gradient of these transcription factors regulates the transition from stem cell to differentiation states. We show how this gradient separates developmental and environmental responses in growth regions to the fluctuating auxin signal that is upstream of both. Finally, we provide evidence how control of the direction of cell division, which is of key importance for the formation of plant tissues, is connected to the auxin signalling process.

13:55 – 14:20

COORDINATING TISSUES DURING AXOLOTL LIMB REGENERATION

Tanaka, Elly

Institute of Molecular Pathology, Vienna, Austria

Regrowth of a severed limb in the axolotl is a spectacular example of regeneration—the remaining portion of the limb is able to activate stem cells so that they replace the appropriate part of the limb, and rebuild the complex architecture of the different, interacting cell types. This process occurs in three morphologically and molecularly definable stages, wound-healing, blastema formation, and patterning. I will talk about our work that has identified wound signals that initiate regeneration, and how the connective tissue cells orchestrate the building of the blastema and the patterning of the regenerate. A stable positional code is maintained in the adult limb that is central for controlling the amputation specificity and controlling that the correct parts of the limb are produced.

14:20 – 14:45

EPITHELIAL STEM CELLS AND REGENERATIVE MEDICINE

Pellegrini, Graziella¹, Rama, Paolo², Hirsch, Tobias³, Rothoef, Tobias⁴, Teig, Nortbert⁴, Bauer, Johann⁵ and De Luca, Michele⁶

¹University of Modena and Reggio Emilia, Modena, Italy, ²Cornea and Ocular Surface Unit, San Raffaele Scientific Institute, Milan, Italy, ³Department of Plastic Surgery, Burn Centre, BG University Hospital Bergmannsheil, Ruhr University Bochum, Germany, ⁴Department of Neonatology and Pediatric Intensive Care, University Children's Hospital, Ruhr University Bochum, Germany, ⁵EB House Austria and Department of Dermatology, University Hospital of the Paracelsus Medical University, Salzburg, Austria, ⁶Centre for Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

Regenerative medicine has generated many efforts to explore new therapeutic potentials of both somatic and pluripotent stem cells with many possibilities envisaged for therapeutic applications. Hematopoietic and epithelial cells are extensively adopted for tissue regeneration, due to their high proliferative capacity and their accessibility. 30 years ago, the method for producing epidermis was discovered by cultivation from a small skin biopsy, allowing life-saving treatment of thousands of severely burned patients, in the following years. The importance of stem cell content was proven for tissues or organs in different pathologies. For instance, recent developments in cell-based therapy for ocular burns provided support for improvement and standardization of the cure for this disabling disease, causing depletion of limbal stem cells. Indeed, biopsies taken from the healthy eye, or other autologous source as oral mucosa in bilateral blindness, can be used for their content of stem cells. The combined use of cell and gene therapy represents a further scientific approach for the treatment of congenital diseases. This approach has recently been established using genetically modified epidermal cells for life-saving treatment on severe genetic diseases, as epidermolysis bullosa. Gene therapy, cell therapy, and tissue engineering have the potential to revolutionize the treatment of disease and injury. Attaining marketing authorization for such Advanced Therapy Medicinal Products (ATMPs) requires a rigorous scientific evaluation by the European Medicines Agency - authorization is only granted if the product can fulfil stringent requirements for quality, safety and efficacy. *Ex vivo* expanded autologous human corneal epithelium, a novel treatment for eye burns, is one of the few ATMPs, to have been granted marketing authorization and is the first claiming a specific amount of stem cells. This presentation highlights the peculiarities of EU rule compliant medicinal products, and specifically discusses how the manufacture had to be updated to achieve authorization. The result is that patients will have access to a therapy that is manufactured to high commercial standards, and is supported by robust clinical safety and efficacy data.

WEDNESDAY 20 JUNE 2018

14:50 - 15:10

THE ISSCR TOBIAS AWARD LECTURE: A PROSPECTIVE ANALYSIS OF HUMAN LEUKEMOGENESIS

Eaves, Connie J.

*Terry Fox Laboratory, BC Cancer Agency, Vancouver,
BC, Canada*

Targeting early events in the leukemogenic process has been a long sought strategy to more effectively treat and perhaps eventually prevent human leukemias. To this end, the increasing resolution and decreasing cost of genomic sequencing has enabled a large spectrum of acquired mutations associated with this process to be identified from analyses of patients' samples. The sequence of acquisition of mutations in these cells and their subclonal evolution can then be retrospectively inferred from analyses of the representation of each mutation in the sample. Drawbacks of this approach are the limitations in the size and site of the samples obtainable, their genomic diversity both between and within patients, and the contributions of non-genomic mechanisms to the altered properties of the cells. An alternative approach is to use protocols that allow the process of leukemogenesis to be tracked prospectively. However, until recently, this was difficult to achieve de novo starting from primary sources of human hematopoietic cells. As a result, most studies have relied on the use of mouse models or immortalized cell lines to generate transformed hematopoietic cells, despite the recognition that these poorly recapitulate the leukemias that appear in patients. This presentation will summarize a new description of the diversity of primitive human hematopoietic cell states that are potential targets for leukemic transformation, their ability to undergo this process, and factors that affect it.

WEDNESDAY, 20 JUNE, 16:00 - 18:00

PLENARY II: RECAPITULATING DEVELOPMENT FROM STEM CELLS

Plenary Room, Ground Level

16:05 - 16:30

MECHANISM AND RECONSTITUTION IN VITRO OF GERM CELL DEVELOPMENT IN MICE, MONKEYS, AND HUMANS

Saitou, Mitinori

Kyoto University, Kyoto, Japan

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 ro-

bust capacity both for spermatogenesis and oogenesis. We have also shown that human iPSCs (hiPSCs) with a primed pluripotency robustly generates human PGCLCs (hPGCLCs) with a property of human early PGCs. Moreover, by investigating the development of cynomolgus monkeys, we have defined a developmental coordinate of the spectrum of pluripotency among mice, monkeys, and humans, and have made an unexpected finding that the germ cell lineage in primates is specified in the amnion. I would here discuss our efforts towards understanding the mechanism of and reconstituting in vitro of germ cell development in mice, monkeys, and humans.

16:30 - 16:55

PANCREAS ORGANOIDS TO DECONSTRUCT NORMAL AND PERTURBED DEVELOPMENTAL MECHANISMS IN MOUSE AND HUMAN

Grapin-Botton, Anne, Gonçalves, Carla, Figueiredo-Larsen, Manuel, Yennek, Siham, Nakamura, Akino, Azad, Ajuna, Larsen, Michael, Beydag-Tasöz, Belin Selcen, Borup Kjær Petersen, Maja, Ramond, Cyrille, Kim, Yung Hae, Honoré, Christian and Scharfmann, Raphael

DanStem, University of Copenhagen, Denmark

Organoids representing a diversity of tissues have recently flourished, bridging the gap between cell lines or primary cells grown on the bottom of culture plates and experiments performed in vivo. Being small and amenable to continuous monitoring they offer the opportunity to scrutinize the dynamics of organ development, which includes the exciting prospect of observing aspects of human embryo development live. Though not recapitulating all facets of physiology, these miniature organs generated in a dish are simpler than the whole organ and offer an opportunity to manipulate culture conditions in isolation from the rest of the embryo and from the mother. Their ability to self-organize, that is to differentiate and organize cells in space, calls for the identification of the simple rules that underlie this capacity. We initially established 3D culture conditions that enable the efficient expansion of dissociated mouse embryonic pancreatic progenitors. With this system, we revealed that pancreas progenitors behave differently in 2D and 3D and that they are sensitive to the stiffness and nature of the 3D environment. Two media compositions were established that unfold different responses in progenitors. A first medium balances long lasting progenitor expansion and endocrine cell production in spheres. A second medium balances progenitor expansion and acinar cell production and enables the formation of a branched network of ducts, in a manner and timing similar to the developmental process. Focusing on the initial conditions leading to these organoids, we observed that the organoids formed if enough cells were clustered and identified a cooperative community effect. Assembling defined numbers of Notch active and inactive cells shows that their interaction is needed to initiate organoid formation and fuel growth. We also used this model to investigate how the branched structure of the pancreatic ducts emerges from the initial small cell

aggregates. Developing the model to study human development and model disease, we will present recent data showing the robust expansion, differentiation and morphogenesis of human pancreatic spheres and organoids derived from embryonic stem cells. Benchmarking these systems to human embryos enables us to assess their relevance and their use to model neonatal diabetes.

16:55 – 17:20

VASCULAR NICHE ANGIOCRINE SIGNALS DICTATE ORGANOTYPIC STEM CELL REGENERATION

Rafii, Shahin

*Cornell Medical College and Angiocrine Bioscience,
New York, NY, U.S.*

Stem cell self-renewal and fate determination require niche-derived signals. However, the source of the niche cells and signals that regulate regeneration are unknown. Tissue-specific endothelial cells (ECs) by oscillating the ultradian production of stimulatory and inhibitory angiocrine factors establish an instructive vascular niche that choreographs organ regeneration and stem cell self-renewal, such as hematopoietic stem cells (HSCs). To uncover the mechanism by which ECs regulate stem cell homeostasis, we have devised a tissue-specific vascular niche platform for expansion of HSCs and for generating vascularized tissue-specific 3D organoids. Co-culture of adult marrow-derived mouse or human HSCs with ECs results in > 50 fold clonal HSC self-renewal with long-term multi-lineage engraftment potential. Vascular niche cells also specify pluripotent-independent conversion of readily accessible adult ECs into engraftable HSCs. To prove this, we transduced human or mouse adult mature ECs with Runx1 /Spi1/Gfi1/FosB transcription factors along with vascular niche-induction enabling step-wise conversion of ECs into immunocompetent HSCs. Clonal populations of converted HSCs expanded on vascular niche and reconstituted hematopoiesis in rodents. Co-infusion of the ECs along with HSCs augmented hematopoietic recovery. To translate the potential of vascular niche to clinic, we have engineered ECs capable of vascularizing epithelial, hepatic, pancreatic, neural and cardiac 3D organoid cultures. Cross talk of ECs with tissue-specific stem cells promotes proper patterning of organoids into functional tissues. We show that transplantation of ECs stimulates organ repair without provoking maladapted fibrosis. We have acquired an IND approval from FDA to perform the First-In-Human co-transplantation of HSCs with vascular niche cells to accelerate hematopoietic recovery. These clinical trials will set the stage for reconstructing and remodeling vascular niche in vivo for treatment of acquired, inherited, and malignant stem cell disorders. Tissue-specific vascular-stem cell organoid cultures facilitate screening by gene-editing and small molecule libraries to identify unknown vascular niche signals that coordinate stem cell self-renewal and differentiation for functional organ repair.

17:20 – 17:30

POSTER TEASERS

W-2064

HETEROCHROMATIN CONDENSATION IS
MEDIATED BY JMJD1A AND JMJD2C DURING
PHYSIOLOGICAL STEM CELL AGING

Jiang, Xiaohua (Cynthia)

The Chinese University of Hong Kong, Hong Kong

W-3069

INTEGRATIVE MOLECULAR ANALYSES
REVEAL DISTINCT REPROGRAMMING
TRAJECTORIES INTO STATES OF NAIVE AND
PRIMED HUMAN INDUCED PLURIPOTENCY?

Liu, Xiaodong

Monash University, Australia

W-1081

THE ROLE OF TRANSLATION IN HUMAN
KERATINOCYTE CELL FATE DETERMINATION

Lewicka, Aleksandra

University of Cambridge, U.K.

W-1020

MOLECULAR MECHANISMS REGULATING
MUSCLE STEM CELLS QUIESCENCE AND
EARLY ACTIVATION

Relaix, Frederic

*INSERM U955-E10 IMRB, Faculté de médecine UPEC,
France*

W-1100

A METHOD TO ISOLATE AND TRANSPLANT
MOUSE HEMATOPOIETIC STEM CELLS ALONG
WITH THEIR NICHE ALLOWING FUNCTIONAL
HEMATOPOIETIC STEM CELL ENGRAFTMENT
WITHOUT MYELOABLATION

Borrelli, Mimi R.

*Department of Plastic and Reconstructive Surgery,
Stanford University, U.S.*

WEDNESDAY 20 JUNE 2018

17:30 – 17:55

**THE ANNE MCLAREN MEMORIAL
LECTURE: DEVELOPMENTAL
TRAJECTORY OF THE MOUSE EPIBLAST
DEFINES THE DEVELOPMENTAL
CORRELATE OF EMBRYO-DERIVED
PLURIPOTENT STEM CELLS**

Tam, Patrick P.L

*Children's Medical Research Institute, Westmead,
NSW, Australia*

The basic body plan of the embryo is visualised by the regionalization of cell fates in the primary germ layers during gastrulation. The collation of stage-wise fate maps enables the reconstruction of the developmental trajectory of lineage differentiation of cells in the germ layers. Transcriptome analysis of the mouse embryo across the developmental stages from pre-gastrulation to late gastrulation has defined the developmental progression and provides the molecular annotation of the genealogy and the transcriptional and signalling activity of spatially registered sub-populations of cells in the germ layer. The developmental-spatial transcriptome presents a refined perspective of the developmental trajectory and lineage relationship of the multipotent tissue progenitors during germ layer differentiation. In relevance to the biology of stem cells, the transcriptome knowledge provides the developmental correlates for tracking the state of pluripotency, the embryological counterpart and the lineage trajectory of the embryo-derived pluripotent stem cells and the molecular activity underpinning the acquisition of lineage propensity, and for the rationalization of the methodology of directed differentiation.

THURSDAY, 21 JUNE, 09:00 – 11:10

PLENARY III: SYSTEMS BIOLOGY OF HETEROGENEITY

Plenary Room, Ground Level

09:15 – 09:40

STEM CELL HETEROGENEITY IN THE ADULT HIPPOCAMPUS

Guillemot, Francois, Blomfield, Isabelle, Harris, Lachlan and Urban, Noelia

The Francis Crick Institute, London, UK

Stem cells in the hippocampus of the adult brain produce neurones that have important functions in memory and mood control. Most adult hippocampal stem cells are quiescent while a small fraction proliferate and produce neurones in response to various physiological stimuli or to injury. How stem cells compute the diverse stimuli and downstream niche signals they receive to produce appropriate numbers of adult neurones remains an open question. We found that the transcription factor *Ascl1* is essential for activation of hippocampal stem cell. We also obtained evidence that *Ascl1* expression is controlled by different post-translational mechanisms at different stages in the hippocampal stem cell lineage. *Ascl1* is transcribed in most quiescent stem cells but *Ascl1* protein accumulation in these cells is suppressed by the transcriptional repressor *Id4*, via sequestration of *Ascl1* dimerisation partner and degradation of monomeric *Ascl1*. *Ascl1* protein is also actively degraded in proliferating hippocampal stem cells, by a different mechanisms involving the E3 ubiquitin ligase *Huwe1*. We are characterising the niche signals that controlling *Ascl1* protein levels via regulation of *Id4* and *Huwe1*. Further investigation of *Huwe1* function in proliferating hippocampal stem cells has shown that active elimination of the pro-activation factor *Ascl1* is essential for a fraction of these cells to return to quiescence. Moreover, examination of *Huwe1* function in mice of different ages has revealed that stem cells that have previously proliferated and have returned to quiescence (which we call 'resting stem cells') have a unique role in maintaining homeostatic hippocampal neurogenesis. In contrast, stem cells that have not previously proliferated ('dormant stem cells') have a limited role in homeostatic neurogenesis, suggesting they may serve as a reserve stem cell population. We are currently investigating whether resting and dormant stem cell populations are differentially activated by niche signals and by physiological neurogenic and injury stimuli.

09:40 – 10:05

SINGLE CELL ANALYSIS OF HUMAN PREIMPLANTATION EMBRYOS AND PLURIPOTENT CELLS

Lanner, Fredrik

Karolinska Institute, Stockholm, Sweden

Our research focuses on understanding how pluripotency is established and controlled in the human embryo. We have recently undertaken two approaches to explore how the pluripotent cells emerge in the human embryo using single cell RNA sequencing and developed new tools to track naïve and primed pluripotent cells. These data show that pluripotent epiblast cells emerge coincidentally with blastocyst formation. The data further suggest that female cells undergo X-chromosome dosage compensation prior to implantation. In contrast to the mouse, *XIST* is transcribed from both alleles throughout the progression of this expression dampening, and X-chromosome genes maintain biallelic expression while dosage compensation proceeds. In vitro, pluripotent cells are thought to exist in naïve and primed states, and provide important models to investigate the earliest stages of human development. Naïve cells can be obtained through primed-to-naïve resetting, however, there are no reliable methods to prospectively isolate unmodified naïve cells during this process. Comprehensive profiling of cell-surface proteins by flow cytometry in naïve and primed pluripotent cells. Several naïve-specific, but not primed-specific, proteins were expressed by pluripotent cells in the human preimplantation embryo. Naïve-specific cell-surface proteins were induced during primed-to-naïve resetting and enabled the isolation and characterization of live naïve cells and intermediate cell populations. This analysis revealed distinct transcriptional and X-chromosome inactivation changes associated with early and late stages of naïve cell formation. Thus, identification of state-specific proteins provides a robust set of molecular markers to unambiguously define human pluripotent state, and allows new insights into the molecular events leading to naïve cell resetting.

10:05 – 10:30

THE HEMATOPOIETIC AND ERYTHROID HIERARCHIES THROUGH THE LENS OF SINGLE CELL TRANSCRIPTOMICS

Socolovsky, Merav, Tusi, Betsabeh, Wolock, Sam, Weinreb, Caleb, Hwang, Yung and Hidalgo, Daniel

Department of Molecular, Cell and Cancer Biology, University of Massachusetts Medical School, Worcester, MA, U.S.

The formation of red blood cells begins with the differentiation of multipotent haematopoietic progenitors. Reconstructing the steps of this differentiation represents a general challenge in stem-cell biology. Here we used single-cell transcriptomics, fate assays and a theory that allows the prediction of cell fates from population snapshots, to demonstrate that mouse hematopoietic pro-

genitors differentiate through a continuous, hierarchical structure into seven blood lineages. We uncovered coupling between the erythroid and the basophil or mast cell fates, a global haematopoietic response to erythroid stress and novel growth factor receptors that regulate erythropoiesis. We defined a flow cytometry sorting strategy to purify early stages of erythroid differentiation, completely isolating classically defined burst-forming and colony-forming progenitors. We also found that the cell cycle is progressively remodelled during erythroid development and during a sharp transcriptional switch that ends the colony-forming progenitor stage and activates terminal differentiation. Our work showcases the utility of linking transcriptomic data to predictive fate models, and provides insights into lineage development in vivo.

10:30 – 10:40

POSTER TEASERS

T-2074

GENERATION OF INNER EAR ORGANOID ENRICHED WITH MECHANOSENSITIVE VESTIBULAR HAIR CELLS DERIVED FROM HUMAN PLURIPOTENT STEM CELLS

Mattei, Cristiana

Melbourne School of Engineering, The University of Melbourne, VIC, Australia

T-2162

UTILIZING RNA SEQUENCING TO IDENTIFY CANCER-RELATED MUTATIONS IN HUMAN PLURIPOTENT STEM CELLS

Avior, Yishai

The Hebrew University, Israel

T-1030

SINGLE-CELL TRANSCRIPTOME ANALYSIS OF EARLY MOUSE CARIOGENESIS AND PERTURBATION UPON HAND2 LOSS

De Soysa, Yvanka

University of California, San Francisco and Gladstone Institutes, U.S.

T-1051

SINGLE CELL RNA-SEQ REVEALS DACH1 EXPRESSION SEGREGATES LYMPHOID AND MYELOID FATE IN EARLY HAEMATOPOIESIS

Tian, Luyi

Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia

T-2003

CLONAL LINEAGE TRACING AND SINGLE CELL ANALYSES OF NEURAL STEM AND PROGENITOR CELLS IN THE MOUSE EMBRYONIC VENTRAL FOREBRAIN GERMINAL ZONE

Yamine, Samantha

Department of Molecular Genetics, University of Toronto, Canada

10:40 – 11:05

THE ERNEST MCCULLOCH MEMORIAL LECTURE: MAKING ISLET CELLS FOR DIABETICS

Melton, Douglas A.

Harvard University and Harvard Stem Cell Institute, Cambridge, MA, U.S.

Beta cell insufficiency in Type 2 diabetes and beta cell loss in Type 1 diabetes lead directly to a dependence on insulin injections. An alternative approach is produce human beta cells, and other islet endocrine cells, for transplantation which would, in principle, relieve patients of regular finger pricks and insulin injections and provide superior metabolic control. Advances in controlling the directed differentiation of stem cells into functional human islets cells, and protecting them from immune attack following transplantation, will be described.

THURSDAY, 21 JUNE, 13:15 – 15:15

CONCURRENT IA: MECHANISMS OF REPROGRAMMING 1: TO PLURIPOTENCY

Melbourne Room 1, Level 2

13:20 – 13:45

ACQUISITION OF NAÏVE PLURIPOTENCY IN MICE AND MEN BY MODULATING TGF-BETA SIGNALING PATHWAY: TWO SIDES OF THE SAME COIN?

Baharvand, Hossein

Royan Institute, Teheran, Iran

Mouse embryonic stem cells (ESCs) cultured in the presence of inhibitors of TGF β and FGF signaling pathways (dubbed R2i) exhibit typical features of ground state pluripotency in which stem-cell pluripotency is established and maintained by efficient blockade of endogenous differentiation pathways. R2i allows for efficient pluripotent stem cell generation from mouse and rat preimplantation blastocysts as well as from primordial germ cells (PGCs). R2i as same as the well-known 2i condition which include the FGF and GSK3 inhibitors could support the criteria of

ground state pluripotency. However, R2i exhibits more efficiency in controlling pluripotency, genomic integrity and ESC generation from single blastomeres obtained from mouse pre-implantation embryos and embryonic germ cell (EGCs) derivation from mouse PGCs. High throughput transcriptome analysis indicated that in spite of the high similarity between 2i and R2i grown ESCs, BMP4 signaling pathway is highlighted in R2i cells. Moreover, the proteome and miRNome analysis indicated the differences in traditional serum/LIF cultured- and the ground state (2i and R2i)-cultured ESCs. We found that the focal adhesion signaling pathway significantly downregulated and glycolysis signaling pathway upregulated in ground state conditions. Moreover, the ground-state ESCs express a distinct set of miRNAs compared with serum/LIF grown ESCs in that way most “ground-state miRNAs” are encoded by an imprinted region on chromosome 12 within the *Dlk1-Dio3* locus. Our time course transcriptome analysis during ESC generation from inner cell mass (ICM) in R2i regimen indicated that DNA methyltransferases and epithelial to mesenchymal transition blockage play pivotal roles in launching the ESC self-renewal program. In contrast to the mouse context, however, it seems that TGF- β signaling plays a stimulatory role in generation and maintenance of human naïve pluripotency, which is obtained through the activation of nuclear receptors. We found that the brief treatment with two chemical agonists of nuclear receptors or TGF β as the alternative is sufficient to induce naïvety. Indeed, activation of TGF β pathway promotes key features of naïvety in human pluripotent stem cells. TGF β signaling might be the key feature that distinguishes mouse from human naïvety.

13:45 - 14:00

IDENTIFYING HETEROGENEITY OF GROUND STATE PLURIPOTENCY IN MOUSE EMBRYONIC STEM CELLS

Horie, Kyoji¹ and Yoshida, Junko²

¹*Department of Physiology II, Nara Medical University, Kashihara, Japan,* ²*Nara Medical University, Kashihara, Japan*

Mouse embryonic stem cells (ESCs) are maintained in pluripotent states in serum free medium in the presence of Mek and Gsk3 inhibitors and LIF (2i/LIF), which is called a ground state culture condition. Core pluripotency transcription factors known to fluctuate under serum/LIF such as Nanog are homogeneously expressed under 2i/LIF, implicating that ground state pluripotency is static in nature. However, recent reports of single cell transcriptome analyses revealed heterogeneously expressed gene modules in ground state, with the significance of this heterogeneity remains elusive. Here we report the heterogeneity of ground state ESCs was associated with their differentiation potency. A gene trap vector using Venus as a reporter was randomly inserted genome-wide for the trapped gene expression. Thousands of single cell-derived colonies were microscopically observed and clones showing heterogeneous Venus expression at the single cell level were identified. Venus-positive and -negative cells were

sorted in each clone and their differentiation potency was compared. From this screen, a clone showing distinct characteristics between Venus-positive and -negative cells was identified. Expression of Venus was reversible: Venus-positive cells could be derived from Venus-negative cells, and vice versa. In this clone, a noncoding gene with no known function was inserted with Venus. In vitro, Venus-positive cells formed dome-shaped colonies with sharp edges on culture compared with Venus-negative cells. Distinct differentiation potency was noted between Venus-positive and -negative cells by in vitro differentiation assays, indicating the heterogeneity of differentiation potency of undifferentiated ESCs. This hypothesis was further supported by RNA-seq analysis of undifferentiated ESCs, in which distinct gene ontology was enriched between Venus-positive and -negative cells. Unexpectedly, Venus-negative cells showed high expression of two-cell stage embryo-specific markers (e.g. *Zscan4* and *MERVL*), suggesting that Venus-negative cells have early stage embryonic characteristics. Finally, these results demonstrate the functional heterogeneity of ground state pluripotency and that this condition is not in a static state but is dynamically fluctuating.

14:00 - 14:15

TFAP2C REGULATES TRANSCRIPTION IN HUMAN NAIVE PLURIPOTENCY BY OPENING ENHANCERS

Clark, Amander¹, Pastor, William², Liu, Wanlu³, Chen, Di³, Ho, Jamie³, Kim, Rachel³, Hunt, Timothy³ and Jacobsen, Steven⁴

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Naïve human embryonic stem cells (hESCs) largely recapitulate the transcriptional state of pre-implantation epiblast. In contrast, primed hESCs more closely resemble post-implantation epiblast. Therefore, naïve and primed hESCs constitute a developmental model for understanding the earliest pluripotent stages in human embryo development. To identify new transcription factors that differentially regulate the unique pluripotent stages, we mapped open chromatin using ATAC-Seq and found enrichment of the AP2 transcription factor binding motif at naïve-specific open chromatin. We determined that the AP2 family member TFAP2C is upregulated during primed to naïve reversion and becomes widespread at naïve-specific enhancers. Using CRISPR/Cas9 we show that TFAP2C functions to maintain pluripotency and repress neuroectodermal differentiation during the transition from primed to naïve by facilitating the opening of enhancers proximal to pluripotency factors. Additionally, we identify a previously undiscovered naïve-specific OCT4 enhancer enriched for TFAP2C binding. Taken together, TFAP2C establishes and maintains naïve human pluripotency and regulates OCT4 expression by mechanisms that are distinct from mouse.

14:15 - 14:30

EPIGENETIC AND GENETIC EFFECTS OF GENDER ON REPROGRAMMING TO IPS CELLS AND PLURIPOTENCY

Pasque, Vincent

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Pluripotency can be established from somatic cells by reprogramming approaches and also captured from early embryos. However, how gender affects reprogramming processes and pluripotency remains unclear. We have recently isolated isogenic male and female mouse induced pluripotent stem cells (iPSCs). Here, I will present new studies combining DNA methylation profiling, transcriptional profiling, pluripotency exit measurements, chromatin profiling, growth and genetic analyses, and functional experiments to investigate the transcriptional, epigenetic and genetic effects of gender on the induction, maintenance and exit from pluripotency. I will show that the transcriptional state, DNA methylation, exit from pluripotency and cellular growth of female iPSCs differs from that of male iPSCs, partly mimicking early mammalian embryo development. I will present evidence that X chromosome loss in female iPSCs resolves gender-specific differences but does not restore imprint methylation. I will show that DNA hypomethylation and delayed pluripotency exit can be molecularly uncoupled in female embryonic stem (ES) cells through manipulation of the X-linked MAPK inhibitor *Dusp9*. I will also present evidence that the open chromatin landscape of ES cells is modulated by gender at thousands of chromatin regions and reveal the transcriptional regulatory logic by which gender influences pluripotency. Defining the mechanisms regulating the establishment, maintenance and exit from pluripotency *in vitro* and *in vivo* and understanding how these mechanisms are influenced by gender will have important implications for development and regenerative medicine.

Funding Source: The Research Foundation - Flanders (FWO) (Odysseus Return Grant G0F7716N to V.P.), the KU Leuven Research Fund (BOFZAP starting grant St-G/15/021BF to V.P., C1 grant C14/16/077 to V.P. and Project financing).

14:30 - 14:45

RECONSTRUCTION OF CELLULAR REPROGRAMMING LANDSCAPES AND TRAJECTORIES BY ANALYSIS OF LARGE-SCALE SINGLE-CELL GENE EXPRESSION

Shu, Jian^{1,2}, Tabaka, Marcin^{1,2}, Schiebinger, Geoff¹, Cleary, Brian¹, Subramanian, Vidya¹, Solomon, Aryeh¹, Berube, Peter¹, Lee, Lia^{1,2}, Brumbaugh, Justin³, Hochedlinger, Konrad⁴, Regev, Aviv¹, Jaenisch, Rudolf² and Lander, Eric¹

¹Broad Institute, Cambridge, MA, U.S., ²Whitehead Institute, Cambridge, MA, U.S., ³Massachusetts General Hospital, Boston, MA, U.S., ⁴Harvard University, Cambridge, MA, U.S.

Understanding the molecular programs that guide cellular differentiation during development is a major goal of modern biology. Here, we developed an approach, WADDINGTON-OT, for inferring developmental landscapes, probabilistic cellular fates and dynamic trajectories from large-scale single-cell RNA-seq (scRNA-seq) data collected along a time course. We demonstrated the power of WADDINGTON-OT by applying it to study around 300,000 scRNA-seq profiles collected during reprogramming of fibroblasts to iPSCs by the Yamanaka factors. We applied this strategy to an additional 200,000 scRNA-seq profiles of other reprogramming cocktails, with the goal of discovering the inherent mechanisms of iPSC reprogramming. We construct a high-resolution map of reprogramming that rediscovers known features; uncovers new alternative cell fates; predicts the origin and fate of any cell class; highlights senescent-like cells that may support reprogramming through paracrine signaling; and implicates regulatory models in particular trajectories. Our approach provides the first high resolution roadmap of different reprogramming cocktails and a general framework for cell fate conversions in natural and induced settings.

14:45 - 15:10

NOVEL FUNCTIONS OF RNA-BINDING PROTEINS IN TRANSCRIPTION REGULATION AND STEM CELL PLURIPOTENCY

Shen, Xiaohua and Bi, Xianju

Tsinghua University, Beijing, China

Much of the developmental complexity of higher eukaryotes is thought to arise from gene regulation rather than from an increase in the number of protein-coding genes. RNA may represent a hidden layer of regulatory information in complex organisms. Noncoding RNAs have been increasingly recognized as important regulators of transcription and chromatin structure. The fact that RNA-binding proteins (RBPs) must be enlisted to mediate RNA functions raises the possibility that RBPs might participate in transcription control. I will discuss recent progresses we have made in RBP-mediated regulations of gene expression and stem cell pluripotency.

THURSDAY, 21 JUNE, 13:15 – 15:15

CONCURRENT IB: DISEASE MODELING

Melbourne Room 2, Level 2

13:20 – 13:45

MOUSE MODELS OF GASTRIC CANCERS

Yang, Xiao

State Key Laboratory of Proteomics, Beijing Institute of Lifeomics, Beijing, China

Gastric cancer is the second leading cause of cancer-related death worldwide, the molecular mechanisms underlying the pathogenesis of gastric carcinomas remain to be fully defined. To better understand the genetic mechanisms controlling the function of gastric epithelial cells in the homeostasis maintenance of the gastric epithelium, we established 4 transgenic mouse lines in which the Cre recombinase were expressed in various gastric epithelial cells and generated different kinds of mouse models of gastric cancers. We have previously shown that inactivation of PTEN in mouse gastric epithelium initiates spontaneous carcinogenesis with complete penetrance by 2 months of age, providing the *in vivo* causal link between the dysregulation of PTEN/Akt signaling and gastric tumorigenesis. Using the inducible Cre-LoxP system to delete Smad4 and PTEN genes in murine gastric Lgr5+ stem cells as well as marked mutant Lgr5+ stem cells and their progeny with Cre-reporter Rosa26tdTomato, rapid onset and progression from microadenoma and macroscopic adenoma to invasive intestinal-type gastric cancer (IGC) were found in the gastric antrum of double mutant mice. In contrast, Smad4 and PTEN deletions in differentiated cells, including antral parietal cells, pit cells and corpus Lgr5+ chief cells, failed to initiate tumor growth. All these data demonstrated that gastric Lgr5+ stem cells were cancer-initiating cells and might act as cancer-propagating cells that contribute to malignant progression. The function of E-cadherin in gastric antral Lgr5+ cells in the maintenance of gastric epithelial homeostasis will also be discussed.

13:45 – 14:00

GENETIC NEUROSCIENCE: HOW HUMAN GENES AND ALLELES SHAPE NEURONAL PHENOTYPES

Mitchell, Jana M.¹, Nemesh, James², Mello, Curtis², Ghosh, Sulagna³, Eggan, Kevin³ and McCarrroll, Steven²

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The high polygenicity of neuropsychiatric disorders - shaped by thousands of common and rare variants, and by different combinations of risk alleles in each individual - presents formidable challenges for biology. As these

variants are often incompletely penetrant or of weak-effect, it would be enormously valuable if cellular studies could learn from vast numbers of variants simultaneously. We have been working to develop a novel strategy for population-scale cellular studies: pooling cell lines from increasing numbers of individuals into reaction chambers, then using sequencing-based strategies for deconvoluting cells' identities as part of a phenotypic read out. This allows us to address two key challenges; 1) Scale - we can investigate phenotypes from hundreds of cell lines at once; and 2) Variance, control, and reproducibility -pooling cell lines reduces technical noise arising from well-to-well variation and downstream molecular processing. Using this experimental paradigm, the polygenicity of these disorders - which historically has been viewed as a weakness - can be transformed into a scientific strength. Our approach combines single-cell RNA sequencing with mosaic culture systems to allow us to link RNA expression profiles with an individual's genotype. We found that co-culturing cell lines in this way greatly reduces variance; the coefficient of variation between cell lines cultured individually with those co-cultured simultaneously dropped markedly from 0.20 to 0.08. We directly tested the association between gene expression and cis-regulatory variation to identify expression quantitative trait loci (eQTL). These "population-in-a-dish" analyses allow us to map changes in direction and magnitude of gene expression directly back to regulatory variants implicated in disease. We have identified hundreds of eQTLs in pools of pluripotent stem cells, and in pools of cells differentiated *in-vitro* towards neural precursors and more mature, upper-layer cortical excitatory neurons. These experiments lay the framework for future investigations aimed towards investigating the effects of disease-associated variation on neuronal physiology, and represent a crucial step towards elucidating the molecular pathways onto which these genetic signals converge.

14:00 – 14:15

NUTRACEUTICAL RESCUE OF PATHOLOGICAL CHANGES IN IPSC-DERIVED NEURAL CELL TYPES FROM A CHILDHOOD LEUKODYSTROPHY CAUSED BY MUTATIONS IN ASPARTATE TRNA SYNTHETASE (DARS)

Wolvetang, Ernst J.¹, He, Ruojie², Endes, Carola³, Ovchinnikov, Dmitry³, Sun, Jane³, Mar, Jessica³, Powell, Joseph³, Froehlich, Dominique⁴, Klugmann, Matthias⁴, Salomons, Gaia Salomons⁵, Wolf, Nicole⁵, van der Knaap, Marjo⁵ and Vanderver, Adeline⁶

¹Stem Cell Engineering Group, The Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Brisbane, Queensland, Australia, ²Sun Yat-Sen University, Guangzhou, China, ³The University of Queensland, Brisbane, Australia, ⁴The University of New South Wales, Sydney, Australia, ⁵VU University Medical Center, Amsterdam, Netherlands, ⁶Children's Hospital of Philadelphia, PA, U.S.

The DARS gene codes for Aspartate-tRNA synthetase (AspRS) and is mutated in patients with Hypomyelination with Brain Stem and Spinal Cord Involvement and Leg Spasticity (HBSL). How AspRS mutations lead to focal hypomyelination and cognitive impairment, and why there is inter-patient variability in severity and onset has remained unclear, and no treatment is available. We reprogrammed HBSL patient fibroblasts into foot-print free iPSC, and show that HBSL-iPSC derived cortical neurons exhibit increased ER-stress, increased apoptosis, and gene expression changes consistent with defective neuronal function and protein translation. We further find HBSL-iPSC derived astrocytes show defects in activation, whereas single cell RNAseq reveals specific mitochondrial gene expression differences in HBSL oligodendrocytes, indicating AspRS deficiency affects each of the three cell types that control CNS myelination differently. Importantly, we are able to show that supplementation of cortical neuronal cultures with the nutraceutical L-Ornithine-L-Aspartate rescues the neuronal phenotypes, indicating this may be a therapeutic option for HBSL patients.

Funding Source: Supported by: The Mission Massimo Foundation and the ARC SRI "Stem Cells Australia".

14:15 - 14:30

USING INDUCED SENSORY HAIR CELLS FOR HIGH THROUGHPUT SCREENING TO IDENTIFY OTOPROTECTANTS

Menendez, Louise¹, Gopalakrishnan, Suhasni², Trecek, Talon², Yu, Haoze², Llamas, Juan², Makmura, Welly², Segil, Neil² and Ichida, Justin²

¹Department of Neuroscience, University of Southern California, Los Angeles, CA, U.S., ²University of Southern California, Los Angeles U.S.

Hearing loss affects 360 million people worldwide and the leading cause is loss of sensory hair cells in the cochlea. Hair cells are scarce and very fragile, making studies difficult. Here we used direct reprogramming to generate induced sensory hair cells (iHCs) in vitro. Our results demonstrate that a specific set of hair cell transcription factors is sufficient for reprogramming mouse fibroblasts towards a hair cell fate. The iHCs resemble primary mouse hair cells at a transcriptional and functional level. The transcriptional profile of iHCs successfully recapitulates 72% of primary hair cell genes and shuts down 79% of the starting fibroblast genes. The functionality of the iHCs has been assayed by their ability to take up styryl dyes in a similar manner as primary hair cells, indicative of a rudimentary mechano-transduction apparatus. Additionally, whole cell patch clamping of the iHCs repeatedly demonstrated positive outward currents that have activation kinetics characteristic of primary hair cell currents. One goal of this in vitro model is to provide a high-throughput system to study the selective vulnerability of sensory hair cells to environmental insults, such as well-known ototoxins like gentamicin, an aminoglycoside antibiotic, and cisplatin, a chemotherapy drug. We performed a longitudinal survival tracking experiment with iHCs to assay

for ototoxin-induced cell death. Time-lapse data showed a clear dose-dependent loss of iHCs in response to the ototoxins. A preliminary otoprotectant screen was performed on iHCs. Our screen examined 640 compounds for their ability to rescue the previously identified ototoxic effect of either gentamicin or cisplatin. The screen identified 8 potentially protective compounds that significantly extended the survival of iHCs by greater than 3 standard deviations from the mean survival of the ototoxin treated control. Some compounds identified are involved in known pathways of hair cell degeneration, and some identified novel targets. We are pursuing these hits by testing them on human iHCs, whole organ of Corti explants and in vivo in mouse models. So far one compound has demonstrated a significant rescue in the whole organ explant. Taken together, in vitro iHCs will help us pursue protective and regenerative initiatives for the vulnerable hair cells of the cochlea.

14:30 - 14:45

ENUCLEATION IN INDUCED RED BLOOD CELLS: A PLATFORM FOR AUTOLOGOUS CELL THERAPY AND IN VITRO MODELING OF SICKLE CELL ANEMIA

Rosanwo, Tolulope O.¹, Clark, Martha², Vo, Linda³, Kinney, Melissa¹, North, Trista¹ and Daley, George¹

¹Boston Children's Hospital, Boston, MA, U.S.,

²Harvard TH Chan School of Public Health, Boston, U.S.,

³University of California San Francisco, U.S.

Human induced pluripotent stem cells (hiPSCs) hold tremendous promise for disease modeling and the development of novel therapeutic treatments for sickle cell anemia (SCA). hiPSCs can theoretically produce all cell types including induced red blood cells (iRBCs). Sickle cell patients could benefit from autologous, engineered red blood cells as these patients have rare blood types, are frequently allo-sensitized to blood products, and at risk of iron overload from recurrent transfusions. However, in vitro modeling of SCA as well as iRBC production from hiPSCs has been hampered by their inability to differentiate into terminally-mature, enucleated, beta globin-expressing red blood cells. Here, we describe strategies to improve in vitro production of iRBCs. We generated hiPSCs from sickle cell patients with hemoglobin SS disease seen at our hematology clinic at Boston Children's Hospital. Using a cocktail of transcription factors that promote self-renewal and multipotency expressed under the control of a doxycycline-regulated promoter (ERG, HOXA9, RORA, SOX4, MYB), we generated conditionally immortalized hematopoietic progenitors that serve as a renewable source of robust erythroid cells in vitro. Erythroid progenitors differentiated from these lines underwent globin-switching once transfused into immunodeficient mice, with a 27% induction of beta globin expression. An in vitro protocol incorporating human plasma can be used to produce 30-40% beta-globin-expressing cells. 10-50% of generated iRBCs are also enucleated. Preliminary iRBC analysis reveals nearly 36% of the enucleated population to be RNA negative erythrocytes and 64% RNA positive

reticulocytes. With an expandable source of erythroid progenitors capable of producing mature red cells, we hope to assess the feasibility of this platform for autologous cell therapies. In future studies, we anticipate the improvement of the sickling model via a robust induction of beta-globin expression. The generation of hiPSC-derived SCA models will be critical in broadening the current understanding of the molecular mechanisms of this disease, and the development of improved pharmacological treatments for the treatment of SCA.

Funding Source: Howard Hughes Medical Institute, Doris Duke Charitable Foundation, National Institute of Diabetes and Digestive and Kidney Disease, National Heart Lung and Blood Institute: Progenitor Cell Translational Consortium.

14:45 – 15:00

IPSC-DERIVED NEUROSPHEROIDS RECAPITULATE DEVELOPMENT AND PATHOLOGICAL SIGNATURES OF HUMAN BRAIN MICROENVIRONMENT

Terraso, Ana P.^{1,2}, Simão, Daniel ^{1,2}, Bayó-Puxan, Neus^{3,4,5}, Arez, Francisca^{1,2}, Silva, Marta M.^{1,2}, Sousa, Marcos F.^{1,2}, Gomes-Alves, Patricia^{1,2}, Raimundo, Nuno⁶, Kremer, Eric J.^{3,4} and Brito, Catarina^{1,2}

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Brain microenvironment plays important roles in neurodevelopment and pathology. Neural cell culture typically relies on the use of heterologous matrices that poorly resemble brain ECM or reflect its pathological features. We have shown that perfusion bioreactor-based 3D differentiation of iPSC-derived human neural stem cells (hiPSC-NSC) sustains the concomitant differentiation of the three neural cell lineages (pR-neurospheroid). Here, we hypothesized that if the pR-neurospheroid strategy would also allow deposition of native neural ECM, it would be possible to (i) mimic cellular and microenvironment remodeling occurring during neural differentiation, without the confounding effects of exogenous matrices and (ii) recapitulate pathological phenotypic features of diseases in which alterations in homotypic/ heterotypic cell-cell interactions and ECM are relevant. Quantitative transcriptome (NGS) and proteome (SWATH-MS) analysis showed that neurogenic developmental pathways were recapitulated in our system, with significant changes in cell membrane and ECM composition, diverging from 2D differentiation. We observed a significant enrichment in structural proteoglycans typical of brain ECM, such as neurocan,

versican, brevican and tenascin C, a downregulation of basement membrane constituents (e.g., laminins, collagens and fibrillins) and higher expression of synaptic and ion transport machinery. pR-neurospheroids were generated using hiPSC-NSC derived from Mucopolysaccharidosis type VII (MPS VII) patient. MPS VII is a neuronopathic lysosomal storage disease caused by deficient β -glucuronidase (β -gluc) activity, leading to glycosaminoglycan (GAGs) accumulation in the brain. The main MPS VII molecular hallmarks were recapitulated, e.g., accumulation of GAGs. MPS VII pR-neurospheroids showed reduced neuronal activity and disturbance in network functionality, with alterations in connectivity and synchronization, not observed in 2D cultures. These data provide insight into the interplay between reduced β -gluc activity, GAG accumulation, alterations in the neural network, and its impact on MPS VII-associated cognitive defects.

Funding Source: SFRH/BD:/78308/2011;/52202/2013;/52473/2014, FCT, Portugal and iNOVA4Health-UID/Multi/04462/2013, FCT/ MEC, Portugal.

THURSDAY, 21 JUNE, 13:15 – 15:15

CONCURRENT IC: CARDIAC DEVELOPMENT AND DISEASE

Room 219/220, Level 2

13:20 – 13:45

CARDIAC MICROTISSUES FROM HPSC IN MODELLING CARDIOVASCULAR DISEASE

Mummery, Christine, Bellin, Milena, Giacomelli, Elisa, van Meer, Berend, Orlova, Valeria, Sala, Luca and Tertoolen, Leon

Leiden University Medical Center, Leiden, Netherlands

Derivation of cardiovascular cell types from human pluripotent stem cells derived from patients or introducing targeted mutations is an area of growing interest as a platform for drug discovery and toxicity. Our lab has been investigating organs on chip and microtissue solutions in which cardiomyocytes and cardiac vascular and stromal cells are present. This promotes cardiomyocyte maturation and in combination with new methods for functional phenotyping, we have been able to quantify the outcomes of drug and disease mutation responses in situ. The use of isogenic pairs has proven very important since variability between “healthy control” hiPSC lines is often greater than the difference between a diseased cells and its isogenic control. hiPSC derived cardiomyocytes with mutations in ion channels and other genes can accurately predict changes in cardiac electrical properties and reveal drug sensitivities also observed in patients.

13:45 – 14:00

PATIENT DERIVED-IPS CELLS IDENTIFY A NOVEL PROTECTIVE FACTOR AGAINST ATHEROSCLEROSIS

Toyohara, Takafumi¹, Roudnicky, Filip², Florido, Mary¹, Nakano, Toshiaki³, Ptaszek, Leon⁴, Yu, Haojie¹, Lee, Minjin⁵, Friesen, Max¹, Davidow, Lance⁵, Rubin, Lee⁵, Pereira, Alexandre⁶, Aikawa, Masanori³ and Cowan, Chad¹

¹Beth Israel Deaconess Medical Center, Boston, MA, U.S., ²Roche pRED (Pharmaceutical Research and Early Development), Basel, Switzerland, ³Center for Interdisciplinary Cardiovascular Sciences, Cardiovascular Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, U.S., ⁴Cardiac Arrhythmia Service, MGH Heart Center, Massachusetts General Hospital, Boston, MA, U.S., ⁵Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, U.S., ⁶Laboratory of Genetics and Molecular Cardiology, Heart Institute, University of São Paulo Medical School, Brazil

Cardiovascular disease (CVD) is the most common cause of death in patients with type II diabetes mellitus (T2DM). Susceptibility to CVD varies, and some T2DM patients appear protected from CVD. The mechanism for this protective effect has not been clarified. We propose to study this protective phenotype with patient-derived induced pluripotent stem cells (iPSCs), which can be used to model CVD in a dish and shed light on the underlying mechanisms. To this end we have generated iPSCs from T2DM patients with or without CVD, and subsequently differentiated these into human endothelial cells (ECs) as well as vascular smooth muscle cells (VSMCs). In comparing the gene expression profiles in the ECs and the VSMCs, we found an esterase, arylacetamide deacetylase (AADAC) increased significantly in VSMCs derived from T2DM patients without CVD. To investigate the function of AADAC, we overexpressed AADAC in human primary and human iPSC-derived VSMCs. AADAC overexpression reduced the number of lipid droplets per cell significantly. Cellular migration, proliferation and apoptosis were also significantly decreased with higher levels of AADAC. We attempted to validate these findings in a murine model by generating VSMC-specific AADAC overexpressing mice on an apolipoprotein E (ApoE) knockout background. Mice with increased AADAC showed dramatically ameliorated atherosclerotic lesions in their aorta compared to non-overexpressing ApoE mice. Murine VSMCs isolated from mice overexpressing AADAC displayed a phenotype of decreased lipid droplets, cell migration, proliferation and apoptosis, all of which are consistent with our human data. Our findings suggest that AADAC protects T2DM patients from CVD by upregulating lipid metabolism, reducing migration, proliferation and apoptosis thereby protecting VSMCs from atherogenic phenotypes. Our data indicate that iPSCs are a robust tool to interrogate a patient's clinical status, and that we can identify CVD-protective mechanisms by leveraging this technology. Taking

advantage of protective mechanisms such as the one established in this study is of paramount importance to combat the ongoing CVD global epidemic. We believe this avenue of research into AADAC has tremendous future therapeutic potential.

14:00 – 14:15

PROFILING PROLIFERATIVE CELLS AND THEIR PROGENY IN DAMAGED MURINE HEARTS

Kretzschmar, Kai¹, Post, Yorick¹, Bannier-Hélaouët, Marie¹, Mattiotti, Andrea², Drost, Jarno³, Basak, Onur⁴, van den Born, Maïke¹, Gunst, Quinn², Versteeg, Danielle¹, Kooijman, Lieneke¹, van der Elst, Stefan¹, Li, Vivian⁵, van Es, Johan¹, van Rooij, Eva¹, van den Hoff, Maurice² and Clevers, Hans¹

¹Hubrecht Institute, Utrecht, Netherlands, ²Academic Medical Centre Amsterdam, Netherlands, ³Princess Maxima Centre for Paediatric Oncology, Utrecht, Netherlands, ⁴University Medical Centre Utrecht, Netherlands, ⁵The Francis Crick Institute, London, Netherlands

The capacity of the adult mammalian heart to functionally regenerate upon injury remains controversial. Different cardiac stem cell (CSC) populations have been reported to contribute to tissue renewal after insult, yet their functional significance for myocardial regeneration remains disputed. Furthermore, the proliferative capacity of resident non-cardiomyocyte cell lineages has been largely neglected. Here we perform single-cell messenger RNA sequencing and genetic lineage tracing using two Ki67 knock-in mouse models that allow sorting and unbiased mapping of proliferating cells and their progeny in homeostatic and regenerating murine hearts. We find that cardiomyocyte proliferation is largely restricted to the early postnatal growth phase, while non-cardiomyocyte cardiac cell lineages actively cycle also in the homeostatic and damaged adult myocardium. Proliferative post-damage fibroblasts display a gene-expression pattern similar to that of neonatal cardiac fibroblasts, while no significant numbers of cardiomyocytes re-enter the cell cycle upon damage. We find follistatin-like 1 (Fstl1), previously described as a cardiomyogenic factor of epicardial origin, to be specific to cardiac fibroblasts and to be strongly induced upon cardiac injury. Genetic lineage tracing from the Fstl1 locus reveals that these fibroblasts generate the fibrotic scar tissue, yet do not transdifferentiate into cardiomyocytes. Genetic deletion of Fstl1 in cardiac fibroblasts results in a severe phenotype with high mortality due to cardiac rupture upon cardiac injury. In sum, we find no evidence for the existence of a quiescent CSC population, for transdifferentiation towards cardiomyocytes, or for significant numbers of cardiomyocytes that can re-enter the cell cycle in response to cardiac injury and contribute to the myocardial lineage. However, resident cardiac fibroblasts that proliferate upon myocardial infarction are critical to maintain post-damage tissue integrity, as they generate a fibrotic scar to prevent cardiac rupture.

14:15 - 14:30

NEW STRATEGIES FOR ACCELERATING CARDIAC REGENERATION

Rosenthal, Nadia A.

The Jackson Laboratory, Bar Harbor, ME, U.S.

Regeneration in vertebrates is an evolutionary variable that hinges on the rapid transition from wound healing to restoration of organ form and function after tissue damage. Analysis of regenerative capacity in an unbiased screen of genetically defined recombinant inbred mouse panels has yielded dramatic intra-species variation, with distinct gene networks underlying the repair of heart, muscle and skin. Using combination of genetic manipulation and pharmacological blockades we have shown how modifying the profile of immune cell infiltration can facilitate or prevent cardiac repair, revealing that diversity in regenerative capacity is dependent on immune composition and response, and uncovering immune tolerance as a critical component of the regeneration process, suggesting new cell targets for clinical intervention. The diverse regenerative capacity of adult mammalian organs is also reflected in the tissue-specific composition and transcriptomic profiles of resident immune cell subsets and the stromal cells with which they interact, highlighting the potential for more genetically precise, organ-specific treatments of degenerative diseases.

14:30 - 14:45

THE TRANSCRIPTIONAL LANDSCAPE OF CARDIAC DIFFERENTIATION AT SINGLE CELL RESOLUTION

Palpant, Nathan¹, Friedman, Clayton², Nguyen, Quan², Lukowski, Samuel², Helfer, Abbigail², Chiu, Han², Voges, Holly², Baillie, Greg², Senabouth, Anne², Christ, Angelika², Bruxner, Timothy², Murry, Charles³, Wong, Emily², Ding, Jun⁴, Wang, Yuliang³, Hudson, James², Bar-Joseph, Ziv⁴, Tam, Patrick⁵ and Powell, Joseph²

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Differentiation into diverse cell lineages requires the orchestration of gene regulatory networks guiding diverse cell fate choices. Utilizing human pluripotent stem cells, we measured expression dynamics of 17,718 genes from 43,168 cells across five time points over a thirty day time-course of in vitro cardiac-directed differentiation. We used unsupervised clustering to identify transcriptional networks underlying lineage derivation of 15 subpopulations including mesoderm, definitive endoderm, vascular endothelium, cardiac precursors, and definitive cardiac fates including contractile cardiomyocytes and non-contractile derivatives. Utilizing customized machine learning algorithms, we analyzed scRNA-seq data to identify tran-

scription factor regulatory networks linking the trajectory of subpopulations in vitro with cell types derived during cardiac development in vivo. We leveraged this data to study gene networks governing cardiomyocyte differentiation in vivo to advance translational applications of stem cells in disease modelling and therapies. Among a network of known genetic drivers of differentiation, we identified dysregulation of the non-DNA binding homeodomain protein, HOPX as a candidate cause for the immature state of in vitro derived cardiomyocytes. Utilizing genetic approaches coupled with engineered heart tissues, we determined that HOPX is functionally required for molecular and physiological cardiac maturation in vitro. While HOPX is expressed in cardiac progenitor cells (CPC) in vivo, we show during in vitro differentiation that HOPX has a repressive chromatin state in day 5 CPCs with delayed onset of expression in only 16% of day 30 definitive hPSC-derived cardiomyocytes. To recapitulate in vivo development, we screened for mechanisms promoting HOPX expression in CPCs compared to small molecule differentiation alone. Our results identified mechanisms driving hypertrophy in CPCs as essential for HOPX expression and gene networks associated with cardiomyocyte maturation. Taken together, we utilized single cell analysis of cardiac in vitro differentiation to identify mechanisms for activating gene networks in CPCs as they occur during in vivo heart development. These findings will facilitate the utility of hPSCs for cardiac translational applications.

Funding Source: This work was supported by the Australian Research Council (SR1101002).

14:45 - 15:10

CARDIAC DEVELOPMENT: BASIS FOR DISEASE AND REGENERATION

Srivastava, Deepak

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Heart disease is a leading cause of death in adults and children. We, and others, have described complex signaling, transcriptional and translational networks that guide early differentiation of cardiac progenitors and later morphogenetic events during cardiogenesis. By leveraging these networks, we have reprogrammed disease-specific human cells in order to model genetically defined human heart disease in patients carrying mutations in cardiac developmental genes. These studies revealed mechanisms of haploinsufficiency and we now demonstrate the contribution of genetic variants inherited in an oligogenic fashion in congenital heart disease. We also utilized a combination of major cardiac developmental regulatory factors to induce direct reprogramming of resident cardiac fibroblasts into cardiomyocyte-like cells with global gene expression and electrical activity similar to cardiomyocytes, and now have revealed the epigenetic mechanisms underlying the cell fate switch. Most recently, we identified an approach to unlock the cell cycle in adult cardiomyocytes by introducing fetal cyclins and cyclin dependent kinases, and have been able to induce resident, post-mitotic cardiomyocytes to undergo cell division efficiently enough to regenerate damaged myocardium. Knowledge regarding

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the early steps of cardiac differentiation in vivo has led to effective strategies to generate necessary cardiac cell types for disease-modeling and regenerative approaches, and may lead to new strategies for human heart disease.

THURSDAY, 21 JUNE, 13:15 - 15:15

CONCURRENT ID: EPITHELIAL STEM CELLS

Room 212/213, Level 2

13:20 - 13:45

LET'S TALK ABOUT STROMA: ADIPOCYTES AND FIBROBLASTS IN TISSUE REGENERATION AND REMODELING

Horsley, Valerie, Shook, Brett and Zwick, Rachel
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Multiple stromal cell types support the homeostasis and regeneration of epithelial tissues. However, the function and heterogeneity of mesenchymal cells in epithelial tissues is not well understood. Here, we examined the contribution of mesenchymal cells and mature adipocytes to the regeneration of epithelial tissues using mouse skin wound healing and mammary gland lactation as model systems. Activated mesenchymal cells generate myofibroblasts that produce extracellular matrix (ECM) molecules for tissue resilience and strength and can produce excessive ECM during fibrotic disorders. Using extensive analysis of pro-fibrotic cells during mouse skin wound healing, fibrosis and aging; we identify three major functionally distinct subpopulations of myofibroblasts. Our findings identify multiple populations of fibrotic cells and suggest the pro-fibrotic environment dictates functional myofibroblast heterogeneity; which is driven by fibroblast-immune cell interactions after wounding. In the mammary gland, stromal adipocytes rapidly repopulate the stroma as the epithelial cells regress during involution of epithelial cells following lactation. Using genetic lineage tracing, lipid tracking, and lipidomics, we show that during involution, mature adipocytes undergo hypertrophy to regenerate the stromal MG adipose depot by filling with milk lipid trafficked from epithelial lumen. We find that milk lipid are recycled into adipocytes after lactation, facilitating the epithelial regression and stromal remodeling that occurs during MG involution. Furthermore, we developed a unique tissue and cell type-specific method to ablate MG adipocytes after lactation and demonstrate that in the MG, mature adipocytes are necessary for lipid uptake into epithelial cells and proper epithelial alveolar regression during involution. Our work has profound implications for our understanding of tissue regeneration and remodeling and the contribution of the stroma to these processes.

13:45 - 14:00

BEYOND GOOSEBUMPS: INTERACTIONS BETWEEN THE HAIR FOLLICLE, THE ARRECTOR PILI MUSCLE, AND THE SYMPATHETIC NERVE DURING DEVELOPMENT AND HAIR FOLLICLE REGENERATION

Hsu, Ya-Chieh¹, Schwartz, Yulia², Gonzalez Celeiro, Meryem², Chen, Jyhlong³ and Lin, Sung-Jan³

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Piloerection, commonly known as goosebumps, involves three interconnected cell types: the hair follicle, the arrector pili muscle (APM), and the sympathetic nerve. The interactions between these three cell types during development and adult tissue maintenance remains poorly understood. Here, we identify a central role of the developing hair follicle in regulating the formation of APMs, which then attract sympathetic innervation to the hair follicle stem cells. Although dispensable for hair follicle development, impulses from the sympathetic nerves are crucial for regulating hair follicle stem cell activity during hair follicle regeneration. Formation of the APMs requires Sonic Hedgehog secreted from the developing hair follicles. Once developed, APMs do not undergo turnover, providing a stable anchor that maintains sympathetic innervations to the hair follicle stem cells. APM ablation leads to concurrent loss of sympathetic nerve innervation to the hair follicles. Our results uncover a novel function of APM in bridging the body's sympathetic modulations to influence hair follicle stem cell activity, and illustrate an example for how a developing tissue regulates the establishment of the niche to modulate its regeneration in adulthood. Our results may also explain why hair loss is a common side effect of beta-blockers, which suppress the sympathetic tones, and why loss of APMs is commonly associated with permanent hair loss conditions such as in androgenic alopecia.

14:00 - 14:15

AN EVOLUTIONARILY CONSERVED RIBOSOME-RESCUE PATHWAY MAINTAINS MOUSE EPIDERMAL STEM CELL HOMEOSTASIS

Liakath-Ali, Kif¹, Mills, Eric², Sequeira, Inês¹, Lichtenberger, Beate¹, Pisco, Angela Oliveira¹, Sipilä, Kalle¹, Mishra, Ajay¹, Yoshikawa, Harunori³, Wu, Colin Chih-Chien², Ly, Tony³, Lamond, Angus³, Adham, Ibrahim⁴, Green, Rachel² and Watt, Fiona¹

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Ribosome-associated mRNA quality control mechanisms ensure fidelity of protein translation. Although extensively studied in yeast, little is known about their role in mam-

malian tissues, despite emerging evidence that stem cell fate is controlled by translational mechanisms. One evolutionarily conserved component of the quality control machinery, Dom34/Pelota (Pelo), rescues stalled ribosomes. Here we show that Pelo is required for mammalian epidermal homeostasis. Conditional deletion of Pelo in those murine epidermal stem cells that express Lrig1 results in hyperproliferation and abnormal differentiation. In contrast, deletion in Lgr5+ stem cells has no effect and deletion in Lgr6+ stem cells has only a mild phenotype. Loss of Pelo results in accumulation of short ribosome footprints and global upregulation of translation rather than affecting expression of specific genes. Translational inhibition by rapamycin-mediated down regulation of mTOR rescues the epidermal phenotype. Our study reveals a novel role for the ribosome-rescue machinery in mammalian tissue homeostasis and an unanticipated specificity in its impact on different stem cell populations.

14:15 - 14:30

ACTIVATION OF NEUREGULIN1/ERBB SIGNALLING PROMOTES INTESTINAL STEM CELL PROLIFERATION AND IMPROVES TISSUE REGENERATION FOLLOWING DAMAGE

Jarde, Thierry¹, Rossello, Fernando², Kurian Arackal, Teni², Flores, Tracey², Giraud, Megane², Prasko, Mirsada², Nefzger, Christian², Abe, Shin-ichi³, Polo, Jose² and Abud, Helen²

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Defining signals that regulate intestinal stem cells (ISCs) may enable stem cell pools to be manipulated in degenerative diseases and intestinal pathologies. The Neuregulin1/ErbB signalling pathway plays a pivotal role in regulating aspects of tissue homeostasis and regeneration in the nervous system. However, the function of this pathway in the intestinal epithelium is currently unknown. We examined the expression of Nrg1 and its receptors in the small intestine using immunofluorescence and qRT-PCR. We observed that supporting niche cells express Nrg1, while ISCs express ErbB receptors, suggesting that Nrg1/ErbB signalling may directly regulate ISCs. To investigate the functional activity of Nrg1 in the intestine, 12 week-old mice were injected with 15ug Nrg1 for 5 days. Activation of Nrg1/ErbB signalling increased cell proliferation in the intestinal crypts by 43% and caused alterations in cellular differentiation. The requirement for Nrg1 was assessed by inducing loss of Nrg1 in transgenic mice. Loss of Nrg1 resulted in a significant decrease in cell proliferation within crypts in both ISCs and progenitor cells. To characterise the molecular changes induced by Nrg1 signalling in ISCs, RNA sequencing was performed on ISC and progenitor cell populations isolated from Nrg1-treated and control animals. Nrg1 treatment produced a proliferative molecular signature in both cell types. Importantly, the ISC population became more homogeneous and expressed higher

levels of stem cell markers. The potential role of Nrg1/ErbB signalling during tissue regeneration was investigated using two mouse models of injury/regeneration (irradiation and 5-FU treatment). Interestingly, the expression of Nrg1 in both models was elevated 5-10 fold during the intestinal regenerative phase. This was reinforced by using in vitro organoids where Nrg1 significantly promoted organoid growth and the formation of colonies from single ISCs. Importantly, the intestinal regenerative response following damage was significantly improved when mice were treated with Nrg1. Taken together, our results demonstrate that Nrg1 is a crucial niche signal that regulates ISC proliferation. Manipulating the Nrg1/ErbB signalling pathway during intestinal tissue regeneration has potential therapeutic applications.

Funding Source: This work is supported by an National Health and Medical Research Council project grant and a Monash University Strategic grant.

14:30 - 14:45

ELUCIDATING THE RADIATION RESISTANCE MECHANISMS IN THE REGENERATIVE MOUSE INTESTINE USING SINGLE CELL RNA SEQUENCING

Ayyaz, Arshad¹, Kumar, Sandeep¹, Ghoshal, Bibaswan¹, Trcka, Daniel¹, Gregorieff, Alex² and L. Wrana, Jeffrey¹

¹Lunenfeld-Tanenbaum Research Institute, Toronto, ON, Canada, ²McGill University, Montreal, PQ, Canada

The intestinal epithelium completely turns over every week in mice and every 2-3 weeks in humans. The multipotent Lgr5+ crypt base columnar (CBC) cells are responsible for constantly replenishing the epithelium with fresh cells under homeostatic conditions throughout the animals' life span. However, in response to injury, such as ionizing radiation (IR), the majority of Lgr5+ cells are lost, but then re-emerge post-IR and are indispensable for a successful recovery. It remains unclear how these resilient Lgr5+ stem cells are generated. To investigate their population dynamics at the single cell level, we performed single cell RNA sequencing on 4500 cells isolated from the mouse small intestine without or after 3 days whole body IR exposure. Unsupervised clustering classified differentiated cell types into separate groups that could be identified by the expression of their corresponding lineage markers. In response to IR we found significant changes in the cellular composition of the intestine that included depletion of about 75% of Paneth cells, 50% of Tuft cells and 30% of Goblet cells, with a concomitant increase in the proportion of enterocytes (ECs) and enteroendocrine (EE) cells. We also observed a loss of 90% of Lgr5+ cells and in particular Lgr5high cells were undetectable after 3 days post-IR. To enrich for stem cells, we next repeated this strategy on isolated crypts, which led to a 2.1-fold enrichment of Lgr5+ cells under homeostatic conditions, whereas the number of Lgr5high cells in IR-treated samples remained negligible (2 of 4500 cells). Intriguingly, unsupervised clustering of crypt cells revealed a cell population that displayed heterogeneous expression of stem

cell markers and could be divided by low or high expression of proliferative markers. We called these two classes the 'revival' and 'proliferative' groups. The revival stem cell compartment was composed of slowly cycling cells and was marked by YAP target gene expression, while the proliferative compartment expressed high levels of CBC markers. We propose that damage to the intestine leads to the emergence of a distinct regenerative stem cell that reconstitutes the homeostatic Lgr5 compartment.

Funding Source: Canadian Institutes of Health Research (CIHR). Terry Fox Research Institute. University of Toronto's Medicine by Design which receives funding from the Canada First Research Excellence Fund (CFREF).

14:45 - 15:10

REGULATION OF EPIDERMAL STEM CELL FATE BY NICHE-DERIVED SIGNALS AND FORCES

Wickström, Sara

Max Planck Institute for Biology of Ageing, Cologne, Germany

Our research aims to uncover how complex but stereotyped tissues are formed, maintained and regenerated through local growth, differentiation and remodeling. To decipher this fundamental question we need to understand how single cell behaviors are coordinated on the population level and how population-level dynamics is coupled to tissue architecture. Uncovering these regulatory principles will further facilitate development of stem cell (SC) therapies and effective treatments against cancers. As a self-renewing organ maintained by distinct stem cell populations, the epidermis represents an outstanding, clinically highly relevant research paradigm to address these questions. We apply mouse genetics and molecular cell biology, combined with state-of-the art biological imaging, biophysics, biochemistry and theoretical approaches to study stem regulation and tissue homeostasis/aging in this system. In my presentation I will discuss our recent research on stem cell-niche interactions in cell fate decisions and plasticity, and the role of mechanical forces in these processes.

THURSDAY, 21 JUNE, 13:15 - 15:15

CONCURRENT IE: HOMEOSTASIS, METABOLISM AND AGING

Room 203/204, Level 2

13:20 - 13:45

AWAKENING STEM CELLS IN THE BRAIN

Brand, Andrea and Otsuki, Leo

University of Cambridge, U.K.

The systemic regulation of stem cells ensures they meet the needs of the organism during growth and in response

to injury. A key control point is the decision between quiescence and proliferation. *Drosophila* neural stem cells (NSCs) enter quiescence in late embryogenesis and are reactivated post-embryonically in response to a nutrition-dependent signal from the fat body. The fat body performs many of the storage and endocrine functions of the vertebrate liver and adipose tissue and acts as a sensor, coupling nutritional state to organismal growth. We showed that the nutritional stimulus transduced by the fat body induces the expression of insulin/IGF-like peptides (dILPs) in the blood brain barrier glia, which overlie the quiescent stem cells. We found that insulin signalling is essential for NSCs to exit quiescence. Insulin signalling can also promote proliferation in vertebrate neural stem cells, suggesting that the mechanisms controlling stem cell reactivation may be conserved. We are investigating the systemic and local signals that regulate neural stem cell quiescence and reactivation.

13:45 - 14:00

EPIGENETIC REGULATION OF LIPID METABOLISM IN NEURAL STEM CELL FATE DECISION

Syal, Charvi¹, Sarma, Sailendra Nath², Seegobin, Matthew², Thomas, Jacob³ and Wang, Jing²

¹*Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada,* ²*Ottawa Hospital Research Institute, Ottawa, ON, Canada,* ³*University of Western Ontario, London, ON, Canada*

Lipids, often considered little more than structural components of a cell, have recently been identified as prominent regulators of neural stem and progenitor cell (NPC) function, under both physiological and pathological conditions. However, our knowledge of molecular aspects of regulation of lipid metabolism and its specific role in determination of NPC function is lacking. Previously, we identified that the atypical protein kinase C (aPKC)-mediated phosphorylation of CBP (CREB binding protein) at Ser436, activated by age-related intrinsic signals and metformin stimulation, was able to promote neuronal differentiation of adult NPCs. We have now identified monoglyceride lipase (Mgll) as the direct target of this pathway, wherein an active aPKC-CBP pathway represses Mgll expression in adult NPCs to promote their differentiation. Mgll, an enzyme that hydrolyses the endocannabinoid, 2-arachidonoyl glycerol (2-AG) to produce arachidonic acid (ARA), is thus, a key regulator of two critical lipid components in the brain as well as a potential modulator of NPC function. We observed elevated Mgll levels, concomitant with neuronal differentiation deficits in NPCs isolated from sub-ventricular zone of transgenic CBP-S436A mice, that lack a functional aPKC-CBP pathway. Genetic knockdown of Mgll in these CBP-S436A NPCs rescued their differentiation defects. In addition, we found that CBP-S436A NPCs exhibit enhanced proliferation at the expense of differentiation as an outcome of increased Mgll levels, implicating Mgll as a dynamic switch that regulates NPC function by altering lipid composition (2-AG versus ARA). Interestingly, we also found that NPCs from

an Alzheimer's disease (AD) model, the 3xTg mice, closely mimic CBPS436A NPC behaviour in vitro. 3xTg NPCs exhibit attenuation of the aPKC-CBP pathway, which is associated with elevated Mgl1 expression and increased NPC proliferation at the expense of differentiation in culture, similar to CBPS436A NPCs. Reactivation of the aPKC-CBP-Mgl1 pathway in these AD NPCs mitigates their differentiation deficits. These findings thus suggest that attenuation of aPKC-CBP mediated Mgl1 repression results in neuronal differentiation deficits in NPCs, contributing to AD predisposition.

Funding Source: Natural Sciences and Engineering Research Council of Canada (NSERC); Scottish Rite Charitable Foundation of Canada.

14:00 - 14:15

CONTROL OF PLURIPOTENT STEM CELL FATE DECISIONS BY METABOLIC FLUX

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¹Center for Molecular Medicine, University of Georgia, Athens, GA, U.S., ²University of Georgia, Athens, GA, U.S.

As human pluripotent stem cells (hPSCs) exit pluripotency they are thought to switch from a glycolytic mode of energy generation to one more dependent on oxidative phosphorylation. In this presentation, we show that although metabolic switching occurs during early mesoderm and endoderm differentiation, elevated glycolytic flux is maintained and essential during early ectoderm specification. Metabolic switching is therefore not an obligatory event required for exit from pluripotency. Elevated glycolysis is required for self-renewal of hPSCs and requires elevated MYC/MYCN activity. In endoderm and mesoderm, decreased MYC/MYCN transcriptional activity coincides with metabolic switching, but this is reversed by ectopically restoring MYC activity. MYC activity is therefore necessary and sufficient for metabolic switching. In nascent ectoderm, sustained MYCN activity maintains the transcription of 'switch' genes that are rate-limiting for metabolic activity and lineage commitment. This study identifies MYC and MYCN as developmental regulators that couple metabolism to pluripotency and cell fate determination. This general mechanism is likely to have direct implications for MYCs role in reprogramming to the pluripotent state.

14:15 - 14:30

SIRT1 ENHANCES THE SURVIVAL OF HUMAN EMBRYONIC STEM CELLS BY PROMOTING DNA REPAIR

Kim, Dong-Wook

Department of Physiology, Yonsei University College of Medicine, Seoul, Korea

Human embryonic stem cells (hESCs) hold great promise for the treatment of many currently incurable diseases through cell replacement therapy. Sirtuin1 (SIRT1), an NA-

D⁺-dependent class III histone deacetylase, is abundantly expressed in hESCs and has been reported to play a role in regulating early differentiation and telomere elongation. We found that blocking the function of SIRT1 in hESCs induced massive cell death, thus leading us to hypothesize that SIRT1 is required for hESC survival. Either blocking the function or decreasing the level of SIRT1 dramatically promoted cell death in hESCs, but not in differentiated cells such as fibroblasts. SIRT1 inhibition-mediated cell death was preceded by increased DNA damage. Our detailed mechanistic study showed that the increased DNA damage caused by SIRT1 down-regulation was at least partially due to decreased levels of DNA repair enzymes such as MSH2, MSH6, and APEX1. Furthermore, we observed p53 activation followed by the overexpression of PUMA and BAX, two pro-apoptotic p53 target genes, after SIRT1 inhibition. Owing to these events, apoptotic cell death was induced in hESCs in the absence of SIRT1, thus suggesting that SIRT1 acts as a guardian of pluripotent stem cells. Together, our results demonstrated that SIRT1 is required to maintain a high level of the DNA repair proteins MSH2, MSH6, and APEX1 and to prevent massive hESC death. This study provides valuable insights into the mechanism of SIRT1-mediated hESC survival and should contribute to the development of safe and effective cell replacement therapies.

Funding Source: This research was supported by the Bio and Medical Technology Development Program of the NRF funded by the Korean government, MSIT(2017M3A9B4042580).

14:30 - 14:45

FUNCTIONAL REJUVENATION OF AGED INTESTINAL STEM CELLS BY METABOLIC INTERVENTION AND DIRECT REPROGRAMMING

Nefzger, Christian M.¹, Jarde, Thierry¹, Horvay, Katja¹, Rossello, Fernando¹, Srivastava, Akanksha², Prasko, Mirsada¹, Paynter, Jacob¹, Sun, Yu¹, Liu, Xiaodong¹, Chan, Eva¹, Li, Jinhua¹, Pflueger, Jahnviz², Knaupp, Anja¹, Nilsson, Susan³, Rackham, Owen⁴, Lister, Ryan², Abud, Helen¹ and Polo, Jose¹

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Intestinal stem cells (ISCs) drive epithelial homeostasis and regeneration following damage and these processes are impaired with age, however the exact reason of this decline is unknown. In order to uncover the underlying mechanism for functional differences in aged stem cells we determined the molecular and functional changes occurring in the ISC niche during the aging process. We found widespread transcriptional changes associated with reduced Wnt signalling and decreased metabolic activity. Importantly, we show that elevation of Wnt signalling only

partially rescued ISC defects. However, metabolic intervention restored Wnt signaling state, transcriptional signature and organoid formation frequency to levels found in young animals. Furthermore, we identified key drivers of an “aged” transcriptional network and demonstrated that forced expression of these factors in organoids derived from aged stem cells rescued their regenerative defects and re-established metabolic potential. Our data demonstrate that different molecular changes associated with aging stem cells can be efficiently reversed, which has implications for aging intervention strategies. Collectively, we anticipate that our findings will open the door for future clinical applications in improving regeneration of the gastrointestinal tract.

14:45 – 15:10

METABOLIC DETERMINATION OF CELL FATE THROUGH SELECTIVE INHERITANCE OF MITOCHONDRIA

Katajisto, Pekka, Dohla, Julia, Englund, Johanna, Amaral, Ana, Gebert, Nadja, Salminen, Ella, Gopalakrishnana, Swetha, Kakela, Reijo and Ori, Alessandro

University of Helsinki, Finland, and Karolinska Institutet, Helsinki, Sweden

In order to maintain homeostasis, tissue renewing adult stem cells are controlled by multiple mechanisms balancing self-renewal and differentiation. As fate changes in stem cells are paralleled by profound metabolic rewiring, cellular metabolism provides one possible level for such control. We have studied the role of cellular metabolism in the context of asymmetric cell divisions to address how metabolism is determined immediately after cell division, and whether asymmetric fate determination is controlled by metabolism. We have discovered that the chronological age of mitochondria inherited from the mother cell, determines daughter cell metabolism and fate upon asymmetric division in stem-like human mammary epithelial cells (HMECs). Old mitochondria are apportioned selectively to the differentiating daughter cell, while progeny omitting old mitochondria retains stem-like properties. Age-specific isolation and profiling of mitochondria revealed that protein and lipid composition, as well as organelle function, changes as mitochondria mature, and results in more active oxidative metabolism in old mitochondria. Upon asymmetric segregation, inherited mitochondrial metabolism prompts metabolic bias in daughter cells, and has the capacity to preserve stem-like properties or induce differentiation. Pharmacologic modulation immediately after cell division can mitigate the inherited metabolic bias and alter fate of daughter cells. Our results demonstrate that cell fate programs are susceptible to modulation by metabolism immediately after division of stem-like cells, and that the asymmetric apportioning of old mitochondria may be one of the first fate determinants in adult stem cell divisions.

THURSDAY, 21 JUNE, 16:00 – 18:00

CONCURRENT IIA: GENE EDITING

Melbourne Room 1, Level 2

Sponsored by The Allen Institute for Cell Science

16:05 – 16:30

GENE EDITING: OPTIMIZATION AND APPLICATION IN PRIMARY CELLS

Wang, Haoyi, Mu, Wei, Xiang, Guanghai and An, Chenrui

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CRISPR-Cas9 system has become the tool of choice for gene editing. To facilitate its application in primary cells, we optimized the sgRNA to improve its stability and reduce its immunogenicity. We enhanced the sgRNA stability by adding 5' cap and 3' polyA tail to in vitro transcribed (IVT) sgRNA (indicated as CTsgRNA). Using CTsgRNAs, we achieved significantly higher gene editing and activation efficiency in human cells compared to unmodified sgRNAs. In addition, we found that IVT sgRNAs induced type I interferon (IFN) release, which led to poor survival of human CD34+ HSPCs, CD3+ T cells and chimeric antigen receptor (CAR)-T cells. By treating the IVT sgRNA with calf intestine phosphatase (CIP), we were able to eliminate the IFN induction effect of IVT sgRNAs, and achieve significantly better cell survival without affecting gene editing efficiency. To improve the gene editing efficiency in human pluripotent stem cells, we compared the efficiency of introducing indels, precise point mutation, and transgene integration in primed human embryonic stem cell culture and three naïve culture systems. Naïve culture conditions in general had higher efficiency. 5i naïve system in particular had a more consistent improvement, with targeted transgene insertion efficiency reaching 20% without any selection.

16:30 – 16:45

ENDOGENOUS GENE TAGGING WITH CRISPR/CAS9 TO ILLUMINATE CELL ORGANIZATION AND DYNAMICS

Gunawardane, Ruwanthi

Allen Institute for Cell Science, Seattle, WA, U.S.

The Allen Institute for Cell Science is creating a dynamic visual model of hiPSC organization to understand and predict normal and pathological cell states. Towards this goal, we have created the “Allen Cell Collection”; an open source collection of fluorescently tagged human induced pluripotent stem cell (hiPSC) lines representing the major organelles of the cell. Our approach utilizes CRISPR/Cas9 to introduce fluorescent tags via homology driven repair (HDR) into the genomic locus of interest. Editing yields

isogenic hiPSC lines expressing fusion proteins unique to each cell line under endogenous regulation. Live cell imaging, image analysis, computational modeling, and open distribution of tools and data to the scientific community define our endeavor. Here we present the CRISPR/Cas9- based gene editing strategy and workflow used to generate ~25 GFP-tagged clonal hiPSC lines representing the major organelles of the cell including the nucleus, mitochondria, adhesions, cytoskeleton, golgi and ER. We have also developed related editing methods for introducing red fluorescent proteins, tagging dual structures, safe harbor edits, and differentiation specific gene tagging. We will describe our genotyping strategy to identify clones harboring precisely incorporated FP tags including off-target and NGS analysis and present trends observed during precise editing. Clonal lines also undergo various quality control assays for ensuring genomic stability, pluripotency, and confirmation of subcellular localization prior to use in live cell imaging and distribution. We will highlight the utility of these cell lines for generating image-based integrated models of cell organization and dynamics and discuss the potential applications of these endogenously tagged lines for basic science and disease modeling.

16:45 – 17:00

SELF-CLEAVING GUIDE RNAs FOR SELECTIVE EXPANSION OF PRECISELY GENE EDITED HEPATOCYTES IN VIVO

Grompe, Markus¹, Tiyaboonchai, Amita², Nygaard, Sean² and Vonada, Anne²

¹Papé Family Pediatric Research Institute, Oregon Health and Science University, Portland, OR, U.S.,

²Oregon Health and Science University, Portland, OR, U.S.

Transplantation of cells that have been manipulated by precise gene editing is an attractive approach for cell-based therapies, especially for genetic disorders. However, gene editing by homologous recombination is inherently inefficient. One strategy to achieve a higher overall efficiency of gene editing is to selectively expand cells that have acquired the desired targeting event in vivo after transplantation. This can be achieved by linking the wanted genetic modification to a selectable gene disruption cassette in cis, such that growth selection can happen only if proper gene targeting has been achieved. Using a factor 9 expressing Generide rAAV vector targeted to the albumin locus we previously showed that an shRNA embedded in a microRNA within an intron can protect hepatocytes from a hepatotoxic drug and result in high transgene levels. While this approach can work, shRNAs usually only knock down a gene by ~ 80-90%, thus limiting its utility for drug protection regimens. In contrast, complete gene knockouts can be achieved by CRISPR-cas9 cutting. In order to generate selectable CRISPR-mediated gene knockouts, it is necessary to restrict its endonuclease activity to only cells that have proper gene targeting. This strategy requires that the gRNA expression is driven by a tissue-specific pol2 promoter. Here we show

that flanking gRNAs with self-cleaving ribozymes permits proper processing of active gRNA from pol2 transcripts. In *Fah*^{-/-} mice, loss of *Hpd* or *Hgd*, genes upstream of *FAH* in tyrosine degradation, provides a selective advantage for hepatocytes. We observed strong in vivo selection of albuminF9 generide AAV vectors harboring self-cleaving gRNA (scgRNA) against *Hpd* and *Hgd*. Superphysiologic levels of human F9 were seen in *Fah*^{-/-} mice treated with these vectors and then taken off NTBC. In order to broaden this paradigm, we engineered a system that renders hepatocytes resistant to the hepatotoxic drug acetaminophen. A scgRNA designed to knock out NADPH-cytochrome P450 reductase (*Cypor*) was incorporated into the albumin-hF9 gene ride vector. Loss of *Cypor* prevents the conversion of acetaminophen into its toxic metabolite. Acetaminophen treatment resulted in the expansion of *Cypor* null hepatocytes to ~45% of the liver mass and therapeutic levels of human F9 expression.

17:00 – 17:15

IN VIVO SIMULTANEOUS TRANSCRIPTIONAL ACTIVATION OF MULTIPLE GENES IN THE BRAIN USING CRISPR-DCAS9-ACTIVATOR TRANSGENIC MICE

Zhou, Haibo¹, Liu, Junlai², Zhou, Changyang¹, Gao, Ni¹, Rao, Zhiping¹, Li, He¹, Hu, Xinde¹, Li, Changlin¹, Yao, Xuan¹, Shen, Xiaowen¹, Sun, Yidi³, Wei, Yu¹, Liu, Fei¹, Ying, Wenqin¹, Zhang, Junming¹, Tang, Cheng¹, Zhang, Xu¹, Xu, Huatai¹, Lin, Linyu¹, Cheng, Leping¹, Huang, Pengyu² and Yang, Hui¹

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Despite rapid progresses in the genome-editing field, in vivo simultaneous overexpression of multiple genes remains challenging. We generated a transgenic mouse using an improved dCas9 system that enables simultaneous and precise in vivo transcriptional activation of multiple genes and long noncoding RNAs in the nervous system. As proof of concept, we were able to use targeted activation of endogenous neurogenic genes in these transgenic mice to directly and efficiently convert astrocytes into functional neurons in vivo. This system provides a flexible and rapid screening platform for studying complex gene networks and gain-of-function phenotypes in the mammalian brain.

Funding Source: National Science and Technology Major Project, CAS Strategic; Priority Research Program, the MoST863 Program, NSFC grants, China Youth; Thousand Talents Program, Break through project of Chinese Academy of Sciences.

THURSDAY 21 JUNE 2018

17:15 - 17:30

FIRST-IN-HUMAN STUDY OF FEASIBILITY, SAFETY AND ENGRAFTMENT OF ZINC FINGER NUCLEASE CCR5-MODIFIED CD34+ HEMATOPOIETIC STEM/PROGENITOR CELLS IN HIV-1 (R5) INFECTED SUBJECTS

Stan, Rodica¹, Cardoso, Angelo¹, Krishnan, Amrita¹, Kim, Teresa¹, Torres-Coronado, Monica¹, Gardner, Agnes¹, Killion, Salena², Holmes, Michael², Lee, Gary², Greengard, Judy¹, Dubois-Stringfellow, Nathalie², Win, Sandra³, Pushkin, Richard³, Lalezari, Jay³, Mills, Anthony⁴, Mitsuyasu, Ronald⁵, Conner, Ed² and Zaia, John¹

¹City of Hope, Duarte, CA, U.S., ²Sangamo Therapeutics, Richmond, CA, U.S., ³Quest Clinical Research, San Francisco, CA, U.S., ⁴Mills Clinical Research, Los Angeles, CA, U.S., ⁵University of California, Los Angeles CARE Center, Los Angeles, CA, U.S.

We developed a novel therapeutic strategy for HIV-1 infection by engineering HIV-resistant immune cells via gene editing of autologous hematopoietic stem/progenitor cells (HSPC). A Zinc Finger Nuclease (ZFN) mRNA construct was designed to selectively disrupt the chemokine receptor 5 (CCR5), a co-factor required for HIV-1 infection of human cells, in HSPC. ZFN-CCR5-HSPC were manufactured and infused as an autologous "transplant" after busulfan conditioning. Preliminary results are now available from the ongoing safety/feasibility clinical trial (NCT02500849). R5-tropic HIV-1 infected subjects who were aviremic and had suboptimal CD4 counts (≥ 200) and ZFN-HSPC products were manufactured for 3 subjects in each cohort. The products had between $2.15E+06$ and $11.5E+06$ CD34+ cells/kg body weight. The median CCR5 disruption evaluated by MiSeq was 20% indels for the investigational products manufactured for Cohort 1 and 25% for Cohort 2. Median exposure to busulfan (AUC) was 9,340 Qmol*min in Cohort 1 and 12,773 Qmol*min in Cohort 2. All subjects received the anticipated number of busulfan doses, except one in Cohort 1, who metabolized busulfan slowly and achieved the target AUC with the test dose (3.2 mg/kg). Subjects in Cohort 1 engrafted by Day +15 (ANC ≥ 500 /Ql for 3 consecutive days), and those in Cohort 2 engrafted by Day +14. Only one subject had a platelet count below 20k/Ql (Cohort 2) at Day +11. The CD4 counts dropped significantly in all subjects post mobilization and collection, and then had a delayed recovery to the levels prior to mobilization. This is the first-in-human use of ZFN genome editing of HSPC, and preliminary data show that conditioning with busulfan and infusion of autologous CCR5-ZFN-modified HSPC are safe and well tolerated in HIV-infected subjects.

Funding Source: This study is funded through a strategic partnership between California Institute for Regenerative Medicine (CIRM), grant SP3A 07536, and Sangamo Therapeutics.

17:30 - 17:55

HUMAN DEVELOPMENT AND DISEASE THROUGH THE LENS OF PLURIPOTENT STEM CELLS

Huangfu, Danwei

Developmental Biology Program, Memorial Sloan Kettering Cancer Center, New York, NY, U.S.

My laboratory is interested in understanding pancreatic development and disease through applying genetic approaches in human pluripotent stem cells (hPSCs), including embryonic and induced pluripotent stem cells (hESCs and hiPSCs). Combining CRISPR/Cas-mediated gene editing and stem cell technologies, our reverse genetics approach has revealed the roles of key transcription factors pancreatic development and diabetes. Using the forward genetics approach, we performed a number of genome-wide knockout screens for identification of developmental regulators. We also applied both forward and reverse genetic approaches to our stem-cell based system for study of epigenetic mechanisms underlying lineage differentiation focusing on DNA methylation. Together our findings establish the use of hPSCs as a genetic model system for studying human disease and developmental mechanisms.

THURSDAY, 21 JUNE, 16:00 - 18:00

CONCURRENT IIB: NEURAL DEVELOPMENT

Melbourne Room 2, Level 2

16:05 - 16:30

REGULATION OF NEURAL STEM/PROGENITOR CELL FATE DURING 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 symmetrically to increase their pool size (expansion phase). They then divide asymmetrically and give rise to neuronal and glial cell types in a region- and developmental stage-dependent manner and with high precision (neurogenic and gliogenic phases, respectively). We have previously shown that Polycomb group (PcG) complex and high mobility group A (HMGA) proteins play pivotal roles in driving the fate switches of NSCs associated with the transition from the neurogenic phase to the gliogenic phase. At this meeting, we would like first to focus on how these and other proteins control the fate of NPCs. Second, we will address 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.

16:30 – 16:45

AKNA, A NEW CENTROSOMAL PROTEIN REGULATES EMT-LIKE FEATURES OF NEUROGENESIS BY MICROTUBULE ORGANIZATION

Camargo Ortega, Germán D.¹, Falk, Sven¹, Johansson, Pia¹, Peyre, Elise², Sahu, Sanjeeb³, Broix, Loic², De Juan Romero, Camino⁴, Draganova, Kalina¹, Vinopal, Stanislav⁵, Geerlof, Arie⁶, Feederle, Regina⁶, Shao, Wei⁷, Shi, Song-Hai⁷, Hauck, Stefanie⁶, Bradke, Frank⁵, Borrell, Victor⁴, Tiwari, Vijay⁸, Huttner, Wieland⁹, Wilsch-Braeuninger, Michaela⁹, Nguyen, Laurent² and Goetz, Magdalena¹

¹Helmholtz Zentrum Muenchen and University of Munich, Germany, ²University of Liege, Belgium, ³Institute of Molecular Biology, Mainz, Germany, ⁴Universidad Miguel Hernandez, Alicante, Spain, ⁵Center for Neurodegenerative Diseases, Bonn, Germany, ⁶Helmholtz Zentrum Muenchen, Munich, Germany, ⁷Memorial Sloan Kettering Cancer Center, New York, U.S., ⁸previously at Institute of Molecular Biology, Mainz, Germany, ⁹Max Planck Institute of Molecular Cell Biology and Genetics, Dresden, Germany

Understanding mechanisms regulating neural stem cell (NSC) homeostasis and their fate commitment is fundamental for their efficient manipulation and future use in regenerative medicine. Our laboratory interrogates pathways regulating NSC self-renewal or differentiation into transit-amplifying progenitor cells by genome-wide expression analysis of subsets of NSCs in the developing and adult brain. These studies have proven successful for the identification of novel regulators of neurogenesis and brain folding also key in direct neuronal reprogramming. Here we choose to examine the role of the putative AT-hook containing transcription factor Akna as we found it to have elevated mRNA expression in differentiating NSCs (generating transit-amplifying progenitors) while self-renewing NSCs have lower expression levels. We show that Akna is instead a novel bona fide centrosomal protein, mainly localizing at subdistal appendages of the mother centriole where it is necessary and sufficient to confer microtubule organizing activity via microtubule anchoring and to promote microtubule nucleation to the interphase centrosome. We show the importance of this process in the epithelial-mesenchymal transition (EMT)-like delamination of NSC subtypes thereby promoting cells to move towards the subventricular zone (SVZ) where transit-amplifying progenitors reside and remain there until Akna levels decrease again, concomitant with the loss of centrosomal MTOC activity in mature neurons. Together with a similar function in human cerebral organoids, our work demonstrates a novel mechanism regulating NSC maintenance versus differentiation, serving to expand

the SVZ and numbers of transit-amplifying progenitors in ontogeny and phylogeny. Furthermore, the role of Akna has broader relevance beyond the developing brain as it is necessary for dissociation of junctional complexes in other true epithelial cells undergoing EMT. Akna is required for mesenchymal transformation and thus, highlights the importance of centrosomal microtubule organization in other contexts of development and cancer.

16:45 – 17:00

MAKE DO AND MAKE NEW: HOW ZEBRAFISH RAPIDLY REGENERATES SPINAL CORD INJURY

Kaslin, Jan¹, Vandestadt, Celia², Castillo, Hozana², Khabooshan, Mitra², Li, Mei², Hamimi, Mustafa², Schulze, Keith³ and Anko, Minna-Iiisa²

¹Monash University, Australian Regenerative Medicine Institute, Melbourne, Australia, ²Australian Regenerative Medicine Institute, Melbourne, VIC, Australia, ³Monash Micro Imaging (MMI), Melbourne, Australia

Zebrafish have a remarkable capacity to regenerate following spinal cord injury. While many factors controlling neurogenesis have been identified, the cellular mechanisms regulating global neural regeneration are largely unknown. We used in vivo imaging to pin-point specific cells and signals that control spinal cord regeneration in zebrafish. Surprisingly, we identified two temporally and mechanistically distinct waves of cellular regeneration in the spinal cord. The initial wave of regeneration relying on cell migration of neural precursors to the lesion site, enabling rapid functional recovery, and the activation of quiescent neural stem and progenitor cells (NSCs). This is then followed by the second wave of regeneration which largely driven by regenerative neurogenesis. Neurogenesis compensates for both the loss of tissue at injury site as well as the cells depleted from proximal areas due to early migration. Furthermore, we find that inflammation and leukocytes play a critical role in differentially regulating cell recruitment and activation of NSCs after injury. The two waves of regeneration demonstrate how the zebrafish are able to rapidly regain motor function after complete ablation, but also gradually replenish lost tissue over time. Taken together, our data suggest that inflammation driven recruitment of neural precursors play an unanticipated role in neural repair.

Funding Source: This work was supported by a NHMRC project grant.

THURSDAY 21 JUNE 2018

17:00 - 17:15

NEW INSIGHTS ON HUMAN CORTICAL DEVELOPMENT AND MICROCEPHALY USING SINGLE ORGANOID AND SINGLE CELL RNASEQ

Elkabetz, Yechiel

Genome Regulation, Max Planck Institute for Molecular Genetics, Berlin, Germany

Methods for deriving cortical progenitors from PSCs are highly variable due to the immense complexity of cortical cell and identity and the lack of efficient readout for the desired cortical starting population. We generated organoids (3D) and rosettes (monolayers) and systematically compared inhibitor-free, dual SMAD inhibition, WNT inhibition and combined dual SMAD and WNT inhibition and performed extensive RNA-Seq for multiple, individually analyzed organoids and single cell RNA-Seq alongside comprehensive cellular and cytoarchitectural analysis for early and late derived cultures. PCA combined with enrichment analysis with human brain transcriptomic datasets reveals that dual SMAD inhibition promotes thalamic and midbrain/hindbrain fates, while combined dual SMAD and WNT inhibition exclusively specifies dorsal pallium progenitors that ultimately develop into the four lobes of the neocortex. On the other hand, the medial pallium (archicortex) that constitutes the cortical hem and that later develops into the hippocampus can be well induced by both treatments and also quite prominent transcriptionally in inhibitor-free derived organoids. Cortical deep and upper layer markers eventually appear in all derivation methods, due to their expression in non-cortical areas in vivo - proving them problematic for demonstrating cortical fate. Nonetheless, only under combined inhibition, cortical layers including the important CUX2 upper layer marker appears homogeneous. We show that only neocortical progenitors (derived by combined inhibition) demonstrate early enhanced Notch activation and robust ability to radially organize, and propose that these two features - when overlapping - serve well as an efficient readout for successful transition towards neocortical, but not more posterior brain starting populations. Strikingly, organoids harboring microcephaly a centrosomal mutation displays specific loss of neocortical cells and massive apoptosis in these Notch active radially organized regions only if derived by exclusively under triple inhibition - demonstrating neocortex-specific cell death. Thus, combined inhibition is indispensable for standardized modeling of corticogenesis and demonstrating cortex-specific defects associated with microcephaly.

17:15 - 17:30

AN INTRINSIC MECHANISM CONTROLS REACTIVATION OF NEURAL STEM CELLS BY SPINDLE MATRIX PROTEINS

Wang, Hongyan

Duke-National University of Singapore (NUS) Medical School, Singapore

The switch between quiescence and proliferation is central for neurogenesis and its alteration is linked to neurodevelopmental disorders such as microcephaly. However, intrinsic mechanisms that reactivate *Drosophila* larval neural stem cells (NSCs) to exit from quiescence are not well established. Here we show that the spindle matrix complex containing Chromator (Chro) functions as a key intrinsic regulator of NSC reactivation downstream of extrinsic insulin/insulin-like growth factor signalling. Chro also prevents NSCs from re-entering quiescence at later stages. NSC-specific in vivo profiling has identified many downstream targets of Chro, including a temporal transcription factor Grainy head (Grh) and a neural stem cell quiescence-inducing factor Prospero (Pros). We show that spindle matrix proteins promote the expression of Grh and repress that of Pros in NSCs to govern their reactivation. Our data demonstrate that nuclear Chro critically regulates gene expression in NSCs at the transition from quiescence to proliferation.

17:30 - 17:55

USING PLURIPOTENT STEM CELLS TO DECIPHER HUMAN-SPECIFIC MECHANISMS OF BRAIN DEVELOPMENT

Vanderhaeghen, Pierre

University of Brussels ULB, Belgium

The cerebral cortex is the most complex structure in our brain, and has undergone major and rapid complexification during recent evolution, mostly related to increased neuronal number and connectivity. Pluripotent stem cells constitute a promising tool for the modelling of human brain development and diseases. Here we will describe how corticogenesis from pluripotent stem cells, whether in vitro or using xenotransplantation, can be used to identify novel molecular and cellular mechanisms linking human brain development and evolution, from neurogenesis to synaptogenesis.

THURSDAY, 21 JUNE, 16:00 - 18:00

CONCURRENT IIC: ROAD TO THE CLINIC 1

Room 219/220, Level 2

16:05 - 16:30

CAR T CELL THERAPY: THE CD19 PARADIGM AND BEYOND

Wang, Xiuyan

Memorial Sloan Kettering Cancer Center, U.S.

Chimeric Antigen Receptor modified T cells targeting CD19 have demonstrated remarkable potency in B cell malignancies. Advances in the selection of optimal T cells and genetic engineering are poised to broaden T-cell-based therapies and foster new applications in infectious diseases and autoimmunity. We recently demonstrated

that the targeting of CD19-specific CAR to the T-cell receptor α constant (TRAC) locus results in more uniform CAR expression in human peripheral blood T cells, and enhances T-cell potency, with edited cells vastly outperforming conventionally generated CAR T cells in a mouse model of acute lymphoblastic leukemia. We are presently scaling up the cGMP manufacture of TRAC-CAR T cells to test their safety and efficacy in a clinical trial where responses and toxicities will be compared with those encountered with current CAR therapies. In addition, CAR T cells can be generated in vitro from pluripotent stem cells as an alternative to manipulating mature T cells, offering potential access to an unlimited source of therapeutic T lymphocytes. We have demonstrated that iPSC-derived T cells expressing a CAR can eradicate tumors in vivo, providing a foundation for further exploiting the potential of self-renewing stem cells to engineer therapeutic T cells. The combination of iPSC technology and immune engineering may thus provide an opportunity to generate T cells that uniquely combine favorable attributes including antigen specificity, lack of alloreactivity, enhanced functional properties, and histocompatibility.

16:30 – 16:45

HUMAN ESC-CARDIOMYOCYTES RESTORE FUNCTION IN INFARCTED NON-HUMAN PRIMATE HEARTS

Murry, Charles E.

Institute for Stem Cell and Regenerative Medicine, University of Washington, Seattle, WA, U.S.

Much of the burden of heart disease arises from the heart's inability to regenerate new myocardium after injury. Pluripotent stem cell-derived cardiomyocyte grafts can remuscularize substantial amounts of infarcted myocardium and beat in synchrony with the heart but in some settings cause ventricular arrhythmias. It is unknown whether human cardiomyocytes can restore cardiac function in a physiologically relevant large animal model. Here we show that transplantation of 750 million cryopreserved human embryonic stem cell-derived cardiomyocytes (hESC-CMs) enhances cardiac function in macaque monkeys with large myocardial infarctions. Infarction was induced by inflating a balloon catheter in the mid-LAD artery for 3 hours followed by reperfusion. After induction of immunosuppression, hESC-CMs or vehicle control were delivered surgically via trans-epicardial injection. One month after hESC-CM transplantation, global left ventricular ejection fraction (LVEF; MRI) significantly improved compared to vehicle-injected hearts, and by 3 months post-engraftment there was >90% recovery of function. Grafts averaged 11.6% of infarct size, formed electromechanical junctions with the host heart and by 3 months contained 99% ventricular myocytes. A subset of animals experienced graft-associated ventricular arrhythmias, shown by electrical mapping to originate from a point-source functioning as an ectopic pacemaker. In conclusion, remuscularization of the infarcted macaque heart with human myocardium provides durable improvement in left ventricular function. We predict that, with prop-

er management of arrhythmias, human cardiomyocyte grafts can induce similar improvements in human hearts.

16:45 – 17:00

THE ADULT HUMAN EPCAM+CD24+CD133+ CHOLANGIOCYTE AS A BIPOTENTIAL HUMAN HEPATIC PROGENITOR AND TRANSPLANTABLE REGENERATIVE THERAPY FOR BILIARY DISEASE

Hallett, John M.¹, Lu, Wei-Yu², Ferrira-Gonzalez, Sofia², Man, Tak Yung², Thomson, John², O'Duibhir, Eoghan², Gadd, Victoria², Dwyer, Benjamin², Thirlwell, Kayleigh³, Fraser, Alasdair³, Hay, David², Oniscu, Gabriel² and Forbes, Stuart²

¹Scottish Centre for Regenerative Medicine, University of Edinburgh, U.K., ²University of Edinburgh, U.K., ³Scottish National Blood Transfusion Service, Edinburgh, U.K.

There is no effective regenerative therapy for advanced biliary diseases. Liver transplantation can be curative however demand exceeds organ availability. We have analysed EpCAM+CD24+CD133+ cholangiocytes as a transplantable cell therapy. Human livers deemed unsuitable for organ transplantation were studied. EpCAM+CD24+CD133+ (triple +ve) cells represented 1% of the total cholangiocyte yield. Following single cell isolation and organoid culture, triple +ve cells had a greater colony forming ability than EpCAM+CD24+CD133- (dual +) cells (1.67 relative increase $p < 0.01$). RNA seq analysis showed that triple +ve cells highly expressed Sox 9 and FoxA2. Fatty livers had increased numbers of K19 +ve cholangiocytes (2.2% vs 0.62%) and showed upregulation of gene groups associated with positive regulation of cell proliferation ($p = 1.2 \times 10^{-2}$) and extracellular matrix organisation ($p = 2.7 \times 10^{-3}$) in keeping with a cholangiocyte driven regenerative response to injury. Triple +ve cells were maintained in culture for over 1 year, whilst dual +ve cells could only be maintained for 15 weeks. Triple +ve cells could be differentiated towards a hepatocyte lineage (positive staining for CYP2D6 and albumin and negative for CK19) unlike dual +ve cells which maintained a biliary phenotype. The Krt19CreERM2fl/fl Rag2^{-/-} Il2rg^{-/-} mouse was developed as a novel immunodeficient model of biliary injury and senescence. Induced mice had activation of p21 and p53 in intra and extrahepatic bile ducts, increased serum markers of biliary disease, fibrosis (1.44% vs 0.87% $p = 0.005$) and histological changes compared to controls. When one million triple +ve cells were transplanted into the Krt19CreERM2fl/fl Rag2^{-/-} Il2rg^{-/-} model of biliary disease all animals treated survived well to day 42 with normalising liver biochemistry and liver histology with human cells engrafting within the biliary tract. Controls had deranged liver biochemistry, necrotic and inflamed livers and reached clinical endpoints for euthanasia. In conclusion, triple +ve cells isolated from discarded human livers, are clonogenic in vitro, functionally engraft and rescue a model of severe biliary disease, indicating a potential future cell therapy.

17:00 – 17:15

ISOLATION AND TRANSPLANTATION OF HUMAN PLURIPOTENT STEM CELL-DERIVED MIDBRAIN DOPAMINERGIC PROGENITORS INTO PARKINSONIAN RATS

de Luzy, Isabelle R.¹, Kauhausen, Jessica², Gantner, Carlos², Niclis, Jon³, Pouton, Colin⁴, Thompson, Lachlan² and Parish, Clare²

¹*Stem Cells and Neural Development, Florey Institute of Neuroscience and Mental Health, Melbourne, VIC, Australia*, ²*Florey Institute of Neuroscience and Mental Health, Melbourne, Australia*, ³*Centre for Translational NeuroMedicine, Copenhagen, Denmark*, ⁴*Monash Institute of Pharmaceutical Sciences, Melbourne, Australia*

Human pluripotent stem cells are a promising tool for the cellular replacement of degenerated ventral dopaminergic neurons (vmDA) in Parkinson's disease. Despite the successful generation of bona fide vmDA neurons in vitro, the asynchronous and heterogeneous nature of the differentiations results in transplants consisting of proliferative, immature and terminally differentiated cells. To ensure safety and maximal functional benefit of stem cell-derived vmDA grafts it will be imperative to remove poorly specified and potentially tumorigenic cells prior to clinical translation. Here, we have utilized two novel hESC knock-in reporter lines expressing eGFP under the LMX1A and PITX3 promoters, enabling selective isolation of early and late VM progenitors by FACS following in vitro differentiation. For both reporter lines, Unsorted, GFP+ and GFP- cells were transplanted into Parkinsonian nude rats. Only animals receiving Unsorted or LMX1A-GFP+ cell grafts showed progressive improvements in motor function. Postmortem histological analysis revealed small grafts from PITX3-GFP+ cells, suggesting isolation of these late progenitors was not compatible with cell survival and integration. In contrast, LMX1A-GFP+ grafts were highly enriched for vmDA neurons, and importantly excluded all 5-HT serotonergic neurons (known to underpin graft-induced-dyskinesias) as well as reduced proliferative populations (that could lead to neural overgrowths). Grafts derived from LMX1A-GFP+ cells innervate developmentally relevant targets whilst LMX1A-GFP- cell grafts largely innervated non-dopaminergic nuclei. The identification of a target, such as LMX1A, to isolate vmDA progenitors capable of surviving and integrating, while simultaneously eliminating unwanted cell populations is highly relevant, given the rapid advancement of PSCs towards the clinic and the likely requirement for more stringent safety and standardization measures.

17:15 – 17:30

INTRACEREBRAL TRANSPLANTATION OF NEURAL STEM CELL LINE, NSI-566, IN CHRONIC ISCHEMIC STROKE PATIENTS FOR TREATMENT OF PARALYSIS

Johe, Karl K.¹, Zhang, Guangzhu², Li, Ying², Reuss, James³, Ulmer, John⁴, Li, James⁵, Xu, Shuangshuang⁵, Wang, Feng⁵, Hazel, Thomas¹, Hand, Holly¹, Dai, Yiwu², Zhang, Hongtian², Hong, Peng², Liu, Nan², He, Jianghong², Wu, Cuiying², Zhang, Ping², Feng, Huiru², Lu, Xiangdong², Johe, Karl¹ and Xu, Ruxiang²

¹*Neuralstem, Inc., Germantown, MD, U.S.*, ²*Affiliated BaYi Brain Hospital, Army General Hospital of People's Liberation Army (PLA), Beijing, China*, ³*Prism Clinical Imaging, Inc., Elm Grove, WI, U.S.*, ⁴*Medical College of Wisconsin, Milwaukee, WI, U.S.*, ⁵*Suzhou Neuralstem Biopharmaceutical, Suzhou Industrial Park, China*

Paralysis due to ischemic stroke is a major cause of prolonged neurological disability world-wide and in particular in China and Asian countries. There are currently no effective therapies to reverse the paralysis. We have investigated the feasibility and safety of transplanting human neural stem cells to reverse the paralysis in stably hemiparetic stroke patients. Neural stem cells are the precursor cells present in the neuroepithelium along the neuraxis during mammalian fetal development. NSI-566, the investigational product used in this study, is a stable cell line consisting of neural stem cells derived from a single human fetal spinal cord tissue, expanded only by epigenetic means with no genetic modification. This cell line is also being tested in clinical trials in the U.S. for treatment of amyotrophic lateral sclerosis (NCT01348451) and spinal cord injury (NCT01772810). In a single-site, Phase I study, 3 cohorts (n=3/cohort) were transplanted with ascending doses of NSI-566, which involved a one-time stereotactic, intracerebral injection of 1.2×10^7 , 2.4×10^7 , or 7.2×10^7 cells. Immunosuppression therapy with tacrolimus was maintained for 28 days. All subjects had chronic motor stroke, verified by MRI, initiated between 5 and 24 months prior to surgery, with Modified Rankin Score of 2, 3, or 4 and Fugl-Meyer Motor Score of 55 or less. Safety was the primary objective. Changes in Fugl-Meyer Motor Scale, Modified Rankin Scale, and NIH Stroke Scale were measured as secondary outcomes. Changes in FDG-PET, functional MRI, and structural MRI were measured as exploratory outcomes. Twelve-month clinical data of the combined nine participants were analyzed using the Wilcoxon signed rank test. At the 12-Month Visit, compared to Baseline, the mean Fugl-Meyer Motor Score (FMMS, total score of 100) showed 15.6 points of improvement (p=0.0078), the mean Modified Ranking Score (MRS) 0.8 points of improvement (p=0.031), and the mean NIH Stroke Scale (NIHSS) 3.2 points of improvement (p=0.016). The stem cell treatment was well tolerated at all doses. Longitudinal MRI studies showed evidence of graft survival and cavity-filling in all 9 patients. There was no death or any serious adverse event related to the treatment. This result warrants further study with larger cohorts with a randomized control arm.

17:30 – 17:55

A PIPELINE OF INNOVATIVE CELLULAR MEDICINES FOR CURRENTLY INTRACTABLE, ADVANCED-STAGE DISEASES

Simmons, Paul J.

Research and New Product Development, Mesoblast Limited, Melbourne, VIC, Australia

Mesoblast's allogeneic, 'off-the-shelf' mesenchymal lineage cell product candidates are being evaluated in a range of advanced-stage diseases with high, unmet medical needs, including cardiovascular diseases, musculoskeletal disorders, immune-mediated and inflammatory conditions and oncologic and hematologic diseases. The Company has established what it believes is the industry's most clinically advanced and diverse portfolio of cell-based product candidates with three programs in Phase 3 clinical studies. Consistent and durable clinical outcomes have been demonstrated across multiple difficult-to-treat diseases. Our lead mesenchymal precursor cell (MPC) product candidates under investigation are MPC-150-IM for advanced heart failure, MPC-06-ID for chronic low back pain due to disc degeneration and MPC-300-IV for biologic refractory rheumatoid arthritis and diabetic nephropathy. The Phase 3 trial of Mesoblast's allogeneic mesenchymal stem cell product candidate MSC-100-IV (remestemcel - L) in children with steroid refractory acute Graft versus Host Disease (a GVHD) has successfully met the primary endpoint of Day 28 overall response (OR, complete + partial response) rate. This represents an important milestone towards delivering a potentially effective treatment for this very serious and life-threatening condition and a further step towards Mesoblast's goal to have the first industrially manufactured allogeneic stem cell product approved in the United States.

THURSDAY, 21 JUNE, 16:00 – 18:00

CONCURRENT IID: TISSUE ENGINEERING

Room 212/213, Level 2

Sponsored by eLife Sciences

16:05 – 16:30

ORGANOID DEVELOPMENT BY DESIGN

Lutolf, Matthias P.

École Polytechnique Fédérale de Lausanne (EPFL), Switzerland

Organoids form through poorly understood morphogenetic processes in which initially homogeneous ensembles of stem cells spontaneously self-organize in suspension or within permissive three-dimensional extracellular matrices. Yet, the absence of virtually any predefined patterning influences such as morphogen gradients or mechanical cues results in an extensive heterogeneity. Moreover,

the current mismatch in shape, size and lifespan between native organs and their in vitro counterparts hinders their even wider applicability. In this talk I will discuss some of our ongoing efforts in developing programmable organoids that are assembled by guiding cell-intrinsic self-patterning through tissue engineering.

16:30 – 16:45

MECHANICS-GUIDED DEVELOPMENTAL PATTERNING OF NEUROECTODERM TISSUE FROM HUMAN PLURIPOTENT STEM CELLS

Xue, Xufeng¹, Sun, Yubing², Resto Irizarry, Agnes³, Studer, Lorenz⁴ and Fu, Jianping³

¹Mechanical Engineering, University of Michigan, Ann Arbor, MI, U.S., ²University of Massachusetts, Amherst, MA, U.S., ³University of Michigan, Ann Arbor, MI, U.S., ⁴Memorial Sloan-Kettering Institute, New York, NY, U.S.

Classic embryological studies have successfully applied genetics and cell biology principles to understand embryonic development. However, it remains unresolved how mechanics, as an integral part for shaping development, is involved in controlling tissue-scale cell fate patterning. Here we report a micropatterned human pluripotent stem (hPS) cell-based neuroectoderm developmental model, wherein pre-patterned geometrical confinement induces emergent patterning of neuroepithelial (NE) and neural plate border (NPB) cells, mimicking neuroectoderm regionalization during early neurulation. Specifically, microcontact printing is utilized to generate circular shaped hPS cell colonies with defined sizes. Neural induction of hPS cell colonies leads to autonomous regionalization of NE and NPB cells, with PAX6+ NE cells preferentially localized at colony central region and PAX3+, ZIC1+ and MSX1+ NPB cells concentrated at colony periphery, forming a concentric ring-shaped tissue sheet consistent with neuroectoderm patterning. Importantly, strong correlations between spatial regulations of cell shape, cytoskeletal contractility and BMP activity are observed during emergent neuroectoderm patterning of hPS cell colonies. Using microcontact printing to obtain patterned single hPS cells with prescribed spreading areas as well as a custom designed microfluidic device for stretching hPS cell colonies, we further show that cell shape and mechanical force can directly activate BMP-SMAD signaling and thus repress NE but enhance NPB differentiation. All together, we show that autonomous patterning of neuroectoderm tissue with proper NP and NPB regionalization emerges de novo as the tissue physically takes shape and self-assemble in pre-patterned geometrical confinements. Self-organization of morphogenetic cues, including cell shape and cytoskeletal contractility, could provide positional information and directly feed back to mediate BMP activity and thus dictate spatial regulations of NE and NPB lineage commitments during neuroectoderm patterning. This study provides a novel hPS cell-based model to understand the biomechanical principles that guide

neuroectoderm patterning, thereby useful for studying neural development and diseases.

Funding Source: National Institutes of Health (R21 EB017078 and R01 EB019436), National Science Foundation (CMMI 1129611, CBET 1149401, and CMMI 1662835), and American Heart Association (12SDG12180025).

16:45 – 17:00

THREE-DIMENSIONAL iPSC-DERIVED HUMAN ARTIFICIAL SKELETAL MUSCLES MODEL MUSCULAR DYSTROPHIES AND ENABLE MULTILINEAGE TISSUE ENGINEERING

Tedesco, Francesco Saverio¹, Maffioletti, Sara², Sarcar, Shilpita², Henderson, Alexander², Mannhardt, Ingra³, Pinton, Luca², Moyle, Louise², Steele-Stallard, Heather², Cappellari, Ornella⁴, Wells, Kim⁴, Ferrari, Giulia², Mitchell, Jamie², Tyzack, Giulia², Kotiadis, Vassilios², Khedr, Moustafa², Ragazzi, Martina², Wang, Weixin², Duchon, Michael², Patani, Rickie², Zammit, Peter⁵, Wells, Dominic⁴ and Eschenhagen, Thomas³

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Generating artificial human skeletal muscle is instrumental for investigating muscle pathology and therapy. However, most bioengineering platforms are challenged by the limited expansion potential and differentiation ability of tissue-derived myogenic cells. Moreover, although there is an increasing need to develop clinically-relevant, multilineage, patient-specific models, no such isogenic human skeletal muscle model has been derived to date. These obstacles negatively impact on the translational potential of these platforms to develop novel therapies for muscle diseases. To overcome these limitations, we generated three-dimensional (3D) artificial skeletal muscle tissue from human pluripotent stem cells, including induced pluripotent stem cells (iPSCs) from patients with Duchenne, limb-girdle and congenital muscular dystrophies. 3D skeletal myogenic differentiation of pluripotent cells was induced within hydrogels under tension to provide alignment. Artificial muscles recapitulated key characteristics of human skeletal muscle tissue and could be implanted into immunodeficient mice. Importantly, pathological cellular hallmarks of severe (and currently incurable) muscular dystrophies could be modeled with higher fidelity using this 3D platform than standard bi-dimensional cultures. Finally, we show generation of fully human iPSC-derived complex multilineage models, containing key isogenic cellular constituents of normal skeletal muscle, including vascular endothelial cells, pericytes and motor neurons. These results lay the foundation for a human skeletal mus-

cle organoid-like platform for complex disease modelling, regenerative medicine and drug development.

Funding Source: EU FP7 grant 602423 (PluriMes), IMI grant 115582 (EBiSC), BBSRC, Fundació La Marató de TV3, MuscularDystrophyUK and European Research Council. F.S.T. is funded by an NIHR Academic Clinical Fellowship.

17:00 – 17:15

BIO-ENGINEERING TRANSPLANTABLE HUMAN VASCULARISED LIVER ORGANIDS

Yap, Kiryu K.^{1,2}, Gerrand, Yi-Wen², Taylor, Caroline¹, Poon, Christopher¹, Kramer, Anne³, Pera, Martin⁴, Yeoh, George³, Morrison, Wayne^{1,2,5} and Mitchell, Geraldine^{1,2,5}

¹O'Brien Institute, Department of St Vincent's Institute, Fitzroy, VIC, Australia, ²University of Melbourne Department of Surgery at St Vincent's Hospital Melbourne, Fitzroy, VIC, Australia, ³Harry Perkins Institute for Medical Research and Centre for Medical Research, University of Western Australia, Perth, Australia, ⁴The Jackson Laboratory, Bar Harbor, ME, U.S., ⁵Australian Catholic University, Fitzroy, VIC, Australia

Bio-engineered liver organoids offer a regenerative alternative to donor-derived organ transplantation and a platform for drug testing and disease modelling. Transplantable liver organoids with intrinsic micro-vasculature were developed using human liver progenitor cells (LPC) as a parenchymal cell source, liver sinusoidal endothelial cells (LSEC) to generate liver-specific vasculature, and adipose-derived mesenchymal stem cells (ASC) as support cells. Cells in a 10:10:1 ratio (LPC:LSEC:ASC, total 1 million cells) were mixed in a human liver-derived extracellular matrix hydrogel and seeded into a porous polyurethane scaffold (NovoSorb™, 3mm diameter, 0.8mm thickness, bio-absorbable and FDA-approved). Between day 1 and 3 in culture, organoids upregulated key liver genes (HNF4 α , albumin, HGF, CYP3A4). Functional assays demonstrated albumin secretion, urea production, bile acid excretion, and CYP3A4 activity, which all increased over time. Capillary and bile canaliculi-like structures were also observed. Concurrent organoids were developed by replacing liver gel with Matrigel (a commonly used hydrogel derived from mouse sarcoma extracellular matrix). In all gene and functional parameters, liver gel organoids outperformed Matrigel organoids. For in vivo studies, liver gel organoids were transplanted into an "in vivo bioreactor" (a protective chamber surgically placed around an artery/vein to induce capillary sprouting and create a highly vascularised space) created in the groin of immuno-deficient SCID mice. At 14 days, functional human blood vessels perfused by mouse blood and clusters of differentiating human hepatocytes were present. Measurable levels of human albumin were secreted into the mouse circulation by transplanted organoids (n=4, human albumin in mouse serum 25.339 Qg/mL). In conclusion, functional human vascularised liver organoids can be engineered using a combination of LPC/LSEC/ASC, enhanced by liver-specific extracellular matrix.

Notably, all components were human-derived. Proof-of-concept transplantation studies indicate organoid survival/function in immuno-deficient mice. Longer time-points and transplantation in a humanised mouse model of liver disease are currently underway to assess the therapeutic efficacy of this organoid approach.

17:15 - 17:30

CO-EMERGENCE OF MULTIPLE RESPIRATORY HINDBRAIN POPULATIONS FROM HUMAN PLURIPOTENT STEM CELLS

Butts, Jessica, Mihaly, Eszter and McDevitt, Todd
Gladstone Institutes, San Francisco, CA, U.S.

The hindbrain is the most conserved central nervous system structure in vertebrates and is critical to the control of autonomic function, including respiration. V2a and V0V interneurons (IN) as well as chemosensitive neurons are critical populations in the phrenic circuit that provide input to respiratory control centers. Damage to these populations by cervical spinal cord injury or disease (i.e. ALS) dramatically diminishes respiration. There are currently no in vitro sources to study their development and functional interactions, thus, the objective of this work was to co-emerge critical hindbrain populations from human pluripotent stem cells (PSC). We have previously described a protocol to generate V2a IN from PSC using retinoic acid, sonic hedgehog (Shh), and Notch inhibition. HOX gene expression from single cell RNA sequencing on day 17 cultures revealed the IN population was primarily hindbrain and cervical (HOXA3, HOXB1, HOXB6). K-means clustering of 15 principle components identified 5 distinct clusters that described the cell population. Transcription factors expressed in the hindbrain were among the top 10 genes expressed in the 3 largest clusters: PHOX2A/PHOX2B (chemosensitive neurons), LHX5/PAX2 (V0V IN), and CHX10/SOX14 (V2a IN). To modulate relative proportions of co-emerged V0V and V2a IN, the concentration of purmorphamine (pur), a Shh agonist, was varied analogous to signaling in the developing neural tube, where a ventral-to-dorsal gradient of Shh gives rise to V0v (dorsal, low Shh) and V2a (ventral, high Shh) IN. In in vitro cultures, low pur concentration (10nM) resulted in higher LHX5 (10.48%) and lower CHX10 (3.87%) expression while higher concentration (100nM) resulted in lower LHX5 (2.7%) and higher CHX10 (11.43%) expression, consistent with developmental Shh signaling. To interrogate how these populations organize and mature, the differentiation was performed in suspension. The aggregates doubled in size after 100 days in culture to become >1mm in diameter. Additionally, NeuN+, Neurofilament+, and VGlut2+ neurons were identified throughout the aggregate with GFAP+ glia along the edges. Together, this study reports a tunable system to co-emerge multiple respiratory hindbrain populations from human PSC, which can be further evaluated to model disease and development.

Funding Source: California Institute of Regenerative Medicine (CIRM), The Roddenberry Foundation.

17:30 - 17:55

ENGINEERING HUMAN TISSUES FOR REGENERATIVE MEDICINE AND STUDY OF DISEASE

Vunjak-Novakovic, Gordana, Ronaldson-Bouchard, Kacey, O'Neill, John and Liu, Bohao
Columbia University, New York, NY, U.S.

Tissue engineering is becoming increasingly successful with authentically representing the actual environmental milieu of the development, regeneration and disease. The classical paradigm of tissue engineering involves an integrated use of human stem cells, biomaterial scaffolds (providing a structural and logistic template for tissue formation) and bioreactors (providing environmental control, and dynamic sequences of molecular and physical regulatory factors). This biomimetic approach is designed to recapitulate the critical aspects of tissue development, regeneration and disease. Living human tissues are being engineered from various types of human stem cells, and tailored to the patient and the condition being treated. A reverse paradigm is now emerging with the development of platforms for modeling of integrated human physiology, using micro-tissues derived from human iPS cells and functionally connected by vascular perfusion. In all cases, the critical questions relate to our ability to recapitulate the cell niches, using bioengineering tools. This talk will discuss some recent advances in regenerative engineering of whole organs (lung, heart, bone) and recapitulation of human physiology using microphysiological platforms with interconnected human tissues derived from the patient's iPSCs.

THURSDAY, 21 JUNE, 16:00 - 18:00

CONCURRENT IIE: MUSCLE STEM CELLS

Room 203/204, Level 2

16:05 - 16:30

INTRINSIC AND EXTRINSIC REGULATION OF THE MUSCLE STEM CELL NICHE

Tajbakhsh, Shahragim
Pasteur Institute, Paris, France

The microenvironment is critical for the maintenance of stem cell populations, and it can be of cellular and non-cellular nature, including secreted growth factors and extracellular matrix (ECM) as well as intrinsic regulators. Skeletal muscle satellite (stem) cells are quiescent during homeostasis and they are mobilised to restore tissue function after muscle injury. Although certain signalling pathways that regulate quiescence have been identified, the mechanisms by which niche molecules regulate stem cell properties remain largely unknown. We have identified Notch signalling as a major regulator of the muscle stem cell niche. Specifically, Notch/RBPJ-bound regulatory ele-

ments are located adjacent to specific collagen genes in adult muscle satellite cells. These molecules are linked to the ECM and constitute putative niche components. Notably, satellite cell-produced collagen V (COLV) is a critical component of the quiescent niche, as conditional deletion of Col5a1 leads to anomalous cell cycle entry and differentiation of satellite cells. Strikingly, COLV, but not collagen I and VI, specifically regulated quiescence through Calcitonin receptor mediated activity, therefore, a Notch/COLV signalling cascade cell-autonomously maintains the stem cell quiescent state, and raises the possibility of a similar reciprocal mechanism acting in diverse stem cell populations. In other studies, we have identified a microRNA pathway that is regulated by Notch, and it required for stabilizing muscle stem cells in their niche.

16:30 – 16:45

ERBB3 AND NGFR MARK A DISTINCT SKELETAL MUSCLE PROGENITOR CELL IN HUMAN DEVELOPMENT AND HPSCS

Hicks, Michael¹, Hiserodt, Julia², Paras, Katrina², Xi, Haibin², Young, Courtney², Saleh, Kholoud², Evseenko, Denis³, Spencer, Melissa², Van Handel, Ben² and Pyle, April²

¹*Microbiology, Immunology, and Molecular Genetics, University of California, Los Angeles, CA, U.S.,*

²*University of California, Los Angeles, CA, U.S.,*

³*University of Southern California, Los Angeles, U.S.*

Human pluripotent stem cells (hPSCs) can be directed to differentiate into skeletal muscle progenitor cells (SMPCs). However, the myogenicity of hPSC-SMPCs relative to human fetal or adult satellite cells remains unclear. HPSC-SMPCs derived by directed differentiation are less functional in vitro and in vivo compared to human satellite cells. Utilizing RNA-SEQ, we identified cell surface receptors ERBB3 and NGFR that demarcate myogenic populations, including PAX7 progenitors in human fetal development and hPSC-SMPCs. We demonstrated that hPSC skeletal muscle is immature, but inhibition of TGF- β signaling during differentiation improved fusion efficiency, ultrastructural organization, and expression of adult myosins. This enrichment and maturation strategy restored dystrophin in hundreds of dystrophin-deficient myofibers after engraftment of CRISPR/Cas9-corrected Duchenne muscular dystrophy hiPSC-SMPCs. Post-engraftment, hiPSC-SMPCs not fused with myofibers were re-isolated from wild type or diseased muscle and single-cell RNA-SEQ used to determine in vivo cell fate and maturation. The work provides an in-depth characterization of human developmental myogenesis, and identifies candidates that improve the in vivo myogenic potential of hPSC-SMPCs to levels equal to directly-isolated human fetal muscle cells.

Funding Source: Eli and Edythe Broad Stem Cell Research Center Postdoctoral Fellowship.

16:45 – 17:00

STEM CELL-MACROPHAGE INTERACTIONS REGULATE VERTEBRATE MUSCLE REGENERATION: INSIGHTS FROM ZEBRAFISH

Ratnayake, Dhanushika and Currie, Peter

Australian Regenerative Medicine Institute, Clayton, VIC, Australia

Studying muscle regeneration through in vivo imaging has the potential to reveal phenomena that might not be observed by in vitro studies. Zebrafish are a key vertebrate model system for high-resolution live imaging due to their optical transparency and the genetic tools available for lineage analysis. Here we use the zebrafish system to characterize stem cell-macrophage interactions during muscle regeneration. Nitroreductase-mediated genetic ablation of macrophages prior to injury resulted in a muscle regeneration deficit, due at least in part to a failure of stem cell migration into the wound site. Remarkably, in vivo cell tracking identified distinct macrophage populations based on cell behaviour: a “transient” injury responding population that migrate into the wound site and phagocytose cellular debris, making the environment conducive for repair; and a long-term injury responding macrophage population that “dwells” in the wound site throughout the repair process, continuously extending cytoplasmic protrusions to physically interact with injury responding stem and progenitor cells. We hypothesize that “dwelling” macrophages regulate regeneration by providing environmental and positional information to stem cells via these physical interactions, and are currently focused on characterizing the signalling pathways that mediate these processes.

17:00 – 17:15

DEFINING HUMAN IN VIVO SKELETAL MUSCLE DEVELOPMENT AND IN VITRO PLURIPOTENT STEM CELL MYOGENESIS AT SINGLE CELL RESOLUTION

Xi, Haibin¹, Langerman, Justin², Sabri, Shan², Gonzalez, Karen², Young, Courtney², Fujiwara, Wakana², Mota, Andrea³, Marzi, Julia⁴, Liebscher, Simone⁴, Van Handel, Ben⁵, Evseenko, Denis⁵, Spencer, Melissa², Schenke-Layland, Katja⁴, Plath, Kathrin² and Pyle, April²

¹*Microbiology, Immunology and Molecular Genetics, University of California Los Angeles, CA, U.S.,*

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⁴*Eberhard Karls University Tübingen, Germany,*

⁵*University of Southern California, Los Angeles, CA, U.S.*

Skeletal muscle progenitor cells (SMPCs) derived from human pluripotent stem cells (hPSCs) are promising sources for regenerative medicine in treating muscle wasting disorders including muscular dystrophies and sarcopenia. Nevertheless, the current hPSC directed myogenic differentiation protocols result in highly heterogeneous cell

populations with immature SMPCs that are unsuitable for clinical implementation. These drawbacks are reflective of insufficient SMPC specification *in vitro*, due to lack of knowledge of human skeletal myogenesis *in vivo*. Using single cell RNA-sequencing (scRNA-seq), we profiled human limb myogenic cells from early week 5 embryos to adulthood. We observed heterogeneity of *in vivo* SMPCs at individual stages and more strikingly, across development. We confirmed the dynamic expression pattern of key myogenic transcriptional factors as well as unique cell surface marker expression in distinct SMPC populations by IHC. Next, to define the *in vitro* SMPCs derived from hPSCs, we generated a knock-in PAX7-GFP reporter hPSC line using CRISPR/Cas9. We differentiated them, sorted the GFP⁺ (PAX7⁺) cells at different time points, and performed scRNA-seq. Interestingly, we found that the early wave of PAX7⁺ cells are mainly composed of SOX2⁺ neural lineage cells, both neurogenic and myogenic cells co-exist during intermediate period, whereas the myogenic cells dominate at later differentiation time points. Similar to the *in vivo* cells, we observed extensive heterogeneity of the *in vitro* SMPCs. In mice myofibers are known to be critical for early SMPC development. Thus, we utilized our reporter cells to enrich PAX7⁺ SMPCs during myogenic differentiation, cultured them in the absence or presence of myotubes, and re-isolated the PAX7⁺ cells via FACS. Intriguingly, the PAX7⁺ cells cultured with myotubes display gene expression patterns resembling a transition from early embryonic to later fetal stage, such as decreased PAX3 and increased COL15A1 expression. Overall, our study comprehensively profiled the human myogenic cells across different stages during both *in vivo* development and *in vitro* hPSC differentiation. This work can serve as a resource for advancing our knowledge of human myogenesis and guide the generation of optimal cells for translational applications in muscle diseases.

17:15 - 17:30

BAMBI-MEDIATED SIGNALING PATHWAY IS INVOLVED IN SATELLITE CELLS QUIESCENCE AND ACTIVATION

Xie, Liwei¹, Yao, Xiangping^{1,2}, Chen, Shujie¹, Yu, Taiyong², Yang, Gongshe² and Xu, Guohuan¹

¹Guangdong Institute of Microbiology, Guangzhou, China, ²Northwest A and F University, Xian, China

BAMBI is bone morphogenic protein and activin membrane-bound inhibitor, which regulates cell proliferation and differentiation through the interaction with TGF- β and Wnt/ β -catenin signaling pathway. Previous work in C2C12 myoblast demonstrated the BAMBI is a key factor regulating the differentiation. In present work, our preliminary data suggest that BAMBI protein is detected both in the cytosolic fraction instead of the membrane of skeletal muscle and in satellite cells. Skeletal muscle-specific knockout of BAMBI leads to upregulation of Pax7 and MyoD expression, followed with spontaneous activation of satellite cells, which lead us to generate the hypothesis that BAMBI-mediated signaling pathway is involved in regulating satellite cells quiescence and activation, lead-

ing to the switch of muscle fiber type. To test the hypothesis, TA cross-section staining and single myofiber isolation and immunostaining indicated that BAMBI is detected in both myofiber and satellite cells. MCK-Cre-mediated deletion of BAMBI in skeletal muscle leads to the spontaneous activation of satellite cells with the upregulation of Pax7 and MyoD. Long-term deletion of BAMBI causes the fiber type switch from TCA-based Type I fiber to glycolysis-based Type IIB fiber. Mice with the dysfunction of the BAMBI gene in skeletal muscle also fails to regenerate upon the CTX-induced muscle regeneration compared with the control mice. Further investigation will delve into the molecular mechanism of BAMBI in fiber type switch and satellite cell physiology and pathogenesis.

17:30 - 17:55

IN VIVO GENE EDITING IN MUSCLES AND MUSCLE STEM CELLS

Wagers, Amy

Harvard University, Cambridge, MA, U.S.

The *in vivo* delivery of genome modifying enzymes, including CRISPR/Cas9 gene editing complexes, holds significant promise for both therapeutic applications and functional genetic screening in muscle and other tissues. In this context, delivery to endogenous tissue stem cells, including muscle satellite cells which provide an enduring source of myofiber replacement in homeostasis and in response to regenerative cues, is of particular interest. We previously developed an adenoassociated virus- (AAV-) based system for local and systemic delivery to skeletal muscle of experimentally engineered programmable Cas9 nuclease. Application of this system to delete specific gene sequences in a mouse model of Duchenne Muscular Dystrophy (DMD) demonstrated simultaneous targeting in multiple organs of therapeutic interest, with restoration of the mutated Dystrophin protein reading frame, recovery of muscle function, and establishment of a pool of modified muscle stem cells capable of participating in subsequent muscle regenerative events. In recent work, we have further adapted this approach to enable templated sequence replacement via homology-directed repair, raising the possibility of accomplishing sequence-directed, systemically disseminated DNA replacement *in vivo* in postnatal muscle and muscle stem cells. We have also demonstrated the capacity of AAV-delivered genome modifying enzymes to target non-muscle progenitors in distinct anatomical niches, indicating the robustness and potential generalizability of this approach as a new experimental alternative to conventional transgenic/knockout mouse models and *ex vivo* transduction strategies. Taken together, these results suggest exciting new opportunities for manipulating stem cell function experimentally and for therapeutic intervention to achieve functional recovery of disease-relevant gene products and promote endogenous repair activity across organ systems.

FRIDAY, 22 JUNE, 09:00 – 11:15

PLENARY IV: NEW TECHNOLOGIES IN STEM CELL ENGINEERING

Plenary Room, Ground Level

09:00 – 09:25

IN VIVO BRAIN ORGANOID MODEL OF VASCULARIZED AND FUNCTIONAL PSC-DERIVED HUMAN BRAIN ORGANOID

Gage, Fred H., Mansour, Abed AlFattah, Gonçalves, Tiago, Johnston, Stephen and Parylak, Sarah

The Salk Institute for Biological Studies, La Jolla, CA, U.S.

Stem cells have the remarkable ability to self-organize in three-dimensional (3D) space into organ-like structures termed Organoids. By harnessing this property, researchers have been able to create such organoids for several tissues that better recapitulate the complexity and physiological properties of tissues and organs. Despite many reports describing the generation of human neural organoids, the generation of vascularized and functional neural organoid graft is not described yet. Here we describe the generation of vascularized, and electrophysiologically active, human cerebral-organoids by transplantation of organoids grown in vitro to an adult mouse brain. Engrafted mice were viable, and exhibit long and high survival rates. Moreover, histological and immunostaining analysis revealed intact grafts with mature neurons, and extensive axonal trajectories from the implant to multiple regions of the host mouse brain. Importantly, live imaging on of the implanted organoids using two-photon microscopy revealed neuronal activity, and intensive vascular network with active blood flow within the organoid. Moreover, our method creates opportunities for noninvasive recording of neuronal activity with high spatial and temporal resolution deep within organoid-brain chimera. This powerful combination of in vitro 3D human neural structures, and an in vivo rich environment in the animal brain provides a promising novel approach with broad applications for degenerative and regenerative medicine.

09:25 – 09:50

EXPLOITING TARGETED (EPI)GENOME EDITING FOR THERAPEUTIC APPLICATIONS

Lombardo, Angelo

San Raffaele Telethon Institute for Gene Therapy, Milan, Italy

The development of targeted technologies able to precisely edit the genome and its regulatory code is opening novel exciting perspectives for the treatment of inherited and acquired diseases. These technologies hold the promise of in situ correction of genetic defects, targeted integration of exogenous transgene expression cassettes, and fine-tuning modulation of endogenous gene expres-

sion via transcriptional and epigenetic reprogramming. We have recently described a novel editing approach that exploits epigenetics and programmable DNA binding domains to permanently silence gene expression. During my talk, I will discuss critical aspects affecting efficiency of this novel approach and propose possible therapeutic targets that may benefit from targeted epigenetic editing. Furthermore, I will extend on the power of genome editing to discuss a synthetic biology approach aiming at generating immune-stealth human stem cells, which may provide an indefinite source of off-the-shelf cells for transplantation.

09:50 – 10:15

3D EPIGENOME RECONFIGURATION IN BRAIN DEVELOPMENT AND NEURODEGENERATIVE DISEASE

Phillips-Cremins, Jennifer E.

Perelman School of Medicine University of Pennsylvania, Philadelphia, PA, U.S.

The Cremins Lab focuses on higher-order folding of the genome and how epigenetic marks work through long-range regulatory mechanisms to govern neural cell fate in the mammalian brain. Much is already known regarding how transcription factors and epigenetic marks work in the context of the linear genome to regulate neuronal development and function. Yet, severe limitations still exist in our ability to apply this knowledge to engineer neuron fate at will or correct brain diseases in vivo. The overarching goal of the Cremins lab is to obtain detailed mechanistic understanding of how the genome is folded and reconfigured during neural lineage commitment and synaptogenesis and how these folding patterns influence the specificity, maturation and pruning of neuronal connections in healthy mammalian brain development. We also study how the genome is misfolded in neurodegenerative disease and we develop tools to engineer 3D genome folding on demand. Addressing this knowledge gap will provide an essential foundation for our long-term goal to engineer the 3-D genome to control neural cell fate in debilitating neurodevelopmental and neurodegenerative diseases.

10:15 – 10:40

WHOLE-ORGANISM CLONE-TRACING USING SINGLE-CELL SEQUENCING

van Oudenaarden, Alexander M.

Hubrecht Institute-KNAW and University Medical Center, Utrecht, Netherlands

Embryonic development is one of the most crucial periods in the life of a multicellular organism. A limited set of embryonic progenitors gives rise to all cells in the adult body. Determining which fate these progenitors acquire in adult tissue is a major challenge and requires the simultaneous measurement of clonal history and cell-type at single-cell resolution. Clonal history has traditionally been

quantified by microscopically tracking cells during development, monitoring the heritable expression of genetically encoded fluorescent proteins and, most recently, by utilizing next generation sequencing technology exploiting somatic mutations, transposon tagging, viral barcoding, and CRISPR/Cas9 genome editing strategies. Single-cell transcriptomics on the other hand, provides a powerful technology platform for cell-type classification in an unbiased manner. However, integrating both measurements for many single cells has been a major hurdle. Here, we present ScarTrace, a single-cell sequencing strategy that allows us to simultaneously quantify information on clonal history and cell type for thousands of single cells obtained from different organs from adult zebrafish. Using this approach we show that all blood cells in the kidney marrow arise from a small set of multipotent embryonic progenitors that give rise to all blood cell types. In contrast, we find that cells in the eyes, brain, and caudal tail fin arise from many embryonic progenitors, which are more restricted and produce specific cell types in the adult tissue. Next we use ScarTrace to explore when embryonic cells commit to forming either left or right organs using the eyes and brain as a model system. Lastly we monitor regeneration of the caudal tail fin and identify a subpopulation of resident macrophages that have a clonal origin that is distinct from other blood cell types. We envision that ScarTrace will have major applications in other experimental model systems to match embryonic clonal origin to adult cell-type to ultimately reconstruct how the adult body was built from a single cell.

10:40 - 10:45

POSTER TEASERS

F-2048

BMP PATHWAY AS THE MASTER REGULATOR OF THE SLOW CYCLING, CHEMO-RESISTANT CANCER STEM CELL COMPARTMENT IN HUMAN EPITHELIAL CARCINOMA

Syeddasli, Naisana

University of Sydney, Australia

F-2129

MAPPING CELLULAR REPROGRAMMING VIA POOLED OVEREXPRESSION SCREENS WITH PAIRED FITNESS AND SINGLE CELL RNA-SEQUENCING READOUT

Parekh, Udit

University of California, San Diego, CA, U.S.

F-2088

GUIDED SELF-ASSEMBLY OF SOX2+SOX9+ HUMAN LUNG PROGENITORS INTO SIMPLIFIED DEVELOPMENTALLY INSPIRED TUBULAR ARCHITECTURE

Soleas, John P.

Institute of Biomaterials and Biomedical Engineering, University of Toronto, Canada

F-3038

PATIENT-DERIVED IPSC-BASED DRUG DISCOVERY PLATFORM HIGHLIGHTS RAPAMYCIN AS A DRUG CANDIDATE FOR FIBRODYSPLASIA OSSIFICANS PROGRESSIVA (FOP)

Hino, Kyosuke

iPS Cell-Based Drug Discovery, Sumitomo Dainippon Pharma Co., Ltd., Japan

10:45 - 11:10

ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE: CONTROL HUMAN PLURIPOTENT STEM CELL FATE USING CHEMICAL APPROACHES

Chen, Shuibing

Weill Cornell Medical College, New York, NY, U.S.

Human pluripotent stem cells (hPSCs) provide unlimited starting material to generate differentiated cells that can be used to build a functional organ. Essential to this pursuit is an efficient way to differentiate hPSCs into specific types of mature cells. Cell-permeable small molecules that can modulate the function of specific proteins provide a convenient and efficient approach to controlling stem/progenitor cell fate. Our laboratory has an in house chemical library containing 6,000 chemicals, including kinase inhibitors, signaling pathway regulators, nature products and FDA-approved drugs, and protein library containing 400 growth factors. Using high content and high throughput screening approaches, we have identified a series of small molecules that control stem cell self-renewal, differentiation and reprogramming. In addition, we have identified small molecules that direct hPSC differentiation into certain cell types, including pancreatic endocrine cells, pancreatic ductal epithelial cells, cardiac SA nodal cells, trophoblast cells, and colonic organoids. Using hPSCs derived tissues or organoids, we have established several in vitro and in vivo platforms to study the role of genetic factors and environmental factors in the progression of diabetes, pancreatic cancer, colorectal cancer, and virus infection. Recently, we performed a high content chemical screen using human embryonic stem cell derived cortical neuron progenitor cells (hNPCs). Hippelastine hydrobromide (HH) was discovered to inhibit ZIKV infection in hNPCs. The hit compound was further confirmed for its

anti-ZIKV effect using human fetal-like forebrain organoids and adult mouse model. This stem cell-based screen followed by validation using human forebrain organoids and a mouse model identifies drug candidates for the treatment of ZIKV infection and ZIKV-related neurological complications in fetal and adult patients.

FRIDAY, 22 JUNE, 13:15 - 15:15

CONCURRENT IIIA: ORGANOID IN MODELING DISEASE AND DEVELOPMENT

Melbourne Room 1, Level 2

Sponsored by Decibel Therapeutics

13:20 - 13:45

INTESTINAL ORGANOID FOR CYSTIC FIBROSIS MODELING

Beekman, Jeffrey

University Medical Center Utrecht, Netherlands

We use intestinal organoids to model cystic fibrosis, a life-shortening monogenetic diseases characterised by aberrant epithelial ion and fluid transport due to CFTR mutations. Forskolin that raises cAMP and opens the CFTR ion channel induces rapid luminal fluid secretion in rectal organoids, which leads to organoid swelling in a fully CFTR-dependent manner. This assay can be used to quantitate individual CFTR function, and also individual response to novel pharmacotherapies (CFTR modulators) that restore CFTR function in a CFTR mutation and patient-specific manner. Data will be presented that show correlations between in vitro forskolin-induced organoid swelling and in vivo indicators of disease severity or therapeutic response. We also developed a high throughput screening assay to screen organoids from people with rare CFTR mutations ($n > 170$) for response to clinically available CFTR modulators and > 1400 FDA-approved drugs. On a whole, our data demonstrate that organoids recapitulate individual therapeutic response, and support that clinically annotated biobanks of individual stem cells could be patient-friendly options to select optimal individualised therapies in progressive diseases.

13:45 - 14:00

PROGRAMMABLE MICROFLUIDIC SYNTHESIS OF SYNTHETIC HUMAN EMBRYO-LIKE ENTITIES

Fu, Jianping¹, Zheng, Yi², Xue, Xufeng², Shao, Yue², Nasr Esfahani, Sajedeh², Wang, Sicong² and Gumucio, Deborah²

¹*Mechanical Engineering, Biomedical Engineering, Cell and Developmental Biology, University of Michigan, Ann Arbor, MI, U.S.*, ²*University of Michigan, Ann Arbor, MI, U.S.*

Most of our current knowledge of mammalian embryology is derived from studies of the mouse embryo. However, mammalian development involves substantial divergence in the mechanism and order of cell-fate allocations among species, and there has been a critical lack of information regarding human development due to the scarcity of human embryo specimens. Leveraging the self-organizing properties of human pluripotent stem (hPS) cells, recent developments of synthetic human entities with embryo-like features (SHEEFs) have sparked great interests in using such synthetic models to advance human embryology, embryo toxicology, and reproductive medicine. However, existing SHEEF systems rely on uncontrolled, spontaneous organization and development of hPS cell cultures in ill-defined environments without any spatial constraints. Such lack of controllability and reproducibility significantly hinder the full potential of the SHEEFs for their uses in embryo toxicological screening and drug testing or mechanistic investigations of human embryogenesis. Herein, we report a novel microfluidic strategy to achieve programmable, scalable, robust synthesis of SHEEFs using hPS cells. By asymmetrically applying agonists and/or antagonists in a highly controlled manner using microfluidics - both spatiotemporally and in terms of dosage, we have successfully developed a hPS cell-based, synthetic embryological model of human post-implantation development that recapitulates multiple embryogenic events including amniotic cavity formation, amnion-epiblast patterning, primordial germ cell (PGC) specification, and development of the primitive streak with controlled anteroposterior polarity. Enabled by this novel microfluidic synthesis system, we further discover that the amnion, as a unique keystone during early human embryo development, functions as a signaling center for PGC specification and controls the proper developmental sequence by triggering the onset of gastrulation from the posterior epiblast. We envision that our microfluidic synthesis system for SHEEFs, given its controllability, scalability, and compatibility with live-cell imaging, will provide a powerful synthetic embryological platform that open up previously inaccessible phases of the human life cycle to experimental study.

Funding Source: National Institutes of Health (R01 DK089933), Natural Sciences and Engineering Research Council of Canada, and University of Michigan Mechanical Engineering Startup Fund.

14:00 - 14:15

SINGLE CELL TRANSCRIPTOMICS OF GENE-EDITED HUMAN CEREBRAL ORGANIDS REVEALS NEURON-SPECIFIC PATTERNING DEFECTS AND A TREATMENT-RESPONSIVE GLIAL INFLAMMATORY SIGNATURE IN TUBEROUS SCLEROSIS

Salick, Max R.¹, Goold, Carleton², Ihry, Robert², Biag, Jonathan², Ho, Daniel², Kommineni, Sravya², Kulkarni, Tripti², Raymond, Joe², Henry, Beata², Altshuler, Bob², Kirkpatrick, Nathaniel², Chen, Julie², Ye, Chaoyang², Randhawa, Ranjit², Bilican, Bilada², Fletcher, David², Worringer, Kathleen², Dolmetsch, Ricardo² and Kaykas, Ajamete²

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Tuberous sclerosis complex (TSC) is a systemic disease caused by a heterozygous germline mutation in the TSC1 or TSC2 genes, which occurs in 1 out of 6,000 live births. Symptoms arise during development when somatic mutations in the affected gene lead to loss of heterozygosity, resulting in unchecked mTOR activity. This leads to a range of symptoms in the heart, lung, kidneys, skin, and other organs; however, the most severe symptoms arise when these somatic mutations occur in the brain. When this happens, hamartomas form in distinct regions of the cortex, along with severe epilepsy, intellectual disability, and often autism. There are several unique hallmarks of the afflicted region, including dysmorphic neurons, balloon cells, and disrupted cortical architecture. To model this disease in vitro we produced TSC2^{-/-} human embryonic stem cell and induced pluripotent stem cell lines using an inducible CRISPR/Cas9 system. Neurons differentiated from these stem cell lines replicated several of the disease phenotypes, such as S6 phosphorylation and neuron size, which are then corrected by RAD001, an effective mTOR inhibitor. We then produced cerebral organoids to mimic human brain development, which we treated with DMSO or RAD001, followed by dissociation and single cell sequencing using a 10X Chromium system. Analysis of the single cell data revealed distinct mutation effects in the neuronal and glial populations, which were largely corrected in the RAD001-treated cerebral organoids. Network analysis revealed a disruption in telencephalon patterning in the neurons, which was confirmed in follow-up two-dimensional differentiation studies. Single-cell analysis revealed a strong inflammatory signal in the mutant astrocytes, which was particularly rescued in the RAD001-treated samples. Lastly, we conducted an aptamer-based screen of secreted proteins from WT and TSC2^{-/-} neurons. Considerable differences in the secretome of these cultures suggests that the healthy tissue surrounding the hamartomas may also be involved in the disease phenotype. This study marks the first known investigation of isogenically-controlled disease models, along with a treatment response, using droplet single cell

transcriptomics, and may play a key role in understanding the complex physiology behind tuberous sclerosis.

Funding Source: Funding was provided by the Novartis Institutes for Biomedical Research and the NIBR Postdoctoral Program.

14:15 - 14:30

HIGH THROUGHPUT SINGLE CELL RNA-SEQ OF DEVELOPING MOUSE KIDNEY AND HUMAN KIDNEY ORGANIDS REVEALS A ROADMAP FOR RECREATING THE KIDNEY

Combes, Alexander^{1,2}, Phipson, Belinda², Zappia, Luke², Lawlor, Kynan², Er, Pei², Oshlack, Alicia² and Little, Melissa²

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Recent advances in our capacity to differentiate human pluripotent stem cells to human kidney tissue are moving the field closer to novel approaches for renal replacement. Such protocols have relied upon our current understanding of the molecular basis of mammalian kidney morphogenesis. To date this has depended upon population based-profiling of non-homogenous cellular compartments. In order to improve our resolution of individual cell transcriptional profiles during kidney morphogenesis, we have performed 10x Chromium single cell RNA-seq on over 6000 cells from the E18.5 developing mouse kidney, as well as more than 7000 cells from human iPSC-derived kidney organoids. We identified 16 clusters of cells representing all major cell lineages in the E18.5 mouse kidney. The differentially expressed genes from individual murine clusters were then used to guide the classification of 16 cell clusters within human kidney organoids, revealing the presence of distinguishable stromal, endothelial, nephron, podocyte and nephron progenitor populations. Despite the congruence between developing mouse and human organoid, our analysis suggested limited nephron maturation and the presence of 'off target' populations in human kidney organoids, including unidentified stromal populations and evidence of neural clusters. This may reflect unique human kidney populations, mixed cultures or aberrant differentiation in vitro. Analysis of clusters within the mouse data revealed novel insights into progenitor maintenance and cellular maturation in the major renal lineages and will serve as a roadmap to refine directed differentiation approaches in human iPSC-derived kidney organoids.

Funding Source: This work was supported by the Australian Research Council (DE150100652), the National Health and Medical Research Council, and the National Institutes of Health Rebuilding a Kidney consortium (DK107344).

14:30 – 14:45

HUMAN INTESTINAL ORGANOID AS A MODEL FOR INTESTINAL FAILURE AND ABERRANT LIPID METABOLISM IN PATIENTS WITH DGAT1 DEFICIENCY

van Rijn, Jorik M.¹, van Haaften Visser, Désirée², van der Doef, Hubert³, van Hoesel, Marliek², van Vugt, Anke², Kokke, Freddy², Stigter, Edwin², Lichtenbelt, Klaske², Massink, Maarten², Duran, Karen², Verheij, Joke³, Lugtenberg, Dorien⁴, Nikkels, Peter², Brouwer, Henricus⁵, Verkade, Henkjan³, Scheenstra, Rene³, Spee, Bart⁶, Nieuwenhuis, Edward², Coffey, Paul², van Haaften, Gijs², Houwen, Roderick² and Middendorp, Sabine²

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Patient-derived stem cell organoids provide researchers with an increasingly well described patient-specific model of disease. Especially human intestinal organoids have been shown to reflect the donor's epithelial characteristics in a highly representative fashion. Here, we have used small intestinal organoids as a disease model for three patients with a novel mutation in the gene encoding diacylglycerol-acyltransferase 1 (DGAT1), a defect which has previously been described to cause intestinal failure. Symptoms of this chronic condition include severe early-onset diarrhoea, vomiting, and protein losing enteropathy on ingestion of dietary lipids. In healthy individuals, DGAT1 catalyses the formation of triacylglycerol from diacylglycerol and acyl-CoA, which is necessary for lipid metabolism in the intestine. The DGAT1 mutation we found led to loss of protein due to immediate proteasomal degradation. Using thin-layer chromatography, we show that DGAT1 deficiency specifically altered triacylglycerol metabolism in enterocytes. Furthermore, we found that DGAT1 mutant organoids show impaired lipid droplet formation upon incubation with oleic acid. In addition, DGAT1 mutant organoids were more sensitive to OA-induced caspase-3 mediated cell death compared to healthy control organoids. We confirmed these DGAT1-dependent functional differences through CRISPR/Cas9-guided deletion of DGAT1 in healthy control intestinal organoids. In conclusion, we show for the first time the importance of DGAT1 in human gut epithelium and link DGAT1 deficiency to altered lipid metabolism and fat intolerance. By developing several functional assays to model DGAT1 deficiency in-vitro, we furthered our understanding of the pathophysiology of disease and enabled the screening for potential novel therapeutics. Our data once again emphasize the strength of organoids in patient-specific disease modelling and their use in personalized drug screening.

Funding Source: This work was supported by the Netherlands Organisation for Scientific Research (NWO; VIDI 016.146.353) to SM.

14:45 – 15:10

BRAIN ORGANOID AS A MODEL SYSTEM FOR NEURODEVELOPMENT AND EVOLUTIONARY STUDIES

Muotri, Alysson

University of California, San Diego, La Jolla, CA, U.S.

The complexity of the human brain, with thousands of neuronal types, permits the development of sophisticated behavioral repertoires, such as language, tool use, self-awareness, symbolic thought, cultural learning and consciousness. Understanding what produces neuronal diversification during brain development has been a longstanding challenge for neuroscientists and may bring insights into the evolution of human cognition. Human pluripotent stem cells have the ability to differentiate in specialized cell types, such as neurons and glia. Moreover, induced pluripotent stem cells can be achieved from living individuals by reprogramming somatic cells that would capture their entire genome in a pluripotent state. From these pluripotent state, it is possible to generate models of the human brain, such as brain organoids. We have been using brain-model technology (BMT) to gain insights on several biological processes, such as human neurodevelopment and evolution. We also applied BMT to measure the impact of genetic variants in autism spectrum disorders and for evolutionary studies. The reconstruction of human synchronized network activity in a dish can help to understand how neural network oscillations might contribute to the social brain. Our findings suggest a potential bridge to the gap between the microscale in vitro neural networks electrophysiology and non-invasive electroencephalogram.

FRIDAY, 22 JUNE, 13:15 – 15:15

CONCURRENT IIIB: NERVOUS SYSTEM DISEASE

Melbourne Room 2, Level 2

13:20 – 13:45

USING STEM CELLS FOR DRUG DISCOVERY IN NEUROSCIENCE

Dolmetsch, Ricardo

Novartis Institutes for BioMedical Research, Inc., Cambridge, MA, U.S.

Drug development in neuroscience has been particularly challenging over the last two decades. A major limitation has been the lack of predictive preclinical models that can be used at early stages of drug discovery to select and optimize drug candidates. iPSC-derived neurons have the potential to improve our drug discovery pipeline by providing human cellular models of neurological and psychiatric disease. We have built a platform for generating iPSC derived neurons, engineering them using CRISPR

Cas9 and using them to conduct both high throughput screens and secondary hit selection and optimization assays. I will discuss our efforts to optimize this system and some of the learnings that we have made along the way. I will also discuss our ongoing programs to develop drugs for neurodevelopmental diseases using human induced pluripotent stem derived neurons. I will discuss our efforts in Spinal Muscular Atrophy, Dravet Syndrome and Phelan McDermid Syndrome and discuss some of the challenges ahead.

13:45 - 14:00

FINDING YOUR PLACE: CONTROL OF CELL MIGRATION DURING FETAL BRAIN DEVELOPMENT AND NEURONAL MIGRATION DISORDER IN HUMANS

Heng, Julian

Curtin Health Innovation Research Institute, Curtin University, Perth, Western Australia, Australia

The development of neural circuits during fetal brain development relies on the timely production of neurons, their correct placement as well as their capacity to form appropriate connections with other brain cells. Abnormal cell migration during fetal brain development can lead to disruptions in the development and functional organisation of neural circuits which subserve mental function. We have identified the heterogeneous ribonuclear protein U-like 2 (HNRNPUL2) as a mediator of cell migration during fetal brain development. Through a series of functional studies in mice, we demonstrate that appropriate levels of HNRNPUL2 are essential to radial migration by neuroprogenitor/stem cells and postmitotic neurons of the embryonic cerebral cortex, and that a rare missense variant likely causes periventricular nodular heterotopia, a neuronal migration disorder in humans. These findings broaden our understanding of the mechanisms for cell migration and support the accurate genetic diagnosis of neuronal migration disorder in humans.

Funding Source: This research was supported by a Career Development Fellowship (ID:1011505) from the National Health and Medical Research Council of Australia.

14:00 - 14:15

SPINAL CORD EPENDYMAL CELLS ARE FUNCTIONALLY HETEROGENOUS AND CONTAIN A SMALL SUBPOPULATION OF NEURAL STEM CELLS

Stenudd, Moa, Sabelström, Hanna and Frisé, Jonas
Karolinska Institutet, Stockholm, Sweden

The neural stem cells in the adult spinal cord are ependymal cells. Ependymal cells self-renew slowly during physiological conditions, but they start dividing rapidly in vitro and after spinal cord injury. After injury, they generate astrocytes in the glial scar and remyelinating oligodendrocytes. Without the injury response by ependymal cells,

spinal cord injuries grow deeper, more neurons die and the normally occurring slight recovery of function is attenuated. Spinal cord ependymal cells are known to show molecular heterogeneity, but it has remained unclear if stem cell properties are shared between all ependymal cells or held only by some. We examined the functional heterogeneity among ependymal cells by fate mapping two small subpopulations that can be recombined and heritably labelled in *Glast-CreER* and *Troy-CreER* mice. We found that *Glast-CreER* recombined cells self-renew inefficiently in vitro, while the *Troy-CreER* recombined population contains almost all efficiently self-renewing cells. Our results suggest the *Glast-CreER* recombined cells act as progenitor cells in vitro, while the *Troy-CreER* recombined subpopulation harbours nearly the entire in vitro stem cell capacity of the adult spinal cord. After spinal cord injury, *Glast-CreER* recombined ependymal cells do not contribute to glial scar formation. On the contrary, we show that *Troy-CreER* recombined ependymal cells divide rapidly to generate astrocytes in the glial scar and oligodendrocytes. Using single-cell fate mapping, we explore the expansion and spread of migrating clones generated from individual *Troy-CreER* recombined ependymal cells. Furthermore, we confirm that *Troy-CreER* recombined ependymal cells typically stay by the central canal when they generate migrating progeny, likely by undergoing asymmetric cell division. We conclude that a subpopulation containing less than 10% of the ependymal cells harbours nearly the entire in vitro neural stem cell capacity of the adult spinal cord. *Troy-CreER* recombined ependymal cells contribute to scar formation after injury and maintain their own population while they generate migrating progeny. The small *Troy-CreER* recombined neural stem cell population may pose an interesting target for therapeutic intervention after spinal cord injury.

Funding Source: Swedish Research Council, the Swedish Cancer Society, the Swedish Society for Strategic Research, Tobias Stiftelsen, AFA Försäkringar, StratRegen at Karolinska Institutet and Torsten Söderbergs Stiftelse.

14:15 - 14:30

MUTATIONS IN *ACTL6B* CAUSE AUTISM AND EPILEPSY AND LEAD TO LOSS OF DENDRITES IN HUMAN NEURONS

Bell, Scott¹, Rousseau, Justine², Peng, Huashan³, Jefri, Malvin³, Wu, Hanrong³, Theroux, Jean-Francois³, Ernst, Carl³ and Campeau, Phillippe²

¹*Integrated Program of Neuroscience, McGill University, Montreal, Canada*, ²*Montreal University, Canada*, ³*McGill University, Montreal, Canada*

We identified nineteen families with undiagnosed neurodevelopmental disorders that all possessed mutations in *ACTL6B*, a crucial regulator of dendrite formation that had not been previously identified to contribute to human disease. Ten families were found to have bi-allelic mutations in *ACTL6B*, presenting symptoms of epileptic encephalopathy and spasticity, and nine families were

found to have de novo heterozygous missense mutations and displayed intellectual disability, autism, and Rett-like stereotypies. Generating iPSC-derived neurons from an affected individual revealed that mutations in ACTL6B result in increased binding of the BAF complex to an enhancer driving increased expression of SEMA4D, a key inhibitor of dendrite outgrowth. Patient cells were also observed to have abnormal cell differentiation, including a profound loss of dendrites. Both the increased SEMA4D expression and loss of dendrites was reversed upon CRISPR/Cas9-mediated mutation correction of the patient line. To examine the effect of ACTL6B on human neuronal development, a CRISPR/Cas9 mediated ACTL6B knock-out (KO) neuronal line was generated, and was observed to also present severe deficits in dendritogenesis and increased SEMA4D expression. Moreover, the introduction of three different ACTL6B mutations identified in patients into ACTL6B KO neurons all resulted in further increases in SEMA4D expression, whereas re-introduction of wild-type ACTL6B resulted in downregulation of SEMA4D expression. This study provides the first ever description of a novel genetic disease caused by mutations in ACTL6B and identifies aberrantly high inhibition of dendritogenesis through SEMA4D signalling as a likely mechanism contributing to the pathology of the disease.

Funding Source: Carl Ernst and Phillippe Campeau are supported by the Canadian Institute for Health Research (CIHR), as well as the Fonds de Recherche en Santé Québec (FRQS).

14:30 - 14:45

TRANSPLANTATION OF HUMAN EMBRYONIC STEM CELL DERIVED DOPAMINERGIC NEURONS IN AN ACCELERATED ALPHA-SYNUCLEIN RAT MODEL OF PARKINSON'S DISEASE

Hoban, Deirdre B.¹, Breger, Ludivine¹, Wahlestedt, Jenny¹, Cardoso, Tiago¹, Mattsson, Bengt¹, Luk, Kelvin², Björklund, Anders¹ and Parmar, Malin¹

¹Lund University, Sweden, ²University of Pennsylvania, Philadelphia, PA, U.S.

Preclinical validation studies to assess the therapeutic potential of human embryonic stem cell (hESC) derived dopaminergic (DA) neurons have mostly been performed in the 6-hydroxydopamine (6-OHDA) model of Parkinson's disease (PD). However, this model does not reflect the pathological features or progressive nature of PD. Here, we aim at assessing how the transplanted cells survive, mature, integrate and innervate the existing circuitry in a novel accelerated model of PD, whereby preformed human alpha-synuclein fibrils and AAV6 human alpha-synuclein are unilaterally injected into the rat substantia nigra. This model gives rise to alpha-synuclein pathology, inflammation and progressive loss of DA cells from the substantia nigra and terminals in the striatum. After allowing the pathology to develop for 8 weeks, we then transplanted hESC-derived DA neurons into the striatum and assessed their survival, maturation, integration and innervation at

6 weeks post-transplant. Post mortem histology revealed that transplanted cells were capable of innervating the dopamine depleted striatum in a similar, biologically-relevant pattern previously seen in the 6-OHDA model. We also used monosynaptic tracing based on modified rabies virus to assess that the pathology present in this model did not inhibit the ability of the graft to integrate into the host circuitry, meaning that the grafted cells are able to receive appropriate and sufficient synaptic contact with the host central nervous system. Finally, on closer examination, we found preliminary evidence of alpha-synuclein pathology in the grafted region of the striatum, indicating possible host-to-graft transfer of alpha-synuclein pathology. Further studies to confirm this observation, and to examine a longer time-point where we can assess the maturation and function of the transplanted cells, and if this is affected by the potential pathology transfer, are currently underway. This will give us a better understanding of the performance of these cells in a more clinically relevant, novel alpha-synuclein model of PD, thus adding to the body of knowledge required as this cell replacement therapy progresses to clinical trials.

Funding Source: New York Stem Cell Foundation (NYSCF); The Swedish Research Council; The European Research Council (ERC); NeuroStemCellRepair (EU); Parkinsonfonden; Bagadilc; MultiPark; Malin Parmar is a NYSCF-Robertson Investigator.

14:45 - 15:10

GDNF ENHANCES THE FUNCTIONAL INTEGRATION OF HUMAN PLURIPOTENT STEM CELL-DERIVED DOPAMINE GRAFTS IN A RAT MODEL OF PARKINSON'S DISEASE

Parish, Clare¹, Gantner, Carlos¹, Kauhausen, Jessica¹, de Luzy, Isabelle R.¹, Niclis, Jonathan¹, Penna, Vanessa¹, Bye, Christopher¹, Pouton, Colin², Kirik, Deniz³ and Thompson, Lachlan¹

¹The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia, ²Monash Institute of Pharmaceutical Sciences, Melbourne, Australia, ³Lund University, Sweden

The derivation of neurotransmitter and region specific neuronal populations from human pluripotent stem cells (hPSC) provides impetus for advancing cell therapies into the clinic. At the forefront is our ability to generate mid-brain dopaminergic (DA) progenitors, suitable for transplantation in Parkinson's disease. However, pre-clinical studies have highlighted the relatively low proportions of DA neurons within these grafts and their inferior plasticity, particularly in comparison to human fetal grafts. Here we sought to examine whether modification of the host environment, through the viral delivery of a developmentally critical molecule, glial cell-line derived neurotrophic factor (GDNF), could improve graft integration and function in Parkinsonian rodents. Utilising LMX1A- and PITX3-GFP hPSC reporter lines, we tracked the response of DA progenitors implanted into either a GDNF-rich environment or following delayed delivery of the neurotrophin. Early

exposure of the graft to GDNF promoted survival of DA and non-DA cells, leading to enhanced motor recovery in PD rats. Delayed overexpression of intrastriatal GDNF also promoted motor recovery in transplanted rats, not through neuroprotection, but alternate selective mechanisms including enhanced DA graft plasticity, increased activation of striatal neurons and elevated DA metabolism. These results highlight the potential of targeted neurotrophic gene therapy strategies to improve hPSC graft outcomes.

FRIDAY, 22 JUNE, 13:15 – 15:15

CONCURRENT IIIC: MECHANISMS OF REPROGRAMMING 2: TRANSDIFFERENTIATION BETWEEN LINEAGES

Room 219/220, Level 2

13:20 – 13:45

CELL-TYPE- AND STAGE-SPECIFIC CONSTELLATIONS OF ENHANCERS CONTROL COMPLEX GENE EXPRESSION PROGRAMS IN THE NERVOUS SYSTEM

Wichterle, Hynek, Closser, Michael, Guo, Xiaoyun, Kopunova, Rachel, Patel, Tulsii, Guo, Yuchun, Rhee, Ho Sung, Ruan, Yijun and Gifford, David

Columbia University, New York, NY, U.S.

Cellular complexity of the nervous system demands a commensurate complexity of the regulatory system controlling cell type-specific patterns of gene expression. Using embryonic stem cell-derived motor neurons we discovered a unique architecture of enhancer elements associated with neuronal genes. Genome-wide maps of enhancer-promoter interactions revealed that most genes induced in motor neurons are regulated by constellations of distributed enhancers spanning extensive genomic territories, rather than by localized super-enhancers. Meta-analysis of regulatory regions associated with genes expressed in other neuronal populations suggests that distributed enhancers are not a unique property of spinal motor neurons, but are broadly employed in the regulation of gene expression within the nervous system. Furthermore, within individual neuronal cell types, these constellations of enhancers are highly dynamic, exhibiting temporal specificity. Together, our findings support the view that neuronal genes are associated with large non-coding genomic territories, accommodating uniquely large numbers of cell-type- and cell-stage-specific regulatory elements controlling complex patterns of gene expression within the nervous system.

13:45 – 14:00

USING A PREDICTIVE COMPUTATIONAL ALGORITHM TO ESTABLISH A UNIVERSAL TRANSCRIPTION FACTOR ENHANCED DIFFERENTIATION FRAMEWORK

Chen, Joseph¹, Tiedemann, Mathew¹, Brewster, Kaitlyn¹, Liu, Xiaodong¹, Manent, Jan¹, Grubman, Alexandra¹, Gough, Julian², Rackham, Owen³, Nefzger, Christian¹, Polo, Jose¹

¹Monash University, Australia ²Cambridge Biomedical Campus, United Kingdom, ³Duke-National University of Singapore Medical School, Singapore

The ability of pluripotent stem cells (PSCs) to generate virtually any cell type in the body holds great promise in regenerative medicine and disease modeling. Many strategies, adapted from our understanding of developmental biology, have aided us in optimizing specific culture conditions that facilitate the differentiation of target cell types. However, in recent years, a number of studies suggested the use of transcription factors (TFs), master regulators of cell identity, to improve the yield, speed and/or specificity of differentiation. These novel TF-based strategies were discovered through empirical testing of a large number of TF combinations that have been associated with the target cell type, a very complex, laborious and inefficient process. Unfortunately, the identification of key TFs to enhance differentiation of PSCs is currently limited to specific cell lineages which have been extensively studied (e.g. neurons, blood and muscle). In spite of this, we and others have previously developed computational frameworks to accurately predict the TFs required for cell conversion into target cell types. We adopted our predictive algorithm, Mogrify, to predict TFs which will enhance the differentiation of PSCs into cells of all three germ layers. We show that co-expression of the predicted key TFs for PSC to keratinocyte differentiation gave rise to cells acquiring keratinocyte-like morphologies and expressing keratinocyte markers (K1 and K14) in half the time compared to the standard baseline differentiation method. Similarly, enhanced differentiation into cells of other germ layers using separate sets of predicted TFs yielded the desired cells in less than half the time compared to control cultures. Through this approach, we have established new enhanced differentiation protocols for a variety of lineages and cell types which were previously unreported. Accordingly, Mogrify enables the identification of key TFs that can enable cell fate conversion as well as develop enhanced differentiation protocols for the generation and enrichment of target cell types from pluripotent stem cells for potential therapeutic downstream applications.

14:00 - 14:15

DIRECT REPROGRAMMING OF MOUSE FIBROBLASTS INTO FUNCTIONAL SKELETAL MUSCLE PROGENITORS

Bar-Nur, Ori¹, Gerli, Mattia², Di Stefano, Bruno², Almada, Albert², Galvin, Amy², Coffey, Amy², Huebner, Aaron², Feige, Peter³, Verheul, Cassandra², Ott, Harald², Tajbakhsh, Shahragim⁴, Rudnicki, Michael³, Wagers, Amy² and Hochedlinger, Konard²

¹Center for Regenerative Medicine, Massachusetts General Hospital, Harvard University, Boston, MA, U.S., ²Harvard University, Boston, MA, U.S., ³Ottawa Health Research Institute, Canada, ⁴Institut Pasteur, Paris, France

Skeletal muscle harbors quiescent stem cells termed satellite cells and proliferative progenitors termed myoblasts, both of which play pivotal roles during muscle regeneration and hold promise for the treatment of muscle-associated disorders. However, current technology does not allow permanent capture of cell populations with myogenic potential *in vitro*. We report that ectopic expression of the myogenic transcription factor MyoD, combined with exposure to three small molecules, readily reprograms mouse fibroblasts into induced myogenic progenitors (iMPCs) that can be propagated extensively while retaining the ability to produce contractile myotubes. Immature iMPCs express markers of skeletal muscle stem and progenitor cells, including Pax7 and Myf5, and can differentiate into Dystrophin-expressing myofibers upon transplantation into a mouse model of Duchenne Muscular Dystrophy. Notably, a subset of transplanted iMPCs maintain Pax7 expression *in vivo* and sustain regenerative responses in a serial injury model, consistent with stem cell-like properties. We further provide evidence that functional progenitor cells can be established from explanted muscle tissue following small molecule exposure alone. These findings reveal a novel and robust approach to derive expandable myogenic stem/progenitor cells with characteristics of satellite cells from different somatic tissues.

14:15 - 14:30

A SOFTWARE TOOL FOR DESIGNING TRANS-DIFFERENTIATION EXPERIMENTS WITH COMBINATIONS OF TRANSCRIPTION FACTORS

Appleton, Evan¹, Ng, Alex² and Church, George²

¹Department of Genetics, Harvard Medical School, Boston, MA, U.S., ²Harvard Medical School, Boston, MA, U.S.

A current focus in the stem cell field is to develop methods for direct cell-type conversions. This can be accomplished in a variety of ways including surface-condition based methods, media growth factor methods and genetic methods. Many recent successes rely primarily on the use of genetic methods - specifically directed differentiation via transcription factor (TF) over-expression.

When using TF over-expression based methods, a majority of the work comes down to identifying the subset of TFs in the genome that can successfully convert cell type 'A' to cell type 'B' when overexpressed. Historically this identification process has been rooted in expert knowledge from groups that had extensive expertise in the genetics of one or more cell type. While this approach has resulted in some significant successes, these methods are generally low-throughput and many valuable conversions are still unknown. Furthermore, recent work in our group has resulted in the definition and production of a 'TFome' of all known TFs in the human genome composed of ~1768 genes - thus exhaustively screening all possible combinations of TFs of even a relatively small size is essentially impossible with current methods. Some recent efforts have instead attempted to approach this problem computationally using transcriptomics data to identify TF combinations that are likely candidates to perform a specific conversion, although these methods have a few key limitations - they exclusively rely on sometimes sparse transcriptomics data, they output one final solution as opposed to an experimental design, they do not leverage other types of next-generation sequencing data, and they have no intrinsic feedback loop for evaluating outcomes to automatically design the next round of experiments. Here we present a software tool that uses open-chromatin data and transcriptomics data to output an experimental design in which a subset of the human TFome is multiplexed to identify cells that seem to be most successful in that screen. The most promising candidates from this screen are then sequenced for RNA expression and open chromatin and the data is used to inform the next multiplex experiment. This tool is first being applied to known TF-based conversions, but is being developed as generally as possible for use as a tool for any desired novel conversion.

Funding Source: This work was funded under the IARPA Fun GCAT Program PTE Federal Award No: W911NF-17-2-0089.

14:30 - 14:45

MITOCHONDRIAL DYNAMICS DETERMINES HUMAN EMBRYONIC STEM CELL FATES

Lacey, Joanne¹, Hill, Christopher¹, Mortiboys, Heather¹, Rodriguez, Tristan² and Barbaric, Ivana¹

¹University of Sheffield, UK, ²Imperial College London, UK

Human pluripotent stem cells (hPSCs) may provide an unlimited source of cells of therapeutically relevant cell types, due to their ability to self-renew *in vitro* for long periods of time, whilst retaining the ability to differentiate into all of the cell types in the body. Unlocking the therapeutic potential of hPSCs relies on our ability to control stem cell fates, i.e. self-renewal, differentiation and death. However, the detailed molecular mechanisms governing the stem cell fate decisions remain largely unknown. Given the importance of mitochondria for multiple essential cellular processes, such as energy metabolism and apoptosis, we posited that mitochondrial dynamics can influence hPSC fate decisions. Mitochondria are dynamic

organelles which undergo cycles of fusion (mediated predominantly by MFN1, MFN2 and OPA1) and fission (mediated by DRP1). In order to elucidate the effects of mitochondrial dynamics on hPSC fate determination, we have used CRISPR-Cas9 genome editing to generate knock out cell lines of the mitochondrial fusion (MFN1, MFN2 and OPA1) and fission (DRP1) factors. We show that deletion of MFN1, MFN2, OPA1 and DRP1 generates distinct mitochondrial fragmentation and fusion phenotypes. Our preliminary data supports our hypothesis that mitochondrial shape impacts stem cell fate decisions. Lending weight to this hypothesis is our finding that the spontaneously arisen genetic variants in hPSC cultures display distinct mitochondrial phenotypes linked to improved survival and reduced differentiation of variant cells. Overall, our findings provide important insights into the underlying mechanisms of stem cell maintenance, which has important implications for the translational goals of hESC research for regenerative medicine.

Funding Source: This work was supported by a grant from the Medical Research Council (MR/N 009371/1).

14:45 – 15:00

HYPERTRANSCRIPTION DRIVES CELLULAR REPROGRAMMING

Babos, Kimberley N.¹, Galloway, Kate² and Ichida, Justin²

¹*Department of Development, Stem Cells, and Regenerative Medicine, University of Southern California, San Gabriel, CA, U.S.*, ²*University of Southern California, Los Angeles, CA, U.S.*

Cellular reprogramming requires massive transcriptional realignment, and only a small fraction of cells successfully process the demands of transcription factor-mediated reprogramming to convert into an alternative cellular identity. We examined the cellular processes that drive reprogramming to identify why conversion rarely occurs. Previous work in iPSC reprogramming identified fast-cycling, hyperproliferating cells as a privileged population. To determine how hyperproliferating cells contribute to conversion to a post-mitotic cell type, we isolated hyperproliferating cells undergoing conversion to induced motor neurons (iMNs). We observe that hyperproliferating cells reprogram to iMNs with significantly higher frequency. Genetic perturbation via a p53 mutant (p53DD) significantly increases the population of hyperproliferating cells and magnifies conversion 100-fold. We also find that addition of p53DD provides an extensive reprogramming boost across species and protocols. In investigating the mechanisms that promote reprogramming, we identified hypertranscription is a primary driver of conversion. By measuring transcription rate through 5-ethynyl uridine incorporation, we observe that addition of the reprogramming factors induces a wave of hypertranscription early in reprogramming. Inclusion of p53DD sustains the window of hypertranscription. By driving a global transcriptional increase using an hRASV12 mutant, conversion is significantly enhanced. We identified a rare population of hyperproliferating, hypertranscribing cells (HHCs). The

population size of HHCs in converting cultures correlates with conversion efficiency. By profiling cells early in conversion, we find that cells driven with hypertranscription increase expression of transcriptional machinery and DNA repair pathways. We specifically identify topoisomerase expression as a key parameter modulating the cell's ability to maintain the population of HHCs by balancing hypertranscription and hyperproliferation. Finally, hypertranscription significantly increases functional and molecular properties of engineered cells to mimic their in vivo surrogates. By providing the context to drive and sustain hypertranscription, we robustly generate reprogrammed cells with signatures of maturity.

FRIDAY, 22 JUNE, 13:15 – 15:15

CONCURRENT IIID: HEMATOPOIESIS

Room 212/213, Level 2

13:20 – 13:45

MODELING NORMAL AND MALIGNANT HAEMATOPOIESIS USING HUMAN PLURIPOTENT STEM CELLS

Elefanty, Andrew George, Ng, Elizabeth, Bruveris, Freya, Nafria I Fedi, Monica, Leitoguinho, Ana Rita, Motazedian, Ali, Kusur, Jasna, McDonald, Penny, Labonne, Tanya and Stanley, Edouard

Murdoch Children's Research Institute, Parkville, VIC, Australia

It has been an ongoing challenge to dissect the mechanisms underlying the normal development of haematopoiesis. Even with access to developing embryos, the replication of the processes that guide a cell from pluripotency to mesoderm to either an extra- or an intra-embryonic haemogenic endothelium and then to yolk sac-like or AGM-like blood cells have remained very difficult. In this presentation I will discuss what we have learnt about the steps involved in these processes from studies using gene-targeted and reporter cell lines. Finally, we have begun to model human leukaemias in vitro and I will share data from our latest insights on the initial steps of the neoplastic process.

13:45 - 14:00

YAP REGULATES HEMATOPOIETIC STEM CELL FORMATION IN RESPONSE TO THE BIOPHYSICAL FORCES OF BLOOD FLOW

Lundin, Vanessa¹, Theodore, Lindsay², Wrighton, Paul³, Sousa, Patricia², Han, Areum², Hwang, Katie³, Goessling, Wolfram³, Ingber, Donald⁴, Daley, George² and North, Trista²

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Hematopoietic stem cells (HSCs) are specified during embryonic development from hemogenic endothelial cells (HEC) along the ventral surface of the dorsal aorta (VDA). Prior studies from our labs demonstrated that HSC emergence follows the onset of blood flow, which exposes the vascular endothelium to biomechanical forces. To better understand how these forces drive HSC production, we engineered a human biomimetic aorta-on-a-chip platform and subjected induced pluripotent stem cell (iPS)-derived HEC to wall shear stress (WSS) or circumferential stretch (CS). RUNX1, the main transcription factor involved in HSC specification, was upregulated by both WSS and CS compared to static control cells. Interestingly, YAP (Yes-associated protein) target genes ANKRD1 and CTGF were also upregulated after exposure to CS; this induction was abolished in the presence of a Rho inhibitor, indicating a role for Rho-YAP mechano-transduction in mediating the effect of blood flow on HECs. To determine whether these findings pertain *in vivo*, we utilized an inducible zebrafish Yap overexpression (Yap-OE) model, which significantly increased runx1+ in the VDA. This effect was sustained throughout development, as Yap-OE also significantly increased the number of Cd41+ HSCs in the caudal hematopoietic tissue as well as rag1+ lymphoid progenitors in the thymus. Similar results were found following knockdown of *lats1/2*, negative regulators of endogenous Yap. In contrast, *yap*^{-/-} knockout embryos exhibited a significant reduction in runx1 expression. Activation of Yap through Rho-GTPase stimulation significantly increased runx1 expression in silent heart morphant embryos that lack circulation, but was ineffective in *yap* mutants, indicating that Rho-Yap influences HSC formation downstream of blood flow. *In vitro*, YAP activation in iPS-derived HEC mediated via Rho-GTPase stimulation or LATS1/2 knockdown increased RUNX1 levels and colony forming potential, demonstrating that biophysical forces from blood flow can be mimicked by YAP modulation. Together, our findings reveal a functional intersection between mechano-transductive Rho-YAP activation and RUNX1-dependent HSC production, which may be exploited to improve *in*

vitro human HSC differentiation protocols from pluripotent stem cell sources.

14:00 - 14:15

LIVER-DERIVED SYSTEMIC THROMBOPOIETIN IS REQUIRED FOR BONE MARROW HEMATOPOIETIC STEM CELL MAINTENANCE

Ding, Lei, Decker, Matthew, Leslie, Juliana and Liu, Qingxue

Columbia University Medical Center, New York, NY, U.S.

Hematopoietic stem cells (HSCs) depend on extrinsic cues for their maintenance. Currently, only local signals from the bone marrow niche have been shown to sustain adult HSCs. This has raised the fundamental question of whether systemic factors may play critical roles in HSC maintenance. We assessed the *in vivo* functional source of thrombopoietin (TPO), a key cytokine required for maintaining bone marrow HSCs. It was previously shown that Tpo translation is under stringent control. We engineered a novel Tpo^{DsRed-CreER} knockin mouse by recombining DeRed and CreER into the endogenous locus of Tpo. This is the first genetic tool for *in vivo* labeling of cells that translate Tpo transcripts. We found that TPO protein was expressed in liver hepatocytes but not cells in the bone marrow. To functionally identify the physiological source of Tpo *in vivo*, we generated a floxed allele of Tpo and conditionally deleted it from a variety of candidate cell populations. Deletion of Tpo from hematopoietic cells, osteoblasts, or bone marrow mesenchymal stromal cells did not affect HSC number or function. Strikingly, when Tpo was deleted from hepatocytes, HSCs were nearly completely depleted from the bone marrow. Inducible deletion of hepatic Tpo in adult mice by a hepatocyte-specific Cre-bearing adenovirus had the same effect as deletion by a transgenic Cre line. This suggests a continuous, rather than developmental, dependence on hepatic TPO. Thus a long-range regulatory factor - systemic TPO made in the liver by hepatocytes - is required for adult bone marrow HSC maintenance.

14:15 - 14:30

THE SPLICEOSOMAL COMPONENT SF3B1 IS ESSENTIAL FOR ZEBRAFISH HEMATOPOIETIC STEM CELL FORMATION THROUGH REGULATION OF THE JAK/STAT SIGNALING PATHWAY

Potts, Kathryn S.¹, Cameron, Rosannah², McKinstry, Mia¹, Gupta, Varun¹, Bai, Xiaoying³ and Bowman, Teresa¹

¹*Albert Einstein College of Medicine, Bronx, NY, U.S.*, ²*Ferrier Research Institute, Victoria University of Wellington, Wellington, New Zealand*, ³*University of Texas, Dallas, TX, U.S.*

Hematopoietic stem cells (HSCs) sustain multilineage hematopoiesis for the lifetime of an organism. During em-

bryogenesis, HSCs emerge from specialized hemogenic endothelial (HE) cells in the dorsal aorta through an endothelial-to-hematopoietic transition (EHT). While much is known about transcription factors in HSC specification, it is poorly defined how RNA processing influences HSC fate choices. Using zebrafish loss-of-function mutants for the spliceosomal component splicing factor 3b, subunit 1 (sf3b1), we identified that impaired splicing hindered HSC production, specifically at the EHT. Loss-of-function sf3b1hi3394 mutants have diminished expression of HE and HSC markers runx1 and gata2b at 24 hours post fertilization (hpf) and cd41:gfp+ HSCs are significantly reduced by flow cytometry. However, the pan-endothelial marker kinase insert domain receptor-like (kdrl) and the aorta-specific markers notch1b and notch3 are expressed normally. Therefore, although sf3b1 is ubiquitously expressed, HE and HSCs are more sensitive to its loss than other endothelial cells. We performed RNA-sequencing on purified kdrl:gfp+ endothelial cells from sf3b1 mutant and wildtype siblings at 24 hpf. Nearly 900 genes were mis-spliced, 144 of which were differentially expressed. Many of these genes are involved in mRNA processing and Janus Kinase (Jak)/Signaling Transducer and Activator of Transcription (Stat) signaling, including interleukin 6 signal transducer (il6st), the gene encoding the IL6-family common receptor Glycoprotein 130 (Gp130). To determine if mis-spliced il6st was sufficient to perturb HSCs, we used antisense morpholino (MO) injections and CRISPR/Cas9 mutagenesis. il6st MO-injected wildtype embryos mimicked the il6st exon-skipping event observed in sf3b1 mutants. HSC quantitation by cd41:gfp+ flow cytometry and runx1 and gata2b in situ hybridization revealed significantly diminished HSCs, phenocopying the sf3b1 mutants. Stat3 is a major transcription factor mediating Gp130-activated gene expression. Consistent with this role, we found that overexpression of a constitutively active form of Stat3 significantly suppressed the HSC defects in sf3b1 mutants. Together, these data indicate that Sf3b1-mediated splicing regulation of the Jak/Stat pathway is critical for HSC emergence.

Funding Source: Gabrielle's Angel Foundation, American Cancer Society RSG-129527-DDC, Kimmel Foundation, the EvansMDS Foundation, the New York State Department of Health Contract C30292GG, and the National Institute of Health.

14:30 - 14:45

ROS SUPPRESSION THROUGH P53 ACTIVITY AND A REMODELED MITOCHONDRIAL NETWORK DETERMINES THE FATE OF FUNCTIONAL HUMAN HEMATOPOIETIC STEM CELLS DURING EX-VIVO EXPANSION

Papa, Luena¹, Djedaini, Mansour², Zimran, Eran², Ge, Yongchao², Sebra, Robert², Sealfon, Stuard² and Hoffman, Ronald²

¹Hematology/Oncology, Mount Sinai, New York, NY, U.S., ²Mount Sinai, New York, U.S.

The development of ex-vivo strategies to expand human hematopoietic stem cells (HSCs) is needed to increase the limited numbers of HSCs present in umbilical cord blood (UCB) units that are used for allogeneic transplantation. Such strategies are intended to generate HSCs with metabolic and gene expression profiles that closely resemble fully functional HSCs. Recently, we have shown that ex-vivo treatment of UCB-CD34⁺ cells with a combination of cytokines and valproic acid (VPA) increases substantially the numbers of functional HSCs, which contribute to long-term multilineage hematopoietic reconstitution in NSG mouse models. In this report, we demonstrate that VPA treatment orchestrates and coordinates cellular mechanisms that drive UCB-CD34⁺ cells into a primitive state in which they acquire and retain phenotypic, transcriptomic and primitive mitochondrial profiles, all of which are characteristics of long-term HSCs. High throughput RNA-seq performed with both single cells and a bulk of CD34⁺ cells revealed that VPA triggers the transcription of long-term HSC phenotypic markers. The VPA-expanded cells exhibited a transcriptomic profile that is distinct from that of the uncultured UCB-CD34⁺ cells since it is highly enriched for gene sets that comprise long-term human HSC signatures. UCB-CD34⁺ cells acquire this HSC profile during early periods of treatment with VPA and can retain it while HSC numbers increase. Remarkably, our data link the acquisition of the HSC phenotype to the remodeling of the mitochondrial network and p53 activation and establish both as critical regulators of ROS, a determinant of the HSC fate. The expanded HSCs obtained a low mitochondrial mass, reduced membrane potential and low ROS levels. Conversely, loss of this HSC phenotype is coupled to an increased mitochondrial activity. Our data demonstrates that a further decrease in the mitochondrial activity and ROS generation enhances the capacity of VPA to trigger acquisition and maintenance of the stem cell status. VPA activates antioxidant defense mechanisms that rely on the p53-MnSOD axis. Failure to activate the p53-MnSOD axis compromised HSC expansion. These studies indicate that ROS suppression through the coordination of p53 activity and mitochondrial remodeling determines the fate of HSCs during ex-vivo expansion with VPA.

Funding Source: NYSTEM.

14:45 - 15:00

CONSTITUTIVE DELETION OF AP2A2 RESULTS IN FETAL LIVER HAEMATOPOEISIS EXHAUSTION DUE TO LOSS OF HSC QUIESCENCE AND PERTURBED ASYMMETRICAL:SYMMETRICAL HSC FATE

Ting, Stephen¹ and Rhost, Sara²

¹Australian Centre for Blood Diseases, Monash University, Melbourne, VIC, Australia, ²Monash University, Melbourne, VIC, Australia

We identified the polarity gene, Ap2a2 as an enhancer of mouse long-term HSC function via a candidate over-expression / transplantation screen, and a potential HSC cell fate determinant during live cell HSC videomicroscopy.

py. We hypothesised Ap2a2-transduced HSCs acquired in-vitro quiescence. Using the Tet-On H2B-GFP mouse line where HSC self-renewal is restricted to dormant GFP-high (CD150⁺48⁻LSK - SLAM) HSCs - We transduced vector versus Ap2a2 into H2B-GFP HSCs for an in-vivo pulse-chase transplantation assay. This showed a relative 3-fold increase in the dormant GFP-high SLAM HSC subpopulation of Ap2a2-transduced HSC recipients. We also present two new mouse transgenic lines: an Ap2a2-LacZ reporter and constitutive Ap2a2 knock-out (KO). X-Gal/FDG staining of bone marrow (BM) cells confirmed higher endogenous Ap2a2 expression in LT-HSCs via lacZ mean fluorescence intensity in the SLAM long-term (LT-) versus short-term (ST- CD150⁺48⁻LSKs) HSCs. Analyses of heterozygote Ap2a2 KO matings with an expected 25% Ap2a2^{-/-} Mendelian inheritance showed an Ap2a2^{-/-} frequency at E14.5 (N=164 embryos); E16.5-E18.5 (N=114 embryos) and at weaning (N=148 mice) of respectively, 30%; 19%; 11%. E14.5 Ap2a2^{-/-} embryos had smaller livers but twice as many LT-SLAM HSCs, which was confirmed by limit dilution assay (Ap2a2^{+/+} 1/150,891; Ap2a2^{-/-} 1/78,971 via ELDA). Ki67/DAPI cell cycle analyses showed specific loss of G0 in E14.5 LT- versus ST-HSCs. At E16.5-E18.5, there were embryonic Ap2a2^{-/-} survivors and non-survivors with now, no difference in FL LT-HSC absolute numbers, but survivor FL LT-HSCs showing recuperated G0 with differentiation (i.e. equivalent to Ap2a2^{+/+} total FL cells) as opposed to resorbed non-survivor embryos with continued loss of G0 and failed differentiation. Functionally, E14.5 Ap2a2-null FL cells have maintained in-vitro and in-vivo splenic colony formation but significantly impaired competitive transplant reconstitution. Numb staining of Ap2a2^{-/-} E14.5 LT-HSCs showed perturbed asymmetrical to symmetrical divisions. We conclude Ap2a2 is crucial for stage-specific FL HSC expansion via maintenance of a G0 quiescent HSC subpopulation that links HSC fate/differentiation and with constitutive Ap2a2 deletion - an in-vivo FL HSC exhaustion phenotype ensues.

Funding Source: NHMRC project grants 1006420 and 1047554; NHMRC RD Wright, Career Development Grant.

FRIDAY, 22 JUNE, 13:15 – 15:15

CONCURRENT IIIIE: STEM CELLS IN ORGAN DEVELOPMENT AND MAINTENANCE

Room 203/204, Level 2

13:20 – 13:45

SPERM STEM CELLS: THEIR CONTEXT-DEPENDENT BEHAVIOR

Yoshida, Shosei

National Institute for Basic Biology, Aichi, Japan

Tissue stem cells play different roles in different contexts: in addition to the homeostasis of cycling tissues, stem

cells also support post-insult regeneration or post-transplantation repopulation. This motivates the potential use of stem cells for applications. Interestingly, it has been known in many tissues that different populations of cells contribute differently to these stem cell functions, although the same term “stem cells” is used. In particular, differentiation-destined populations may retain the stem cell potential, and revert back to the self-renewing pool with high probability on regeneration or transplantation. Mouse spermatogenesis is amongst such tissues whose study revealed the context-dependent behaviors of tissue stem cells. Among a number of advantages of this system for tissue stem cell research, it should be emphasized that this may be the only tissue in which the stem cell behavior can be analyzed at a single cell resolution, using pulse-labeling and live-imaging studies, both in homeostasis and after transplantation. In this session, the behavior of sperm stem cells following transplantation into germ cell-depleted host testes will be discussed in comparison with that in homeostasis. Further, our attempt to modulate their fates to enhance the potential usefulness of transplantation will be introduced.

13:45 – 14:00

ATR MEDIATED REPLICATION-STASIS CONTROLS MUSCLE STEM CELL QUIESCENCE

Salvi, Jayesh, van Velthoven, Cindy, Antoine de Morree, Antoine and Rando, Thomas
Stanford University, CA, U.S.

A distinguishing feature of adult mammalian stem cells is their ability to remain in a non-cycling, quiescent state. Muscle stem cells (mSCs) are a prime model of quiescent stem cells and are required for skeletal muscle regeneration. Understanding of quiescence regulation in mSCs is limited, and it is unclear what factors prevent the initiation of DNA replication and cell-cycle entry in the quiescent state. Furthermore, the molecular checkpoints that regulate the transition of mSCs from a quiescent to activated state remain uncharacterized. To gain insight into mSC quiescence we utilized TU (thiouracil) and Ribosome-tag sequencing to label nascent RNA transcripts in vivo and sensitive capillary western blot techniques to confirm protein expression ex vivo. Surprisingly, we find that multiple replication associated factors are transcribed and translated in quiescence. Intriguingly, mSCs display hallmarks of stalled replication, namely punctate RPA foci. Concurrently, we find that the replication stress response protein, ATR (Ataxia Telangiectasia and Rad3-Related Protein) is abundant and active in quiescent but not activated mSCs, suggesting quiescent mSCs are in a state of replication stress. To discern the role of ATR in mSCs we generated mSC specific conditional ATR knockout mice. ATR ablation results in increased mSC proliferation as measured by EDU incorporation and ki67 staining. Moreover, we observe increased number and clusters of mSCs on single myofibers in ATR knockout but not wild-type mice. Importantly, over-expression of an ATR activating protein, ETAA1 (Ewings Tumor-Associated Antigen 1) suppresses mSC proliferation in wild-type but not ATR ablated cells.

These data suggest that ATR induces replication-stasis to maintain quiescence and that ATR activity can be manipulated to control mSC cell-cycle entry and proliferation. We propose a model in which mSCs are poised for replication and the ATR cascade fulfills a novel role in repressing premature stem cell activation. To further elucidate the mechanism by which ATR governs mSC quiescence we will perform phosphoproteomic analysis and aim to discover novel factors involved in stem cell maintenance that may lead to targeted therapeutics for treatment of diseases such as muscular dystrophies.

Funding Source: Human Frontier Science Program - Long-term Fellow.

14:00 - 14:15

IDENTITY AND DYNAMICS OF MOUSE MAMMARY STEM CELLS DURING BRANCHING MORPHOGENESIS

Scheele, Colinda¹, Hannezo, Edouard², van Rheenen, Jacco¹ and Simons, Benjamin³

¹Netherlands Cancer Institute, Amsterdam, Netherlands, ²IST Austria, Vienna, Austria, ³Cavendish Laboratory, Cambridge, UK

During puberty, the mouse mammary gland develops from a small rudimentary tree into a highly branched epithelial network of ducts. Much effort has been invested in finding mammary stem cell (MaSC) markers, but so far a unifying MaSC marker is lacking. Owing to the absence of exclusive stem cell markers, the number, location, fate, and dynamics of MaSCs, which drive branching morphogenesis, are unknown. Therefore, we developed a unique multi-disciplinary approach to define the identity of MaSCs during pubertal mammary morphogenesis. Using unbiased lineage tracing, in vivo imaging, whole gland reconstructions, single cell mRNA sequencing, and modelling we determined the dynamics of mammary gland morphogenesis from a single MaSC level to the organ scale. Using this combination of tools, we uncovered for the first time the identity and dynamics of the MaSCs that drive pubertal mammary gland development. On the single cell level we found that the majority of terminal end bud cells function as highly proliferative, lineage-committed MaSCs that are heterogeneous in their expression profile and short-term contribution to ductal extension. Yet, through cell rearrangements during terminal end bud bifurcation, each MaSC is able to contribute actively to long-term growth. On the organ scale, based on quantitative analyses of large-scale mammary gland reconstructions, we built a model to quantitatively explain how the MaSCs together drive the growth and the shape of the mammary gland. We found that branching follows from the proliferation of equipotent terminal end buds that stochastically branch, and randomly explore their environment. Growing terminal end buds compete for space, and become proliferatively inactive when in close proximity with neighboring ducts. This simple model of branching and annihilating random walks explains all features and heterogeneity in size and branching patterns observed in

mammary glands. Together, our study shows that the behavior of MaSCs is not directly linked to a single expression profile. Instead, morphogenesis relies upon heterogeneous MaSC populations that together drive the complex branched epithelium, which develops as a self-organized process without the need of a deterministic sequence of genetically programmed events.

14:15 - 14:30

EVOLUTIONARILY DISTINCTIVE MECHANISMS OF HUMAN GERM CELL LINEAGE SPECIFICATION

Kojima, Yoji¹ and Saitou, Mitinori²

¹Department of Life Science Frontiers, Center for iPS Cell Research and Application (CiRA), Kyoto, Japan, ²Faculty of Medicine, Kyoto University, Kyoto, Japan

Little has been known about germ cell specification in human since it occurs shortly after implantation and unapproachable. Here, we established knockout hiPSCs by introducing frame shift mutation in the developmental genes using CRISPR/Cas9 system, and performed the induction of human primordial germ cell-like cells (hPGCLCs) from hiPSCs via a state named incipient mesoderm-like cells (iMeLCs). By analyzing the differentiation competency of these knockout lines and the transition of their transcriptome towards hPGCLCs, we have elucidated the hierarchy of transcription factors and signaling pathways for germ cell specification in human that is different from that of well-studied mice system. Human PGCLCs specification does not require T as in mice, but instead, T-box family member EOMES activates the expression of SOX17, which in turn, induces BLIMP1 expression, the driver of the downstream germ cell genes such as NANOS3. Furthermore, TFAP2C which act downstream of BLIMP1 in mice, is expressed earlier than BLIMP1 in human. It is activated by BMP signaling in a SOX17-independent manner, and is required not to initiate but to maintain the expression of BLIMP1. Our findings elucidate the evolutionarily divergence in molecular cascade of germ cell specification and provides foundation for further study of human germ cell development.

14:30 - 14:45

ESTROGEN REGULATES HEPATOBILIARY FATE DECISIONS DURING VERTEBRATE DEVELOPMENT

Goessling, Wolfram¹, Chaturantabut, Saireudee², Shwartz, Arkadi², Garnaas, Maija², Labella, Kyle², Cutting, Claire², Carroll, Kelli³, Budrow, Nadine², Palaria, Amrita⁴, Gorelick, Daniel⁵, Tremblay, Kimberly⁴ and North, Trista³

¹Genetics Division, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, U.S., ²Brigham and Women's Hospital/Harvard Medical School, Boston, MA, U.S., ³Boston Children's Hospital, Boston, MA, U.S., ⁴University of Massachusetts, Amherst, MA, U.S., ⁵Baylor College of Medicine, Houston, TX, U.S.

During liver development, bipotential progenitor cells called hepatoblasts differentiate into hepatocytes and biliary epithelial cells (BECs) to ensure a functional liver required to maintain organismal homeostasis. The developmental cues controlling the differentiation of committed progenitors into these cell types are incompletely understood. Here, we discover an essential role for estrogen in vertebrate liver development to regulate hepatobiliary fate decisions. Exposure of zebrafish embryos to 17 β -estradiol (E2) during liver development from 48-72 hours post fertilization significantly decreased hepatocyte-specific gene expression, liver size, and hepatocyte number. In contrast, pharmacological blockade of estrogen synthesis or nuclear estrogen receptor signaling enhanced liver size and hepatocyte marker expression. Transgenic reporter fish demonstrated nuclear estrogen receptor activity in the developing liver. Chemical inhibition and morpholino knockdown of nuclear estrogen receptor 2b (*esr2b*) increased hepatocyte gene expression and blocked the effects of E2. Engineered *esr2b*^{-/-} mutant zebrafish exhibited significantly increased hepatocyte lineage markers with no impact on liver progenitor specification. Time-lapse imaging of bigenic hepatocyte-biliary reporter fish after E2 exposure revealed enhanced biliary epithelial differentiation at the expense of hepatocyte fate, while genetic loss of *esr2b* impaired biliary lineage commitment. E2 enhanced BMP activity, as demonstrated in fluorescent reporter fish and by p-SMAD Western blot, while the BMP inhibitor dorsomorphin reversed the E2-induced effects on hepatobiliary fate, demonstrating the importance of BMP in mediating the estrogen effect. To demonstrate evolutionary conservation, human iPSC-derived hepatoblasts were exposed to E2 or the ESR modulator fulvestrant: estrogen increased biliary differentiation at the expense of hepatocytes, while ESR blockade had an inverse effect. Our studies identify E2/ESR2/BMP signaling as an important regulator of hepatobiliary fate decisions during vertebrate liver development. These results have significant clinical implications for infants exposed to estrogenic compounds during pregnancy and in vitro differentiation of hepatocytes and biliary cells.

Funding Source: NIH R01DK090311; PEW Charitable Trusts.

14:45 – 15:10

THE ROLE OF DISTINCT POPULATIONS OF MUSCLE STEM CELLS DURING REGENERATION AND ORGAN GROWTH

Currie, Peter

Australian Regenerative Medicine Institute, Melbourne, VIC, Australia

Skeletal muscle is an example of a tissue that deploys a self-renewing stem cell, the satellite cell, to effect regeneration. Recent in vitro studies have highlighted a role for asymmetric divisions in renewing rare “immortal” stem cells and generating a clonal population of differentiation-competent myoblasts. However, this model has lacked in vivo validation. We have defined a zebrafish muscle stem cell population analogous to the mamma-

lian satellite cell and image the entire process of muscle regeneration from injury to fiber replacement in vivo. This analysis reveals complex interactions between satellite cells and both injured and uninjured fibers and provides in vivo evidence for the asymmetric division of satellite cells driving both self-renewal and regeneration via a clonally restricted progenitor pool. In contrast to regeneration, organ growth requires a careful balance between cell commitment and stem cell self renewal to maintain tissue growth trajectories. While the processes that regulate resident stem cells during regeneration and disease have received much attention, the basis of stem cell deployment during organ growth remains poorly defined. Using imaging and fate mapping techniques in zebrafish we identify a lifelong stem cell pool that exhibits extensive clonal drift, shifting from the random deployment of a large population of stem cells during larval growth, to the reliance on a small number of dominant stem cell clones to fuel adult muscle growth. We further reveal that self renewal and clonal drift of growth specific muscle stem cells requires the activity of specific genes and cell cycle control. We define a distinct mechanism for the regulation of the stem cells required for organ growth and in the process provides a molecular understanding of the mechanisms underlying clonal drift in vivo.

FRIDAY, 22 JUNE 13:15 – 14:55

CONCURRENT IIIF: ETHICS AND REGULATORY CONSIDERATIONS

Room 106, Level 1

13:20 – 13:35

“YOU MUST CLICK THE BUTTON AND DONATE”: ONLINE CROWDSOURCING TO FUND UNPROVEN STEM CELL TREATMENTS

Tanner, Claire¹, Sipp, Doug², Turner, Leigh³ and Munsie, Megan⁴

¹Centre for Stem Cell Systems, The University of Melbourne, VIC, Australia, ²RIKEN Center for Developmental Biology, Kobe, Japan, ³Centre for Bioethics, University of Minnesota, Minneapolis, U.S., ⁴The Centre for Stem Cell Systems, The University of Melbourne, Australia

Many people who undergo unproven stem cell-based interventions seek financial support from their communities to fund what are often costly treatments and associated expenses. Crowdsourcing has been identified as a key way people raise funds for a host of medical treatments, however little is known about people’s use of online fundraising sites to fund unproven stem cell-based interventions. This paper draws on quantitative and qualitative data collected from two popular contemporary fundraising sites (GoFundMe.com and YouCaring.com) in order to garner insight how these sites are being used across different geographical locations to fund purported ‘stem

cell treatments' that have no or weak scientific basis. In addition to mapping the use and success of these online campaigns by people with different health conditions in different locations, we consider the range of visual and discursive techniques that are employed to attract funds for treatments. In so doing we consider how the practices of online crowdsourcing enact certain 'realities' about potential patients, stem cells and their therapeutic potential. To conclude we consider the socio-cultural and ethical implications of online crowdsourcing for non-evidenced based treatments in the context of national and global healthcare.

13:35 - 13:50

THE VIEWS AND PRACTICES OF AUSTRALIAN DOCTORS ON THE MANAGEMENT OF PEOPLE'S PURSUIT OF UNPROVEN STEM CELL-BASED INTERVENTIONS

Fahd, Saad, Munsie, Megan, Tanner, Claire and Temple-Smith, Meredith

The University of Melbourne, VIC, Australia

The phenomenon of stem cell tourism - where people are travelling domestically and abroad to seek purported stem cell 'treatments' with little to no evidence of safety and or benefit- has been recognised as a significant issue that exposes people to the risk of financial exploitation, physical and psychological harm. Patient handbooks exist to support patients in these positions, and suggest they seek advice from their treating doctor or General Practitioner (GP) when contemplating stem cell-based interventions (SCBIs). However, little is known about GP's views on or knowledge about SCBIs, or their experiences fielding patient enquiries about them. To address this gap, our qualitative study explores the experiences, views and practices of Australian GPs in the management of people's pursuit of unproven SCBIs. Sixteen GPs participated in semi-structured interviews. The study found that GPs are often faced with enquiries about SCBIs and lack confidence in responding to them. GP's responses to enquiries about SCBIs also varied - ranging from encouraging/discouraging the pursuit of SCBIs, to leaving the decision to pursue SCBIs to the patient. The adoption of the latter position may be leaving vulnerable patients independently navigating the complex information about these costly and risky non-evidenced based treatments. Such findings highlight the need for future development of tailored resources for GPs, and appropriate dissemination strategies to maximise their use by GPs, in order to better equip them with the necessary tools to improve their care of people considering undergoing these treatments. These steps are critical for assisting Australian GPs in providing adequate and consistent support for patients contemplating SCBIs.

13:50 - 14:05

STEM CELL REGISTRIES: SCIENCE OR SCIENTISM?

Hendl, Tereza^{1,2}, Lipworth, Wendy³, Munsie, Megan², Kerridge, Ian³ and Lysaght, Tamra⁴

¹*Sydney Health Ethics, The University of Sydney, Australia* ²*The University of Melbourne, VIC, Australia*, ³*The University of Sydney, Australia*, ⁴*The National University of Singapore, Singapore*

Autologous stem cell therapy is a contested area. Discussions about it centre to large extent on the appropriateness of "innovating" outside the context of clinical trials. Supporters of unregulated access to autologous stem cell interventions have argued for freedom to innovate outside of clinical research. However, critics of the weakly regulated stem cell market have argued that experimental interventions should only be offered outside the formal context of clinical trials if scientific data is collected in order to assess safety and efficacy in the "real world". In response, the stem cell industry has established registries collecting data about stem cell interventions and argued that these registries validate "innovative" clinical practice with autologous stem cells. In this presentation, we challenge the notion that stem cell registries substitute for research. Drawing on a critical exploration of established registries collecting data about clinically unproven stem cell interventions, and their comparison with registries tracking clinically proven and justified treatments, we argue that registries of unproven stem cell interventions have many methodological flaws. Moreover, we problematise the very idea of establishing registries to track scientifically unproven clinical practice as a form of scientism and a marketing tool serving to validate clinically unjustified procedures.

Funding Source: This presentation was produced as part of the ARC-funded Linkage Project Regulating autologous stem cell therapies in Australia.

14:05 - 14:20

WHAT DO WE KNOW ABOUT PROVIDERS OFFERING UNPROVEN STEM CELL INTERVENTIONS?

Master, Zubin¹, Fu, Wayne², Chau, Beth³, Fojtik, Joseph⁴, Snyder, Gregory⁵ and Turner, Leigh⁶

¹*Biomedical Ethics Research Program, Mayo Clinic, Rochester, MN, U.S.*, ²*Albany Medical College, Albany, NY, U.S.*, ³*Mayo Clinic, Rochester, MN, U.S.*, ⁴*Illinois Department of Financial and Professional Regulations and Mercy Health Systems, McHenry, IL, U.S.*, ⁵*Federation of State Medical Boards, Mound, MN, U.S.*, ⁶*University of Minnesota, Minneapolis, MN, U.S.*

The direct-to-consumer marketing of unproven stem cell interventions (SCIs) is an important public health and patient safety issue. In the U.S., there are more than 351 businesses operating 570 clinics with the highest numbers seen in California, Florida and Texas. Much is known

about the marketing practices of such clinics. However, researchers have not systematically examined clinicians associated with such businesses. In this study, we analyze the backgrounds and credentials of providers who offer unproven SCIs in California, Florida and Texas. After identifying providers listed on clinic websites in the three states, we queried publically available databases (NPIdb, FSMB docInfo and state medical board) to identify backgrounds, degrees, specialties and disciplinary actions. Preliminary results show 234 providers in Florida, 209 in California, and 160 in Texas with a combined 3.5:1 male to female ratio. The majority of businesses (61%) have 1-3 providers. Solo practices are most common (40%). Few businesses have 4-10 or more than 10 providers. Interestingly, one business in Florida has 37 providers while another in Texas lists 33 practitioners. In all three states, most providers are medical doctors (67%) followed by nurses (6%), podiatrists (5%), chiropractors (3%), physical therapists (3%), scientists (2%) and dentists (1%). Providers self-reported over 30 clinical specialties. In all three states, the majority of medical providers are orthopedists with 31% receiving residency and 35% receiving fellowship training. With slight differences among states, anesthesiology, family medicine, and physical medicine and rehabilitation were among the top residencies while fellowship training focused on pain and sports medicine. When examining disciplinary actions against clinical providers irrespective of where they practiced, we found an average rate of 9.3%. Future work will include a detailed examination of disciplinary actions and scope of practice. These preliminary results show that most providers offering unproven SCIs are medically trained, male and in an orthopedic specialty. Characterizing providers' backgrounds is a key step in helping state medical boards better address the phenomenon of clinicians marketing and providing unproven SCIs.

14:20 - 14:35

RECONSIDERING THE 14-DAY RULE: CONTRASTING DIFFERENT PATHWAYS FOR HUMAN EMBRYO RESEARCH LIMITATIONS

Matthews, Kirstin R.W.¹, Iltis, Ana², Robert, Jason³ and de Melo-Martín, Inmaculada⁴

¹*Baker Institute for Public Policy, Rice University, Houston, TX, U.S.*, ²*Wake Forest University, Winston Salem, NC, U.S.*, ³*Arizona State University, Tempe, AZ, U.S.*, ⁴*Weill Cornell Medical College, Cornell University, New York, NY, U.S.*

Human embryo research is restricted in many countries to the 14th day of development, a stage prior to the formation of the primitive streak—an observable, early step towards the formation of neural tissue. In 2016, scientists published the first reports cultivating human embryos to this time point, stopping because of the restriction rather than for scientific or research-related reasons. Many scientists and ethicists are now challenging the validity of the deadline. They argue that important knowledge could be gained by extending the limit or eliminating restrictions on embryo research altogether. Others believe the

guideline is justifiable. They suggest that science and the desire to obtain important knowledge alone do not justify human embryo research past day 14. Instead, they argue that moral, ethical, and societal considerations beyond the possibility of securing new knowledge should be a part of the discussion when deciding about public policies. This presentation will explore the scientific, policy, and ethical considerations relevant to re-examining the 14-day rule. It will highlight differing paths and options countries might take in reconsidering the 14-day rule. Furthermore, it will present a preliminary framework integrating scientific, policy, and ethical perspectives. The framework will be based on discussions with developmental biologists, policy scholars, philosophers, and ethicists as well as public perspectives and will depict a range of ethical and political concerns. It will specifically highlight concerns regarding discrete time points in early human development and will describe policy challenges for different national policies.

14:35 - 14:50

THE EUROPEAN HUMAN PLURIPOTENT STEM CELL REGISTRY (HPSCREG): ESTABLISHING A FRAMEWORK FOR ATTESTING ETHICAL AND LEGAL PROVENANCE OF HPSC LINES

Isasi, Rosario¹, Stacey, Glyn² and Kurtz, Andreas³

¹*Dr. John T. Macdonald Foundation Department of Human Genetics, University of Miami, FL, U.S.*, ²*International Stem Cell Banking Initiative, London, UK*, ³*Universitätsmedizin Berlin (Charité), Berlin, Germany*

The Human Pluripotent Stem Cell Registry (hPSCReg) is the largest, international, freely accessible global registry for human pluripotent stem cell lines (hPSC-lines). Established in 2007, and supported by the European Commission, hPSCReg is an open platform for coordination and cooperation in the area of hPSC research and application. Its purpose is to avoid redundancy and ensuring comparable quality standards in hPSC research. hPSCReg aims to collaborate with registries and cell banks worldwide. The registry allows searching for cell lines and for information available about these cell lines. New cell lines can be registered and information to already registered cell lines can be added. Registration of a cell line in hPSCReg confirms ethical procurement and scientific evidence for pluripotency to the global community. The registry collects, validates and stores additional information related to the pluripotent cell lines. Registration of cell lines in hPSCReg provides visibility, confidence in ethical provenance, validation of characterization data and comparability with other registered lines. In this presentation we will outline hPSCReg's framework for attesting ethical and legal provenance of cell lines as well as the procedure adopted for cell line certification. In addition, we will highlight the mechanisms established for handling cases in which no complete tracing of ethical provenance is possible. Final-

ly, we will outline hPSCReg's proposed modular standard consent for hESC and hiPSC.

Funding Source: European Commission, H2020, Grant Agreement Number: 726320.

FRIDAY, 22 JUNE, 16:00 – 18:00

PLENARY V: STEM CELL BASED DISEASE MODELING

Plenary Room, Ground Level

Sponsored by Burroughs Wellcome Fund

16:00 – 16:25

HUMANIZED PATIENT-SPECIFIC GLIAL CHIMERIC MICE FOR MODELING NEUROLOGICAL AND NEUROPSYCHIATRIC DISEASE

Goldman, Steven A.

University of Copenhagen, Denmark and University of Rochester Medical Center, Rochester, NY, U.S.

The neurodegenerative and neuropsychiatric disorders have typically been thought of as neuronal in etiology. Yet the macroglial cells - astrocytes, oligodendrocytes and glial progenitor cells - are the most prevalent cells in the brain, and their causal involvement in the neurodegenerative diseases has only recently been appreciated. This talk will focus on the potential utility of glial progenitor cell transplantation as a means of both modeling and treating not only the diseases of myelin loss - which have long been studied as potential beneficiaries of glial progenitor cell therapy - but also those neurodegenerative and neuropsychiatric disorders with significant glial involvement. In that regard, I will discuss the production and use of humanized glial chimeric mice, which are produced by transplanting human glial progenitors into neonatal immune deficient mice. In these mice, the human glial progenitor cells out-compete their murine counterparts to eventually dominate the glial population of the host brains. Human glial chimerization has significant effects on neurophysiology, cognition and behavior, which suggest the importance of human-specific glial attributes to neural network function. By generating glial chimeric mice using patient-derived hiPSC-derived glial progenitors, we may therefore now investigate the causal contributions of human glial pathology to human brain disease, by producing patient- and disease-specific glial chimeras. Using this approach, we have identified significant contributory roles for glial pathology in diseases as varied as childhood-onset schizophrenia and Huntington disease, and have validated the corresponding efficacy of glial replacement as a treatment approach for the latter. Human iPSC-derived glial chimeric mice thus provide us a new model system by which to study not only the myelin disorders, but also the entire range of neurodegenerative and neuropsychiatric diseases in which glia may causally participate, while

identifying those that may benefit from glial replacement therapy as well.

16:25 – 16:50

CLONING OF MACAQUE MONKEYS BY SOMATIC CELL NUCLEAR TRANSFER

Sun, Qiang, Liu, Zhen, Cai, Yijun, Wang, Yan, Nie, Yanhong, Zhang, Chenchen, Xu, Yuting, Zhang, Xiaotong, Wang, Zhanyang, Lu, Yong and Poo, Muming

Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

Generation of genetically uniform non-human primates may help to establish animal models for primate biology and biomedical research. In this study, we have successfully cloned cynomolgus monkeys (*Macaca fascicularis*) by somatic cell nuclear transfer (SCNT). We found that injection of H3K9me3 demethylase Kdm4d mRNA and treatment with histone deacetylase inhibitor trichostatin A at one-cell stage following SCNT greatly improved blastocyst development and pregnancy rate of transplanted SCNT embryos in surrogate monkeys. For SCNT using fetal monkey fibroblasts, 6 pregnancies were confirmed in 21 surrogates and yielded 2 healthy babies. For SCNT using adult monkey cumulus cells, 22 pregnancies were confirmed in 42 surrogates and yielded 2 babies that were short-lived. In both cases, genetic analyses confirmed that the nuclear DNA and mitochondria DNA of the monkey offspring originated from the nucleus donor cell and the oocyte donor monkey, respectively. Thus, cloning macaque monkeys by SCNT is feasible using fetal fibroblasts.

16:50 – 17:15

STEM CELLS AND CARDIOVASCULAR GENOMICS FOR PRECISION MEDICINE

Wu, Joseph C.

Stanford University School of Medicine, Stanford, CA, U.S.

The prospect of changing the plasticity of terminally differentiated cells toward pluripotency has completely altered the outlook for biomedical research. Human induced pluripotent stem cells (iPSCs) confer considerable advantages over conventional methods of studying human diseases. Here I will discuss, in a comprehensive manner, the recent advances in iPSC technology in relation to disease modeling, cardiovascular genomics, and precision medicine.

FRIDAY 22 JUNE 2018

17:25 - 17:50

ISSCR INNOVATION AWARD LECTURE: LIFE-SAVING REGENERATION OF THE ENTIRE HUMAN EPIDERMIS BY TRANSGENIC STEM CELLS

De Luca, Michele

Centre for Regenerative Medicine, University of Modena and Reggio Emilia, Modena, Italy

Laminin beta3-deficient generalized Junctional Epidermolysis Bullosa is the first genetic disease targeted by transplantation of epidermal cultures originated from transgenic epidermal stem cells. A seven-year-old child, carrying a homozygous acceptor splice site mutation (C1977-1G> A, IVS 14-1G> A) within intron 14 of LAMB3 and suffering complete life-threatening epidermal loss on 80% of his body surface, was treated with autologous epidermal cultures transduced with a MLV-derived retroviral vector carrying the LAMB3 cDNA under the control of the viral LTR. Several skin biopsies were taken to perform histological analysis, immunofluorescence, in situ hybridization and genome-wide analysis of the retroviral integration sites. The regenerated epidermis was normal-looking, remained mechanically stable throughout the entire follow-up period (almost 3 years) and did not form blisters, even upon shear force. We observed a proper expression and location of laminin 332 in the basal lamina. In situ hybridization performed using vector-specific LAMB3 probes showed homogenous expression of LAMB3 mRNA in all epidermal layers, confirming that the regenerated epidermis consists only of transgenic keratinocytes. Histological analysis showed a normal and fully differentiated epidermis with a normal dermal-epidermal junction. Electron Microscopy confirmed the presence of well-defined, organized hemidesmosomes comparable to those of healthy controls. The proviral integration pattern was maintained in vivo and epidermal renewal did not cause any clonal selection. Clonal tracing showed that the human epidermis is sustained not by equipotent progenitors, but by a limited number of long-lived stem cells, detected as holoclones, that can extensively self-renew in vitro and in vivo and produce progenitors that replenish terminally differentiated keratinocytes.

SATURDAY, 23 JUNE, 09:00 – 11:10

PLENARY VI: CANCER STEM CELLS

Plenary Room, Ground Level

09:00 – 09:25

GENETIC AND EPIGENETIC DEREGLATION OF ADULT STEM CELLS

Bardin, Allison

Institut Curie, Paris, France

Mutations arising in adult stem cells often lead to the initiation of pre-cancerous lesions providing a selective fitness advantage. Further genetic and epigenetic deregulation drive evasion of cellular checkpoints and promote tumor evolution. Therefore, an understanding of the mechanisms influencing genetic and epigenetic deregulation in adult stem cells will provide insight into cancer initiation and development. Our recent work in *Drosophila* and that of others in mammalian model systems have demonstrated that adult stem cell mutation is frequent and can have significant phenotypic consequences on adult tissues. Importantly, the underlying causes driving mutational processes remain to be fully understood. Using the *Drosophila* adult intestinal stem cells as a genetic model system, we are exploring how genetic and epigenetic factors can influence adult stem cells. Our data demonstrate that, during aging, the stem cell genome becomes mutated through large deletions and structural variations, single nucleotide variants, and transposon-mediated processes that can drive neoplastic growth. Our current work exploring how these mutational processes are influenced by the environment and how genomic and epigenetic features of the genome may contribute to stem cell mutation, will be discussed. In addition, we have gained insight into how epigenetic deregulation can drive excessive stem cell self-renewal: through a genetic screen, we have identified the chromatin-remodeling factor Kismet (CHD7/CHD8) as playing an essential role in limiting stem cell self-renewal. Inactivation of kismet leads to unregulated stem cell proliferation through excess EGFR signaling. Altogether, our findings elucidate important genetic and epigenetic control mechanisms in adult stem cells acting to limit stem cell self-renewal properties and pre-cancer-like growth.

09:25 – 09:50

STEM CELL SIGNALS IN CANCER HETEROGENEITY AND THERAPY RESISTANCE

Reya, Tannishtha

University of California, San Diego School of Medicine, La Jolla, U.S.

Our research focuses on the signals that control stem cell self-renewal and how these signals are hijacked in cancer. Using a series of genetic models, we have studied how classic developmental signaling pathways such as Wnt, Hedgehog and Notch play key roles in hematopoietic

stem cell growth and regeneration and are dysregulated during leukemia development. In addition, using real-time imaging strategies we have found that hematopoietic stem cells have the capacity to undergo both symmetric and asymmetric division, and that shifts in the balance between these modes of division are subverted by oncogenes. Further, regulators of this process, including the cell fate determinant Musashi, are critical players in driving progression of solid and liquid cancers and could serve as targets for diagnostics and therapy. Ongoing work is focused on understanding the mechanisms that drive therapy resistance after drug delivery, as well as developing high resolution *in vivo* imaging approaches to map normal stem cell behavior and interactions within living animals, and to define how these change during cancer formation.

09:50 – 10:15

LGR5+ STEM CELLS IN EPITHELIAL MAINTENANCE, REPAIR AND CANCER OF THE MOUSE STOMACH

Barker, Nick and Leushacke, Marc

Institute of Medical Biology, Singapore

We have identified Lgr5 as a facultative component of the Wnt receptor complex specifically expressed on cycling stem cells in the intestine, colon, pyloric stomach, hair-follicles, ovary and embryonic kidney. Long-term ablation of the Lgr5+ cell compartment *in vivo* severely impairs epithelial homeostasis in both the pyloric antrum and the corpus, establishing the Lgr5+ populations as being critical for daily maintenance of the gastric mucosa. Employing new, non-variegated Lgr5-2A-CreERT2/EGFP/DTR mouse models we now identify a subset of Lgr5-expressing chief cells responsible for epithelial repair in the corpus stomach following parietal cell atrophy. These Lgr5+ chief cells drive gastric metaplasia *in vivo* following K-RAS mutation. We additionally characterize the transcriptomes Lgr5+ stem cells in mouse intestine, colon and stomach, revealing new gastric stem cell-specific markers that can be used to isolate human gastric stem cells for regenerative medicine applications and for use in selectively targeting cancer-causing mutations to the Lgr5+ stem cell compartment in mice as a means of evaluating their contribution to gastric cancer initiation and progression.

10:15 – 10:40

GETTING ABREAST OF THE MAMMARY EPITHELIAL DIFFERENTIATION HIERARCHY

Visvader, Jane E¹, Fu, Nai Yang¹, Rios, Anne², Pal, Bhupinder¹, Chen, Yunshun¹, Vaillant, Francois¹, Capaldo, Bianca¹, Dawson, Caleb¹, Smyth, Gordon¹ and Lindeman, Geoffrey¹

¹Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, ²Princess Maxima Centrum, Utrecht, Netherlands

Breast cancer is a highly heterogeneous disease at both the molecular and pathological levels. To understand this

heterogeneity and the 'cells of origin' of breast cancer, it is important to dissect the normal mammary epithelial hierarchy. Despite accumulating evidence for a mammary differentiation hierarchy, the basal compartment comprising stem cells remains poorly characterized. Through gene expression profiling of Lgr5+ versus Lgr5- basal epithelial cells, we identified a novel marker Tspan8 that led to the fractionation of three distinct mammary stem cell (MaSC) subsets in the adult gland. These exist in a largely quiescent state but differ in their repopulating ability, spatial localization, and their molecular signatures. Interestingly, the dormant MaSC subset localizes to the proximal region of the gland throughout life. These cells appear to originate from the embryonic mammary primordia before switching to a quiescent state post-natally but can be recruited into the cell cycle in response to hormones. Recent single cell gene expression analyses have revealed unexpected complexity within the basal and luminal compartments. Moreover, analyses at different stages of development have provided insights into the earliest 'lineage priming' events and a large-scale shift in the gene expression program near the onset of puberty. In a further layer of investigation, lineage tracing studies combined with 3D confocal imaging has enabled the visualization of large regions of intact tissue at cellular resolution and provided insights into the normal differentiation hierarchy as well as potential 'cells of origin' of breast cancer.

10:40 - 11:05

Speaker Rescheduled From Presidential Symposium

ORGAN REGENERATION AND ANTI-AGING STRATEGIES

Belmonte, Juan Carlos Izpisua

Salk Institute for Biological Studies, La Jolla, CA, U.S.

Aging can be defined as the progressive decline in the ability of a cell or organism to resist stress and disease. Recent advances in cellular reprogramming technologies have enabled detailed analyses of the aging process, often involving cell types derived from aged individuals, or patients with premature aging syndromes. In my talk I will discuss how cellular reprogramming allows the recapitulation of aging in a dish, describing novel experimental approaches to investigate the aging process. Finally, I will explore the role of epigenetic dysregulation as a driver of aging, discussing how epigenetic reprogramming may be harnessed to ameliorate aging hallmarks, both in vitro and in vivo. A better understanding of the reprogramming process may indeed assist the development of novel therapeutic strategies to extend a healthy lifespan.

SATURDAY, 23 JUNE, 13:15 - 15:15

CONCURRENT IVA: ROAD TO THE CLINIC 2

Melbourne Room 1, Level 2

13:20 - 13:45

THE LONDON PROJECT TO CURE BLINDNESS AT 10 YEARS, HAVE WE FOUND A CURE?

Coffey, Peter

University College London, UK

The London Project to Cure Blindness aimed to bring to clinic within 5 years a cell therapy for Age-related macular degeneration (AMD). In 2013, UK regulatory approval was granted by the Medicines and Healthcare products Regulatory Agency to treat 10 patients who had AMD associated with an untreatable subretinal bleed or rips in the retinal pigmented epithelial layer (RPE). Two patients with subretinal bleeds were implanted with patches of stem cell derived RPE in the summer of 2015. The journey to clinic and the visual outcome will be presented.

13:45 - 14:00

USE OF HUMAN INDUCED PLURIPOTENT STEM CELLS TO PRODUCE CYTOKINE AUTONOMOUS, CHIMERIC ANTIGEN-DIRECTED NATURAL KILLER CELLS WITH IMPROVED ANTI-TUMOR ACTIVITY

Kaufman, Dan S¹, Lee, Tom², Li, Ye¹, Bjordahl, Ryan², Mahmood, Sajid², Zhu, Huang¹, Bonello, Gregory² and Valamehr, Bahram²

¹Department of Medicine, University of California, San Diego, La Jolla, CA, U.S., ²Fate Therapeutics, La Jolla, CA, U.S.

Natural killer (NK) cells are potent anti-tumor cells that play an important role in innate and adaptive immunity. Multiple clinical studies have demonstrated that adoptive transfer of allogeneic NK cells can induce durable remissions to cancers that have relapsed or are refractory to standard treatments. While most of the clinical anti-tumor efficacy has been against acute myelogenous leukemia, here we use human induced pluripotent stem cells (iPSCs) to produce standardized, engineered NK cells that have directed and more potent activity against both liquid and solid tumors. Using this iPSC platform, we evaluated combinations of NK cell-specific chimeric antigen receptors (CARs) with an autonomous protein to create a highly effective, persistent, and targeted NK cell therapy. The NK cell optimized CAR (NK-CAR) backbone contains the NKG2D transmembrane domain, the 2B4 co-stimulatory and the CD3 ζ signaling domains to mediate a strong increase in NK cell signaling. To provide directed anti-tumor activity, anti-mesothelin and anti-CD19 scFvs were added to the NK-CAR backbone, engineered into the iPSC and

subsequently differentiated to CAR-expressing NK cells. Using an ovarian cancer xenograft model, a single dose of NK-CAR^{meso} NK cells markedly inhibited tumor growth and mediated enhanced survival (84 days) compared to controls, including NK cells harboring a T-cell CAR construct ($p < 0.002$). We next engineered an IL-15RF fusion protein to provide self-stimulating signals to support NK cell function and persistence. The IL-15RF construct was created by fusing mature IL-15R α to IL-15 at the C-terminus through a flexible linker. The design mimics the trans-presentation of IL-15 bound to IL-15R α that is presented to IL-15R β/γ C dimer to initiate signaling. While both iPSC-derived NK cells (iNKs) and iNKs bearing IL-15RF expanded in vitro in a similar manner in the presence of soluble IL-15 and IL-2 (2040- and 3615-fold expansion), only the iNKs bearing IL-15RF significantly proliferated in the absence of cytokines (10- vs. 701-fold expansion). Together, these strategies allow us to produce cytokine-autonomous, NK cells suitable for an “off-the-shelf” approach to provide standardized CAR-targeted immunotherapy against both solid and liquid tumors.

Funding Source: National Institutes of Health, California Institute for Regenerative Medicine, Fate Therapeutics.

14:00 - 14:15

INDUCED PLURIPOTENT STEM CELL DERIVED 3D ENGINEERED EYE TISSUES TO RESTORE BLINDING EYE DISEASES

Bharti, Kapil¹, Sharma, Ruchi², Song, MinJae², Rising, Aaron², Amaral, Juan² and Maminishkis, Arvydas²

¹National Eye Institute, Bethesda, MD, U.S., ²National Institutes of Health, Bethesda, MD, U.S.

Age-associated ocular diseases macular degeneration (AMD) and diabetic retinopathy (DR) affect millions of people world-wide. In advanced stages these diseases lead to atrophy of the retina, the retinal pigment epithelium (RPE), and the choroid - leading to blindness. We are developing 2D and 3D ocular tissues of various complexities as potential tissue therapies for ocular atrophy of different severity. We have developed clinical-grade RPE-patch with functional and mature RPE cells derived from patient-specific induced pluripotent stem cells (iPSCs). This RPE-patch is delivered to the back of the eye on a biodegradable scaffold and will serve as an autologous “replacement” patch in cases where RPE monolayer atrophies. Preclinical IND-enabling studies related to the RPE-patch have been completed and a phase I trial will be initiated later in 2018. Recently, we have expanded this product to include iPSC-derived micro-vessels that are bioprinted on the opposite side of the RPE-patch. These vessels behave similar to native choroidal vessels - they fenestrate and proliferate in response to RPE induced changes in secretion of VEGF and other cytokines. This combined RPE/“choroid” construct will be used as a potential tissue therapy for deeper RPE and choroidal atrophy in advanced AMD and DR. Currently, we are developing a more complex 3D retina/RPE/choroid tissue that will

be used in the case of complete retina/RPE/choroid atrophy in late-stage diseases. We have developed methods and tools to surgically deliver these tissues to the back of the eye. In addition, we have developed devices to ship cryopreserved tissue to surgery suites. Our work provides potential tissue therapies for several blinding eye diseases.

14:15 - 14:30

THE PRECLINICAL STUDY OF IPSC-DERIVED CTL THERAPY FOR EBV-ASSOCIATED LYMPHOMA

Ando, Miki¹, Ando, Jun², Ishii, Midori³, Sakiyama, Yumi⁴, Harada, Sakiko¹, Honda, Tadahiro¹, Fujita, Masako⁴, Komatsu, Norio¹ and Nakauchi, Hiromitsu⁵

¹Department of Hematology, Juntendo University School of Medicine, Bunkyo-ku, Japan, ²Juntendo University School of Medicine, Bunkyo-ku, Japan, ³Department of Orthopedic Surgery, Bunkyo-ku, Japan, ⁴The Institute of Medical Science, The University of Tokyo, Minato-ku, Japan, ⁵Stanford University School of Medicine, Stanford, CA, U.S.

Extranodal natural killer (NK)/T cell lymphoma, nasal-type (ENKL) is an aggressive lymphoma, relatively common in Asia. These lymphomas rapidly disseminate to various sites in advanced stage, resulting in a miserable outcome. Development of an effective salvage therapy is an urgent issue. Antigen-specific cytotoxic T lymphocytes (CTL) therapy can induce durable remission in selected tumors such as melanomas and virus-related tumors. As ENKLs are invariably infected by Epstein-Barr virus (EBV), these lymphomas should be a good target of CTL therapy. However, CTLs continuously exposed to viral or tumor antigens are known to often become exhausted. Antigen-specific CTLs generated from iPSCs have higher proliferative capacity and longer telomeres than the original CTLs and are functionally rejuvenated (rejT). For clinical translation, the tumorigenic potential of iPSCs and the malignant transformation of differentiated iPSCs are major safety concerns. To address these issues, we introduced inducible caspase-9 (iC9)-based safeguard system into iPSCs. iC9-rejTs have strong anti-tumor effect against EBV-infected tumors in vivo and the system provides a reliable safeguard for rejT therapy. We are doing a preclinical study utilizing rejT therapy to EBV-associated lymphomas. 10 patients with EBV-associated lymphoma, which includes ENKL, Hodgkin lymphoma and MTX-related lymphoproliferative disorder were enrolled in this study and had common HLA types such as A2402 and A0201. Two patients with advanced ENKL died before generation of EBV-CTLs had even started. We could generate 12 types of EBV-CTL clones from 7 of the patients and T-iPSCs were subsequently established from each CTL clone. All T-iPSCs derived from various EBV antigen-specific CTLs efficiently differentiated into rejTs. These rejTs had equally high specificity while showing stronger cytotoxicity (45-90%) against EBV-infected tumor cell lines when compared to the original EBV antigen-specific CTLs (40-78%). Conversely, less than 10% of non-specific killing

SATURDAY 23 JUNE 2018

against HLA-mismatched cells was observed. We believe that rejT therapy provides a promising and safe approach to “off-the-shelf therapy” for EBV-associated lymphomas.

Funding Source: This work was supported by JSPS KAKENHI Grants 16K09842.

14:30 – 14:45

A SOLUTION FOR CELL THERAPY SAFETY

Monetti, Claudio¹, Liang, Qin², Shutova, Maria², Neely, Eric², Hacibekiroglu, Sabiha², Yang, Huijuan², Kim, Christopher², Zhang, Puzheng², Mileikovsky, Maria², Sung, Hoon-Ki³ and Nagy, Andras²

¹panCELLa, Toronto, ON, Canada, ²Lunenfeld-Tanenbaum Research Institute, Sinai Health System, Toronto, Canada, ³The Hospital For Sick Children Research Institute, Toronto, Canada

Safety concerns are one of the most important factors limiting the wide-scale implementation of cell-based therapy to treat disease. Here, we introduce a concept and an associated genome-editing strategy that addresses this challenge. The solution proposed is based on a Fail-Safe system, where a negative selectable marker is transcriptionally linked to the expression of an endogenous cell division essential locus (CDEL). A cell is defined as a “FailSafe cell” if its FailSafe system is functional. From our system, we can calculate a FailSafe Level (FSL), which estimates the probability that a therapeutic batch of cells will contain a non-FailSafe cell. Our prototypes for CDEL and suicide gene are CDK1 and HSV-TK, respectively. We successfully introduced this system in both mouse and human ES cells, showing that it does not interfere with the developmental potential of the cells. Furthermore, we show that proliferating cells can be completely and selectively eliminated by activating the suicide gene, both in vitro and in vivo. After a brief treatment with the pro-drug for the suicide gene, the teratomas generated in mice by FailSafe ESCs were induced into a stable and dormant ectopic tissue for more than one year. Based on our definition of FSL, we used mathematical modeling to quantify the risk of generating non-FailSafe cells when producing numbers of cells relevant to cell therapies. We then describe how the FSL can be increased by introducing the FailSafe system homozygously and into more than one gene. This design to generate safe cells is already being applied to several disease models in the lab, for example multiple sclerosis (see N Payne’s abstract), and non-human primates (see K Davidson’s abstract). The true power of the FailSafe system will be highlighted when used in combination with an allograft tolerance system (see J Harding’s abstract), that will lead to the generation of off-the-shelf and safe cell therapy products. To bring this product closer to the clinic, the company panCELLa Inc. was created, and we are currently developing and optimizing procedures to introduce the FailSafe system in clinically-relevant cell lines.

Funding Source: Funding support to Dr. Andras Nagy from CIHR foundation scheme, Canadian Research Chair and Medicine by Design (University of Toronto).

14:45 – 15:10

RESTORING ENTERIC NERVOUS SYSTEM FUNCTION AND ALTERING THE GASTROINTESTINAL TRANSCRIPTOME WITH IMPLANTED NEURAL CREST CELLS DERIVED FROM HPSC

Grikscheit, Tracy C¹, Schlieve, Christopher R¹, Spence, Jason², Huang, Sha², Fowler, Kathryn¹ and Thornton, Matt³

¹The Saban Research Institute at Children’s Hospital Los Angeles, CA, U.S., ²University of Michigan Medical School, Ann Arbor, MI, U.S., ³Department of Obstetrics and Gynecology, University of Southern California, CA, U.S.

Acquired or congenital disruption in enteric nervous system (ENS) development or function can lead to significant dysmotility or obstruction. ENS restoration through cellular transplantation may provide a cure for enteric neuropathies. We have previously generated human pluripotent stem cell (hPSC)-derived tissue-engineered small intestine (TESI) from human intestinal organoids (HIOs). However, HIO-TESI fails to develop an ENS. ENS components derived exclusively from hPSCs can restore ENS function in HIO-TESI. hPSC-derived enteric neural crest cell (ENCC) supplementation of HIO-TESI establishes sub-mucosal and myenteric ganglia, repopulates various subclasses of neurons, and restores neuroepithelial connections and neuron-dependent contractility and relaxation in ENCC-HIO-TESI. RNA sequencing identified differentially expressed genes involved in neurogenesis, gliogenesis, gastrointestinal tract development, and differentiated epithelial cell types when ENS elements are restored during in vivo development of HIO-TESI. Our findings validate an effective approach to restoring hPSC-derived ENS components in HIO-TESI and may indicate their potential for the treatment of enteric neuropathies.

SATURDAY, 23 JUNE, 13:15 – 15:15

CONCURRENT IVB: EPIGENETICS AND GENETIC REGULATORY NETWORKS

Melbourne Room 2, Level 2

13:20 – 13:45

EXPANDED CELL FATE POTENTIAL IN EMBRYONIC STEM CELLS

He, Lin

University of California, Berkeley, CA, U.S.

Embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) efficiently generate all embryonic cell lineages but rarely generate extraembryonic cell types. We found that microRNA miR-34a deficiency expands the developmental potential of mouse pluripotent stem

cells, yielding both embryonic and extraembryonic lineages and strongly inducing MuERV-L (MERVL) endogenous retroviruses, similar to what is seen with features of totipotent two-cell blastomeres. miR-34a restricts the acquisition of expanded cell fate potential in pluripotent stem cells, and it represses MERVL expression through transcriptional regulation, at least in part by targeting the transcription factor that regulate MERVL induction. Our studies reveal a complex molecular network that defines and restricts pluripotent developmental potential in cultured ESCs and iPSCs.

13:45-14:00

MODELLING TRANSCRIPTIONAL VARIABILITY IN SINGLE CELL RNA-SEQ DATA DURING HUMAN EMBRYOGENESIS CAPTURES CHANGES IN THE REGULATION OF CRITICAL DEVELOPMENTAL GENES

Mason, Elizabeth A.¹, Ghazanfar, Shila², Lanner, Fredrik³, Yang, Jean², Wells, Christine⁴

¹Department of Anatomy and Neuroscience, The University of Melbourne, Australia, ²School of Mathematics and Statistics, The University of Sydney, Australia, ³Department of Clinical Science, Intervention, and Technology, Karolinska Institute, Sweden, ⁴Department of Anatomy and Neuroscience, University of Melbourne, Australia

Molecular variability in human stem cell populations is thought to reflect an inability of in vitro culture systems to recapitulate the complex signalling environment of the developing embryo. We present an alternative theory: that expression variability is a natural feature of embryogenesis, and measuring the expression variability of a gene informs the level of regulation imposed on it. Variability itself is rarely the focus of analysis; instead most transcriptional studies use linear models to identify the differentially abundant genes between phenotypes. This framework successfully characterizes average differences between populations, but cannot account for stochastic differences captured by single cell RNA-seq (scRNA-seq) experiments. Accurately determining abundance and variability is further complicated by the sparseness of non-zero expression values in scRNA-seq data. To address these challenges and evaluate gene expression during human pre-implantation embryogenesis, we applied a statistical mixture model to scRNA-seq data. Fitting the model on a gene-by-gene basis allowed us to evaluate shifts in the proportion of cells expressing a given gene (λ), and also the mean (Q) and standard deviation (σ) of expression. From here, a correlation based analysis evaluated whether abundance (Q) and variability (σ) capture different aspects of transcriptional regulation. While each metric largely identified the same genes, the number and nature of relationships between them differed. Indeed, genes sharing correlated patterns of variability during development were enriched for motifs associated with developmental transcription factors (e.g. HIC2, PPAR γ , E2F4 and ZNF692). Variability detected specific regulatory rela-

tionships during development, with less redundancy than abundance. Our approach provides a gene-centric platform to evaluate population-based parameters of gene expression, while preserving the complexity of scRNA-seq data.

14:00 - 14:15

THE RETROTRANSPOSON LINE1 REGULATES EARLY EMBRYONIC IDENTITY

Percharde, Michelle¹, Lin, Chih-Jen², Bulut-Karslioglu, Aydan³, Yin, Yafei⁴, Peixoto, Gabriel³, Biechele, Steffen³, Shen, Xiaohua⁴ and Ramalho-Santos, Miguel³

¹Eli and Edythe Broad Center for Regeneration Medicine, University of California, San Francisco, CA, U.S., ²University of Edinburgh, UK, ³University of California, San Francisco, CA, U.S., ⁴Tsinghua University, Beijing, China

Transposable elements (TEs) make up nearly half of mammalian genomes and are often described as genome parasites or 'junk DNA'. LINE1 retrotransposons are the most abundant TE class and their expression is thought to be largely deleterious for cells. However paradoxically, LINE1 is highly expressed during early development. Here we report that LINE1 plays essential roles in mouse embryonic stem (ES) cells and in pre-implantation embryos. This function is dependent upon LINE1 RNA and is independent of LINE1 retrotransposition activity. In ES cells, LINE1 acts as a nuclear RNA scaffold that recruits Nucleolin and Kap1/Trim28 to repress Dux, the master activator of a transcriptional program specific to the totipotent 2-cell embryo. LINE1 depletion causes inappropriate activation of Dux, along with genes and transcripts driven by the 2-cell specific LTR retrotransposon, MERVL. In parallel, LINE1 mediates association of Nucleolin and Kap1 with rDNA, promoting rRNA synthesis and ES cell self-renewal. In embryos, LINE1 is required for Dux silencing, synthesis of rRNA and exit from the 2-cell stage. These results reveal an essential partnership between LINE1 RNA and chromatin factors in the regulation of transcription, developmental potency and ES cell self-renewal. We propose that LINE1 forms an integral part of the transcriptional networks that regulate cellular potency during early mammalian development.

14:15 - 14:30

FUNCTIONAL HIERARCHY OF CHROMATIN CHANGES DURING X-CHROMOSOME INACTIVATION IN MOUSE EMBRYONIC STEM CELLS

Zylicz, Jan Jakub^{1,2}, Bousard, Aurélie², Teixeira da Rocha, Simão³, Syx, Laurène² and Heard, Edith²

¹University of Cambridge, U.K., ²Institut Curie, Paris, France, ³Universidade de Lisboa, Portugal

Development involves the orchestration of elaborate programmes of gene activation and silencing. Chromatin changes accompany this differential use of the genome.

However, there are still few cases where the precise role of chromatin has been established in developmental gene regulation, particularly in the establishment of gene silencing. Here we investigate the hierarchy and functions of chromatin states during initiation of X-chromosome inactivation in mouse embryonic stem cells. We have generated high resolution, allele-specific chromatin and transcription maps during the earliest stages of facultative heterochromatin formation. We define the relative kinetics of chromatin changes at promoters, enhancers and gene bodies. This roadmap of early events during X-chromosome inactivation reveals that transcriptional silencing is tightly coupled to histone deacetylation, and accumulation of the PRC1-dependent H2AK119Ub. Subsequently, active histone methylation marks such as H3K4me3 are removed, followed by the appearance of PRC2-associated H3K27me3. Different regions show different time of onset of these changes but the order of events is globally equivalent. To assess the functional relevance of these chromatin processes we have generated and analysed several mutant ESC lines in which histone deacetylation, polycomb recruitment or gene silencing are affected. We show that specific removal of active histone modifications is functionally involved in the rapid transcriptional silencing of most X-linked loci. We also find that Polycomb-mediated changes may play different downstream roles. This study provides the first detailed epigenomic roadmap of X inactivation and provides important insights into the molecular mechanisms that underlie gene silencing in a developmental context.

Funding Source: Wellcome Trust and European Research Council.

14:30 - 14:45

EPIGENETIC REPROGRAMMING OF THE 3D CHROMATIN LANDSCAPE IN GROUND STATE PLURIPOTENCY

Atlasi, Yaser, Megchelenbrink, Wout, Peng, Tianran, Habibi, Ehsan, Joshi, Onkar, Wang, Shuang-Yin, Poser, Ina, Marks, Hendrik and Stunnenberg, Hendrik
Radboud University, Nijmegen, Netherlands

Enhancer-promoter communication underlies spatiotemporal gene expression. Mechanisms underlying enhancer activation and the extent of enhancer-rewiring during mammalian development are poorly understood. Using a capture HiC approach targeted DNA accessible sites, we generated a comprehensive catalogue of interactions in mouse embryonic stem cells (ESCs) cultured in serum or with two kinase inhibitors (2i-ESCs). These cells represent early stages of embryonic development and display different transcriptional and epigenetic landscapes. Integrative analysis of the transcriptional dynamics, 3D chromatin organization and enhancer activation during serum-to-2i conversion revealed that the extensive transcriptome and epigenome resetting takes place with minimal enhancer-rewiring. Instead, differential gene expression is strongly linked to enhancer activation via H3K27-acetylation within the respective neighborhoods.

Allele specific enhancer analysis and conditional depletion of TFs, reveals an essential role for Esrrb in activation of 2i-specific enhancers. Restoration of polymorphic Esrrb motif using CRISP/Cas9, restores enhancer acetylation in an allele-specific manner. Our study provides conceptual insights into the principles of gene regulation in ESCs and suggest that enhancer activation in early embryonic development is mainly driven by TFs binding in a network of stable enhancer-interactions.

14:45 - 15:00

LAMINA/C REGULATES EPIGENETIC AND CHROMATIN ARCHITECTURE CHANGES UPON AGING OF HEMATOPOIETIC STEM CELL

Grigoryan, Ani¹, Guidi, Novella², Senger, Katharina², Kosyakova, Nadezda³, Liehr, Thomas³, Markaki, Yolanda⁴, Leonhardt, Heinrich⁴, Lipka, Daniel B.⁵, Mulaw, Medhanie A.⁶, Geiger, Hartmut² and Florian, Maria Carolina²

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⁶*University Hospital Ulm, Germany*

Hematopoietic stem cell (HSC) aging, which contributes to the senescent immune remodeling as well to leukemia pathogenesis, is driven by poorly understood epigenetic mechanisms. Here, we analyzed the HSC aging-associated epigenetic drift in terms of structural changes in the distribution of lysine 16 acetylation on histone 4 (H4K16ac), chromosome localization and nuclear structure. Changes in epigenetic architecture were found to be controlled by LaminAC and to be reversible by targeting the activity of the small RhoGTPase Cdc42, which regulates LaminAC expression. Further, LaminAC regulated epipolarity of H4K16ac and the localization of chromosome 11, orchestrating the expression of HSC-specific genes. Thus, we show for the first time that by inhibiting Cdc42 activity in aged HSCs is possible to increase LaminAC expression and rejuvenate the epigenetic and chromatin architecture. These findings extend our understanding of the functional implications of nuclear architecture changes in driving somatic stem cell aging.

SATURDAY, 23 JUNE, 13:15 – 15:15

CONCURRENT IVC: TECHNOLOGY FRONTIERS

Room 219/220, Level 2

Sponsored by AAAS/Science

13:20 – 13:45

INVESTIGATING THE CELLULAR DYNAMICS OF ORGANS DEVELOPMENT AND CANCER USING 3D IMAGING

Rios, Anne

Princess Maxima Centrum, Utrecht, Netherlands

Dr. Rios implemented a novel 3D-imaging approach (with 3D glasses) to perform innovative multicoloured lineage tracing studies to follow the development and fate of mammary stem cells (MaSC) and descendant progenitor cells in vivo in entire mammary gland. As stem cells divide they produce clones of cells; using this imaging technique the fate of these individual clones could be tracked throughout various stages of mammary gland development, including puberty, pregnancy and normal adult homeostasis. This work provided the first in vivo evidence for the existence of bipotent MaSCs, which give rise to the two cell lineages that constitute the mammary ducts, the luminal and the myoepithelial cells, as well as the presence of distinct long-lived unipotent progenitor cells. The cellular dynamics observed at different developmental stages support a model in which both stem and progenitor cells drive morphogenesis during puberty, whereas bipotent MaSCs coordinate ductal homeostasis and remodelling of the adult mouse gland (Nature 2014, Nature Comm. 2016, NCB 2017). We have now specialized this 3D technology combined with the multicolored reporter confetti to detect early aberrant cellular behaviour in models of breast cancer and to visualise how cancerous cells, according to their cell-of-origin, exit normal ductal homeostasis and survive to self-organise into a solid tumour.

13:45 – 14:00

A FLUORESCENT REPORTER OF CELL CYCLE SPEED

Baccei, Anna E.¹, Chen, Xinyue², Hu, Xiao², Hartman, Amaleah², Pearlman Morales, Aria², Lu, Yi-Chien², Lu, Jun², Krause, Diane², Kueh, Hao Yuan³ and Guo, Shangqin²

¹Department of Cell Biology, Yale University, New Haven, CT, U.S., ²Yale University, New Haven, CT, U.S., ³University of Washington, Seattle, WA, U.S.

Cell fate transitions are often accompanied by profound changes in cell cycle dynamics. The ability to identify and isolate live cells with divergent proliferation rates can benefit the study of cell fate control during development, re-generation, reprogramming, and disease. Currently avail-

able strategies to analyze proliferation in live cells focus on specific cell cycle phases; require invasive labeling procedures; lack sensitivity/resolution; or are not tractable for use in vivo. We have developed a genetic reporter that measures the relative cell cycle speed of live cells in a single measurement using two fluorescent wavelengths. This reporter is based on a color-changing Fluorescent Timer (FT) protein (developed by Fedor Subach and colleagues), which emits blue fluorescence when newly synthesized before maturing into a red fluorescent protein. Its ability to report cell cycle speed exploits the different half-life of the blue vs. red form of the same protein molecule. When the FT is expressed at steady-state in a heterogeneously dividing population, faster-cycling cells can be distinguished from slower-cycling cells by the intracellular ratio between the two fluorescent wavelengths as predicted by mathematical modeling. We tagged the FT onto histone H2B to localize signal to the chromatin, facilitating visualization and image processing. Cell cycle perturbation experiments were performed to validate the H2B-FT transgene as a bona fide reporter of cell cycle speed in a variety of cultured mammalian cell lines. Additionally, the H2B-FT color profile faithfully tracked with previously known proliferation kinetics of blood stem and progenitor cell types in vivo in transplanted mouse bone marrow. We generated a mouse allele for inducible expression of the H2B-FT from the endogenous HPRT locus. Using this mouse model, we have been able to obtain new insights into the regulation of hematopoiesis. Because the reporter is compatible with FACS, it is possible to sort subpopulations of cells cycling at different rates for downstream biochemical, genomic, and functional analysis. We anticipate that this technology will be useful in a wide range of cell types and tissue contexts to explore mechanisms linking cell cycle speed and cell fate plasticity.

Funding Source: NIH/NIGMS, T32GM007223.

14:00 – 14:15

RNA SWITCH TECHNOLOGIES TO PURIFY AND PROGRAM TARGET CELL TYPES

Saito, Hirohide

Kyoto University, Kyoto, Japan

The precise identification and purification of target cell types is critical to both study cell function and prepare cells for therapeutic applications. Gene delivery using RNA rather than DNA may be safer owing to a reduced risk of genomic integration. By designing microRNA (miRNA)-responsive mRNAs, we developed a method for high-resolution identification, separation, and purification of target cell types with distinct miRNA activities. We designed mRNAs encoding a protein of interest tagged with complementary sequences of target miRNAs. These miRNA-responsive mRNA switches can control translation of transgenes depending on endogenous miRNA activities and purify variety of target cells, including human ESC/iPSC-derived cardiomyocytes, insulin-producing cells, megakaryocytes, and neurons with high efficiency, accuracy, and safety. Moreover, we prepared a set of “miRNA-responsive, synthetic mRNA library” to rapidly identi-

fy active miRNA profiles in each cell type. For example, we newly identified several miRNAs used as specific markers in human naive and primed pluripotent states. Interestingly, miRNA expression levels analyzed by RNA-Seq did not correlate well with miRNA activities analyzed by our library. Additionally, we recently developed miRNA-responsive CRISPR-Cas9 system in which the genome editing activity of Cas9 can be repressed (OFF) or activated (ON) through endogenous miRNA signatures, generating "miRNA-Cas9 OFF/ON switch" that selectively edits genome of target cells. Possible applications using these RNA switches will be discussed.

14:15 - 14:30

ENHANCED CRISPRa BY THE USE OF BOTH TRANSCRIPTIONAL AND EPIGENETIC ACTIVATORS

Dominguez, Antonia A.¹, Karla, Jaslin², Urke, Amanda³, Naidu, Anika³, Finkbeiner, Steve² and Qi, Lei.³

¹Bioengineering, Stanford University, Stanford, CA, U.S., ²Gladstone Institute, San Francisco, CA, U.S., ³Stanford University, Stanford, CA, U.S.

The ability to directly regulate endogenous gene expression in a sequence-specific manner offers great promises in deepening our understanding of human health and disease. Beyond gene editing, the CRISPR-Cas9 technology offers a gene regulation tool by using the nuclease-deficient dCas9, which does not cleave, but precisely binds to DNA when guided by a single guide RNA (sgRNA). CRISPR activation (CRISPRa) uses dCas9 fusion proteins to recruit transcriptional activators for endogenous gene activation. Strategies to recruit multiple activators to a gene locus have been implemented, such as dCas9-VPR, and have increased the ability to efficiently activate endogenous genes with one sgRNA. Additionally, fusion of the catalytic domain of histone acetyltransferase p300 to dCas9 serves as an epigenetic activator at promoters and enhancers. Here, we implement a strategy that combines both transcriptional and epigenetic activation by pairing transcriptional and epigenetic activators or expressing them sequentially. We have tested the activation of multiple endogenous genes in HEK293T cells and demonstrate that our combined activation system outperforms the individual systems. This combined system allows for a wider dynamic range of activation that can then be modulated by sgRNA selection. Additionally we have engineered these components into an inducible single-vector based CRISPR system that contains selection fluorescence and utilizes the Piggybac transposon system for integration. Coupling these CRISPRa tools, along with CRISPRi, and the ability to model ALS using patient hiPSCs and motor neurons derived from healthy hiPSCs, we are probing the disease-causing mechanism of C9orf72 in Amyotrophic Lateral Sclerosis (ALS). The ability to specifically repress or activate disease targets in a sequence-specific man-

ner offers promise for deepening our mechanistic understanding of not only ALS, but other genetic diseases.

Funding Source: A.A.D is supported by ALS Association Milton Safenowitz Fellowship and the Burroughs Wellcome Fund Postdoctoral Enrichment Program.

14:30 - 14:45

DEVELOPING ALLOGENEIC IMMUNOTHERAPY WITH iPSC DERIVED CYTOTOXIC T AND NK CELLS

Wang, Wen Bo¹, Vodyanyk, Maksym², Zhang, Xing², Brandl, Andrew², Mcleod, Ethan², Slosarek, Erin² and Dao, Monique²

¹Cell Therapy R and D, Cellular Dynamics International (CDI), Madison, WI, U.S., ²Cellular Dynamics International (CDI), Madison, WI, U.S.

Using cutting-edge technologies, Cellular Dynamics International has pioneered techniques for developing and manufacturing induced pluripotent stem cells (iPSCs) and differentiating them into functional human cells. We have demonstrated that footprint free reprogramming technology can be used to generate iPSC lines from normal adult T cells. With the goal of establishing an allogeneic bank of therapeutic T cells for cancer immunotherapy, we have successfully established a number of super-donor iPSC lines from common HLA haplotypes. With feeder-free/serum-free culture conditions, we have developed methods for iPSC differentiation to lymphoid CD34+ precursors, followed by differentiation to CD3+ T and CD56+CD3- NK cells with >100x T or NK cells/iPSC yield during 3-4 weeks. By varying culture conditions, iPSC-derived CD3+ T cells can be generated with different T cell subsets, CD4+ and/or CD8+ cells, T cells expressing TCRgd or TCR ab, T cell-related markers (CD5, CD27), and NK-associated and activation markers (CD94, CD161, CD69). Under defined activation conditions, iPSC-derived T cells could further be expanded to produce homogeneous proliferating T cell cultures with no evidence of exhaustion. Further in vitro studies of iPSC-derived T cells demonstrated their Type 1 cytokine secretion profile (IL2, IFNg, TNF), cytotoxic identity (perforin and granzyme B secretion, target cell cytotoxicity). In combination with chimeric antigen receptor technology, we demonstrate that CD19scFv-CD28z engineered iPSCs could be successfully differentiated into functional T cells with specific cytolytic activity against CD19+ targets. Our results highlight a promising application of iPSCs as a source of allogeneic cytotoxic T and NK cells generated with a defined culture condition built on CDI's industrial human cell production platform. Current studies are in progress to measure the anti-tumor potency of iPSC-derived CAR T cells in vivo and data will be presented.

14:45 – 15:00

GENOME-SCALE CRISPR SCREENING IDENTIFIES NOVEL HUMAN PLURIPOTENT GENE NETWORKS

Kaykas, Ajamete and Ihry, Robert

Novartis Institutes for Biomedical Research, Cambridge, MA, U.S.

The majority of human disease is complex and influenced by many genes. Understanding the genetic modifiers of disease is an important step in the identification of drug targets and treatments. Human pluripotent stem cells (hPSCs) can be used to generate a wide variety of relevant cell-types that are clinically translatable and allow for genetic dissection of disease pathways. Despite the huge potential of hPSCs, their use for genetic screening has been limited because of technical challenges. We have developed a scalable and renewable Cas9/gRNA-hPSC library where loss-of-function mutations can be induced at will. Our inducible-mutant hPSC-library can be used for an unlimited number of unbiased genome-wide CRISPR screens in a variety of hPSC-induced cell types. As proof-of-concept, we performed 3 independent genome-wide screens with this library. We screened for novel genes and pathways involved in 3 of the fundamental properties of hPSCs, their ability to self-renew/survive, differentiate into somatic cell-types, and their inability to survive as single cell clones. We identified the majority of known genes and pathways involved in self-renewal, single cell survival and differentiation, as well as a plethora of novel genes with unidentified roles in these processes. The results of these screens will serve as a resource for the stem cell community for understanding basic hPSC biology. Furthermore, this renewable library can be used to probe for genetic modifiers of any human disease that can be modeled in hPSCs.

SATURDAY, 23 JUNE, 13:15 – 15:15

CONCURRENT IVD: STEM CELLS AND CANCER

Room 212/213, Level 2

13:20 – 13:45

EXPLOITING STEMNESS AS A CANCER CELL VULNERABILITY USING HEPATOCELLULAR CARCINOMA AS A MODEL SYSTEM

Ma, Stephanie

University of Hong Kong, Hong Kong

Our laboratory is interested in understanding the general mechanism of tumorigenesis and developing strategies to target cancer through understanding 'cancer stemness', a property that is closely associated with tumor relapse and the general unfavorable outcome of the disease. Using hepatocellular carcinoma (HCC) as a model system,

we are conducting systematic multidisciplinary studies, involving omics profiling coupled with molecular, cellular, functional and disease modeling approaches, to identify and characterize functional genes and pathways that are operational for cancer stemness. In this talk, I will share some of our recent work on delineating the origins and molecular features of HCC stem cells; and talk about our work on initiating the establishment and characterization of a small-scale HCC organoid bio-bank that is particularly representative of Asian ethnicity.

13:45 – 14:00

INHIBITION OF ROR1 STEM CELL SIGNALING BY CIRMUZUMAB IN CHRONIC LYMPHOCYTIC LEUKEMIA: PHASE 1 CLINICAL TRIAL RESULTS

Kidwell, Reilly L., Choi, Michael, Widhopf, George, Hasan, Md. Kamrul, Chen, Liguang, Yu, Jian, Rassenti, Laura, Pittman, Emily, Messer, Karen, Gutierrez, Charlene, Prussak, Charles, Castro, Januario, Kipps, Thomas and Jamieson, Catriona

Moores Cancer Center, University of California, San Diego, La Jolla, CA, U.S.

Receptor tyrosine kinase like orphan receptor 1 (ROR1) is an onco-embryonic antigen expressed on cancer stem cells (CSCs) but not on normal post-partum tissues. ROR1 is a cell-surface receptor for WNT5A, which induces non-canonical WNT signaling leading to Rho GTPase activation and phosphorylation of hematopoietic lineage cell-specific protein 1 (HS1). Aberrant ROR1 overexpression is linked to CSC self-renewal, making ROR1 a selective target for anti-CSC therapy. As a first-in-class humanized monoclonal antibody developed at UC San Diego, cirmtuzumab is a selective inhibitor of ROR1. We conducted a Phase 1 trial evaluating the safety and biologic activity of cirmtuzumab in patients with chronic lymphocytic leukemia (CLL), a disease in which self-renewing malignant B cells express ROR1, and high levels portend progression. Overall, 26 relapsed/refractory CLL pts were enrolled and received cirmtuzumab at doses ranging from 0.015 to 20 mg/kg for 4 biweekly doses, with PK analyses showing a long plasma half-life (32.4 days). PD analysis confirmed inhibition of Rho GTPases and HS1 phosphorylation within 24 hrs of infusion at doses of 2mg/kg or higher. Inhibition was sustained post-treatment until plasma cirmtuzumab levels became negligible (<200ng/mL). Cirmtuzumab was well-tolerated with no drug-related SAEs, DLTs, or infusion reactions. Despite the limited treatment duration, there were encouraging signs of clinical activity, including reduction in circulating lymphocyte counts, lymph node size, and/or leukemia-cell infiltration of the marrow. Of 22 evaluable pts, 18 had stable disease at the time of response assessment (2 months following the final infusion per iwCLL guidelines). Median time to progression was 259 days (95% CI 168-265 days). Overall, specific inhibition of WNT5A/ROR1 signaling by cirmtuzumab inhibits Rho GTPase activation and HS1 phosphorylation and reduces circulating leukemic cells with early indications of reduced disease progression without significant toxicity. This represents a novel approach to inhibition of CSC

growth/survival signaling, and has a robust application for the treatment of patients with ROR1 expressing cancers/CSCs. It has also prompted a currently enrolling Phase 2 efficacy trial in combination with ibrutinib for relapsed/refractory B cell malignancies.

Funding Source: This clinical trial was supported by a grant from the California Institute of Regenerative Medicine and was conducted in collaboration with Oncternal Therapeutics, Inc.

14:00 - 14:15

MODELLING BREAST CANCER USING CRISPR-CAS9-MEDIATED ENGINEERING OF HUMAN BREAST ORGANOID

Dekkers, Florijn¹, Whittle, James², Chen, Athena², Vaillant, Francois², Liu, Kevin², Dawson, Caleb², Sachs, Norman³, Clevers, Hans¹, Lindeman, Geoff² and Visvader, Jane²

¹Hubrecht Institute for Developmental Biology and Stem Cell Research, Utrecht, Netherlands, ²The Walter and Eliza Hall Institute of Medical Research, Melbourne, Australia, ³Vertex Pharmaceuticals, San Diego, U.S.

Breast cancer evolves from normal epithelium through the accumulation of mutations that result in tumours with complex genomic and biological heterogeneity. Deciphering the critical early events in tumorigenesis that results in this complex biology is essential for understanding the key driver mutations in different breast cancer subtypes. Recently, a human breast organoid technology has been developed to enable genetic modification, long-term expansion and transplantation of breast cancer cells. Here we test the feasibility of generating breast cancer organoids from normal human breast epithelium using CRISPR/Cas9-mediated gene editing. We generated breast organoids from single sorted epithelial cells of normal human reduction mammoplasty samples. Confocal 3D imaging revealed that organoids consist of E-cadherin-positive luminal cells with an outer layer of Keratin 5-positive basal cells. Using CRISPR-Cas9-mediated gene editing, we deleted TP53, PTEN and RB1 in breast organoids and investigated their in vitro growth properties. As expected, mutated organoids demonstrated increased proliferation rates and gained long-term culturing capacity compared to wild-type controls. Engineered breast tumour organoids were transplanted into the mammary fat pad of immunodeficient NOD-SCID-IL2R^{-/-} mice. Notably, transplanted organoids from TP53-PTEN-RB1- but not TP53-PTEN-knockout cells gave rise to tumours that could be serially transplanted. Next generation sequencing analysis indicated that clonal heterogeneity was maintained in organoids in vitro and in tumours propagated in vivo. Based on immunohistochemical staining, tumours (which were ER+PR+HER2-) exhibited features consistent with the luminal subtype of breast cancer. Drug therapy to assess the response to endocrine agents is currently underway. Our study highlights the potential for generating human breast cancer organoids from normal epithelium

that can be applied to understand critical events in early breast cancer tumorigenesis.

Funding Source: Florijn Dekkers is supported by a Marie Skłodowska Curie global individual fellowship of the European Commission.

14:15 - 14:30

REGIONAL VARIATION IN PROLIFERATIVE ACTIVITY OF INTERFOLLICULAR EPIDERMAL PROGENITORS EPIDERMAL AFFECTS SUSCEPTIBILITY TO ULTRAVIOLET INDUCED CARCINOGENESIS

Roy, Edwige, Wong, Ho Yi, Murigneux, Valentine and Khosrotehrani, Kiarash

The University of Queensland, Brisbane, Queensland, Australia

Oncogenic mutations induced by UV can be found in normal skin suggesting that additional factors are necessary to overcome cell intrinsic mechanisms as well as cell of origin restrictions towards tumour formation. A major determinant for a cell to accumulate mutations relies in its ability to persist long term and to give rise to a large clone of mutant cells. In this study, we used multicolour fate tracing (K14Cre/Er:: Rainbow3 mice) to evaluate size changes in clones of epidermal cells in response to chronic suberythemal ultraviolet B radiation injury. Upon tamoxifen injection basal keratinocytes were labelled randomly with one of five possible fluorescent protein combinations and the size of different clones could be evaluated at different time points. Our findings highlight a bimodal progression of epidermal clones. Epidermal clones expanded more if attached to hair follicles (HF) ($P < 0.0001$) compared to those not attached that remained of smaller size despite months of UV irradiation. Although there was globally more epidermal proliferation in the presence of UVB irradiation, proliferating cells were concentrated within 60µm of hair follicle openings and clones distant from hair follicles harboured label retaining cells suggesting their relative slow cycling behaviour. In response to UV, basal cells in proximity of hair follicles were more likely to display nuclear CYCLIN D1 whereas levels of P63, nuclear YAP or P-STAT3 were evenly distributed throughout the surface epidermis. Functionally, microdissection of clones attached or not to hair follicles followed by whole exome sequencing did not reveal any difference in mutation load between proliferative and slow-cycling clones. However in a UVB inducible murine BCC model (K14Cre/ER:: Ptch1lox/+ mice), although keratin17 expressing groups of epidermal cells reflecting hedgehog pathway activation through loss of the second ptch1 allele were evenly distributed across dorsal skin, they were larger in size if attached to hair follicles. Invasive BCCs emanated from hair follicle attached clones. In conclusions, epidermal progenitors in proximity of hair follicles are more proliferative, give rise to larger clones more likely to be affected by a second mutation leading to epidermal carcinogenesis.

14:30 – 14:45

TARGETED INACTIVATION OF ONCOGENIC DRIVERS ORIGINATING FROM ADULT STEM CELLS

Kim, Johnny

Department of Cardiac Development and Remodeling, Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

The most prevalent types of cancer primarily affect tissues containing cells with increased proliferative potential often inferred by resident stem cells (SC) that enable regeneration of the respective tissue. Skeletal muscle regeneration is mediated by activation of rare quiescent muscle SCs that express Pax7. Recently it was shown that germline inactivation of p53 in mdx mice undergoing chronic muscle regeneration develop embryonic rhabdomyosarcomas (ERMS). However the cancer cell of origin and mechanisms of tumor formation under these settings have remained elusive. We identified muscle SCs as a cellular origin of ERMS and show that deactivation of muscle SC quiescence by regeneration is necessary to generate ERMS upon SC specific loss of p53. Purification of lineage-traced tumor cells enabled identification of discrete genomic copy number amplifications that drive tumorigenesis including but not limited to yap1, c-met, cdk4/os9 and c-jun. By reanalyzing human sequencing data including the TCGA PANCAN data set comprising more than 10,000 patients across a broad range of human cancers we discovered novel molecular subtypes of cancer. Importantly, targeted inactivation of identified oncogenes in individual primary tumor cells abolished tumor expansion. Our data indicate the dependence of individual tumors on distinct regulatory networks that originate from adult SCs and underscore the necessity to provide means for personalized therapeutic interventions of cancer.

Funding Source: This work was supported by the Max Planck Society, the DFG (Excellence Cluster Cardio-Pulmonary System (ECCPS)), and SFB TR81 TPO2 and the LOEWE Center for Cell and Gene Therapy.

14:45 – 15:10

DISEASE MODELING OF GASTROINTESTINAL CANCERS USING ORGANOID

Sato, Toshiro

Keio University, Tokyo, Japan

The biological understanding of gastrointestinal cancer requires faithful disease modeling that recapitulates the disease heterogeneity and pathobiological traits of original cancers. We optimized the stem cell niche factor medium for gastrointestinal tumor organoids and established over 100 patient-derived organoid lines from various tissue origins and histological subtypes including previously uncultured rare tumors. Tumor organoids reproduced histopathological grades and differentiation capacities of parental tumors in vitro and upon xenografting. Integrated molecular and biological analyses of tumor organ-

oids revealed their acquisition of niche independency with varying degrees, along with the accumulation of genetic mutations. In general, cancer organoids acquire niche-independent growth capacity through corresponding signal mutations, known as driver gene mutations. However, we noted that some cancers did not follow this rule. For instance, pancreas cancers often gained Wnt-niche independency through an epigenetic reprogramming, and they no longer required Wnt signal activation for their long-term self-renewal in the absence of Wnt pathway mutations. In this session, we would like to show our recent progress in disease modeling using patient-derived cancer organoids and share our biological understanding on how cancers acquire their niche independency to survive and thrive at niche-poor environments.

SATURDAY, 23 JUNE, 13:15 – 15:15

CONCURRENT IVE: STEM CELL NICHES

Room 203/204, Level 2

13:20 – 13:45

DIFFERENTIATION AND SURVIVAL IN THE DROSOPHILA MALE GERM LINE ADULT CELL LINEAGE REQUIRE APICAL POLARITY AND JUNCTIONAL COMPONENTS IN SURROUNDING SOMATIC SUPPORT CELLS

Fuller, Margaret T., Berry, Cameron and Brantley, Susanna

Stanford University School of Medicine, Stanford, CA, U.S.

Interactions with the local microenvironment are required for adult stem cell self-renewal, but also guide stem cell daughters through differentiation. For the *Drosophila* male germ line stem cell lineage, somatic cyst cells are required for daughters of germ line stem cells to initiate differentiation. Two cyst cells form a simple squamous epithelium that encloses one of the two daughters of a stem cell division and maintain this enclosure around the mitotic and meiotic progeny of that founder cell throughout the entire differentiation process. The somatic cyst cells co-differentiate with the germ cells they enclose, suggesting coordinating signals, such as proper development of many organs, ranging from limbs, to hair follicles, mammary glands, or kidneys, requires close-range communication between epithelia and associated mesenchyme. Proper function of the *Drosophila* somatic cyst cells is required for daughters of the germ line stem cell to properly enter a period of transit amplification, to then stop mitotic divisions, and finally to begin preparing for and executing meiosis. Function of tight junction complex components in the somatic cyst cells is required for the germ cells they enclose to survive past the four cell stage of transit amplification. In addition, the *baz/par-6/aPKC* apical polarity complex is required in somatic cyst cells for the germ cells to survive past a later stage of differentiation, immediate-

ly after germ cells exit mitosis and begin to prepare for meiosis. The Par complex prevents death of the neighboring germ cells by antagonizing JNK pathway activity in the somatic cyst cells. Knocking down expression of JNK pathway components in cyst cells that have lost Par complex function rescues survival of the early spermatocytes, suggesting that somatic support cells that have lost polarity actively kill the germ cells they enclose.

13:45 - 14:00

REPROGRAMMING ECTOPIC VASCULAR BLOOD STEM CELL NICHES IN VIVO

Hagedorn, Elliott J.¹, Perlin, Julie¹, Mao, Clara¹, Redfield, Shelby¹, Daily, Madeleine¹, D'Amato, Christopher¹, Li, Brian¹, Riquelme, Raquel¹, Wattus, Samuel¹, Collins, Samantha¹, Holler, Karoline², van Oudenaarden, Alexander³, Junker, Jan Philipp² and Zon, Leonard¹

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The hematopoietic stem and progenitor cell (HSPC) niche is a supportive microenvironment comprised of distinct cell types, including specialized vascular endothelial cells that directly interact with HSPCs and promote stem cell function. Utilizing a new spatial transcriptomics technique called RNA tomography, in combination with tissue-specific RNA-seq, we identified ~20 genes selectively enriched in endothelial cells of the zebrafish fetal hematopoietic niche. Using upstream regulatory sequences for two of these genes, selectin E (*sele*) and *mrc1a*, we generated GFP reporter lines that allowed us to selectively isolate niche endothelial cells. We performed ATAC-seq (an assay for chromatin accessibility) and identified 6,710 regions of chromatin that were open in niche endothelial cells but not endothelial cells from other tissues. Several of these regions were associated with the 20 enriched genes. To evaluate whether these regions might be enhancers we coupled them to GFP and injected them into embryos. To date, 13/19 tested sequences drove GFP in niche endothelial cells. Upon closer examination of the *sele* and *mrc1a* genes, we identified enhancer sequences as short as 158 bp and 125 bp, respectively, which drove niche endothelial-specific expression. A genome-wide motif enrichment analysis of the 6,710 uniquely open chromatin regions revealed that *Ets*, *Sox*, *Gata* and Nuclear Hormone sites were most enriched. Using mutant variants of the 158 bp and 125 bp enhancer sequences, we demonstrated that *Ets*, *Sox* and Nuclear Hormone (RORA/RXRA/NR2F2) sites were independently required for specific transgene expression. We next injected pools of human transcription factors containing at least one member from each of the three families. Strikingly, we found that a combination of ETV2, SOX7 and NR2F2 generated ectopic patches of niche-like endothelial cells that expressed *sele* and *mrc1a*, and were able to recruit and directly interact with *runx1*+ HSPCs, some of which divided. Our results suggest these three factors are sufficient to reprogram niche endothelial

cell identify in vivo and demonstrate that functional aspects of the HSPC niche were recapitulated. These studies have important implications for designing a synthetic vascular niche for stem cells or for modulating the niche in the context of disease therapy.

14:00 - 14:15

MOLECULAR CHARACTERIZATION OF THE HUMAN AND MOUSE ADULT SPINAL CORD STEM CELL NICHES REVEAL A CONSERVED DORSAL-VENTRAL REGIONALISATION AND MSX1+ DORMANT NEURAL STEM CELLS

Hugnot, Jean-Philippe¹, Ripoll, Chantal¹, Gazalah, Hussein¹, Leventoux, Nicolas¹, Calvo, Charles-Felix², Thomas, Jean-Leon³, Lallemand, Yvan⁴ and Bauchet, Luc⁵

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Both in human and mice, the central canal region of the adult spinal cord harbors a niche for neural stem cells. These cells represent an attractive cellular source for endogenous repair of spinal cord lesions due to traumatic injury or neurodegenerative diseases such as ALS. This central canal region is heterogeneous and composed of several cell types. The identity of neural stem cells is still ill-defined and controversial. In order to generate a database for genes expressed in this niche, we performed high throughput RNA profilings of the spinal cord central canal region in human (aged 17 and 46) and mouse. This uncovered the conserved expression of 1200 genes with a high enrichment for ciliogenesis. A conserved set of 120 transcription factors was also identified and IF confirmed the expression of *Sox4*, *Sox9*, *Sox11*, *Meis2*, *Pbx1*, *NFIA*, *Id4*, *Pax6*, *Arx* and *Msx1*. Unexpectedly, we observed that the adult niche maintains the expression of spinal cord developmental genes with a dorsal-ventral regionalized pattern. *Pax6* was excluded from the ventral region which on the contrary contains a group of cells expressing *Arx*, a key gene for SHH signalling. In mouse, *Msx1* expression was restricted to a small number of cells showing low or no proliferation and located in the roof of the niche coinciding with the expression of two morphogens (*BMP6* and *GDF10*). During early spinal cord development, *Msx1* and *Arx* are specifically expressed by roof and floor plate cells then by the dorsal and ventral parts of the presumptive central canal region, highly suggestive of the persistence of roof and floor plate cells in the adult niche. In the brain, neural stem cells express *VEGFR3* (Calvo et al, *Genes Dev.* 2011 Apr 15;25(8):831-44) and using *VEGFR3-YFP* mice, we observed the presence of radial *VEGFR3+* cells in the dorsal and ventral regions of the niche, some of them expressing *Msx1*. Using *Msx1-Tomato* transgenic mice, we found that *Msx1* are not the main source of neural stem cells in the niche however a fraction of these cells can generate multipotent neurospheres which can be passaged at least 9 times and which express *BMP6* and

GDF10. These results indicate that the adult spinal cord niche in mouse and man is a mosaic of cells with different developmental origin and maintaining high levels of neural developmental genes.

Funding Source: AFM, IRME, IRP, ERA NET Neurons, INSERM.

14:15 - 14:30

SUPPRESSIVE ROLE OF BONE MARROW MESENCHYMAL STEM CELL DURING ACUTE MYELOID LEUKEMIA DEVELOPMENT IN MICE

Sandhow, Lakshmi¹, Xiao, Pingnan², Heshmati, Yaser², Kondo, Makoto², Boudierlique, Thibault², Dolinska, Monika², Johansson, Anne-Sofie², Sigvardsson, Mikael³, Ekblom, Marja⁴, Walfridsson, Julian² and Qian, Hong²

¹Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, ²Karolinska Institutet, Stockholm, Sweden, ³Linköping University, Linköping, Sweden, ⁴Lund University, Lund, Sweden

Bone marrow (BM) mesenchymal stem cell (MSC) has been shown to be critical for maintaining normal hematopoiesis and can be altered by leukemic cells. However, the contribution of the MSC to leukemic niche formation and leukemia progression remain poorly understood. We have previously reported Early B-cell Factor 2 (Ebf2) marks native BM MSCs in mice. In the present study, we demonstrated the role of Ebf2⁺ MSC during acute myeloid leukemia (AML) development by using a transplantation-induced MLL-AF9 AML mouse model, cell fate-mapping, multi-colour flow cytometry, and in-vivo MSC depletion. During AML development, the Ebf2⁺ cells dramatically increased and were promoted towards differentiation, reflected in increased proportion of more differentiated mesenchymal progenitor cell (MPC) fraction. By employing triple transgenic Ebf2-CreERT2 x Rosa26-tomato x Ebf2-EGFP mice, we showed that Ebf2⁺ MSC could generate all stromal cell subsets (CD45-TER119-CD31-) including CD51+SCA1+ MSC, CD51+SCA1- MPC and mature stromal cells (CD44+) in AML mouse BM, indicating critical involvement of Ebf2⁺ MSC in leukemic niche formation. Furthermore, the BM MSC/MPC displayed dysregulation of cytokines, such as Cxcl12, Angptl1, Col1a1, Igf1, and Il6, which correlated with AML burden in the BM. Most importantly, depletion of the Ebf2⁺ MSC either prior or after AML transplantation resulted in shorter latency of the AML and reduced survival of the mice, suggesting suppressive role of BM MSCs in MLL-AF9 AML progression. In summary, the Ebf2⁺ MSC/MPCs were critical for maintaining normal hematopoiesis while suppressing AML, however, they could be educated by the infiltrated AML cells to form AML niche favoring the leukemic cell proliferation. Our findings provide cellular and molecular evidence for disease stage-related differential contribution of BM MSC to AML development.

14:30 - 14:45

IDENTIFICATION OF BONE MARROW ENDOTHELIAL STEM CELLS PROMOTING HEMATOPOIETIC RECONSTITUTION POTENTIAL

Domingues, Melanie¹, Oteiza, Ana², McCourt, Peter³, Heazlewood, Chad¹, Williams, Brenda¹, Rossello, Fernando⁴, Nefzger, Christian⁴, Polo, Jose⁴ and Nilsson, Susan¹

¹CSIRO, Clayton, VIC, Australia, ²University of North Norway, Tromsø, Norway, ³University of Tromsø, Norway, ⁴Australian Regenerative Medicine Institute (ARMI)-Monash University, Clayton, Australia

Hematopoietic stem cells (HSC) are capable of the sustained production of all mature blood cells and the transplantation of these cells remains the main treatment option for a range of haematological malignancies. The successful expansion of HSC post-transplant is essential for the bone marrow regeneration post disease treatment. It is well known that the complex microenvironment in which HSC reside is critical for HSC regulation. Although the vascular compartment of the bone marrow niche has long been identified as a major component of HSC regulation and maintenance, little is known about the characteristics or functional capacity of bone marrow sinusoidal endothelial cells. In this study, we identified, prospectively isolated and characterized bone marrow scavenging sinusoidal endothelial cells (BMSEC) utilizing their immense endocytic ability as a functional marker. FITC-labelled advanced glycation end-product modified bovine serum albumin (FA), a ligand for endocytic scavenger receptors specifically labels BM sinusoidal vasculature. Based on the expression of different endothelial markers multiple FA⁺ sub-populations were evident. Analysis of these sub-populations revealed a hierarchically organized system with a stem cell population (BM-ESSC) capable of serial long term BM revascularization and reconstitution of the entire BM sinusoidal endothelial system following transplantation. Importantly, HSC and BM-ESSC populations were shown to be mutually exclusive in terms of cell surface phenotype as well as in their molecular signature both at the population and at the single cell level. Furthermore, we observed that the co-transplantation of enriched populations of BM endothelial scavenging stem and progenitor cells (BM-ESSPC) in combination with hematopoietic progenitor cells (LSK) led to a significant increase in bone marrow cellularity compared to LSK cells alone. We have demonstrated for the first time that the endothelial sinusoidal stem cells (BM-ESSC) are able to revascularise the BM and improve the hematopoietic reconstitution potential of LSK cells following transplantation. Overall, our results suggest that the BM-ESSC could be used as a combination therapy to improve bone marrow transplant outcomes.

SATURDAY 23 JUNE 2018

14:45 – 15:10

PROTEIN C RECEPTOR IN REGULATING MAMMARY STEM CELLS AND BREAST CANCER

Zeng, Yi Arial and Wang, Daisong

Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

The mammary gland is composed of multiple types of epithelial cells that are generated by mammary stem cells (MaSCs) residing at the top of the hierarchy. The identity of MaSCs was unclear. Our study demonstrates that Procr (Protein C receptor), a novel Wnt-target in the mammary gland, marks a population of multipotent MaSC. Procr-expressing cells display high regenerative capacity in transplantation assays and differentiate into all lineages of the mammary epithelium by lineage tracing. In mouse, Procr was required for the mammary development and homeostasis, and was important for the initiation of mammary tumor. Triple-negative breast cancer (TNBC) is a highly aggressive malignancy with no targeted treatment option. We found that PROCR is highly expressed in TNBC patient samples, and associated with poor prognosis. Remarkably, targeting PROCR by a neutralizing antibody inhibits TNBC tumor growth. PROCR represents a surface therapeutic target for human TNBC.

risk of graft-related arrhythmogenesis. This presentation will summarize our recent efforts to: 1) promote the scalable electrophysiological maturation of hPSC-CMs in vitro, 2) develop new optical mapping tools to probe hPSC-CM electrical behavior in vivo, and 3) determine the structural and functional consequence of hPSC-CM transplantation in a highly relevant porcine MI model.

16:30 – 16:55

STRATEGIES TO IMPROVE THE EFFICACY OF CAR T CELLS IN HEMATOLOGIC MALIGNANCIES AND SOLID TUMORS

Riddell, Stanley R, Srivastava, Shivani, Salter, Alex, Pont, Margot, Veatch, Josh, Leung, Isabel and Fraessle, Simon

University of Washington, Seattle, WA, U.S.

Advances in synthetic biology and adoptive T cell transfer are making inroads in cancer therapy. Genetically modified T cells that express synthetic chimeric antigen receptors (CARs) targeting CD19 and BCMA have had success in patients with advanced B cell malignancies and multiple myeloma. Our lab conducted the first clinical trials in which the CD4 and CD8 T cell composition of the CD19 CAR-T cell product is uniform in all patients. This approach identified CAR-T cell dose/response and dose/toxicity relationships not apparent in prior studies, and improved the therapeutic index in B cell tumors. The outgrowth of tumor cells with low or absent antigen expression remains an obstacle for durable remissions in some patients. A larger challenge is to extend CAR-T cell therapy to common solid tumors, where identifying molecules expressed on cancer cells that can be targeted safely remains an obstacle. We developed CARs that target Ig/Fz epitope of the receptor tyrosine kinase like orphan receptor ROR1 expressed in many cancers including non small cell lung cancer (NSCLC) and triple negative breast cancer (TNBC). Unlike hematologic cancers, solid tumors have an immunosuppressive tumor microenvironment (TME), and are often resistant to infiltration by effector T cells. Data from patients with TNBC and NSCLC treated on a clinical trial of ROR1 CAR T cells demonstrates limited CAR T infiltration into tumor masses and less antitumor activity than observed with CAR T cells targeting CD19 in B cell malignancies. To systematically identify and overcome obstacles that may interfere with efficacy of CAR-T cells in solid tumors, we have used an autochthonous K-RAS mutant, P53^{-/-} genetically engineered model of NSCLC that expresses ROR1. This model replicates initiation, progression, and development of the human lung cancer TME, and like in human tumors, ROR1 CAR T cells have partial efficacy and are limited by poor infiltration into the tumor. This model is being used to examine combination therapies with that improve CAR-T cell infiltration and efficacy in solid tumors. The design of logic gated CARs that may allow targeting molecules that are coexpressed on tumor cells and normal cells will be discussed.

SATURDAY, 23 JUNE, 16:00 – 18:15

PLENARY VII: MOVING TO THE CLINIC: GENE AND STEM CELL THERAPIES

Plenary Room, Ground Level

16:05 – 16:30

HEART REGENERATION WITH HUMAN PLURIPOTENT STEM CELL-DERIVED CARDIOMYOCYTES

Laflamme, Michael

Toronto General Hospital Research Institute, University Health Network, Toronto, Canada

Human pluripotent stem cells (hPSCs) have a number of attractive properties for myocardial infarct (MI) repair, including a tremendous capacity for expansion in the undifferentiated state followed by the ability to differentiate into phenotypically unambiguous cardiomyocytes. Our group has contributed to the development of efficient, reliable protocols to generate large quantities of hPSC-derived cardiomyocytes (hPSC-CMs), and we have shown that the transplantation of hPSC-CMs results in the partial remuscularization of injured hearts in multiple preclinical MI models. Despite this, a number of important challenges remain, including concerns about the immature and heterogeneous electrophysiological phenotype of hPSC-CMs, the ability of these cells to undergo appropriate electromechanical integration following transplantation, and the

16:55 - 17:20

THE JOHN MCNEISH MEMORIAL LECTURE:
CLINICAL INVESTIGATION OF GENE TRANSFER
FOR GENETIC DISEASE: RESTORING SIGHT,
MAKING BLOOD CLOT

High, Katherine

Spark Therapeutics, Philadelphia, PA, U.S.

For those with an interest in therapeutics, one of the hopes surrounding the Human Genome Project had been that there would be a rapid expansion of therapeutic options for people born with serious genetic disorders. Clinical gene therapy has required more time to come to fruition in the form of licensed products than most had guessed, although the timelines in clinical development are similar to those seen with other novel classes of therapeutics such as monoclonal antibodies or bone marrow transplantation. In 2017, the US FDA licensed three gene therapy products, two CAR-T cell products for B-cell malignancies, and one AAV vector for a rare form of congenital blindness. This presentation will review the clinical development program that supported the first licensed AAV gene therapy product in the US, for an ultra-rare form of congenital blindness. The presentation will also review data from clinical trials of AAV-mediated gene transfer for hemophilia B and hemophilia A. Similarities and differences in clinical development programs for these two therapeutic areas will be discussed.

17:20 - 18:00

KEYNOTE ADDRESS: CRISPR-CAS SYSTEMS
AND THE FUTURE OF GENE EDITING

Doudna, Jennifer

University of California, Berkeley and HHMI, Berkeley, CA, U.S.

Gene editing with CRISPR technology is transforming biology. Understanding the underlying chemical mechanisms of RNA-guided DNA and RNA cleavage provides a foundation for both conceptual advances and technology development. I will discuss how bacterial CRISPR adaptive immune systems inspire creation of powerful genome engineering tools, enabling advances in both fundamental biology and applications in biomedicine including cell-based therapies. I will also discuss the ethical challenges of some of these applications.

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