Alix Ventures

Market Deep Dive Report

Organoids

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Contents

1. Summary

Organoid technology has seen a rapid advancement in the past decade and a collection of reported organoids resembling breasts, cerebral cortex, intestine, kidney, liver, lung optic cup, pituitary gland, prostate, pancreas and stomach have been developed. The technology, however, is currently in its nascent years and is posed to be used in a number of applications including toxicology, drug discovery, personalized medicine, disease modeling, regenerative modeling, etc.

The market is growing rapidly and is currently dominated by a few players such as STEMCELL Technologies Inc., Cellesce Ltd., Hubrecht Organoid Technology, Organoid Therapeutics, PeproTech, Inc., Thermo Fisher Scientific, Corning Incorporated, and Merck KGgA.

The space has seen a surge of startups in the past few years working on the use of organoids for a myriad applications and our prediction is that it will continue to increase over the projected period and beyond. Startups like Xilis and System 1 Biosciences are using it as a therapeutic platform for drug discovery for cancer and neurological diseases respectively, whereas, Cellesce is trying to meet the rising demand for organoids with their novel bio-processing technology intended towards the growth and expansion of organoids. Owing to the use of big data, automation and software by the startups in the space both traditional biotech along with generalist investors are active in the space. The space has seen a significant rise in VC funding and we believe that the trend will continue in the near future. The technology is still developing and has a number of technical risks such as issues with media standardization, large scale production and vascularization and the startups able to overcome these challenges will emerge as leaders. We expect to see biopharma companies partnering with startups for their platform technology to help with drug discovery and precision medicine. The data collected through biobanks by the startups will be a valuable asset in its own right.

Finally, we believe that this is a great space to look for investments and will remain to be a lucrative space in the future.

2. Market Overview

The organoid market was valued at USD 502 million in 2019 and is expected to grow to a market value of USD 2.74 billion by the end of 2027. This rapid growth is driven by increasing use of organoids in a range of applications, such as pathogenesis, disease modeling, drug screening, biobanking and regenerative medicine. Moreover, the increasing incidence and prevalence of several chronic and infectious diseases, outbreak of the novel coronavirus and significant investments in research and development activities and advancements in big data and technologies like 3D printing is further responsible for the growth . North America currently dominates the organoids market, however, Europe, second largest organoid market, is also projected to witness a rapid growth as well due to investments in research and development on cancer, liver diseases, gastrointestinal diseases for organ regeneration and stem cell research.

2.1 Major Stakeholders

The major stakeholders to consider in this market include pharmaceutical companies, cosmetic companies, startups, academic and research institutes and contract research organizations. The organoid market is dominated by key players such as STEMCELL Technologies Inc., Cellesce Ltd., Hubrecht Organoid Technology, Organoid Therapeutics, PeproTech, Inc., Thermo Fisher Scientific, Corning Incorporated (Life Sciences), and Merck KGgA due to innovative product offerings, robust geographic presence, and large investment in research and development. These players have expanded their product offerings and geographic presence across the globe via adoption of technological advancements, commercialization of organoids technology, alliances with universities, partnerships and acquisitions. Organoids have evolved as a better alternative for animal models for drug discovery and thus organoid based companies have become an ideal partner for large biopharma companies to reduce both capital expenditure and time in the drug development process. Moreover, organoid companies that are able to converge biology and computation/software have become even more lucrative due to their computation/software expertise for partnerships. A recent merger between Cancer Genetics and Stemonix is one such example. The pressure for development of cruelty-free cosmetics by the customers and the political environment and animal testing ban in certain countries have also resulted in a shift towards adoption of alternative testing approaches by the cosmetics industry. L'Oreal's partnership with Organovo was just the beginning and we expect this trend to continue in the upcoming years.

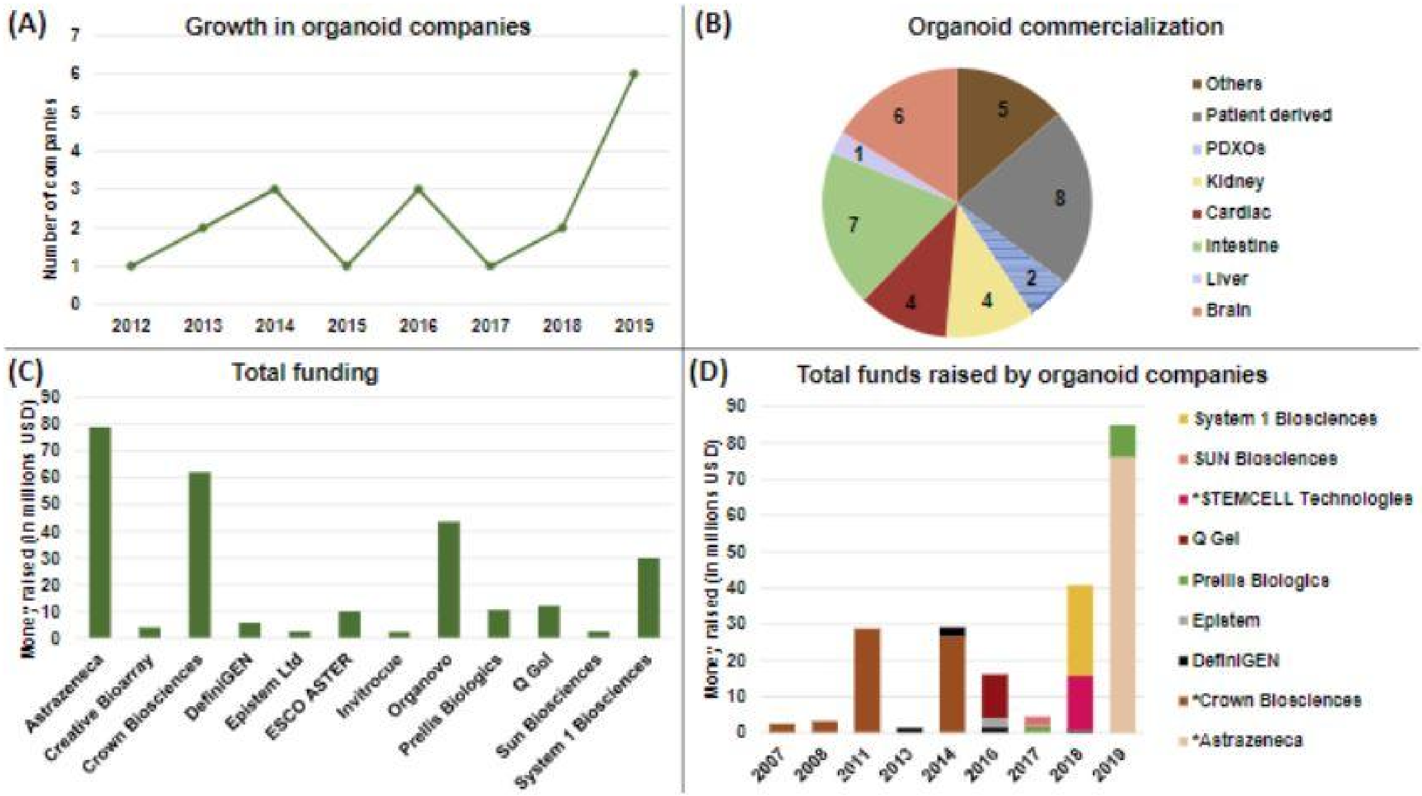
2.2 Analysis of Organoid Companies

Figure 1 depicts the analysis of organoid companies around the world. It shows that the number of companies focusing on commercializing organoids has seen a sharp rise from 2012 to 2019. It is clear that there has been a significant increase in investments in this space in the years the analysis is done and will continue to grow further based on market projections.

Figure 1. Analysis of Organoid companies around the world reproduced from Choudhury et al., 2020, Trends in Molecular Medicine.

3. Technology Overview

3.1 Organoids



There has been a pursuit to develop complex 3D multi-cellular environments that resemble physiological conditions for both academic and research applications such as cancer research, stem cell research, drug discovery, and research pertaining to other types of diseases. This is primarily driven by inaccurate representation of tissue *in vivo* by 2D models, where cells are cultured on plastic or glass substrates. Researchers have now demonstrated that 3D models yield more accurate data about cell-cell interactions, tumor characteristics, drug discovery metabolic profiling, stem cell research and various types of diseases including cancer. Moreover, significant research is now being done in development of artificial organs for both academic and industrial applications. One such 3D cell culture technology known as organoids has gained a lot of traction recently and was awarded the "Method of the Year for 2017".

Organoids also called "mini organs" are a miniaturized version of an organ produced in vitro in three dimensions that shows realistic micro-anatomy. Formally, they are defined as self-organizing 3D structures grown from stem cells that mimic the *in vivo* environment, architecture and multi-lineage differentiation of the original organoids. They can be established from two types of stem cells, one being pluripotent embryonic stem cells (ESCs) or induced pluripotent stem cells (iPSCs) which are collectively known as PSC-derived organoids. Second type of organoids can be derived from adult stem cells (ASCs) which are obtained by resection or biopsy of organs from donors.

Organoids derived from PSCs and ASCs are grown differently and are ideal for different applications. PSCs-derived organoids are first grown in 2D culture where they form spheroids which are then transferred to an extracellular matrix and tissue specific growth factors to develop a particular type of organoid. However, ASC derived organoids are either grown from cell suspension from primary tissue biopsies or from resected tissue material. The ones that evolve from single cell suspension are embedded into an extracellular matrix with a mix of specific growth factors. It typically takes around 3 weeks for them to grow and resemble the structure of a tissue however for a completely mature organoid vascularization is typically achieved by cultivation in bioreactors or by implanting the organoid into an animal model.

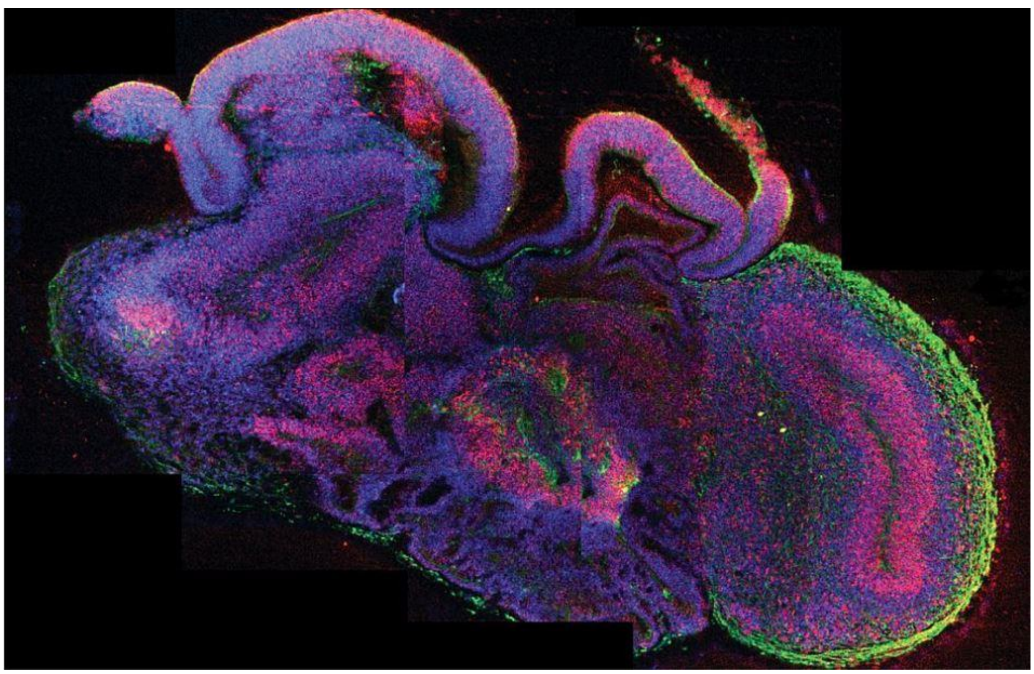


Figure 2. Cross-section of a cerebral organoid culture system. Reproduced from Lancaster et al., 2013, Nature.

3.2 Types of Organoids

A number of different types of organoids have been created to provide researchers with various types of new models for a broad spectrum of tissues. However, this is an on-going process and new forms of organoids are created regularly. To put things into perspective, a total of 45 different types of organoids were created in the year 2010 which in the year 2018 increased to 966 which is an ~21 fold increase.

The list below is in no form comprehensive, however, it describes the most common organoid types.

1. Cancer Organoids

Cancer organoids have been described as potentially the best system to quickly evaluate cancers. Results have shown with high statistical correlation that drugs that work on organoids also work on patients and vice versa. Biobanks of cryopreserved organoids from healthy donors and their tumor counterparts are created for personalized medicine. This potential has also led the Human Cancer Model Initiative (HCMI) to create approximately 1,000 patient-derived cancer cell lines and made available to scientists worldwide for potential use in generating organoid models. HCMI consists of Cancer Research U.K. (CRUK), Hubrecht Organoid Technology (HUB), the Wellcome Sanger Institute (WSI), the National Cancer Institute (NCI), Broad Institute of Harvard and MIT (BROAD), and Cold Spring Harbor Laboratory (CSHL). There are other subtypes of cancer organoids such as colon cancer organoids, colorectal cancer organoids, prostate cancer organoids, breast cancer organoids, Pancreatic organoids, etc.

2. Cerebral Organoid

Cerebral organoids, also called mini-brains are a valuable model in studying numerous applications such as disease modeling, drug discovery, cell therapy, personalized medicine, etc.

It has been used to study viral infections such as zika virus infection in brain organoids. National Institute of Mental Health (NIMH) has developed iPSC-derived organoids from patients with schizophrenia, autistic spectrum disorder (ASD) and bipolar disorder to compare their development to that of healthy controls. Although cerebral organoids have been developed with some degree of success huge improvements are still necessary. Many research labs do not have access to the technology and the cost is also very high. ding of the fundamentals of the particular diseases. The testing of specific gene mutations would help in the development of a general scheme for proper drug administration to patients. The precision medicine approach would lie in the application of medication based on the specific gene variants of the particular patient.

3. Intestinal Organoid

Intestinal organoids are by far the most predominantly used organoids in research and broad clinical applications such as immunology, intestinal biology, stem cell biology, regenerative medicine and tissue engineering. The first mice intestinal organoids were created in 2009 in Hans Clevers lab. Subsequently, human organoids were created from LGR intestinal stem cells from PSCs or primary tissues. Their ability to renew intestinal structures in a relatively short period of time make them an interesting model for many medical applications.

4. Liver Organoid

Liver organoids also known as hepatic organoids consists of a monolayer of epithelial cells that are typically derived from liver ASCs. Recently, researchers have been able to create human cell-derived models bearing a certain disease and it is projected that more of such models will be developed and added to the biobanks over the next few years. This will significantly increase the probability of success of the drug screening process as one of the most common reasons for the drug being pulled out of the clinical trials is liver toxicity. Moreover, clinical trials for human organoid transplantations are planned for this year.

5. Lung Organoid

Lung organoids for both animal and human models currently exist and have a huge potential in modeling disease mechanisms and personalized medicine. In particular, lung cancer is a leading cause of cancer-related death worldwide and having a better cancer model will help researchers understand the different phases of lung cancer. They also have a potential use in drug screening and regenerative medicine.

6. Kidney Organoid

In the last 7 years there has been significant refinement of protocols to generate kidney organoids either derived from human embryonic stem cells or iPSCs and are positioned well to have a transformative impact on applications such as disease modeling, drug screening, efficacy testing, toxicity evaluation and clinical trials in a dish. These organoids have also seen significant efforts towards their vascularization which has always been a concern with organoid systems.

7. Pancreatic Organoid

Pancreatic organoids form an interesting system that can be used to model a healthy ductal pancreas biology and development of disease models of the ductal compartments such as cystic fibrosis. The biggest potential of pancreatic organoids lie in regenerative medicine for curing diabetes. Moreover, they have also been used to model different types of pancreatic cancer and potentially be used in molecular diagnostics and pharmacological testing.

3.3 Organoid Biobanks

An organoid biobank is a platform for collection of organoids. It is a standard approach to keeping organoid samples for ongoing experiments. For instance, Hubrecht Organoid Technology (HUB) is a biobank of patient-derived colon cancer, breast cancer, ovaries, lungs, pancreases and prostate organoids. Similarly, there are other biobanks around the world that store different types of organoids. Summarized below are the different biobanks and types of organoid they store.

Centre	Country	Organoid Type
Institute of Cancer Research	United Kingdom	Cancer
Hubrecht Organoid Technology	The Netherlands	Several Types
The University of Hong Kong	Hong Kong	Cancer
Keio University School of Medicine	Japan	Cancer

Wellcome Sanger Institute	U.S.A	Several Types
Cincinnati Children's Hospital	U.S.A	Several Types
The Princess Margaret Living Biobank	Canada	Cancer
Tokyo Medical and Dental University	Japan	Intestine

3.4 Major Players

All major large cap biopharma companies have committed to the development of AI solutions as a part of their drug discovery process and have disclosed deals and partnerships with academic centers of startups providing such technology. While no company has produced yet a molecule or target that has reached clinical significance, a few startups have stood out as technological leaders:

HUBRECHT ORGANOID TECHNOLOGY

Hubrecht Organoid Technology (HUB) was founded by the Hubrecht Institute, the University Medical Center Utrecht, and the Royal Netherlands Academy of Arts and Sciences (KNAW). HUB`s technology constitutes a paradigm-shifting platform for drug discovery and development, (pre)clinical patient stratification, predictive diagnostics, personalized medicine, clinical trials, regenerative medicine, and companion diagnostics. HUB exploits the pioneering work of Prof. Dr. Hans Clevers, who discovered the HUB Organoid Technology to grow 'mini-organs' – organoids – from epithelial tissue derived adult stem cells (ASCs).

CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

The Cincinnati Children's Hospital Medical Center is a pioneering healthcare institution and one of the top-ranked pediatric research centers in the world. The center tries to bring the organoid technology to the clinic and is the only institution in the U.S. that has an organoid center focused on this goal. They are also a world leader in using animal models for developmental studies and embryonic development. Therefore, they have the unique ability to compare both approaches and are already using organoids for personalized drug screening. They also run the

Center for Stem Cell and Organoid Medicine (CuSTOM), focusing mainly on embryonic organ development.

STEMCELL Technologies Inc.

Stemcell Technologies is a biotech company that provides cell culture and storage media, cell isolation and separation products, cell assays, accessory tools and educational services for life science research. The company also offers contract research services related to cell assays. Stemcell Technologies is also highly involved in organoids, offering culturing media, plastic for organoid cultivation and also readymade frozen organoids.

CrownBio

Crown Bioscience, a global drug discovery and development services company, providing translational platforms to advance oncology, inflammation and autoimmune, cardiovascular and metabolic disease research. They have a strategic partnership with HUB to provide preclinical oncology drug development and validation services using HUB Organoid Technology, including access to HUB's highly characterized tumor organoid biobank.

QGel

QGel is a company that has a library of extracellular matrix samples for cell line and organoid culturing. QGel also offers over 10 types of organ tissue types and cell-lines which can form organoids.

R&D SYSTEMS INC.

R&D systems Inc. offers a variety of products from recombinant proteins, small molecules and peptides to antibodies and cell cultures that include organoids and other 3D culture reagents.

Trevigen Inc.

Trevigen is a biotechnology company focused on products for cancer research and toxicology. The company also offers contract research services to universities and other biomedical companies. They established the Organoid Research Lab (ORL) in 2016. They make a 3D cell culture product named Culturex which is an alternative to Matrigel (Corning Incorporated) and Gletrex (Invitrogen Corp.).

Corning Incorporated

Corning Incorporated is an American multinational technology company that specializes in specialty glass, ceramics, and related materials and technologies including advanced optics, primarily for industrial and scientific applications. Among other things, Corning Inc provides hydrogels such as Corning Matrigel® Matrix and Corning® Collagen are popular scaffold choices to support cell expansion in organoid cultures.

Merck KGaA

Merck KGaA is a leading science and technology company, operating across healthcare, life science and performance materials. They make reagents and media for organoid culture.

4. Historical Context, Key Trends, & Future Development

4.1 History of Organoids

Organoids have become an important discovery today with applications ranging from being an alternative to animal models in drug discovery to artificial organs. However, this pursuit of understanding the biological nature of organization dates back to more than a century. A work by H.V. Wilson in 1907 demonstrated that if a sponge is dissociated into its constituent cells, and these cells are reaggregated randomly, they organize to make a realistic and viable new sponge. Although, the research wasn't aimed to making organoids in the modern sense of the word, this important demonstration that living cells of an adult organism contain sufficient information to guide the formation a multicellular structure without the need for an outside instruction or the need for cells to start from some specific anatomical arrangement contingent on their embryological history was groundbreaking.

Subsequent work pertaining to organoid was done from the point of view of basic developmental biology where embryologists were trying to understand the cellular mechanisms of development and thus, animal sources were preferred for comparison with *in vivo* data. Later, researchers started proposing the idea of studying toxicology with organoids and it became obvious that the use of animal models for the purposes of use of toxicology would have the same issues in extrapolating animal data to humans which we knew were problematic. This along with the vision of making transplantable tissues for human clinical became the primary motivation of using human cells as a starting point. However, it wasn't until the development of the first human embryonic stem cell (hES cell) in 1998 and human-induced pluripotent stem cell (hiPS cell) in 2007 that created a huge interest in development of human organoids for various applications. It was perhaps the groundbreaking works of groups of Yoshiki Sasai and Hans Cleavers that brought significant interest to the field of organoid. Their work promoted the idea that stem cells have the intrinsic ability to self-organize into 3D structures that mimics *in vivo* organs.

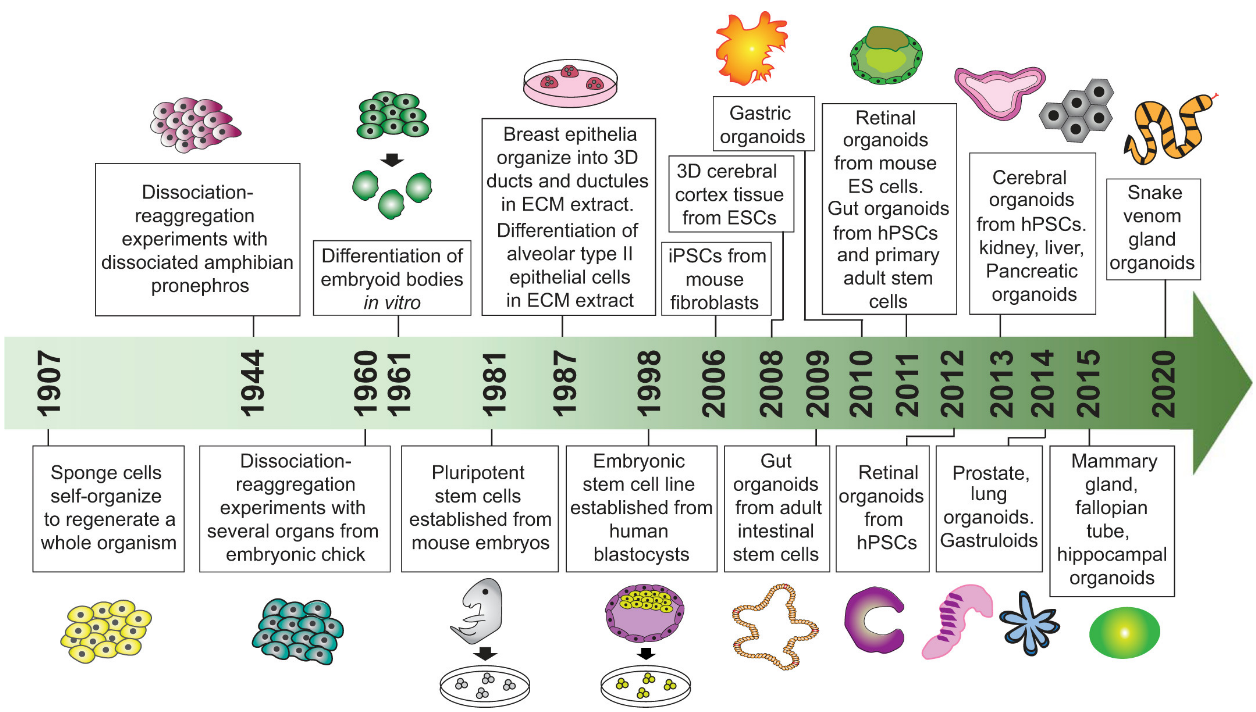


Figure 2. Representation of timeline of the development of organoid cultures. It summarizes key landmark and breakthrough studies leading to the establishment of various organoid technologies. Reproduced from Corrò et al., 2020, American Journal of Physiology-Cell Physiology.

4.2 Key Trends and Future Predictions

After the re-creation of intestinal organoids by Hans Clevers, organoid technology has seen exciting developments. One major event has been the exclusive licensing agreement between Hubrecht Organoid Technology and STEMCELL Technologies Inc. for manufacturing and distributing organoid culture media in 2014 which was a significant and essential step towards widespread use to organoids. Subsequent licensing deals between STEM Cell Technologies and the Cincinnati Children's Medical Center for generating PSC-derived gastrointestinal organoids, including intestinal and stomach cells and exclusive partnership with the Institute of Molecular Biotechnology (IMBA) of the Austrian Academy of Sciences to develop cerebral organoids, or 'mini-brains' has significant pushed the technology forward. Moreover, the project launched by the U.S. National Cancer Institute (NCI) to develop more than 1,000 novel cancer cell models, including organoids, for researchers around the world has led to numerous efforts in advancing the organoid technology in clinical settings.

Aforementioned developments along with the significant advancement in the organoid technology in the past few years have led to the creation of numerous startups trying to use organoids in applications such as drug discovery, toxicology, precision medicine and regenerative medicine. There are a wide range of companies where some are trying to enable growth and expansion of organoids for commercialization whereas others are reinventing the neuro drug discovery by combining brain models, scaled biology and machine learning. It is fair to say that this technology is in its nascent stage and convergence of organoid technology with other biological techniques such as gene editing will lead to a number of interesting applications that will drive patient impact. Furthermore, there are companies that are using machine learning techniques with organoid technology now, it is much more exciting to see the result of these techniques once these startups have collected significant amounts of data over time.

5. Opportunities

The global organoid market has a fragmented landscape with several new players driving intense competition and rising investment in innovation. Moreover, the advancements in Big Data and 3D printing have opened up new avenues for growth. Companies riding this wave of innovation with strong business sense will be far ahead of the competition.

5.1 Current Applications

As an alternative to traditional *in vitro* culture models, organoids have emerged as a superior approach for modeling human developmental biology and diseases. They accurately represent the structure and function of the organ they were derived from and thus have gained popularity in a myriad of applications. Below are some of the key applications of Organoids.

1. **Toxicology**
   Owing to the organoids displaying a very accurate microanatomy. This makes them invaluable for in vitro modeling of drug adverse effects, specifically in organs commonly susceptible to drug-induced toxicities (i.e. gastrointestinal tract, liver, kidney).

2. **Drug Discovery**
   It has become increasingly clear that many cell- and animal-based models are not predictive of clinical efficacy particularly for heterogeneous diseases, such as cancer. Organoids have emerged as a better physiological disease model for efficacy evaluation in preclinical development.

3. **Development**
   Most of our understanding of embryonic development comes from extrapolating observations in mice and other animal models to humans. Human PSC-derived organoids are generated by guided differentiation protocols that mimic developmental processes and can be used to understand developmental biology.

4. **Disease Modeling**
   One exciting application of organoids is modeling pathology and diseases. Due to significant physiological or behavioral differences there is a gap in knowledge in understanding diseases that are difficult or impossible to study in animal models. Organoids can be a cheaper and more tractable alternative for modeling and understanding the pathophysiology of disease for which causes and genetic basis are not well known. An early example is the use of cerebral organoids generated from patient-derived iPSCs to model microcephaly.

Emerging Applications

Although, significant progress is being made in the development of organoid technology, the organoids currently being formed still lack reproducibility, specificity with regard to cell-type(s) composition, uncontrolled size, shape heterogeneity, absence of proper vasculature, and lack of functionality. The convergence of organoid technology with transcriptomics and tissue mechanics will provide new opportunities in numerous applications including human development, personalized and precision medicine.

1. **Regenerative Medicine**
   Given that organoids are a technology that replicate key structural and functional features of human organs. It has a huge potential to impact the field of regenerative medicine. As mentioned previously pancreatic organoids have a huge potential in regenerative medicine to cure diabetes. One promising study is when small intestinal organoids were transplanted in the colon, they successfully retained their original features, like villus formation and the presence of Paneth cells.

2. **Precision Medicine**
   Owing to the tractability and potential to capture patient and tumor type diversity, organoids are well suited for the development of personalized therapeutic approaches. One such example is screening of therapeutics for diversity of cancers captured by organoid biobanks.

5.2 Startups to Watch

The following early stage startups have demonstrated significant promise as up and coming purveyors of novel technology:

XILIS: Xilis has raised $4.85 M in a seed round from Felicis Ventures, 8VC, KdT Ventures, Liquid 2 Ventures, Two Sigma Ventures, Pear Ventures, and Alix Ventures. The company's treatment uses micro-organoids which can be used for testing for drug compatibility faster, enabling healthcare providers to take care of their patients. The founding team is extremely strong.

CELLESCE: Cellesce is a UK based startup that has raised an undisclosed amount from the development Bank of Wales. It has invented a bio-processing technology intended towards the growth and expansion of organoids to assist client organizations in commercializing organoid models which are powerful new enabling technology in drug discovery and regenerative medicine.

SYSTEM1 BIOSCIENCES: System1 Biosciences has raised $25 million of Series A venture funding in a deal led by Charles River Ventures and Pfizer Ventures. They are reinventing neuro drug discovery by combining human brain models, scaled biology and machine learning to decode brain disease, from genetics to neural computation. They harness the resulting deep biological insights to systematically discover and develop novel drugs with greater therapeutic potential.

3DYNAMICS: 3DYNAMICS is an early stage spin-off from Johns Hopkins University School of Medicine funded by a $0.30M grant. They are developing a therapeutics platform designed to generate brain-region-specific organoid in 3D culture. They have also developed a cell culture system consisting of a novel spinning bioreactor platform, called SpinΩ, and a set of methods for differentiation of pluripotent stem cells into region-specific brain organoids and liver organoids. Their technology is scalable and used for pre-clinical drug screening and testing of their efficacy/ toxicity.

PATH BIOANALYTICS: Path Bioanalytics is an early stage grant funded startup that does phenotypic drug discovery and development using patient-derived disease models and AI to advance treatments for targeted patient populations.

KNOWN MEDICINE: Known medicine has raised a total of $150,000 from Kickstart Seed Fund and Forward Venture Capital. The company's platform offers cutting-edge biology research and the newest AI techniques, enabling oncologists to break down a patient's tumor into many micro tumors and treat them with different drugs to find the best one.

CYPRE: Cypre has raised $150,000 of seed funding in the form of convertible debt. They are developing a tumor model platform intended to be used for the transformative 3D cellular research and clinical testing of cancer patients.

DYNOMICS: Dynomics has received $320,000 from Boost VC. They are developing therapeutics to directly target the heart using an authentic human cardiac organoid discovery platform.

5.3 Industry Challenges

5.3.1 Technical Challenges

1. Organoids are only able to recapitulate part of the entire body and may not faithfully capture the stereotypic and complex functions of individual organs. Therefore, they are only able to provide an approximation of the biology of the entire organism, in contrast to the animal model. Therefore, results from organoids have to be complemented by whole organism studies in model systems.
2. Organoid culture uses an animal-based extract, typically Matrigel or Basement membrane extract. These extracts are prone to batch-to-batch variability in their composition, which may affect reproducibility of the experiments. Moreover, they might also carry unknown pathogens and are potentially immunogenic when transplanted to humans which limits their use to transplant settings. There are approaches that can be used for intestinal organoids for short term expansion using clinical grade collagen, however, no such approach exists for long term expansion of intestinal organoids and for expansion of non-intestinal organoids.
3. For ASC-derived organoids, only the epithelial compartment of organs are represented. Therefore, blood vessels, immune cells, stroma, and nerves are lacking. This can possibly be overcome by establishing co cultures which is analogous to what has been done with stem cells.

5.3.2. Ethical and Regulatory Challenges

1. Since organoids are derived primarily from stem cells, the ethical issues surrounding stem cell research and stem cell therapies encompasses organoids as well.
2. Usage of animal-derived ECM 'matrigel' in organoid production is flagged as an ethical concern because of its compatibility issues with humans.

3. To improve the vascularization of organoids, especially cerebral organoids, researchers grew them inside rats. This raises some ethical implications due to a heightened sense of consciousness.
4. Even with all the benefits of a more centralized system, such as an organoid biobank, there are serious considerations related to the confidential information regarding the type of donor, donor consent, etc.

5.3.3 Market Challenges

1. For startups especially, **talent is in short supply**. To succeed in this field, a multidisciplinary skill set including backgrounds in chemistry, biophysics, biology, bioinstrumentation is required. Moreover, if the startup is using AI, that also reduces the supply of the talent pool given an increasing demand for machine learning engineers. For the startup to acquire and keep talent, it becomes important that the founding team is very strong.

6. Conclusions

6.1 Vertical Strengths

- Technology is still in its nascent stage and has significant space for innovation.
- Transformational technology with a very clear value proposition.
- Favorable acquisition and collaboration environment with large biopharmas.
- Market is projected to grow at a high CAGR.

6.2 Vertical Weaknesses

- Ethical challenges around using stem cells for developing organoids.
- Regulatory challenges and concerns related to confidential information regarding the type of donor, donor's consent, etc.
- Difficult for startups to attract talent with expertise in multiple fields

6.3 Opportunity Cost of Capital

Organoid technology is evolving at a fast pace with a relatively large market and thus will drive significant patient impact. In particular, organoids themselves are a platform technology posed to be used in numerous applications including drug discovery, toxicology, precision medicine, regenerative medicine, etc., which makes this vertical particularly lucrative for investment. Companies however, are operating at the forefront of this nascent technology and would need huge support from academic researchers. Nonetheless, this space is ready for more capital and the companies that are able to build early expertise will be able to capture multiple adjacent markets.

6.4 Investment Thesis Areas

This report finds organoid technology as a rich vertical with significant opportunity for startups to thrive. Specifically, companies that are able to address the following needs will have ample ground to build category defining leadership.

1. **Issues with media standardization**: Even though significant efforts are being made in standardizing the media, one major issue around cultivation of media is the composition is not fully standardized and this may cause variability in organoid production. Artificial media isn't developed for most of the organoids and they aren't suitable for long term culture. Moreover, Matrigel which is an extracellular matrix for culturing organoids is known to have batch to batch variability.

2. **Large scale production of organoids**: Very few companies are focusing on large scale production of organoids currently. Scaled manufacturing would be important to lower costs and have a larger impact. Xilis is a startup that is solving for scaling, reducing costs and making organoid development more predictable using its micro organoid technology.
3. **Cost reduction**: Current manufacturing of organoids costs around $3,000. Startups able to reduce the cost of organoid manufacturing will be well positioned.

4. **Vascularization**: The lack of vascularization is a major issue in generating larger organoids (particularly for artificial organ development) which results in limited oxygen

and nutrient delivery to the innermost parts of the organoids. Therefore, companies that are able to solve this problem will have huge potential in the regenerative medicine space. Prof. Roger Kamm's laboratory at MIT has made significant advances in the field.

5. **Improving functionality:** There is a need to improve cellular and morphological complexity of the organoid technology to mimic organs. For instance, inducing properly organized regional identities in brain organoids, or providing a developing branching collecting-duct system in kidney organoids could improve their functionality to the point where they could be used as organs.

7. References & Further Reading

- Commercialization of Organoids
- A brief history of organoids
- Method of the Year 2017: Organoids
- Organoids: A new window into disease, development and discovery
- Organoids and Mini-Organs