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PROGRAM GUIDE

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PLEASE JOIN US FOR THE GLOBAL STEM CELL EVENT OF 2025

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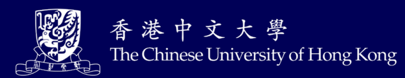

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Dear Colleagues and Friends:

Welcome to Hamburg!

It is thrilling to be back in Europe for our signature event for the first time in nearly a decade – celebrating a tremendous year of progress in stem cell science and applications for human health.

The Program Committee has designed a special event this year. We are seeing stem cell therapies coming to realization in clinical trials and have more talks and sessions on translational stem cell biology than any other ISSCR Annual Meeting in history. This reflects the natural evolution of basic science starting to move toward therapies and demonstrating the potential to help humankind. At the same time, we are delighted that we have been able to balance outstanding basic science alongside those clinical advances throughout the program. As the field is maturing, we are excited about the number of opportunities we are providing to early career investigators coming into the field often starting with basic science questions, which fuel the foundation of the field.

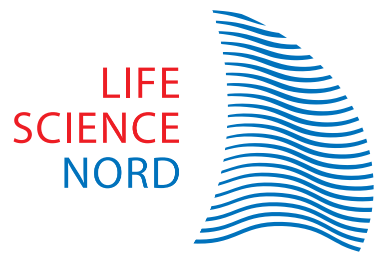
This year, we have also created many opportunities for young scientists to present their work. We have greatly expanded the number of travel awards and have capitalized on the growing interest in community-driven Science Spotlight sessions, organized by post docs and students. Science Spotlights expand on research in emerging fields or specific technologies that drive the field forward, while giving young scientists experience with designing a scientific session. They have been a great addition to the meeting and highlight novel topics, often signaling areas where stem cell science is heading.

We also look forward to vibrant discussion at the poster sessions, with the strongest abstract submission numbers since the pandemic, and to connecting with friends both new and old through our enthusiasm for new discoveries. We always anticipate fantastic talks from our ISSCR Award honorees, Fiona M. Watt, Sergiu P. Paşca, and Jun Wu, and this year is no exception as we hear about the body of work of these extraordinary stem cell scientists. The ISSCR also will tackle provocative conversations around global ethics, policy, and regulation of stem cell science through concurrent sessions lead by our committee members.

Thank you to our stem cell community for joining us this year and to the City of Hamburg, Life Science Nord, Bayer, and BlueRock Therapeutics for their generous support of ISSCR 2024 and coming along with us on this journey to bring our hallmark meeting back to Europe.

The science this year is spectacular. The old-world feel of Hamburg is fabulous. Get ready to enjoy The Global Stem Cell Event of the year!

Amander T. Clark	**Agnete Kirkeby**	**Malin Parmar**
ISSCR President	*Program Co-Chair*	*Program Co-Chair*



Dear delegates of the ISSCR Annual Meeting 2024,

On behalf of the city of Hamburg, it is a great pleasure for me to welcome you all from near and far to our wonderful CCH – Congress Center Hamburg.

We had to wait for quite a long time – our meeting was initially scheduled for 2021. But then Covid-19 changed everything, and our event needed to be postponed. But the ISSCR Annual Meeting is an event worth waiting for, and it is truly an honor to be your co-host together with the Cluster Life Science Nord. You can look forward to four days full of top-class presentations, intensive discussions, and the all-important personal exchange with familiar and new faces from all areas of the stem cell world.

The future starts here. And you are the experts who will play a key role in shaping the future of stem cell research with an open mind and a big heart.

It is a great honor for us that Hamburg is the city where this future takes place. Hamburg and the surrounding region offer one of the leading life science ecosystems. What you can find here is an innovative network where research, industry, startups as well as social and political actors work hand in hand to shape the global healthcare system.

Within the past 20 years, Life Science Nord has evolved into an internationally well-known and respected industry network in Hamburg and Schleswig-Holstein. It actively brings together stakeholders from the biotech, pharma, medtech and digital health sectors and supports them in their progress. Together, we are ambitious to create optimal conditions for researchers and innovators to improve health conditions worldwide.

Hamburg is a great location for cutting-edge research and business opportunities. And beyond this, it is a wonderful place to visit. We therefore hope that you will also find some time to enjoy the stunning Hanseatic charm of our city with its harbor life and its diverse culture. People from all over the world meet here in Hamburg, which is why many of them call it the "Gateway to the World". And if you only have limited time to leave the CCH between your sessions, we recommend a short walk through the Planten un Blomen park adjoining the congress building.

We wish you a fantastic Annual Meeting – and a warm welcome to Hamburg!

Katharina Fegebank
Second Mayor of the Free and Hanseatic City of Hamburg
and Senator in the Ministry of Science, Research, Equality and Districts

Dear friends and colleagues,

Welcome to the 22nd Annual Meeting of the International Society for Stem Cell Research (ISSCR). We, along with our colleagues from BlueRock Therapeutics and Bayer, are excited to welcome you to the premier gathering of researchers in stem cell science and regenerative medicine. We are proud to serve as co-sponsors of this meeting which gathers the brightest minds in stem cell research across the globe to explore significant new advances in the field.

This Annual Meeting is one of the leading opportunities each year for scientific exchange, policy discussion, and public education on the potential that stem cells hold to advance medicine and change the lives of patients.

Throughout the next four days, you will have the chance to participate in poster sessions, plenary talks, concurrent sessions, innovative showcases, and more led by innovators within the field. We encourage you to fully immerse yourself in the experience – seize each opportunity to learn about promising work, forge new connections, catch up with old colleagues, and take the time to relax and enjoy the planned social events.

The future starts here – thank you for being a part of this experience and a member of the innovative community working to transform medicine through the power and promise of stem cells. Enjoy the meeting, we look forward to connecting with you.

Best,

Stefan Irion
Chief Scientific Officer
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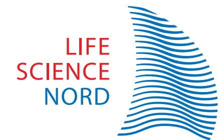

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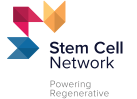

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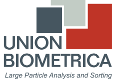

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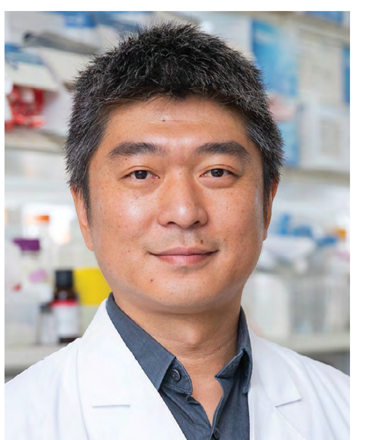
AWARDS

The ISSCR Awards portfolio honors innovation and excellence in the field of stem cell research and regenerative medicine. The awards recognize individual achievements at each career stage, as well as those demonstrating extraordinary public service.

JOIN US ON WEDNESDAY, 10 JULY FOR THE PRESENTATION OF THE 2024 ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD

ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD



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

The 2024 recipient is Jun Wu, PhD, associate professor in the Department of Molecular Biology at the University of Texas Southwestern Medical Center, USA, and a New York Stem Cell Foundation–Robertson Investigator.

Dr. Wu is recognized for his innovative work on creating novel embryonic and extraembryonic stem cells, exploring the mechanisms that limit interspecies chimera formation with human pluripotent stem cells (PSCs), and developing human PSC-based embryo models. Dr. Wu has broadened the understanding of pluripotency by deriving and studying several new types of PSCs with distinct molecular and phenotypic features from different species. His work also includes the generation of PSC-derived interspecies chimeras and the development of an effective and versatile interspecies blastocyst complementation system for the generation of organs and tissues from one species inside another species. Most recently, Dr. Wu's group has developed strategies to generate stem cell-based embryo models from several species, including humans, for studying peri-implantation and peri-gastrulation development in vitro.

The ISSCR Outstanding Young Investigator Award Presentation and Lecture will take place during Plenary II on Wednesday, 10 July, 1:30 PM – 3:35 PM.

JOIN US ON SATURDAY, 13 JULY FOR THE PRESENTATION OF THE 2024 ISSCR PUBLIC SERVICE, MOMENTUM, AND ACHIEVEMENT AWARDS

ISSCR PUBLIC SERVICE AWARD JOINT HONOREES

The ISSCR Public Service Award recognizes outstanding contributions of public service to the field of stem cell research and regenerative medicine.

The ISSCR is honoring Peter W. Andrews, BSc, DPhil, MBA, University of Sheffield, UK, and Tenneille E. Ludwig, PhD, WiCell, USA, with the 2024 ISSCR Public Service Award for their work leading the development of the first international, comprehensive Standards for Human Stem Cell Use in Research. Andrews and Ludwig co-chaired the international collaboration over two years, developing a global reference for rigor and reproducibility in preclinical research, to ultimately strengthen the pipeline of therapies for patients. Standards for Human Stem Cell Use in Research was published in 2023 and has since been adopted by journals, institutions, and funders across the world.

Tenneille Ludwig is the Senior Scientist and Director of the WiCell Stem Cell Bank and a member of the UW-Madison Stem Cell and Regenerative Medicine Center. Peter Andrews is Emeritus Professor of Biomedical Science at the University of Sheffield.

The award will be presented during the Awards and Keynote Session on Saturday, 13 July, 1:30 PM – 3:35 PM.

ISSCR MOMENTUM AWARD

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

The 2024 recipient is Sergiu P. Paşca, MD, Kenneth T. Norris, Jr. Professor and the Uytengsu Director of Stanford Brain Organogenesis, Stanford University, USA.

Dr. Paşca's lab seeks to understand the rules governing human brain assembly and the mechanisms of disease. His laboratory pioneered assembloids, introduced the use of instructive signals to create regionalized neural organoids, and developed integrated human circuits following transplantation. These models have been adopted by hundreds of laboratories worldwide, and Dr. Paşca systematically applied them to gain insights into physiology and disease and to develop therapeutic approaches.

Dr. Paşca will be recognized and deliver the ISSCR Momentum Award Lecture during the Awards and Keynote Session on Saturday, 13 July, 1:30 PM – 3:35 PM.

ISSCR ACHIEVEMENT AWARD

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

The 2024 recipient is Fiona M. Watt, DPhil, FRS, FMedSci, EMBO Director and leader of a research group at EMBL- Heidelberg, Germany.

Fiona Watt is internationally recognized for her work on skin. She found markers to isolate epidermal stem cells and elucidated signaling pathways that regulate stem cell behavior. She uncovered the plasticity of epidermal stem and differentiated cells and discovered how epidermal-dermal communication controls skin homeostasis. Dr. Watt pioneered single-cell analysis, defining how biophysical cues elicit transcriptional responses. She demonstrated the existence of different skin fibroblast lineages, enabling new strategies to treat fibrosis and scarring. Her work has resulted in new insights into how epidermal deregulation leads to tumor formation. Dr. Watt is a member of the EMBO, the Royal Society and the National Academy of Sciences.

Dr. Watt will be recognized and deliver the ISSCR Achievement Award Lecture during the Awards and Keynote Session on Saturday, 13 July, 1:30 PM – 3:35 PM.

The 2024 ISSCR Achievement Award is sponsored by Bayer AG and BlueRock Therapeutics.

2024 TRAVEL AWARDS

CONGRATULATIONS TO THE 2024 TRAVEL AWARD RECIPIENTS

RECIPIENTS OF 2024 ISSCR ZHONGMEI CHEN YONG AWARDS FOR SCIENTIFIC EXCELLENCE

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

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The Tianqiao and Chrissy Chen Institute Fellowship supports members of the *Stem Cell Reports* Early Career Editorial Board (ECEB) by facilitating attendance at the ISSCR Annual Meeting, mentoring opportunities, and the development of educational programming.

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Yue Shao
Yonatan Stelzer
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2024 ISSCR MERIT ABSTRACT AWARDS

The ISSCR recognizes outstanding abstracts with the ISSCR Merit Abstract Awards. These awards are given to ISSCR Student and Postdoc members who have submitted distinguished abstracts as judged by the ISSCR 2024 abstract reviewers. Award recipients will be recognized in Plenary I on Wednesday, 10 July.

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Qiaoling Zhu

PLENARY I: PRESIDENTIAL SYMPOSIUM

Sponsored by: Bayer AG and BlueRock Therapeutics

WEDNESDAY, 10 JULY | 9:30 AM – 11:30 AM

Magdalena Goetz, Helmholtz Zentrum München, Germany

Prof. Dr. Magdalena Goetz, Director of the Institute of Stem Cell Research at the Helmholtz Center Munich and Chair of Physiological Genomics at the Biomedical Center of the Ludwig-Maximilians University in Martinsried/Munich, studied Biology and completed her PhD on the mechanisms of how input connections to the cerebral cortex form during development and how specific neuronal subtypes are specified. Later, she started her own lab at the Max-Planck Institute for Neurobiology and made the breakthrough discovery that radial glial cells are neural stem cells. This inspired her to attempt turning mature glial cells into neurons, a technique she has now developed towards human glia to neuron conversion. Her latest breakthrough discovery is organellar heterogeneity as a key mechanism in development and reprogramming.

Tina Mukherjee, Institute for Stem Cell Science and Regenerative Medicine (InStem), India

Dr. Tina Mukherjee is an Associate Investigator at the Institute for Stem Cell Science and Regenerative Medicine (inStem), Bangalore, where she heads her laboratory as part of the Regulation of Cell Fate theme. The interest of her laboratory lies in understanding the importance of metabolic activity in innate immune development and function. Her lab uses Drosophila to explore the diverse impact of metabolism on innate immune development and function. While this defines their core interest in metabolic regulation of hematopoiesis, they also employ the power of other model systems to uncover the underlying animal physiology that regulates these developmental level immune-metabolic state transitions. This allows them to integrate physiology with immune-development and constitutes their fundamental approach in identifying novel paradigms of myeloid development but also hematopoiesis in general.

Kathrin Plath, David Geffen School of Medicine, UCLA, USA

Dr. Kathrin Plath runs a highly interdisciplinary research program and has made significant contributions to the fields of stem cell biology, gene regulation, epigenetics, and regenerative medicine. She has been at the forefront of studying mechanistically how X-inactivation happens and how somatic cells can be reprogrammed to induced pluripotent stem cells. She serves on the editorial board of *Cell, Science*, and other major journals, and is a Howard Hughes Medical Institute Faculty Scholar.

Sarah Teichmann, Wellcome-MRC Cambridge Stem Cell Institute, UK

Dr. Sarah Teichmann completed her PhD at the MRC Laboratory of Molecular Biology, Cambridge, and was a Beit Memorial Fellow at University College London. She started her group at the MRC-LMB in 2001, and moved to the Wellcome Genome Campus in 2013, where her group was jointly affiliated with the EMBL-EBI and the Wellcome Sanger Institute. In 2016, she was appointed Head of the Cellular Genetics program at the Sanger. Teichmann is a co-founder and co-leader of the international Human Cell Atlas consortium, which aims to create reference maps for cells across all human tissues and co-directs the CIFAR MacMillan Multiscale Human research program. In 2024, Teichmann assumed the position of Chair in Stem Cell Medicine at the University of Cambridge (Cambridge Stem Cell Institute & Dept Medicine).

FEATURED SPEAKERS

JOHN MCNEISH MEMORIAL LECTURE

WEDNESDAY, 10 JULY | PLENARY II: NEW TECHNOLOGIES TO ENGINEER AND PHENOTYPE STEM CELL SYSTEMS

Matthias P. Lutolf, Ecole Polytechnique Fédérale de Lausanne (EFPL), Switzerland

Matthias Lutolf is the founding director of Roche's new Institute for Human Biology (IHB) in Basel, Switzerland. The IHB uniquely bridges academic and pharmaceutical research and is dedicated to research on organoids, human model systems, and translational bioengineering. Lutolf is also a professor at the Swiss Federal Institute of Technology Lausanne (EPFL). He is known for his pioneering work in advanced biomaterials and creatively combining stem cell biology and bioengineering to develop next-generation organoid models that enable better applicability in basic and translational research.

ANNE MCLAREN MEMORIAL LECTURE

THURSDAY, 11 JULY | PLENARY III: EXPLORING THE BASIC PRINCIPLES OF DEVELOPMENT USING STEM CELLS

Alfonso Martinez Arias, Universitat Pompeu Fabra Barcelona, Spain

Alfonso Martinez Arias obtained his PhD from the Universidad Complutense in Madrid, Spain, and his PhD from the University of Chicago, USA. He completed his postdoctoral training at the MRC LMB in Cambridge, UK. After three decades in Cambridge, in 2020 he moved to the UPF in Barcelona, Spain where he is currently an ICREA Research Professor. His interests focus on the way cells interact and use gene regulatory networks to build organisms. Working with pluripotent stem cells, he developed the 'gastruloid' system, which is a model for the study of mammalian gastrulation. He is an elected member of EMBO and in 2012 was awarded the Waddington Medal for his contributions to developmental biology. He has authored two textbooks and a popular science book.

ERNEST MCCULLOCH MEMORIAL LECTURE

THURSDAY, 11 JULY | PLENARY IV: TISSUE ARCHITECTURE AND STEM CELL FUNCTION IN HEALTH AND DISEASE

Elaine Fuchs, The Rockefeller University, USA

Elaine Fuchs is renowned for her research in skin biology, its stem cells, and associated disorders, including cancers and inflammation, and has published more than 370 manuscripts. She received her PhD from Princeton, completed her postdoctorate at MIT, and has been faculty at University of Chicago and now Rockefeller University, where she is an Investigator of the Howard Hughes Medical Institute. Her awards include the National Medal of Science, L'Oreal-UNESCO Award, ISSCR Innovation Award, the Gairdner International Award, and most recently, the Franklin Medal. Fuchs holds membership in the National Academy of Sciences, the National Academy of Medicine, the American Philosophical Society, the Pontifical Academy of Sciences, and the Royal Society.

PATIENT ADVOCATE ADDRESS

SATURDAY, 13 JULY | PLENARY VI: THE CLINICAL REALITY AND PROMISE OF CELL AND GENE THERAPIES

Mikael Rydberg, Lund, Sweden

MR is a 57-year-old married father of five who is still working as a ventilation technician. His symptoms started in 2006 with a tremor in the left arm, and the Parkinson's disease diagnosis was verified by DAT-Scan in 2008. He participated in the TransEuro program in Lund, Sweden, enrolling in the observational cohort in 2011 and was randomized to participate in the transplantation arm of the study in 2015. MR received a staged bilateral transplant of fetal ventral mesencephalic dopaminergic cells. His first transplantation took place in April 2016 to the right putamen. In December 2016 he had a second transplantation, this time to the left putamen, and underwent 12 months of triple immunosuppression therapy.

KEYNOTE ADDRESS

SATURDAY, 13 JULY | PLENARY VII: AWARDS AND KEYNOTE SESSION

Melissa H. Little, Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Denmark and Murdoch Children's Research Institute, Australia

Melissa Little is the CEO of the Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Chief Scientist at the Murdoch Children's Research Institute, and leader of the Kidney Regeneration Laboratory, Melbourne. Little is a former president of the ISSCR and holds an honorary position as Professor in the Department of Pediatrics, University of Melbourne. Internationally recognized for her work on kidney development and pioneering studies into potential regenerative therapies in the kidney, Professor Little's approach to generating kidney organoids from human pluripotent stem cells has been adopted across the globe and is being applied to disease modeling, drug screening, and renal replacement, illustrating the capacity for understanding to be applied to product development.

ISSCR
UPCOMING SYMPOSIA

COPENHAGEN INTERNATIONAL SYMPOSIUM
PSC-DERIVED CELL THERAPIES: CLINICAL ADVANCES, NEXTGEN TECHNOLOGIES, AND THE PATH TO SUCCESS

2-4 OCTOBER 2024 | COPENHAGEN, DENMARK
In partnership with Novo Nordisk

SINGAPORE INTERNATIONAL SYMPOSIUM
STEM CELLS IN TISSUE MAINTENANCE, REPAIR, AND AGING

11-13 DECEMBER 2024 | SINGAPORE
In partnership with Stem Cell Society Singapore (SCSS) & co-sponsored by STEMCELL Technologies

ISSCR CELL THERAPY SUMMIT*

12-13 FEBRUARY 2025 | EDINBURGH, UK
In partnership with Cell and Gene Therapy Catapult

ATHENS INTERNATIONAL SYMPOSIUM
NEURAL DYNAMICS: EXPLORING DEVELOPMENT, DISEASE, AND TREATMENT*

3-4 APRIL 2025 | ATHENS, GREECE
In partnership with Stem Cell Reports & co-sponsored by MaxWell Biosystems

SEATTLE INTERNATIONAL SYMPOSIUM
AI AND MACHINE LEARNING: THE FUTURE OF DIGITAL BIOLOGY*

9-10 OCTOBER 2025 | SEATTLE, USA

BOSTON INTERNATIONAL SYMPOSIUM
LOST IN TRANSLATION: BRIDGING THE GAPS FROM BEDSIDE TO BENCH*

11-12 DECEMBER 2025 | BOSTON, USA

Learn more at ISSCR.org/upcoming-programs

**Title subject to change*

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THE STEM CELL REPORT PODCAST

Join stem cell pioneer and editor-in-chief of *Stem Cell Reports*, Martin Pera, on The Stem Cell Report Podcast as authors go "beyond the paper" and share new insights on their break-throughs and explore questions about the future of the field.

PODCAST GUESTS INCLUDE:

Hans Clevers, MD, PhD

Douglas Melton, PhD

Masayo Takahashi, MD, PhD

Hideyuki Okano, MD, PhD

Fiona Watt, DPhil

Magdalena Zernicka-Goetz, PhD

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thestemcellreport.buzzsprout.com

SCHEDULE AT A GLANCE

WEDNESDAY, 10 JULY

9:00 AM – 9:30 AM	**Refreshment Break**
9:30 AM – 11:30 AM	**Plenary I: Presidential Symposium** *Sponsored by: Bayer AG and BlueRock Therapeutics*
12:00 PM – 1:00 PM	**Innovation Showcases**
1:30 PM – 3:35 PM	**Plenary II**
2:30 PM – 8:00 PM	**Exhibit & Poster Hall Open**
3:35 PM – 4:00 PM	**Refreshment Break**
4:00 PM – 5:30 PM	**Science Spotlights** **Special Session: Equity, Diversity & Inclusion** **Special Session: Career Panel** **COREdinates Focus Session**
5:40 PM – 7:35 PM	**Exhibit Hall Theater Talks**
5:45 PM – 7:45 PM	**Opening Reception & Poster Session I** **Meet-up Hubs**
9:00 PM – 11:00 PM	**Early Career Scientists Social Night*** **Offsite; pre-registration required*

THURSDAY, 11 JULY

8:15 AM – 9:45 AM	**Concurrent Track Sessions** **Evotec Focus Session**
9:30 AM – 10:00 AM	**Refreshment Break**
10:00 AM – 11:45 AM	**Plenary III**
11:00 AM – 6:00 PM	**Exhibit & Poster Hall Open**
12:00 PM – 1:00 PM	**Innovation Showcases**
1:30 PM – 3:00 PM	**Plenary IV** *Sponsored by: Stem Cell Reports*
3:00 PM – 6:00 PM	**Exhibit Hall Pub Crawl**
3:40 PM – 5:35 PM	**Exhibit Hall Theater Talks**
3:45 PM – 5:45 PM	**Poster Session II** **Meet-up Hubs** **Refreshment Break**
6:00 PM – 6:30 PM	**Innovation Showcases**

FRIDAY, 12 JULY

8:15 AM – 9:45 AM	**Concurrent Track Sessions** **Novo Nordisk Focus Session** **BlueRock Therapeutics Focus Session**
9:30 AM – 10:00 AM	**Refreshment Break**
10:00 AM – 11:25 AM	**Plenary V** *Sponsored by: Stem Cell Network*
11:00 AM – 6:00 PM	**Exhibit & Poster Hall Open**
12:00 PM – 1:00 PM	**Innovation Showcases**
1:30 PM – 3:00 PM	**Concurrent Track Sessions** **BIH Focus Session**
3:40 PM – 5:45 PM	**Exhibit Hall Theater Talks**
3:45 PM – 5:45 PM	**Poster Session III** **Meet-up Hubs** **Refreshment Break**
6:00 PM – 7:00 PM	**Innovation Showcases**

SATURDAY, 13 JULY

8:15 AM – 9:45 AM	**Concurrent Track Sessions** **ISSCR Industry Focus Session**
9:30 AM – 10:00 AM	**Refreshment Break**
10:00 AM – 11:35 AM	**Plenary VI** *Sponsored by: Healios K.K.*
1:30 PM – 3:35 PM	**Plenary VII: Awards & Keynote Session**

NETWORKING & EVENTS

ISSCR 2024 offers many opportunities for scientists at all stages of their careers to exchange valuable insights and advice that can advance their research and career. The ISSCR provides various avenues to help scientists foster and strengthen their professional networks. Explore all networking opportunities and events in the Meeting Mobile App.

BLUEROCK CLINICAL TRIALS WORKSHOP SPECIAL SESSION

WEDNESDAY, 10 JULY | 12:00 PM – 1:00 PM

ADVANCES IN THE TREATMENT OF PARKINSON'S DISEASE: THE POSSIBILITIES OF CELL THERAPIES

Presented by: Bayer AG and BlueRock Therapeutics
Organized by: BlueRock Therapeutics

Hall 3, Entrance Level

Parkinson's disease affects more than 8.5 million people worldwide and is the second most common neurodegenerative disease, after Alzheimer's disease. Current pharmacotherapeutic strategies for treating Parkinson's disease motor symptoms include augmenting dopamine levels in the brain through dopamine agonists, enhancing dopamine bioavailability, or limiting levodopa degradation. However, these treatments are associated with motor complications, including the development of dyskinesias and narrowing of the therapeutic window, and adverse effects such as exacerbation of non-motor symptoms. Further, these therapies do not address the loss of dopaminergic neurons; thus, there remains a critical need for novel therapies for Parkinson's disease.

The transplantation of dopaminergic neuronal cells into the putamen is an innovative strategy for restoring dopaminergic function in the brains of people with Parkinson's disease. In this session, we will discuss the advancements in surgical techniques involved in the delivery of cell therapies in the brain. We will also discuss emerging data from the first-in-human phase 1 trial of bemdaneprocel, an hESC derived allogenic, dopaminergic progenitor cell therapy.

PRESENTERS:
David Pedrosa, *Universitätsklinikum Giessen Und Marburg, Standort Marburg, Baldingerstraße, Germany*
Viviane Tabar, *Memorial Sloan Kettering Cancer Center, USA*

CAREER PANEL

WEDNESDAY, 10 JULY | 4:00 PM – 5:30 PM

CAREER PLURIPOTENCY: PIONEERING PATHS IN ACADEMIC AND NON-ACADEMIC SECTORS

Hall X4-9, Level 1

If you find yourself caught up in the excitement yet daunted by the rapid evolution in stem cell research, join our career panel this year. In this session, we will bring together a diverse group of experts to explore the dynamic landscape of stem cell scientists and to discuss the evolving career opportunities in this field. Our panelists will share their professional trajectories, discuss both academic and non-academic paths in stem cell science, and provide insights for young scientists on how to navigate their own journey. Join us for an exciting session that aims to empower you to thrive in the face of career uncertainty.

MODERATOR:
Thomas Hutschalik, *Maastricht University and Ncardia Services B.V., Netherlands*

PANELISTS:
Melissa K. Carpenter, *Carpenter Consulting Corporation, USA*
Giuliana Gagliardi, *European Research Council Executive Agency, Belgium*
Tina Mukherjee, *Institute for Stem Cell Science and Regenerative Medicine (inStem), India*
Marie Engelene Obien, *MaxWell Biosystems, Switzerland*

EARLY CAREER SCIENTISTS SOCIAL NIGHT

WEDNESDAY, 10 JULY | 9:00 PM – 11:00 PM

Start your ISSCR 2024 experience by meeting, mingling, dancing, and socializing with fellow young investigators from around the world. Enjoy light snacks as you network and connect with colleagues in a fun and relaxed atmosphere.

Venue: The KENT Club, Stresemannstraße 163, 22769 Hamburg

SOLD OUT! *This is a ticketed event that requires pre-registration as the venue has limited capacity. Please visit the Registration Desk to inquire about the availability of last-minute tickets.*

Entry to the ISSCR 2024 Annual Meeting Early Career Scientists Social Night requires a meeting badge and government-issued ID with a photo (driver's license, passport, etc.). Attendees must be 21 years or older. The ISSCR does not provide transportation to the venue. Attendees are encouraged to use public transportation (S-Bahn Train S3 or S5), taxi, and/or ride-share service.

This event is exclusively for students and postdoctoral fellows.

Hosted by:

MEET-UP HUBS

Meet-up Hubs are an opportunity for attendees to engage in conversation and networking at these common interest discussion forums.

WEDNESDAY, 10 JULY | 5:45 PM – 6:30 PM

COMPUTATIONAL BIOLOGY

Organized by: Christine Wells, University of Melbourne, Australia and Owen Rackham, University of Southhampton, UK

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

STUDENT AND POSTDOC NETWORKING

Organized by: The ISSCR Early Career Scientist Task Force

Come join the members of the Early Career Scientist Task Force as they discuss evolving career opportunities in stem cell research. Students and postdocs who attended the earlier Career Panel session can continue the conversation, and all students and post docs are encouraged to join in and network with your peers. Bring your questions and considerations about navigating your career journey. Come join the conversation!

RENEW ECR NETWORKING HUB

Organized by: Natalie Charitakis, Murdoch Children's Research Institute, Australia

A space for Novo Nordisk Foundation Center for Stem Cell Medicine, ReNEW, Early Career Researchers from all international hubs to meet and connect with one another. Our goal is to create a vibrant atmosphere where ECRs from three international hubs can come together to collaborate, exchange ideas, and establish professional connections. Here, you'll have the opportunity to delve into stimulating discussions, explore new concepts, and draw inspiration from the projects presented at the event.

This rare chance for our international community of stem cell medicine experts to meet face-to-face promises to strengthen ties and pave the way for future collaborations. Don't miss out on this invaluable opportunity to connect with fellow researchers, expand your network, and contribute to the advancement of stem cell research.

WEDNESDAY, 10 JULY | 7:00 PM – 7:45 PM

INDUSTRY SCIENTISTS NETWORKING

Organized by: The ISSCR Manufacturing, Clinical Translation, and Regulatory Committee

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

UK STEM CELL NETWORK

Organized by: Lyn Healy, Francis Crick Institute, UK

The UK is setting up a network to promote interaction between all stakeholders in the Stem Cell and Regenerative Medicine community. As the meeting this year is in Europe, we predict that many scientists will attend from the UK therefore a meet-up-hub would enable prospective members of the network to gather and discover what the network is planning to establish and how the needs of the community can be addressed, explored and developed. It will afford the community the opportunity to come together and interact on an informal basis, exchange ideas and make new professional contacts. It will also reunite colleagues who might have lost contact over the years since we have been without a network.

STEM CELLS AND CANCER

Organized by: Juli Unternaehrer, Loma Linda University, USA

Let's meet to discuss our work on the interaction of stem cells and developmental pathways with cancer biology.

THURSDAY, 11 JULY | 3:45 PM – 4:30 PM

GET-TOGETHER GERMAN STEM CELL NETWORK

Organized by: The German Stem Cell Network (GSCN)

The meet-up of the German Stem Cell Network (GSCN) is open to all those in the German scientific stem cell community as well as attendees of the 2024 Annual Meeting. We will discuss the dialog platform for stem cell research and national strategies in this field in Germany as well as the ongoing activities of the GSCN.

EARLY CAREER PIS/GROUP LEADERS NETWORKING

Organized by: The ISSCR Early Career Scientists Task Force

If you are an early career Principal Investigator or Group Leader (0-8 years after your final postdoc), we invite you to network with other early career group leader attendees. Join the Early Career Scientist Task Force members at this meet up and bring your challenges to discuss with your peers, or just come to socialize and meet other early career group leaders. Don't miss this unique opportunity to network with your peers from around the world.

STEM CELLS FOR HIRSCHSPRUNG'S DISEASE

Organized by: Peter Andrews, University of Sheffield, UK

Hirschsprung disease (HSCR), a potentially lethal condition affecting 1 in 5,000 newborn children, is caused by the absence of enteric neurons in the distal bowel. This leads to a loss of propulsive gut motility, ultimately resulting in potentially lethal intestinal obstruction. Current treatment is complex, involves surgical removal of the affected region of the bowel, and often leaves patients with lifelong problems. Several groups around the world, that will be present at this ISSCR meeting, are well advanced in developing approaches using pluripotent stem cells or endogenous stem cells to provide enteric neural progenitors for transplant into the affected gut to relieve the condition. This Meet-up will bring together different teams and initiate an ongoing forum for addressing common issues in taking this approach forward to the clinic, e.g., comparing different cell lines, confirming safety, immunogenicity, appropriate clinical parameters and relevant endpoints for first-in-child clinical trials.

THURSDAY, 11 JULY | 5:00 PM – 5:45 PM

MEET THE EDITORS OF STEM CELL REPORTS

Organized by: Stem Cell Reports

Meet the editors of *Stem Cell Reports* to discuss a potential submission, your paper in review or new trends in scientific publishing. Bring your questions about *Stem Cell Reports* and publishing in your society's journal.

POLICY, ETHICS, AND REGULATORY ISSUES

Organized by: The ISSCR Policy Staff

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

LGBTQIA+ STEM CELL NETWORKING

Organized by: Ya-Wan Chen, Icahn School of Medicine at Mount Sinai, USA

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

FRIDAY, 12 JULY | 3:45 PM – 4:30 PM

EUROPEAN RESEARCH COUNCIL (ERC) INFORMATION MEET-UP

Organized by: The European Research Council

A scientific officer from the ERC Executive Agency will answer your questions about the ERC funding opportunities and update you about the recent changes.

STEM CELL PODCAST

Organized by: The Stem Cell Podcast

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

CRYOPRESERVATION OF CELL AND GENE THERAPIES

Organized by: Steve Oh, Independent Cell Therapy Advisor, Singapore

The cell and gene therapy community has spent over 20 years investigating the front end of the manufacturing processes; however, the final cell or secretion products will likely be fresh or frozen in content. This Meet-up will discuss the challenges in delivering frozen cell products. There are seven important topics open for discussion: Primary Containers, Cryopreservation, Storage and Shipping, Stability, Thawing, and Post thaw Analytics.

FRIDAY, 12 JULY | 5:00 PM – 5:45 PM

SELECTION AND TESTING OF CLINICAL-USE-QUALITY IPSCS

Organized by: Pierre Schembri-Wismayer, DeNovo Cell Ltd/University of Malta

In this meet-up, we welcome individuals who group isolating iPSCs, particularly those derived from blood - to learn about optimise methods and quality testing for Clinical level iPSCs.

SUCCESS SYNERGY: NAVIGATING ACADEMIA & INDUSTRY

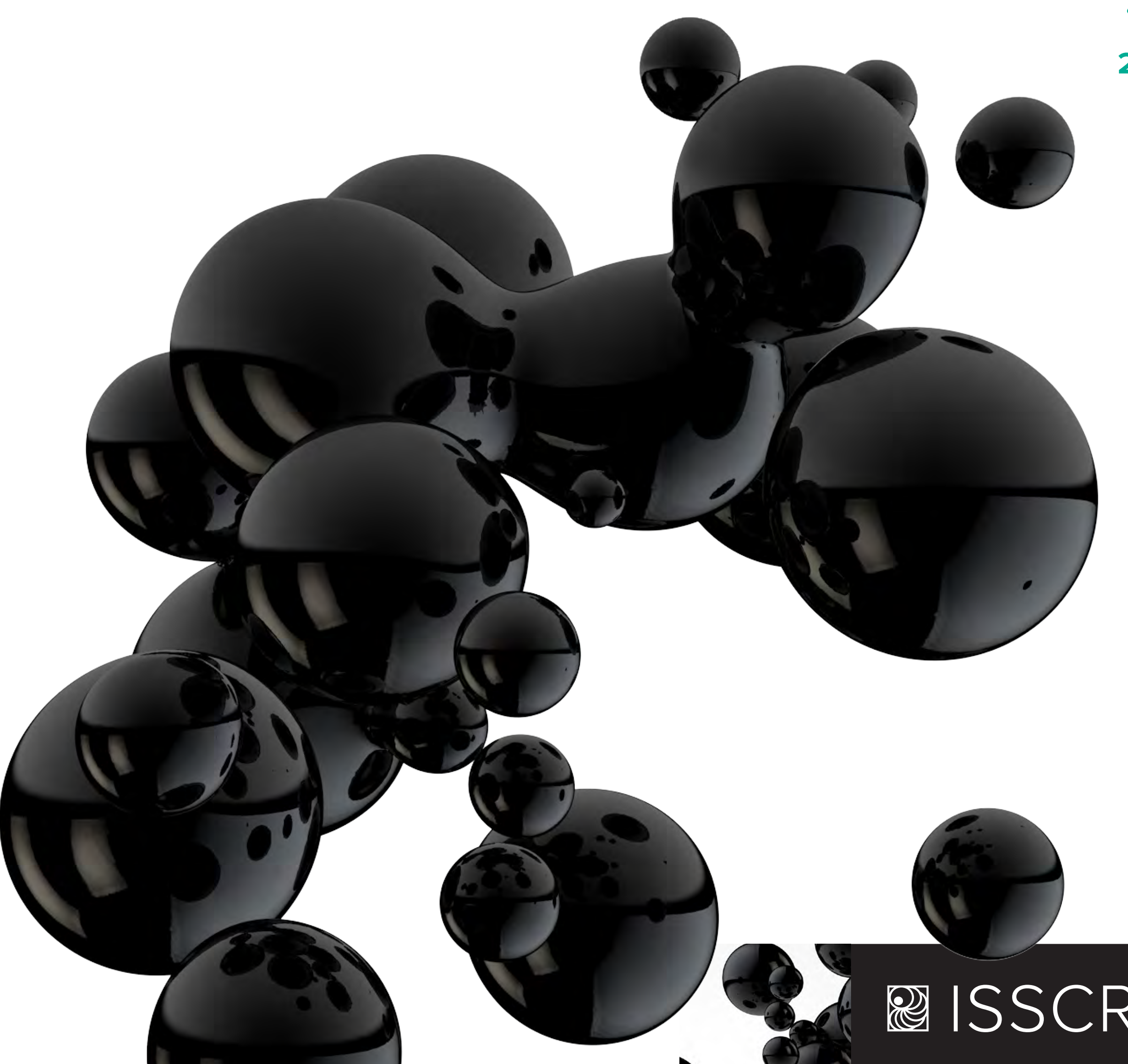
Organized by: Olivia Majhi, Cytogenetics Lab, Department of Zoology, Banaras Hindu University, India

This Meet-up will facilitate networking among students and postdocs while discussing the essential skill sets required for success in academia and industry. This discussion can help the participants understand the soft skills, communication strategies, leadership qualities, collaboration dynamics, time management tactics, and networking strategies crucial for thriving in both academic and industrial environments. From honing soft skills to mastering effective strategies, attendees will gain valuable insights to thrive in diverse professional environments.

HARNESSING STEM CELLS FOR NEXT-GENERATION IMMUNOTHERAPY

Organized by: Ran Jing, Harvard University Medical School, USA

This hub provides a networking opportunity for scientists working on using pluripotent stem cells to study immunology and develop PSC-derived immune cells (T, NK, macrophages, etc.) for cellular immunotherapies.



PUBLIC SYMPOSIUM

PUBLIC PANEL DISCUSSION: STEM CELLS – THE ALL-ROUNDERS AMONG CELLS RESPONSIBLE FOR GROWTH, DISEASES, AND NEW THERAPIES

TUESDAY, 9 JULY | 6:30 PM – 8:30 PM

Panel discussion with stem cell researchers *(Presented in German)*

Admission: FREE!

Program: 6:30 PM: Short films and panel discussion
8:00 PM – 8:30 PM: Conclusion with pretzels and drinks

Venue: University of Hamburg
Main Building, Lecture Hall A
Edmund-Siemers-Allee 1
20148 Hamburg

Hair grows for a lifetime. Wounds heal again. Cells in the blood renew themselves every three months. Stem cells, a very special type of cells in our body, are responsible for these miracles: they can divide, multiply and differentiate into all the different body cells throughout our lives. If errors occur during these fundamental processes, diseases can develop. Research into stem cells therefore provides important insights for medicine. During the panel discussion, the invited scientists will report on the role that mutations or misdirected stem cells play in neurodegenerative diseases, diabetes, or ageing processes.

On the other hand, stem cells can be used to develop new therapies: They can be used to grow small pieces of tissue and organoids and test the effect of drugs on them or use them to replace lost tissue.

Short films will present the scientists' research and the discussion will focus on the status and future of stem cell research and new treatment options. After the event, everyone is cordially invited to continue the discussion over drinks and pretzels.

The event is particularly suitable for students of biology courses and students of life sciences and is a good opportunity to gain insights into stem cell research, science, and medical research and to talk to high-ranking researchers! Please note this program will be in German.

MODERATOR:
Stefanie Seltmann, *Heidelberg University Hospital, Germany*

PANELISTS:

Maike Sander, *Max Delbrück Center Berlin, Germany, specialist for stem cells and diabetes*

Jürgen Knoblich, *Institute of Molecular Biotechnology, Vienna, Austria, specialist for cerebral organoids and neurodegenerative diseases*

Hans Schöler, *Max Planck Institute for Molecular Biomedicine Münster, Germany, specialist in ageing and developmental biology*

Ole Pless, *Fraunhofer Institute for Translational Medicine and Pharmacology ITMP Hamburg, Germany, specialist for rare diseases and drug testing*

PROGRAM SCHEDULE

WEDNESDAY, 10 JULY

Time	Session	Location
9:00 AM – 9:30 AM	**REFRESHMENT BREAK**	Hall 1 Foyer, Level 2
9:30 AM – 11:30 AM	**PLENARY I: PRESIDENTIAL SYMPOSIUM** *Sponsored by: Bayer AG and BlueRock Therapeutics* **Session Chair: Amander T. Clark,** *University of California, Los Angeles, USA*	Hall 1, Level 2
9:30 AM – 9:32 AM	**WELCOME REMARKS**	
9:32 AM – 9:37 AM	**WELCOME FROM SECOND MAYOR HAMBURG AND SENATOR KATHARINA FEGEBANK**	
9:37 AM – 9:39 AM	**REMARKS FROM LIFE SCIENCE NORD**	
9:39 AM – 9:41 AM	**Stefan Irion,** *BlueRock Therapeutics, USA* **REMARKS FROM BAYER AG AND BLUEROCK THERAPEUTICS**	
9:41 AM – 9:46 AM	**Amander T. Clark,** *University of California, Los Angeles, USA* **ISSCR PRESIDENTIAL ADDRESS**	
9:46 AM – 9:50 AM	**RECOGNITION OF ISSCR TRAVEL AND MERIT AWARDEES**	
9:50 AM – 10:15 AM	**Magdalena Goetz,** *Ludwig-Maximilian University of Munich (LMU), Germany* **ORGANELLAR HETEROGENEITY IN STEM CELL DIFFERENTIATION AND REPROGRAMMING**	
10:15 AM – 10:40 AM	**Tina Mukherjee,** *Institute for Stem Cell Science and Regenerative Medicine (inStem), India* **SENSORY PERCEPTION IN DEFINING IMMUNE POTENTIAL: A ROLE BEYOND ITS SENSES**	
10:40 AM – 11:05 AM	**Kathrin Plath,** *University of California Los Angeles School of Medicine, USA* **UNLOCKING THE MYSTERIES OF INCRNA XIST: A JOURNEY OF CONSTANT DISCOVERY**	
11:05 AM – 11:30 AM	**Sarah Teichmann,** *Wellcome-MRC Cambridge Stem Cell Institute, UK* **CELLS, TISSUES & ORGANS: ASSEMBLING THE HUMAN CELL ATLAS**	
12:00 PM – 1:00 PM	**BLUEROCK CLINICAL TRIALS WORKSHOP SPECIAL SESSION: ADVANCES IN THE TREATMENT OF PARKINSON'S DISEASE: THE POSSIBILITIES OF CELL THERAPIES** *Presented by: Bayer AG and BlueRock Therapeutics*	Hall 3, Entrance Level
12:00 PM – 1:00 PM	**INNOVATION SHOWCASES:** see page 51 for details	
	CuSTOMIZING ORGANOIDS FOR DRUG DEVELOPMENT AND REGENERATIVE MEDICINE *Presented by: Ajinomoto Co., Inc.*	Hall G2, Level 2
	TRANSFORMING hiPSC DIFFERENTIATION BY INCREASING EFFICIENCY AND FIDELITY FOR NPCS, HSCS, AND LPCS *Presented by: Cell Microsystems*	Hall G1, Level 2
	STEM CELLS IN LOW EARTH ORBIT: THE NEXT FRONTIER *Presented by: ISS National Laboratory and Sanford Stem Cell Institute at University of California - San Diego*	Hall 4, Entrance Level
	THE FUTURE OF CELL CULTURE: EMPOWERING RESEARCHERS TO MAKE KEY DECISIONS SOONER, ACHIEVE MILESTONES FASTER, AND GET TO CLINIC EARLIER—WITH LOWER ATTRITION RATES *Presented by: Molecular Devices*	Hall Y7-12, Level 2

WEDNESDAY, 10 JULY *Continued*		
	GENETIC WHACK-A-MOLE: BATTLING INSTABILITIES IN iPSCS *Presented by: Pluristyx, Inc.*	Hall X4-9, Level 1
**12:00 PM – 12:25 PM*	**ISSCR STANDARDS IN ACTION: ADVANCEMENTS IN CELL LINE GENERATION AND ORGANOID INNOVATION** *Presented by: STEMCELL Technologies, Inc.*	Hall Y1-6, Level 2
**12:25 PM – 1:00 PM*	**IMPROVING THE GENETIC STABILITY OF SINGLE-CELL-PASSAGED HUMAN PLURIPOTENT STEM CELL CULTURES USING eTeSR™** *Presented by: STEMCELL Technologies, Inc.*	Hall Y1-6, Level 2
1:30 PM – 3:35 PM	TRACK: New Technologies (NT) **PLENARY II: NEW TECHNOLOGIES TO ENGINEER AND PHENOTYPE STEM CELL SYSTEMS** **Session Chairs: Filipe Pereira,** *Lund University, Sweden* **Barbara Treutlein,** *ETH Zurich, Switzerland*	Hall 1, Level 2
1:35 PM – 1:55 PM	**Jonathan Weissman,** *Whitehead Institute for Biomedical Research, HHMI, MIT, USA* **MOLECULAR BIOGRAPHY OF TUMOR EVOLUTION AND NORMAL HEMTOPOIESIS**	
1:55 PM – 2:15 PM	**Fabian Theis,** *Helmholtz Zentrum München, Germany* **MODELING SINGLE-CELL DYNAMICS ACROSS MODALITIES, TIME AND SPACE**	
2:15 PM – 2:35 PM	**Susanne Rafelski,** *Allen Institute for Cell Science, USA* **TOWARD A HOLISTIC AND QUANTITATIVE STEM CELL STATE LANDSCAPE**	
2:35 PM – 3:00 PM	**Matthias Lutolf,** *Institute of Human Biology (IHB) F. Hoffmann-La Roche, Switzerland* **THE JOHN MCNEISH MEMORIAL LECTURE: ENGINEERING NEXT-GENERATION TUMOROIDS FOR PRECISION MEDICINE**	
3:00 PM – 3:03 PM	**ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD PRESENTATION**	
3:03 PM – 3:33 PM	**ISSCR OUTSTANDING YOUNG INVESTIGATOR AWARD LECTURE** **Jun Wu,** *University of Texas Southwestern Medical Center, USA* **THE CURIOUS CASES OF PLURIPOTENT STEM CELL ADAPTATIONS**	
2:30 PM – 8:00 PM	**EXHIBIT & POSTER HALL OPEN**	Hall H, Entrance Level
3:35 PM – 4:00 PM	**REFRESHMENT BREAK**	Hall H, Entrance Level
4:00 PM – 5:30 PM	**PANEL: CAREER PLURIPOTENCY: PIONEERING PATHS IN ACADEMIC AND NON-ACADEMIC SECTORS**	Hall X4-9, Level 1
	TRACK: Ethics, Policy and Standards (EPS) **EQUITY, DIVERSITY, AND INCLUSION IN THE DISH** **Brian Aguado,** *University of California San Diego, USA* **Ralda Nehme,** *Broad Institute of Harvard and MIT and Harvard University, USA* **Raeka Aiyar,** *The New York Stem Cell Foundation (NYSCF) Research Institute, USA* **Magdalena Kasendra,** *Center for Stem Cell & Organoid Medicine (CuSTOM) at Cincinnati's Children's, USA*	Hall G2, Level 2
	FOCUS SESSION: TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY *Organized by: Stem Cell COREdinates* *Supported by: STEMCELL Technologies and Thermo Fisher Scientific*	Hall Y1-6, Level 2
4:00 PM – 5:30 PM	**SCIENCE SPOTLIGHT SESSIONS:** see mobile app for details	
	EXPLORING BIOPHYSICAL CUES: UNRAVELING MECHANOTRANSDUCTION IN PLURIPOTENT STEM CELL DIRECTED DIFFERENTIATION	Hall G1, Level 2
	FRONTIERS IN EPIGENETIC CONTROL FOR ENHANCED STEM CELL THERAPIES	Hall Y7-12, Level 2

Time	Session	Location
	HARVESTING STEM CELL INNOVATION: THE SYMBIOTIC RELATIONSHIP BETWEEN ACADEMIA AND INDUSTRY IN CULTIVATED MEAT DEVELOPMENT	Hall 4, Entrance Level
	CELL POLARITY IN ORGANOID-DERIVED MODELS OF HEALTH AND DISEASE	Hall Z, Level 3
	TRANSLATION OF ACADEMIC RESEARCH: FROM NICE TO HAVE TO CLINICAL IMPERATIVE	Hall 3, Entrance Level
5:40 PM – 7:45 PM	**EXHIBIT & POSTER HALL EVENTS** **Meet-up Hubs:** see page 20 for details **Exhibit Hall Theaters:** see page 61 for details	Hall H, Entrance Level
5:45 PM – 7:45 PM	**OPENING RECEPTION** *Supported by: AMSBIO, bit.bio, PBS Biotech, Qkine, Science Advances/AAAS, and WiCell*	
5:40 PM – 5:55 PM	**HUMAN PLURIPOTENT STEM CELL (HPSC) PLATFORMS FOR TARGET DISCOVERY AND THERAPEUTIC DEVELOPMENT** *Presented by: AstraZeneca*	Exhibit Hall Theater
5:45 PM – 6:30 PM	**COMPUTATIONAL BIOLOGY**	Meet-up Hub
5:45 PM – 6:30 PM	**STUDENT AND POSTDOC NETWORKING**	Meet-up Hub
5:45 PM – 6:30 PM	**RENEW ECR NETWORKING HUB**	Meet-up Hub
5:45 PM – 6:45 PM	**POSTER SESSION I – ODD POSTERS**	
6:00 PM – 6:15 PM	**STREAMLINE YOUR RESEARCH: THE ADVANTAGES OF OUR COMPREHENSIVE GENOMIC INTEGRITY TESTING, CELL AUTHENTICATION, AND MYCOPLASMA DETECTION SOLUTIONS** *Presented by: Stem Genomics*	Exhibit Hall Theater
6:20 PM – 6:35 PM	**ANALYSIS, IMAGING, AND SORTING OF SPHEROIDS, ORGANOIDS, AND 3D CELL CLUSTERS ON THE COPAS VISION** *Presented by: Union Biometrica*	Exhibit Hall Theater
6:40 PM – 6:55 PM	**FROM R&D TO MANUFACTURING: THE CELL AS A PRODUCT** *Presented by: Eppendorf*	Exhibit Hall Theater
6:45 PM – 7:45 PM	**POSTER SESSION I – EVEN POSTERS**	
7:00 PM – 7:15 PM	**INNOVATIVE scFAST-seq TECHNOLOGY: ACCESSING ANALYSIS FROM MUTATION, REGULATION TO EXPRESSION** *Presented by: Beijing SeekGene BioSciences Co. Ltd.*	Exhibit Hall Theater
7:00 PM – 7:45 PM	**INDUSTRY SCIENTISTS NETWORKING**	Meet-up Hub
7:00 PM – 7:45 PM	**UK STEM CELL NETWORK**	Meet-up Hub
7:00 PM – 7:45 PM	**STEM CELLS AND CANCER**	Meet-up Hub
7:20 PM – 7:35 PM	**BIOMANUFACTURING IN LOW EARTH ORBIT: ACCELERATING BREAKTHROUGHS IN REGENERATIVE MEDICINE** *Presented by: Axiom Space*	Exhibit Hall Theater
9:00 PM – 11:00 PM	**EARLY CAREER SCIENTISTS SOCIAL NIGHT** **SOLD OUT!** Pre-Registration required to attend *Hosted by: Life Science Nord and The City of Hamburg* Offsite: The KENT Club, Stresemannstraße 163, 22769 Hamburg Must be 21 or older to attend. Name badge and government ID with photo required for entry.	

THURSDAY, 11 JULY

8:15 AM – 9:45 AM	CONCURRENT TRACK SESSIONS	
8:15 AM – 9:45 AM	TRACK: Disease Modeling and Drug Discovery (DMDD) **ADVANCING IN VITRO MODELS** *Sponsored by: AstraZeneca* **Session Chairs: Gabsang Lee,** *Johns Hopkins School of Medicine, USA* **Ryuji Morizane,** *Massachusetts General Hospital, USA*	Hall 3, Entrance Level
8:20 AM – 8:40 AM	**David Elliott,** *Murdoch Children's Research Institute, Australia* **ENHANCING MATURATION OF STEM CELL-DERIVED CARDIOMYOCYTES**	
8:40 AM – 8:50 AM	**Helmuth Gehart,** *ETH Zürich, Switzerland* **MALIGNANT PLEURAL MESOTHELIOMA ORGANOIDS ENABLE PERSONALIZED MEDICINE FOR A HIGHLY HETEROGENEOUS DISEASE**	
8:50 AM – 9:00 AM	**Deepali Pal,** *University of Bristol, UK* **MICROENVIRONMENT-MEDIATED MECHANISMS DRIVING TARGETABLE LEUKAEMIA DORMANCY**	
9:00 AM – 9:10 AM	**Esther Fousert,** *Leiden University Medical Center, Netherlands* **FROM CELLS TO CURES: HIPSC-DERIVED INNER EAR ORGANOIDS AND RNA THERARPY TO RESOLVE GENETIC HEARING LOSS**	
9:10 AM – 9:20 AM	**Shalaka Chitale,** *CytoTronics Inc., USA* **ELECTRICAL IMAGING: LIVE CELL CHARACTERIZATION FROM STEM CELL BIOLOGY TO PHENOTYPIC DISEASE MODELS**	
9:20 AM – 9:40 AM	**Meritxell Huch,** *Max Planck Institute of Molecular Cell Biology & Genetics (MPI-CBG), Germany* **BUILDING ARCHITECTURE AND COMPLEXITY IN TISSUE-DERIVED LIVER ORGANOIDS**	
8:15 AM – 9:45 AM	TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR) **AGING AND METABOLIC REGULATION OF TISSUE STEM CELLS** *Sponsored by: Stem Cell Reports* **Session Chairs: Elisa Laurenti,** *University of Cambridge, UK* **Sirio Dupont,** *University of Padova, Italy*	Hall Y1-6, Level 2
8:20 AM – 8:40 AM	**Kyoko Miura,** *Kumamoto University, Japan* **INVESTIGATION OF THE MECHANISMS OF AGING- AND CANCER-RESISTANCE IN THE LONGEST-LIVED RODENT, THE NAKED MOLE-RAT**	
8:40 AM – 8:50 AM	**Silvia Sighinolfi,** *IRCCS San Raffaele Scientific Institute, Italy* **INTRACELLULAR IRON OVERLOAD REWIRES HSC METABOLISM BY IMPAIRING MITOCHONDRIAL FITNESS**	
8:50 AM – 9:00 AM	**Jonathan Bayerl,** *University of California, San Francisco, USA* **LONG LIVE THE QUEEN - UNDERSTANDING METABOLISM AND LIFESPAN IN EUSOCIAL SUPER AGERS WITH INDUCED PLURIPOTENT STEM CELLS**	
9:00 AM – 9:10 AM	**Elisa Gabassi,** *University of Innsbruck, Austria* **INDUCIBLE 3D MODELING OF HUMAN BRAIN AGING RECAPITULATES HALLMARKS OF AGING AND IDENTIFIES DISTINCT TRANSCRIPTOMIC SIGNATURES**	
9:10 AM – 9:20 AM	**Rui Yue,** *Tongji University, China* **RECONSTITUTION OF A SOFT BONE MARROW ORGANOID FOR HEMATOPOIETIC STEM CELL REJUVENATION**	
9:20 AM – 9:40 AM	**Salvador Aznar Benitah,** *Institute for Research in Biomedicine (IRB Barcelona), Spain* **ROLE OF CIRCADIAN RHYTHMS IN SYSTEMIC SYNCHRONISATION OF TISSUE FUNCTION: IMPACT IN AGING**	

8:15 AM – 9:45 AM | **TRACK: Clinical Applications (CA)** | Hall Z, Level 3

EMERGING NEW THERAPIES
Sponsored by: Healios K.K.
Session Chairs: Dimitri Kullmann, *University College London (UCL), UK*
Tamar Harel Adar, *Matricelf, Israel*

8:20 AM – 8:40 AM
Ganna Bilousova, *University of Colorado Anschutz Medical Campus, USA*
A PERSONALIZED iPSC-BASED THERAPY FOR RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA DELIVERED VIA CELL SUSPENSION: PRE-CLINICAL DEVELOPMENT

8:40 AM – 8:50 AM
Tatsuma Kondo, *Nagoya University, Japan*
TRANSPLANTATION OF ACTH-SECRETING HUMAN PLURIPOTENT STEM CELL (HPSC)-DERIVED PITUITARY CELLS

8:50 AM – 9:00 AM
Jacqueline Bliley, *Carnegie Mellon University, USA*
BIOENGINEERING AND IN VIVO ASSESSMENT OF 3D BIOPRINTED HUMAN CARDIAC CONDUITS

9:00 AM – 9:10 AM
Shulin Li, *The University of Texas MD Anderson Cancer Center, USA*
ATTIL12-T CELL THERAPY FOR SIMULTANEOUSLY DISRUPTING STROMA/TUMORS AND INDUCTION OF ENDOGENOUS TCR-T CELLS

9:10 AM – 9:20 AM
Holly Voges, *Murdoch Children's Research Institute, Australia*
BIOENGINEERING HUMAN HEART VALVE TISSUE FOR CELLULAR REPAIR USING HUMAN PLURIPOTENT STEM CELLS

9:20 AM – 9:40 AM
Ludovic Vallier, *Berlin Institute of Health at Charite, Germany*
CELL BASED THERAPY AGAINST LIVER DISEASES, WHAT'S NEW?

8:15 AM – 9:45 AM | **TRACK: New Technologies (NT)** | Hall G1, Level 2

IMAGING STEM CELL SYSTEMS ACROSS SCALES
Session Chairs: Miki Ebisuya, *Technische Universität Dresden, Germany*
Ron Weiss, *Massachusetts Institute of Technology (MIT), USA*

8:20 AM – 8:40 AM
Kate McDole, *MRC Laboratory of Molecular Biology, UK*
ILLUMINATING MECHANISMS OF EARLY MOUSE DEVELOPMENT THROUGH ADAPTIVE LIVE-IMAGING

8:40 AM – 8:50 AM
Daniel Postrach, *German Cancer Research Center, Germany*
POLYTOPE: A NOVEL EPITOPE BARCODING SYSTEM FOR ENDOGENOUS FATE-MAPPING VIA MULTIPLEXED IMAGING

8:50 AM – 9:00 AM
Duncan Chadly, *Caltech, USA*
RECORDING AND RECONSTRUCTING CELLULAR HISTORIES IN DIFFERENTIATING PLURIPOTENT STEM CELLS

9:00 AM – 9:10 AM
Ramon Pfaendler, *ETH Zürich, Switzerland*
A SYSTEMS VIEW OF CELLULAR STATE HETEROGENEITY IN HUMAN PLURIPOTENT STEM CELLS

9:10 AM – 9:20 AM
Laura Fischer, *Washington University in St. Louis, USA*
TRACKING AND MITIGATING IMPRINT ERASURE DURING INDUCTION OF NAÏVE HUMAN PLURIPOTENCY

9:20 AM – 9:40 AM
Bernd Bodenmiller, *University of Zurich and ETH Zurich, Switzerland*
HIGHLY MULTIPLEXED IMAGING OF IN SITU TUMOR ECOSYSTEMS TOWARDS PRECISION MEDICINE

THURSDAY, 11 JULY *Continued*

8:15 AM – 9:45 AM	**TRACK: Pluripotency and Development (PD)** **INTEGRATED STEM CELL MODELS OF EARLY EMBRYO DEVELOPMENT** *Sponsored by: Stem Cell Reports* **Session Chairs: Katsuhiko Hayashi,** *Kyushu University, Japan* **Shahragim Tajbakhsh,** *Institut Pasteur Stem Cells and Development, France*	Hall 4, Entrance Level
8:20 AM – 8:40 AM	**Aydan Bulut-Karslioglu,** *Max Planck Institute for Molecular Genetics, Germany* **ADJUSTING MAMMALIAN DEVELOPMENTAL TIMING**	
8:40 AM – 8:50 AM	**Bernardo Oldak,** *Weizmann Institute of Science, Israel* **COMPLETE HUMAN PERI-GASTRULATION STEM CELL DERIVED EMBRYO MODELS WITH ENHANCED DEVELOPMENTAL POTENTIAL AND EFFICIENCY**	
8:50 AM – 9:00 AM	**Anchel de Jaime-Soguero,** *Heidelberg University, Germany* **A SIGNALLING RHEOSTAT CONTROLS CHROMOSOME SEGREGATION FIDELITY DURING EARLY LINEAGE SPECIFICATION AND NEUROGENESIS BY MODULATING REPLICATIVE STRESS**	
9:00 AM – 9:10 AM	**Karlien Van Nerum,** *University of Copenhagen, Denmark* **METABOLIC REWIRING UNDERPINS HUMAN TROPHOBLAST INDUCTION**	
9:10 AM – 9:20 AM	**Raquel Fueyo,** *Stanford University, USA* **ESSENTIAL FUNCTION OF AN HOMINOID-SPECIFIC TRANSPOSON IN HUMAN PREIMPLANTATION DEVELOPMENT**	
9:20 AM – 9:40 AM	**Sophie Petropoulos,** *Karolinska Institutet, Sweden and University of Montreal, Canada* **A COMPREHENSIVE HUMAN EMBRYOGENESIS REFERENCE TOOL USING SINGLE-CELL RNASEQUENCING DATA**	
8:15 AM – 9:45 AM	**FOCUS SESSION: STRATEGIES FOR THE DEVELOPMENT OF ALLOGENIC iPSC-DERIVED CELL THERAPIES** *Organized by: Evotec*	Hall Y7-12, Level 2
8:15 AM – 9:45 AM	**TRACK: Ethics, Policy and Standards (EPS)** **BEST PRACTICES FOR THE DEVELOPMENT OF PSC-DERIVED CELLULAR THERAPIES** *Sponsored by: Burroughs Wellcome Fund*	Hall G2, Level 2
8:15 AM – 8:20 AM	**Kapil Bharti,** *National Eye Institute; National Center for Advancing Translational Sciences, National Institutes of Health, USA* **Jacqueline Barry,** *Cell and Gene Therapy Catapult, UK* **WELCOME AND OVERVIEW**	
8:20 AM – 8:30 AM	**Tenneille E. Ludwig,** *WiCell, USA* **STARTING MATERIALS**	
8:30 AM – 8:40 AM	**Glyn Stacey,** *International Stem Cell Banking Initiative, UK* **BANKING**	
8:40 AM – 8:50 AM	**Ricardo Baptista,** *SmartCella, Sweden* **ANCILLARY MATERIALS & DEVICES**	
8:50 AM – 9:00 AM	**Jacqueline Barry,** *Cell and Gene Therapy Catapult, UK* **REGULATORY CONSIDERATIONS**	
9:00 AM – 9:10 AM	**Derek J. Hei** **DRUG SUBSTANCE AND DRUG PRODUCT**	
9:10 AM – 9:20 AM	**Jeanne Loring,** *Scripps Research Institute and Aspen Neuroscience, USA* **PRECLINICAL CONSIDERATIONS**	

THURSDAY, 11 JULY *Continued*

Time	Session	Location
9:20 AM – 9:30 AM	**Roger A. Barker,** *Wellcome-MRC Cambridge Stem Cell Institute, UK* **CLINICAL CONSIDERATIONS**	
9:30 AM – 9:45 AM	**PANEL DISCUSSION**	
9:30 AM – 10:00 AM	**REFRESHMENT BREAK**	Hall 1 Foyer, Level 2
10:00 AM – 11:45 AM	**TRACK: Pluripotency and Development (PD)** **PLENARY III: EXPLORING THE BASIC PRINCIPLES OF DEVELOPMENT USING STEM CELLS** **Session Chairs: Nicolas Rivron,** *Institute of Molecular Biotechnology, Austrian Academy of Science, Austria* **Hans Schöler,** *Max Planck Institute for Molecular Biomedicine, Germany*	Hall 1, Level 2
10:05 AM – 10:20 AM	**ISSCR BUSINESS MEETING**	
10:20 AM – 10:40 AM	**Jennifer Nichols,** *University of Edinburgh, UK* **INVESTIGATING THE MYSTERY OF HUMAN TROPHECTODERM EXPANSION FOR IMPLANTATION**	
10:40 AM – 11:00 AM	**Maria Elena Torres-Padilla,** *Helmholtz Zentrum München, Germany* **EPIGENETIC MECHANISMS OF CELLULAR PLASTICITY AND REPROGRAMMING TO TOTIPOTENCY**	
11:00 AM – 11:20 AM	**Mansi Srivastava,** *Harvard University, USA* **THE MECHANISMS AND EVOLUTION UNDERLYING PLURIPOTENT STEM CELLS ACROSS ANIMALS**	
11:20 AM – 11:45 AM	**Alfonso Martinez Arias,** *Universitat Pompeu Fabra Barcelona, Spain* **THE ANNE MCLAREN MEMORIAL LECTURE: PLURIPOTENT STEM CELL MODELS OF GASTRULATION: DRAWING LINES**	
11:00 AM – 6:00 PM	**EXHIBIT & POSTER HALL OPEN**	Hall H, Entrance Level
12:00 PM – 1:00 PM	**INNOVATION SHOWCASES:** see page 51 for details	
	UNLOCKING THE POWER OF DETERMINISTIC CELL PROGRAMMING IN BIOMEDICAL RESEARCH AND DRUG DISCOVERY *Presented by: bit.bio*	Hall G2, Level 2
	STEM CELLS: FROM RESEARCH TO MANUFACTURING AND CLINICAL APPLICATIONS *Presented by: Corning Life Sciences*	Hall 3, Entrance Level
**12:00 PM – 12:30 PM*	**CEPT COCKTAIL - A NEW CHEMICAL PLATFORM FOR STRESS-FREE AND SAFE CULTURE OF iPSCS** *Presented by: FUJIFILM*	Hall Y7-12, Level 2
**12:30 PM – 1:00 PM*	**STRATEGIES AND SOLUTIONS FOR ACCELERATING DRUG DISCOVERY AND DEVELOPMENT IN ATMPS AND BIOPHARMA** *Presented by: FUJIFILM*	Hall Y7-12, Level 2
	ADVANCED FUNCTIONAL CHARACTERIZATION OF iPSC-DERIVED IN VITRO MODELS IN DISEASE MODELLING AND ARTIFICIAL INTELLIGENCE *Presented by: MaxWell Biosystems*	Hall 4, Entrance Level
	INNOVATION ACROSS PLURIPOTENT STEM CELL RESEARCH: FROM REPROGRAMMING TO MANUFACTURING AND ORGANOID IMAGING *Presented by: Miltenyi Biotec B.V. & Co. KG*	Hall Y1-6, Level 2
	USING HUMAN PLURIPOTENT STEM CELL-DERIVED NEURAL ORGANOIDS FOR DISEASE MODELING *Presented by: STEMCELL Technologies, Inc.*	Hall G1, Level 2

THURSDAY, 11 JULY *Continued*

Time	Session	Location
	INNOVATION SHOWCASE - THERMO FISHER SCIENTIFIC *Presented by: Thermo Fisher Scientific*	Hall X4-9, Level 1
1:30 PM – 3:00 PM	**TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)** **PLENARY IV: TISSUE ARCHITECTURE AND STEM CELL FUNCTION IN HEALTH AND DISEASE** *Sponsored by: Stem Cell Reports* **Session Chairs: Kim B. Jensen,** *University of Copenhagen, Denmark* **Lucy O'Brien,** *Stanford University, USA*	Hall 1, Level 2
1:35 PM – 1:55 PM	**Cristina Lo Celso,** *Imperial College London, UK* **REGENERATION OF HEALTHY AND MALIGNANT HAEMATOPOIESIS: SIMILAR SIDES OF TWO VERY DIFFERENT COINS**	
1:55 PM – 2:15 PM	**Heinrich Jasper,** *Genentech, USA* **STEM CELL AGING: LOCAL AND SYSTEMIC EFFECTS**	
2:15 PM – 2:35 PM	**Fiona Doetsch,** *University of Basel, Switzerland* **REGULATION AND DIVERSITY OF ADULT NEURAL STEM CELLS**	
2:35 PM – 3:00 PM	**Elaine Fuchs,** *HHMI, The Rockefeller University, USA* **ERNEST MCCULLOCH MEMORIAL LECTURE: MEMORIES FOR BETTER OR FOR WORSE: HOW TISSUE STEM CELLS COPE WITH AND REMEMBER STRESSFUL SITUATIONS**	
3:40 PM – 5:45 PM	**EXHIBIT HALL EVENTS** **Meet-up Hubs:** see page 20 for details **Exhibit Hall Theaters:** see page 61 for details **Exhibit Hall Pub Crawl:** see page 65 for details	Hall H, Entrance Level
3:00 PM – 6:00 PM	**EXHIBIT HALL PUB CRAWL*** **Participating Exhibitors: MCRI iPSC Gene Editing and Derivation Facility, SLAS, PBS Biotech, Axion BioSystems*	
3:40 PM – 3:55 PM	**MOVING iPSC BASED CGT INTO A GMP SETTING** *Presented by: CCRM*	Exhibit Hall Theater
3:45 PM – 4:30 PM	**GET-TOGETHER GERMAN STEM CELL NETWORK**	Meet-up Hub
3:45 PM – 4:30 PM	**EARLY CAREER PIs/GROUP LEADERS NETWORKING**	Meet-up Hub
3:45 PM – 4:30 PM	**STEM CELLS FOR HIRSCHSPRUNG'S DISEASE**	Meet-up Hub
3:45 PM – 5:45 PM	**REFRESHMENT BREAK**	
3:45 PM – 4:45 PM	**POSTER SESSION II – ODD POSTERS**	
4:00 PM – 4:15 PM	**UNVEILING VERLOTM: THE FUTURE OF IMAGE-GUIDED CELL SORTING** *Presented by: NanoCellect Biomedical*	Exhibit Hall Theater
4:20 PM – 4:35 PM	**SCALABLE HUMAN iPSC-TO-3D BIOPRINTING PIPELINE: SUCCESSFUL LARGE-SCALE PRODUCTION USING AUTOMATED BIOREACTOR SYSTEMS** *Presented by: Sartorius Stedim Biotech GmbH*	Exhibit Hall Theater
4:40 PM – 4:55 PM	**CRACKING THE CODE: ACCELERATED DIRECTED DIFFERENTIATION OF HIGH PURITY NEURONS AND NEURAL CREST DERIVATIVES FROM ANY hiPSC LINE** *Presented by: Anatomic Incorporated*	Exhibit Hall Theater
4:45 PM – 5:45 PM	**POSTER SESSION II – EVEN POSTERS**	
5:00 PM – 5:15 PM	**STREAMLINING CELL THERAPY MANUFACTURING WITH ACROBIOSYSTEMS AS YOUR GMP RAW MATERIAL SUPPLIER** *Presented by: ACROBiosystems*	Exhibit Hall Theater

THURSDAY, 11 JULY *Continued*

5:00 PM – 5:45 PM	**MEET THE EDITORS OF STEM CELL REPORTS**	Meet-up Hub
5:00 PM – 5:45 PM	**POLICY, ETHICS, AND REGULATORY ISSUES**	Meet-up Hub
5:00 PM – 5:45 PM	**LGBTQIA+ STEM CELL NETWORKING**	Meet-up Hub
5:20 PM – 5:35 PM	**SOLUTIONS FOR SINGLE CELL AND ORGANOID SORTING AND ISOLATION** *Presented by: Cellenion*	Exhibit Hall Theater
6:00 PM – 6:30 PM	**INNOVATION SHOWCASES:** see page 51 for details	
	REVOLUTIONIZING BRAIN ORGANOID FUNCTIONAL SCREENING: UNVEILING THE POWER OF 3D MICROCHIP TECHNOLOGY FOR ENHANCED LIFE SCIENCES INSIGHTS *Presented by: 3Brain AG*	Hall Y7-12, Level 2
	BIOLAMININ® TECHNOLOGY: SUPPORTING STANDARDIZATION FOR TRANSLATIONAL SUCCESS *Presented by: BioLamina*	Hall G2, Level 2
	STEM CELLS FOR SPECIES DE-EXTINCTION AND CONSERVATION *Presented by: Colossal Biosciences*	Hall Y1-6, Level 2
	ENABLING iPSC INNOVATION: EXPLORE EBiSC'S CELLS, SCIENCE, AND DATA *Presented by: European Bank for iPSCs – EBiSC*	Hall G1, Level 2
	SYNTHETIC PEPTIDE-BASED GROWTH FACTOR ALTERNATIVE AND THEIR APPLICATION *Presented by: PeptiGrowth*	Hall X4-9, Level 1
	EMPOWERING CANCER STUDIES: REVOLUTIONIZING CANCER RESEARCH WITH A UNIVERSAL APPROACH TO ISOLATING STEM CELLS FROM TUMOR BIOPSIES *Presented by: PromoCell GmbH*	Hall 4, Entrance Level
	ADVANCING CELL THERAPIES BY HARNESSING THE POWER OF STEM CELL BIOLOGY & BIOPHYSICS USING THE C-STEM™ TECHNOLOGY PLATFORM *Presented by: TreeFrog Therapeutics*	Hall 3, Entrance Level

FRIDAY, 12 JULY

8:15 AM – 9:45 AM	**CONCURRENT TRACK SESSIONS**	
8:15 AM – 9:45 AM	**TRACK: Clinical Applications (CA)** **GENE THERAPIES** **Session Chairs: Felicia Pagliuca,** *Vertex Pharmaceuticals, USA* **Ludovic Vallier,** *Berlin Institute of Health at Charite, Germany*	Hall G1, Level 2
8:20 AM – 8:40 AM	**Benedikt Berninger,** *King's College London, UK* **ENGINEERING NEURAL CELL FATES BY IN VIVO LINEAGE REPROGRAMMING**	
8:40 AM – 8:50 AM	**Michela Milani,** *IRCCS San Raffaele Hospital, Italy* **LENTIVIRAL VECTOR MEDIATED IN VIVO GENE TRANSFER INTO HEMATOPOIETIC STEM AND PROGENITOR CELLS FOR THE TREATMENT OF FANCONI ANEMIA**	
8:50 AM – 9:00 AM	**Alessandra Ricca,** *San Raffaele Hospital, Italy* **TESTING LENTIVIRAL VECTORS ENCODING FOR CHIMERIC HUMAN GALC ENZYMES TO REFINE HEMATOPOIETIC STEM CELL GENE THERAPY FOR GLOBOID CELL LEUKODYSTROPHY**	
9:00 AM – 9:10 AM	**Carine Bourdais,** *Université de Montpellier, INSERM, CHU Montpellier, France* **COMBINED CELLULAR AND GENE THERAPY TO TREAT PRIMARY CILIARY DYSKINESIA**	

FRIDAY, 12 JULY *Continued*

9:10 AM – 9:20 AM	**Thomas Berger,** *Catalent Cell & Gene Therapy, Germany* **OPTIMIZATION OF A GMP-COMPATIBLE GENE EDITING METHODOLOGY TO GENERATE HUMAN INDUCED PLURIPOTENT STEM CELLS WITH ENHANCED FEATURES FOR THERAPEUTIC APPLICATIONS**	
9:20 AM – 9:40 AM	**Dimitri Kullmann,** *University College London, UK* **GENE THERAPY FOR FOCAL REFRACTORY EPILEPSY**	
8:15 AM – 9:45 AM	**TRACK: New Technologies (NT)** **INTEGRATIVE SINGLE CELL OMICS** *Sponsored by: Stem Cell Reports* **Session Chairs: Baris Tursun,** *University of Hamburg, Germany* **Filipe Pereira,** *Lund University, Sweden*	Hall Z, Level 3
8:20 AM – 8:40 AM	**Barbara Treutlein,** *ETH Zürich, Switzerland* **UNDERSTANDING HUMAN BRAIN ORGANOID DEVELOPMENT WITH INTEGRATIVE MULTI-MODAL SINGLE-CELL TECHNOLOGIES**	
8:40 AM – 8:50 AM	**Christopher Esk,** *University of Innsbruck, Austria* **CEREBRAL ORGANOIDS DISPLAY DYNAMIC CLONAL GROWTH WITH LINEAGE REPLENISHMENT**	
8:50 AM – 9:00 AM	**Enes Ugur,** *Max Planck Institute of Biochemistry, Germany* **BEYOND CURRENT MULTI-MODAL ANALYSES OF SINGLE CELLS: HIGH-RESOLUTION MASS SPECTROMETRY UNRAVELS PROTEIN DYNAMICS IN STEM CELL MODELS**	
9:00 AM – 9:10 AM	**Marieke Van Leeuwen,** *Erasmus MC, Netherlands* **INVESTIGATION LINEAGE FATE DECISIONS IN INTESTINAL EPITHELIUM USING THE DCM-TIME MACHINE**	
9:10 AM – 9:20 AM	**Indranil Singh,** *IRB Barcelona - Institute for Research in Biomedicine, Spain* **HIGH-THROUGHPUT SINGLE-CELL PROFILING OF DNA METHYLATION ALLOWS TRANSGENE-FREE TRACKING OF CLONAL DYNAMICS IN HEMATOPOIESIS**	
9:20 AM – 9:40 AM	**Gonçalo Castelo-Branco,** *Karolinska Institutet, Sweden* **OLIGODENDROGLIA IN DEVELOPMENT AND MULTIPLE SCLEROSIS: INSIGHTS FROM SINGLE-CELL AND SPATIAL OMICS**	
8:15 AM – 9:45 AM	**TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)** **MECHANOBIOLOGY OF STEM CELLS AND TISSUES** **Session Chairs: Kenneth D. Poss,** *Duke University Medical Center, USA* **Peter Reddien,** *Whitehead Institute, MIT, USA*	Hall G2, Level 2
8:20 AM – 8:40 AM	**Sirio Dupont,** *University of Padova, Italy* **A MITOCHONDRIAL MECHANOTRANSDUCTION SIGNALING PATHWAY COORDINATES CELL FATE DIFFERENTIATION IN RESPONSE TO FORCES**	
8:40 AM – 8:50 AM	**Giulia Savorè,** *University of Torino, Italy* **UNRAVELING THE INTERPLAY BETWEEN CARDIAC MECHANOBIOLOGY AND METABOLIC REGULATION IN STEM CELL MODELS**	
8:50 AM – 9:00 AM	**Pamela Wenzel,** *University of Texas Health Science Center at Houston, USA* **FORCE INITIATES MITOCHONDRIAL REMODELING NECESSARY FOR HEMATOPOIETIC STEM CELL FATE**	
9:00 AM – 9:10 AM	**Qiaoling Zhu,** *Tongji University, China* **PROCR+ CHONDROPROGENITORS SENSE MECHANICAL STIMULI TO GOVERN ARTICULAR CARTILAGE MAINTENANCE AND REGENERATION**	

9:10 AM – 9:20 AM **Clementine Villeneuve,** *Max Planck Institute for Molecular Biomedicine, Germany*
TISSUE-SCALE MECHANICS CONTROL STEM CELL FATE AND POSITIONING DURING EPITHELIAL DEVELOPMENT

9:20 AM – 9:40 AM **Eugenia Piddini,** *University of Bristol, UK*
P53-MEDIATED STEM CELL COMPETITION: INSIGHTS INTO MECHANISMS OF CLONAL DOMINANCE

8:15 AM – 9:45 AM **TRACK: Pluripotency and Development (PD)** Hall 3, Entrance Level

NON-INTEGRATED STEM CELL MODELS OF EARLY EMBRYO DEVELOPMENT
Session Chairs: **Aydan Bulut-Karslioglu,** *Max Planck Institute for Molecular Genetics, Germany*
Sophie Petropoulos, *Karolinska Institutet, Sweden and University of Montreal, Canada*

8:20 AM – 8:40 AM **Yasuhiro Takashima,** *Kyoto University, Japan*
NAIVE HUMAN PSCS MODEL PRE- TO POST-IMPLANTATION DEVELOPMENT

8:40 AM – 8:50 AM **Auriana Arabpour,** *University of California, Los Angeles, USA*
PERI-GASTRULATION PATTERNING OF THE HUMAN EMBRYONIC DISC DOES NOT REQUIRE AN EPITHELIAL TO MESENCHYMAL TRANSITION

8:50 AM – 9:00 AM **Jin Zhang,** *Zhejiang University, China*
METABOLIC AND LIPIDOMIC REMODELLING INSTRUCT EARLY MAMMALIAN EMBRYO DEVELOPMENT

9:00 AM – 9:10 AM **Madeleine Linneberg-Agerholm,** *Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW), Denmark*
REGULATIVE DEVELOPMENT IN THE PREIMPLANTATION EMBRYO: A ROLE FOR OCT4 IN PLASTICITY MAINTENANCE IN THE MOUSE PRIMITIVE ENDODERM

9:10 AM – 9:20 AM **Yung Su Kim,** *University of Michigan, Ann Arbor, USA*
SELF-ORGANIZED, PERI-GASTRULATION HUMAN EMBRYO MODEL WITH TRILAMINAR EMBRYONIC DISC-, AMNION-, AND YOLK SAC-LIKE STRUCTURES

9:20 AM – 9:40 AM **Mo Ebrahimkhani,** *University of Pittsburgh, USA*
MODELING POST-IMPLANTATION HUMAN EMBRYOGENESIS TO YOLK SAC BLOOD EMERGENCE

8:15 AM – 9:45 AM **TRACK: Disease Modeling and Drug Discovery (DMDD)** Hall 4, Entrance Level

STEM CELLS FOR PERSONALIZED MEDICINE
Sponsored by: Mytos
Session Chairs: **David Elliott,** *Murdoch Children's Research Institute, Australia*
Sonia Gandhi, *Francis Crick Institute and University College London, UK*

8:20 AM – 8:40 AM **Eva van Rooij,** *Hubrecht Institute, Netherlands*
IDENTIFYING NEW MECHANISMS AND THERAPEUTIC OPPORTUNITIES FOR CARDIOMYOPATHY

8:40 AM – 8:50 AM **Nathalie Saurat,** *MSKCC, USA*
PROGRAMMING AGE IN HUMAN STEM CELL MODELS OF NEURODEGENERATIVE DISEASE

8:50 AM – 9:00 AM **Aman George,** *National Institutes of Health, USA*
GENE THERAPY INDUCES PIGMENTATION IN INDUCED PLURIPOTENT STEM CELLS DERIVED RETINAL PIGMENT EPITHELIUM FROM OCA1A PATIENTS AND ALBINO RAT EYE

9:00 AM – 9:10 AM **Abel Vertesy,** *IMBA - Institute of Molecular Biotechnology Austria, Austria*
HIGH-THROUGHPUT NEURAL CONNECTIVITY MAPPING IN HUMAN BRAIN ORGANOIDS

FRIDAY, 12 JULY *Continued*

Time	Session	Location
9:10 AM – 9:20 AM	**Tianyuan Shi,** *The University of Hong Kong, Hong Kong* **RESTORING DELETED IN LIVER CANCER 1 (DLC1) ISOFORM 1 EXPRESSION IS A MORE EFFECTIVE GENE THERAPY FOR SPINAL MUSCULAR ATROPHY**	
9:20 AM – 9:40 AM	**Jeffrey Beekman,** *University Medical Center Utrecht, Netherlands* **INTESTINAL ORGANOIDS FOR CYSTIC FIBROSIS PRECISION MEDICINE**	
8:15 AM – 9:45 AM	**FOCUS SESSION: PROGRESSING CELL THERAPIES TO CLINIC: UNDERSTANDING THE CELLULAR DRUG PRODUCT** *Organized by: Novo Nordisk A/S*	Hall Y1-6, Level 2
8:15 AM – 9:45 AM	**FOCUS SESSION: REALIZING THE POTENTIAL OF PSC-DERIVED THERAPIES: FROM RESEARCH TO CLINICAL TRANSLATION** *Organized by: BlueRock Therapeutics*	Hall Y7-12, Level 2
9:30 AM – 10:00 AM	**REFRESHMENT BREAK**	Hall 1 Foyer, Level 2
10:00 AM – 11:25 AM	**TRACK: Disease Modeling and Drug Discovery (DMDD)** **PLENARY V: ORGANOID MODELS OF DISEASE** *Sponsored by: Stem Cell Network* **Session Chairs: Christine L. Mummery,** *Leiden University Medical Center, Netherlands* **Hideyuki Okano,** *Keio University, Japan*	Hall 1, Level 2
10:05 AM – 10:25 AM	**Joo-Hyeon Lee,** *University of Cambridge, UK* **LESSONS FROM ORGANOIDS TO STUDY TISSUE REGENERATION AND DISEASE**	
10:25 AM – 10:45 AM	**Sharon Gerecht,** *Duke University, USA* **MICROENVIRONMENTAL REGULATION OF VASCULAR FATE, ASSEMBLY, AND FUNCTION**	
10:45 AM – 11:05 AM	**Flora Vaccarino,** *Yale University, USA* **EXTRACELLULAR MORPHOGENS AND GENOMIC VARIATION INSTRUCT CELL TYPE SPECIFICATION PROGRAMS IN HUMAN PLURIPOTENT CELLS**	
11:05 AM – 11:25 AM	**Toshiro Sato,** *Keio University, Japan* **UNDERSTANDING OF HUMAN ORGAN FUNCTION AND DISEASE USING ORGANOID TECHNOLOGY**	
11:00 AM – 6:00 PM	**EXHIBIT & POSTER HALL OPEN**	Hall H, Entrance Level
12:00 PM – 1:00 PM	**INNOVATION SHOWCASES:** see page 51 for details	
*12:00 PM - 12:30 PM	**CAREER PATHS IN STEM CELLS AND LEO** *Presented by: ISS National Laboratory and Sanford Stem Cell Institute at University of California - San Diego*	Hall 4, Entrance Level
	HIGH-RESOLUTION GENOME INTEGRITY ASSESSMENT IN STEM CELL THERAPY DEVELOPMENT WITH OPTICAL GENOME MAPPING *Presented by: Bionano*	Hall G2, Level 2
	ORGANOIDS: GROW THEM – GLOW THEM. INCREASE YOUR CELL CULTURE CONSISTENCY AND GET THE MOST OUT OF YOUR PRECIOUS SAMPLES WITH BIO-TECHNE REAGENTS *Presented by: Bio-Techne*	Hall G1, Level 2
	KEY REQUIREMENTS FOR EFFICIENT AND LINEAR SCALE-UP OF SHEAR SENSITIVE CELL THERAPY PRODUCTS USING THE VERTICAL-WHEEL BIOREACTOR *Presented by: PBS Biotech*	Hall Y7-12, Level 2
	THINKING OUTSIDE THE DOME: VERSATILE CULTURE METHODS FROM TISSUE-SPECIFIC STEM CELLS *Presented by: STEMCELL Technologies, Inc.*	Hall Y1-6, Level 2

FRIDAY, 12 JULY *Continued*

	LARGE SCALE ENGINEERING EFFORTS IN HUMAN IPSCS TO DECIPHER MOLECULAR AND CELLULAR CHANGES IN DISEASE *Presented by: The Jackson Laboratory*	Hall 3, Entrance Level
1:30 PM – 3:00 PM	**CONCURRENT TRACK SESSIONS**	
1:30 PM – 3:00 PM	**TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)** **MAINTENANCE AND REGENERATION OF TISSUE ARCHITECTURE** **Session Chairs: Eugenia Piddini,** *University of Bristol, UK* **Kyoko Miura,** *Kumamoto University, Japan*	Hall Y1-6, Level 2
1:35 PM – 1:55 PM	**Bon-Kyoung Koo,** *Institute of Molecular Biotechnology (IMBA), Austria and Center for Genome Engineering, Institute for Basic Science, Korea* **RETURN TO HOME-OSTASIS – THE MECHANISM TO RESOLVE INJURY RESPONSE OF THE INTESTINE**	
1:55 PM – 2:05 PM	**Shicong Xie,** *Stanford University, USA* **A CELL SIZE HOMEOSTASIS MECHANISM AUTONOMOUSLY DETERMINES THE TIMING OF THE G1/S TRANSITION FOR MAMMALIAN STEM CELLS IN VIVO**	
2:05 PM – 2:15 PM	**Kerstin Bartscherer,** *Osnabrueck University, Germany* **SPATIAL TRANSCRIPTOMICS REVEAL ASYMMETRIC CELLULAR RESPONSES TO INJURY IN THE REGENERATING SPINY MOUSE (ACOMYS) EAR**	
2:15 PM – 2:25 PM	**Hugo Vankelecom,** *KU Leuven, Belgium* **OVERARCHING SINGLE-CELL MAP AND STEM CELL LANDSCAPE OF THE MOUSE ENDOCRINE PITUITARY ACROSS KEY TIME POINTS OF LIFE IN HEALTH AND DISEASE**	
2:25 PM – 2:35 PM	**Matthew Tierney,** *The Rockefeller University, USA* **VITAMIN A RESOLVES LINEAGE PLASTICITY TO ORCHESTRATE STEM CELL LINEAGE CHOICES**	
2:35 PM – 2:55 PM	**Kenneth Poss,** *Duke University Medical Center, USA* **GENE REGULATORY MECHANISMS OF TISSUE REGENERATION IN ZEBRAFISH**	
1:30 PM – 3:00 PM	**TRACK: New Technologies (NT)** **NOVEL APPROACHES TO PROGRAM AND PERTURB CELL FATE** **Sesson Chairs: Barbara Treutlein,** *ETH Zürich, Switzerland* **Goncalo Castelo-Branco,** *Karolinska Institutet, Sweden*	Hall 4, Entrance Level
1:35 PM – 1:55 PM	**Filipe Pereira,** *Lund University, Sweden* **A COMBINATORIAL TRANSCRIPTION FACTOR SCREENING PLATFORM FOR IMMUNE CELL REPROGRAMMING**	
1:55 PM – 2:05 PM	**Matias Autio,** *Genome Institute of Singapore, A*Star & National University of Singapore, Singapore* **VALIDATED GENOMIC SAFE HARBOUR LOCI & LANDING-PAD CASSETTES ENABLE EASY INTEGRATION AND STABLE TRANSGENE EXPRESSION IN HUMAN PLURIPOTENT STEM CELLS AND DIFFERENTIATED PROGENY**	
2:05 PM – 2:15 PM	**Stepan Jerabek,** *Columbia University, USA* **BASE EDITING IN HUMAN EMBRYOS ENABLES KNOCKDOWN OF PCSK9 WITHOUT DETRIMENTAL CHROMOSOMAL CHANGES**	
2:15 PM – 2:25 PM	**Camila Vazquez Echegaray,** *Lund University, Sweden* **UNCOVERING REGULATORS OF DEGREES OF CELLULAR PLASTICITY BY DIRECT REPROGRAMMING**	

FRIDAY, 12 JULY *Continued*

2:25 PM – 2:35 PM **Gal Keshet (Cleitman Blackstien),** *The Hebrew University of Jerusalem, Israel*
A CRISPR SCREEN COMBINED WITH SINGLE-CELL TRANSCRIPTOMICS IN HUMAN PLURIPOTENT STEM CELLS DEFINES THE HIERARCHY OF TRANSCRIPTION FACTORS GOVERNING PLURIPOTENCY AND DIFFERENTIATION

2:35 PM – 2:55 PM **Baris Tursun,** *University of Hamburg, Germany*
IDENTIFYING NOVEL FACTORS THAT AFFECT CELLULAR REPROGRAMMING BY USING THE GENETIC MODEL ORGANISM C. ELEGANS

1:30 PM – 3:00 PM **TRACK: Clinical Applications (CA)** Hall 3, Entrance Level

PSC-BASED CELL THERAPIES
Sponsored by: Bayer AG and BlueRock Therapeutics
Session Chairs: Benedikt Berninger, *King's College London, UK*
Viviane Tabar, *Memorial Sloan Kettering Cancer Center, USA*

1:35 PM – 1:55 PM **Tamar Harel Adar,** *Matricelf, Israel*
AUTOLOGOUS 3D ENGINEERED TISSUES FOR THERAPEUTIC APPLICATIONS

1:55 PM – 2:05 PM **Edoardo Sozzi,** *Lund University, Sweden*
CO-GRAFT OF DOPAMINE PROGENITORS AND SUPPORTING CELLS TO ENHANCE CELL-BASED THERAPY FOR PARKINSON´S DISEASE

2:05 PM – 2:15 PM **Anne Plant,** *National Institute of Standards and Technology, USA*
LARGE-SCALE LIVE-CELL QUANTITATIVE LABEL-FREE IMAGING OF INDIVIDUAL IPSC FOR MONITORING PLURIPOTENCY

2:15 PM – 2:25 PM **Ian Hay,** *Factor Bioscience Inc., USA*
ENGINEERED IPSC-DERIVED MACROPHAGES EVADE HOST-VERSUS-GRAFT ALLOREACTIVITY AND ENHANCE T CELL CYTOTOXICITY TO TRIPLE NEGATIVE BREAST AND OVARIAN CANCER CELLS IN VITRO

2:25 PM – 2:35 PM **Yoshiki Furukawa,** *Juntendo University School of Medicine, Japan*
GENERATION OF CD4 SINGLE POSITIVE CELLS FROM IPSCS AND INVESTIGATION OF CD4/CD8 T CELL LINEAGE CHOICE

2:35 PM – 2:55 PM **Felicia Pagliuca,** *Vertex Pharmaceuticals, USA*
STEM CELL-DERIVED, FULLY DIFFERENTIATED ISLET CELLS FOR TYPE 1 DIABETES

1:30 PM – 3:00 PM **TRACK: Disease Modeling and Drug Discovery (DMDD)** Hall Z, Level 3

THE USE OF STEM CELLS IN DISEASE MODELING I
Sponsored by: bit.bio
Session Chairs: Guo-li Ming, *University of Pennsylvania, USA*
Meritxell Huch, *Max Planck Institute of Molecular Cell Biology and Genetics, Germany*

1:35 PM – 1:55 PM **Gabsang Lee,** *Johns Hopkins School of Medicine, USA*
ADVANCED HUMAN IPSC-BASED PRECLINICAL MODEL FOR PARKINSON'S DISEASE WITH OPTOGENETIC ALPHA- SYNUCLEIN AGGREGATION

1:55 PM – 2:05 PM **Sara Nolbrant,** *University of California, San Francisco, USA*
INTERSPECIES ORGANOIDS REVEAL HUMAN-SPECIFIC MOLECULAR FEATURES OF DOPAMINERGIC NEURON DEVELOPMENT AND VULNERABILITY

2:05 PM – 2:15 PM **Heein Song,** *Leiden University Medical Center, Netherlands*
APOL1 RISK VARIANTS INDUCE PODOCYTE MITOCHONDRIAL DYSFUNCTION IN PATIENT-DERIVED KIDNEY ORGANOIDS

2:15 PM – 2:25 PM **Alberto Camacho Magallanes,** *Ottawa Hospital Research Institute, Canada*
IDENTIFICATION OF TWIST1 AS A TRUE SYNTHETIC LETHAL TARGET OF TSC2-NULL NEURAL CREST CELLS THROUGH GENOME-WIDE CRISPR KNOCKOUT SCREEN

FRIDAY, 12 JULY *Continued*

Time	Session	Location
2:25 PM – 2:35 PM	**Meiyan Wang,** *Salk Institute for Biological Studies, USA* **ASTROCYTE DIVERSITY CAPTURED IN GLIA-ENRICHED CORTICAL ORGANOID TRANSPLANTED IN MOUSE BRAIN**	
2:35 PM – 2:55 PM	**Sonia Gandhi,** *The Francis Crick Institute and University College London, UK* **THINKING BIG TO SEE SMALL: RESOLVING PROTEINOPATHY IN PATIENT DERIVED STEM CELL MODELS OF PARKINSON'S DISEASE**	
1:30 PM – 3:00 PM	**TRACK: Pluripotency and Development (PD)** **TOTIPOTENCY AND GERM CELL DEVELOPMENT** **Session Chairs: Anne Grapin-Botton,** *Max Planck Institute of Molecular Cell Biology and Genetics, Germany* **Yasuhiro Takashima,** *CiRA and Kyoto University, Japan*	Hall G1, Level 2
1:35 PM – 1:55 PM	**Miguel Esteban,** *Guangzhou Institutes of Biomedicine and Health, China* **INDUCTION, REGULATION, AND APPLICATION OF HUMAN TOTIPOTENT-LIKE CELLS**	
1:55 PM – 2:05 PM	**Miguel Ramalho-Santos,** *Lunenfeld-Tanenbaum Research Institute and University of Toronto, Canada* **LINE1 RNA PREVENTS DEVELOPMENTAL REVERSION OF HUMAN EMBRYONIC STEM CELLS TO THE 8-CELL STATE**	
2:05 PM – 2:15 PM	**Moyra Lawrence,** *Kyoto University, Japan* **PROTEIN NETWORKS UNDERLYING THE MOUSE TOTIPOTENT-LIKE STATE**	
2:15 PM – 2:25 PM	**Maria Rostovskaya,** *Babraham Institute, UK* **MOLECULAR TIMETABLE OF LINEAGE SPECIFICATION IN HUMAN PLURIPOTENT EPIBLAST**	
2:25 PM – 2:35 PM	**Sergiy Velychko,** *Harvard Medical School, USA* **HIGHLY COOPERATIVE CHIMERIC SUPER-SOX INDUCES NAÏVE PLURIPOTENCY ACROSS SPECIES**	
2:35 PM – 2:55 PM	**Katsuhiko Hayashi,** *Kyushu University, Japan* **TITLE NOT AVAILABLE AT TIME OF PUBLISHING**	
1:30 PM – 3:00 PM	**TRACK: Ethics, Policy and Standards (EPS)** **USE OF STANDARDS FOR STEM CELLS IN NON-CLINICAL RESEARCH** **Christine L. Mummery,** *Leiden University Medical Center, Netherlands* **Martin F. Pera,** *The Jackson Laboratories, USA* **Glyn Stacey,** *National Institute for Biological Standards and Control, UK* **Mark R. Kotter,** *bit.bio, UK* **Carlos A. Tristan,** *National Institutes of Health, USA*	Hall G2, Level 2
1:30 PM – 3:00 PM	**FOCUS SESSION: STRATEGIES FOR GENE AND CELL-BASED THERAPIES IN EUROPE** *Organized by: Berlin Institute of Health (BIH) at Charité Berlin*	Hall Y7-12, Level 2
3:40 PM – 5:45 PM	**EXHIBIT HALL EVENTS** **Meet-up Hubs:** see page 20 for details **Exhibit Hall Theaters:** see page 61 for details **Career Exploration Talks:** see page 65 for details	Hall H, Entrance Level
3:40 PM – 3:55 PM	**PROFILING AND PROGRAMMING IN VITRO HUMAN NEURONAL DIVERSITY AT SINGLE-CELL RESOLUTION** *Presented by: Parse Bioscience*	Exhibit Hall Theater
3:45 PM – 5:45 PM	**REFRESHMENT BREAK**	
3:45 PM – 4:30 PM	**EUROPEAN RESEARCH COUNCIL (ERC) INFORMATION MEET-UP**	Meet-up Hub

FRIDAY, 12 JULY *Continued*		
3:45 PM – 4:30 PM	**STEM CELL PODCAST**	Meet-up Hub
3:45 PM – 4:30 PM	**CRYOPRESERVATION OF CELL AND GENE THERAPIES**	Meet-up Hub
3:45 PM – 4:45 PM	**POSTER SESSION III – ODD POSTERS**	
4:00 PM – 4:15 PM	**BEYOND ACADEMIA - SHOWCASING SCIENCE CAREERS WITH SCISMIC** *Presented by: Scismic*	Exhibit Hall Theater
4:20 PM – 4:35 PM	**NUVISAN - THE SCIENCE CRO** *Presented by: NUVISAN*	Exhibit Hall Theater
4:45 PM – 5:45 PM	**POSTER SESSION III – EVEN POSTERS**	
5:00 PM – 5:45 PM	**SELECTION AND TESTING OF CLINICAL-USE-QUALITY iPSCs**	Meet-up Hub
5:00 PM – 5:45 PM	**SUCCESS SYNERGY: NAVIGATING ACADEMIA & INDUSTRY**	Meet-up Hub
5:00 PM – 5:45 PM	**HARNESSING STEM CELLS FOR NEXT-GENERATION IMMUNOTHERAPY**	Meet-up Hub
5:00 PM – 5:46 PM	**CAREER EXPLORATION TALKS** *Sponsored by: Bayer AG and BlueRock Therapeutics*	Exhibit Hall Theater
5:00 PM – 5:15 PM	**Bayer AG and BlueRock Therapeutics**	
5:17 PM – 5:27 PM	**STEMCELL Technologies**	
5:29 PM – 5:34 PM	**European Research Council (ERC)**	
6:00 PM – 6:30 PM	**INNOVATION SHOWCASES:** see page 51 for details	
	CYTOTRONICS PIXEL: ELECTRICAL IMAGING BASED LIVE CELL CHARACTERIZATION FROM STEM CELLS TO PHENOTYPIC DISEASE MODELS *Presented by: CytoTronics*	Hall Y1-6, Level 2
** 6:00 PM – 7:00 PM*	**STEM CELL RESEARCH IN SPACE** *Presented by: Stem Cell Podcast*	Hall 4, Entrance Level

SATURDAY, 13 JULY		
8:15 AM – 9:45 AM	**CONCURRENT TRACK SESSIONS**	
8:15 AM – 9:45 AM	**TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)** **CELLULAR PLASTICITY IN REGENERATION AND CANCER** **Session Chairs: Bon-Kyoung Koo,** *Institute of Molecular Biotechnology (IMBA), Austria and Center for Genome Engineering, Institute for Basic Science, Korea* **Salvador Aznar Benitah,** *Institute for Research in Biomedicine (IRB Barcelona), Spain*	Hall Y7-12, Level 2
8:20 AM – 8:40 AM	**Elisa Laurenti,** *University of Cambridge, UK* **TRACKING HUMAN HAEMATOPOIETIC REGENERATION (AND LOSS OF IT) AT SINGLE CELL RESOLUTION**	
8:40 AM – 8:50 AM	**Mark Schmitt,** *University of Marburg, Germany* **DIFFERENTIATED LINEAGES ARE THE CELLS-OF-ORIGIN OF COLON CANCER IN THE CONTEXT OF INFLAMMATION**	
8:50 AM – 9:00 AM	**Swarnabh Bhattacharya,** *Dana-Farber Cancer Institute/Harvard Medical School, USA* **UNIFIED IDENTITY OF GOBLET AND PANETH CELLS AND CHROMATIN BASIS FOR INTESTINAL EPITHELIAL DIFFERENTIATION**	
9:00 AM – 9:10 AM	**Sandra Gomez Lopez,** *University College London, UK* **FROM AIRWAY BASAL CELLS TO PREINVASIVE LUNG SQUAMOUS CELL DISEASE**	

9:10 AM – 9:20 AM	**Anupama Hemalatha,** *Yale School of Medicine, USA* **LIVE-IMAGING REVEALS METABOLIC REWIRING IN SKIN STEM CELLS THAT DRIVE TOLERANCE TO ONCOGENIC MUTATIONS IN VIVO BY TWO DISTINCT CELL COMPETITION STRATEGIES**
9:20 AM – 9:40 AM	**Peter Reddien,** *Whitehead Institute MIT, USA* **CHOICES IN REGENERATION: HOW PLANARIAN STEM CELLS CHOOSE THEIR FATE**
8:15 AM – 9:45 AM	**TRACK: New Technologies (NT)** — Hall Y1-6, Level 2 **ENGINEERING APPROACHES TO DEVELOPMENTAL AND STEM CELL BIOLOGY** **Session Chair: Kate McDole,** *MRC Laboratory of Molecular Biology, UK*
8:20 AM – 8:40 AM	**Miki Ebisuya,** *Physics of Life TU Dresden, Germany* **STEM CELL ZOO – A PLATFORM TO STUDY SPECIES-SPECIFIC DEVELOPMENT**
8:40 AM – 8:50 AM	**Jianping Fu,** *University of Michigan, Ann Arbor, USA* **A FULLY PATTERNED HUMAN NEURAL TUBE MODEL USING MICROFLUIDIC GRADIENTS**
8:50 AM – 9:00 AM	**Connor Fausto,** *University of Southern California, USA* **CORRECTING KIDNEY ORGANOID PATTERNING WITH SYNTHETIC DEVELOPMENTAL ORGANIZERS**
9:00 AM – 9:10 AM	**Sveva Bottini,** *University of Torino, Italy* **A GENETIC SWITCH FOR GROWTH FACTOR-FREE STEM CELL EXPANSION AND SUBSEQUENT DIFFERENTIATION INTO SKELETAL MUSCLE**
9:10 AM – 9:20 AM	**Suzan Stelloo,** *RIMLS, Radboud University, Netherlands* **DECIPHERING LINEAGE SPECIFICATION DURING EARLY EMBRYOGENESIS USING MULTILAYERED PROTEOMICS**
9:20 AM – 9:40 AM	**Ron Weiss,** *MIT, USA* **MAMMALIAN SYNTHETIC BIOLOGY AND PROGRAMMABLE ORGANOIDS**
8:15 AM – 9:45 AM	**TRACK: Ethics, Policy and Standards (EPS)** — Hall G2, Level 2 **IDENTIFYING THE ETHICAL COMPLEXITIES AND GOVERNANCE IMPLICATIONS FOR EMBRYO MODEL RESEARCH** **Hongmei Wang,** *Institute of Zoology, Chinese Academy of Sciences, China* **Rosario Isasi,** *University of Miami, USA* **Søren Holm,** *University of Manchester, UK* **Sandy Starr,** *Progress Educational Trust (PET), UK*
8:15 AM – 9:45 AM	**TRACK: Disease Modeling and Drug Discovery (DMDD)** — Hall Z, Level 3 **THE USE OF STEM CELLS IN DISEASE MODELING II** *Sponsored by: Institute of Human Biology (IHB, Roche pRED)* **Session Chairs: Jeffrey Beekman,** *University Medical Center Utrecht, Netherlands* **David Elliott,** *Murdoch Children's Research Institute, Australia*
8:20 AM – 8:40 AM	**Ryuji Morizane,** *Massachusetts General Hospital, USA* **ADVANCING DISEASE MODELING AND THERAPEUTICS: KIDNEY ORGANOIDS AND ORGANOID-ON-A-CHIP**
8:40 AM – 8:50 AM	**Jubao Duan,** *University of Chicago/NorthShore University Health System, USA* **SCALED AND EFFICIENT DERIVATION OF FUNCTION ALLELES OF NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS IN HUMAN INDUCED PLURIPOTENT STEM CELLS**
8:50 AM – 9:00 AM	**Carmen Menacho,** *Heinrich Heine University Düsseldorf, Germany* **COMBINED SCREENING STRATEGIES IN INDUCED NEURONS AND MIDBRAIN ORGANOIDS UNVEIL REPURPOSABLE COMPOUNDS FOR THE TREATMENT OF LEIGH SYNDROME**

SATURDAY, 13 JULY *Continued*

9:00 AM – 9:10 AM
Joel Blanchard, *Icahn School of Medicine at Mount Sinai, USA*
ATP13A2 AND POLYAMINE DEFICIENCY CAUSE EPIGENETIC REPROGRAMMING OF HUMAN ASTROCYTES TO A SENESCENT STATE TOXIC TO DOPAMINERGIC NEURONS PROMOTING JUVENILE ONSET PARKINSONS DISEASE

9:10 AM – 9:20 AM
Giovanni Pietrogrande, *The University of Queensland, Australia*
A NEW IMMUNOCOMPETENT BRAIN ORGANOID MODEL TO STUDY DEMYELINATING DISEASES

9:20 AM – 9:40 AM
Guo-li Ming, *University of Pennsylvania, USA*
FUNCTION OF RISK GENES FOR BRAIN DISORDERS IN NEURODEVELOPMENT

8:15 AM – 9:45 AM
TRACK: Pluripotency and Development (PD) — Hall 4, Entrance Level
TISSUE AND ORGAN DEVELOPMENT
Session Chairs: Miguel Estaban, *Guangzhou Institutes of Biomedicine and Health, China*
Mo Ebrahimkhani, *University of Pittsburgh, USA*

8:20 AM – 8:40 AM
Anne Grapin-Botton, *Max Planck Institute of Molecular Cell Biology and Genetics, Germany*
ORGANOID MODELS TO DECIPHER PANCREAS DEVELOPMENT

8:40 AM – 8:50 AM
Wolfram Goessling, *Harvard Medical School/Mass General Hospital, USA*
MACROPHAGES REGULATE PROGENITOR CELL DIFFERENTIATION DURING HEPATOBILIARY DEVELOPMENT AND LIVER REGENERATION

8:50 AM – 9:00 AM
Yanbo Yin, *University of Cambridge, UK*
DEVELOPMENTAL PATTERNING AND CELL-FATE SPECIFICATION OF THE MOUSE COLONIC EPITHELIUM

9:00 AM – 9:10 AM
Julia Batki, *Max Planck Institute for Molecular Genetics, Germany*
CELL FATE REGULATION OF EXTRAEMBRYONIC CELLS IN THE GUT

9:10 AM – 9:20 AM
Juan Alvarez, *University of Pennsylvania, USA*
LINKING CIRCADIAN RHYTHMS TO PANCREATIC BETA-CELL MATURATION

9:20 AM – 9:40 AM
Shahragim Tajbakhsh, *Pasteur Institute, France*
SKELETAL MUSCLE STEM AND NICHE CELL DYNAMICS IN PATHOLOGIES

8:15 AM – 9:45 AM
TRACK: Clinical Applications (CA) — Hall 3, Entrance Level
UPDATES ON CLINICAL TRIALS
Sponsored by: Stem Cell Reports
Session Chairs: Ganna Bilousova, *University of Colorado Anschutz Medical Campus, USA*
Roger A. Barker, *University of Cambridge, UK*

8:20 AM – 8:40 AM
Viviane Tabar, *Memorial Sloan Kettering Cancer Center, USA*
PHASE I CLINICAL TRIAL OF HUMAN ES-DERIVED DOPAMINE NEURONS GRAFTS FOR PARKINSON'S DISEASE: 18 MONTHS DATA

8:40 AM – 8:50 AM
Ruchi Sharma, *NEI/NIH, USA*
A PHASE I/IIA TRIAL TO TEST SAFETY AND FEASIBILITY OF AN AUTOLOGOUS IPS CELL-DERIVED RETINAL PIGMENT EPITHELIUM PATCH IN AGE-RELATED MACULAR DEGENERATION PATIENTS

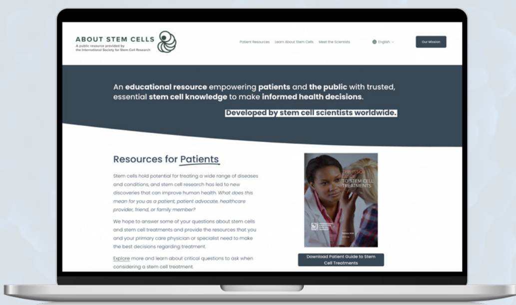
8:50 AM – 9:00 AM
Lisa Ott de Bruin, *Leiden University Medical Centre, Netherlands*
LENTIVIRAL GENE THERAPY TO CORRECT RAG1 DEFICIENCY

9:00 AM – 9:20 AM
Hideyuki Okano, *Keio University, Japan*
FIRST-IN-HUMAN CLINICAL TRIAL OF TRANSPLANTATION OF IPSC-DERIVED NS/PCS IN SUBACUTE COMPLETE SPINAL CORD INJURY: INTERIM REPORT

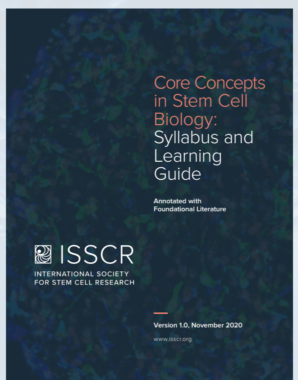
9:20 AM – 9:40 AM
Sonja Schrepfer, *Sana Biotechnology, USA*
HYPOIMMUNE ISLET CELLS MEDIATE INSULIN INDEPENDENCE AFTER ALLOGENEIC TRANSPLANTATION WITHOUT IMMUNOSUPPRESSION

8:15 AM – 9:45 AM	**FOCUS SESSION: INSIGHTS FROM REGULATORS: LESSONS LEARNED FROM THE ISSCR'S REGULATORY LIAISON MEETINGS** *Organized by: ISSCR Industry Subcommittee*	Hall G1, Level 2
9:30 AM – 10:00 AM	**REFRESHMENT BREAK**	Hall 1 Foyer, Level 2
10:00 AM – 11:35 AM	TRACK: Clinical Applications (CA) **PLENARY VI: THE CLINICAL REALITY AND PROMISE OF CELL AND GENE THERAPIES** *Sponsored by: Healios K.K.* **Session Chairs: Roger A. Barker,** *University of Cambridge, UK* **Marinna Madrid,** *Cellino Biotech, USA*	Hall 1, Level 2
10:05 AM – 10:25 AM	**Catherine Priest,** *Neurona Therapeutics, USA* **A PHASE I/II CLINICAL TRIAL OF NRTX-1001 INHIBITORY INTERNEURON CELL THERAPY FOR DRUG-REFRACTORY FOCAL EPILEPSY**	
10:25 AM – 10:45 AM	**Robert Coppes,** *University Medical Center Groningen, Netherlands* **SALIVARY GLAND ORGANOIDS TO TREATMENT RADIOTHERAPY INDUCED XEROSTOMIA**	
10:45 AM – 11:05 AM	**Cristiana Pires,** *Asgard Therapeutics, Sweden* **IN VIVO DIRECT REPROGRAMMING OF TUMOR CELLS TO DENDRITIC CELLS AS A NEW CANCER IMMUNOTHERAPY MODALITY**	
11:05 AM – 11:15 AM	**Mikael Rydberg,** *Sweden* **PATIENT ADVOCATE ADDRESS**	
11:15 AM – 11:35 AM	**Michael Lai,** *HeartWorks, USA* **AUTOLOGOUS IPSC-DERIVED CARDIAC CELL THERAPIES FOR PATIENTS WITH UNIVENTRICULAR CONGENITAL HEART DEFECTS**	
1:30 PM – 3:35 PM	**PLENARY VII: AWARDS & KEYNOTE SESSION** **Session Chairs: Malin Parmar,** *Lund University, Sweden* **Agnete Kirkeby,** *University of Copenhagen, Denmark*	Hall 1, Level 2
1:35 PM – 1:40 PM	**Valentina Greco,** *Yale School of Medicine, Genetics Department & Yale Stem Cell Center, USA* **ISSCR PRESIDENT-ELECT'S ADDRESS**	
1:40 PM – 1:49 PM	**Peter W. Andrews,** *University of Sheffield, UK, Joint Honoree* **Tenneille E. Ludwig,** *WiCell, USA, Joint Honoree* **ISSCR PUBLIC SERVICE AWARD PRESENTATION**	
1:49 PM – 1:52 PM	**ISSCR MOMENTUM AWARD PRESENTATION**	
1:52 PM – 2:22 PM	**Sergiu P. Paşca,** *Stanford University, USA* **ISSCR MOMENTUM AWARD PRESENTATION: HOW THE HUMAN BRAIN BUILDS ITSELF: RECONSTRUCTING NEURODEVELOPMENT WITH STEM CELL-DERIVED ASSEMBLOIDS AND ORGANOIDS**	
2:22 PM – 2:25 PM	**ISSCR ACHIEVEMENT AWARD PRESENTATION** *Sponsored by: Bayer AG and BlueRock Therapeutics*	
2:25 PM – 2:55 PM	**Fiona M. Watt,** *EMBL-Heidelberg, Germany* **ISSCR ACHIEVEMENT AWARD LECTURE: EXPLORING DIFFERENT CELL POPULATIONS IN HEALTHY AND DISEASED SKIN**	
2:55 PM – 3:30 PM	**Melissa H. Little,** *Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Denmark, and Murdoch Children's Research Institute, Australia* **KEYNOTE ADDRESS: MODELLING THE HUMAN KIDNEY FOR DRUG DEVELOPMENT AND TISSUE ENGINEERING**	
3:30 PM – 3:35 PM	**POSTER AWARD ANNOUNCEMENTS AND CLOSING REMARKS**	

ISSCR EDUCATIONAL RESOURCES SUPPORT THE STEM CELL FIELD



Trusted information developed by global experts featuring basic education about stem cells through the latest clinical research.

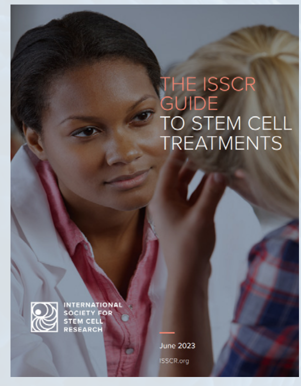


CORE CONCEPTS IN STEM CELL BIOLOGY: SYLLABUS AND LEARNING GUIDE

Support your stem cell curriculum by using the ISSCR's comprehensive and flexible syllabus and learning guide.

CLINICAL DISEASE FACT SHEETS

Stay informed on the current state of stem cell medicine including the clinical status of cell-based therapies and ongoing clinical trials for specific diseases.



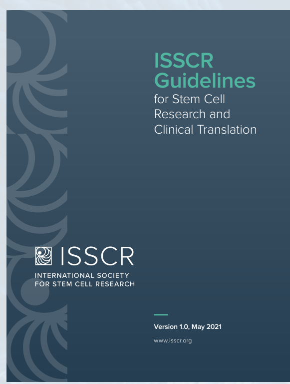
PATIENT GUIDE TO STEM CELL TREATMENTS

Equips patients and families with a trusted resource, empowering them to make safe and informed choices while navigating stem cell treatment options.

STANDARDS FOR HUMAN STEM CELL USE IN RESEARCH

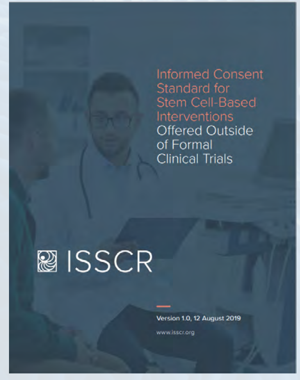
Enhancing rigor and reproducibility in preclinical stem cell research and ultimately strengthening the pipeline of therapies for patients.

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH



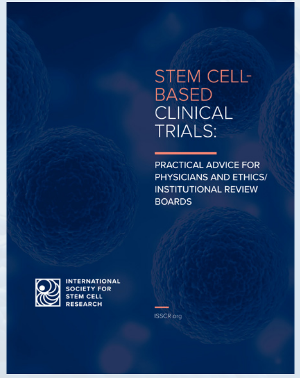
ISSCR GUIDELINES FOR STEM CELL RESEARCH AND CLINICAL TRANSLATION

Adherence to the ISSCR Guidelines provides assurance that stem cell research is conducted with scientific and ethical integrity and that new therapies are evidence-based.



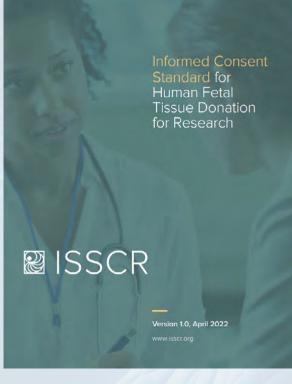
INFORMED CONSENT STANDARD FOR STEM CELL-BASED INTERVENTIONS OFFERED OUTSIDE OF FORMAL CLINICAL TRIALS

A professional standard intended to help patients make an informed decision when offered a stem cell "treatment" outside of a clinical trial.



STEM CELL-BASED CLINICAL TRIALS: PRACTICAL ADVICE FOR PHYSICIANS AND ETHICS/INSTITUTIONAL REVIEW BOARDS

Fundamental questions for clinicians and ethics/institutional review committees to ask when running or reviewing early phase, cell-based clinical trials.



INFORMED CONSENT STANDARD FOR HUMAN FETAL TISSUE DONATION FOR RESEARCH

A professional standard to help ensure women are well informed prior to donating fetal tissue after an elective termination of pregnancy.

EXPLORE ALL ISSCR RESOURCES AT ISSCR.ORG AND ABOUTSTEMCELLS.ORG

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

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PL BioScience GmbH
Proteintech
Proteome Sciences
Qkine
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REPROCELL
Revvity
Sartorius Stedim Biotech GmbH
Scismic
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Sino Biological
Society for Laboratory Automation and Screening (SLAS)
Stem Cell Podcast
Stem Genomics
StemBioSys
STEMCELL Technologies Inc.
StemCultures
SUN bioscience SA
Takara Bio Europe
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Trince Bio
UK Stem Cell Bank
Union Biometrica, Inc.
VectorBuilder Inc.
Viventis Microscopy
WiCell

FOCUS SESSIONS

WEDNESDAY, 10 JULY | 4:00 PM – 5:30 PM

TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY

Organized by: Stem Cell COREdinates

Supported by: STEMCELL Technologies and Thermo Fisher Scientific

Hall Y1-6, Level 2

Stem Cell COREdinates (www.COREdinates.org) is an international consortium of human pluripotent stem cell-focused core facilities that share expertise with protocols, reagents, and technological advancements to establish "best practices" in the maintenance, derivation, differentiation and genetic manipulation of human pluripotent stem cells. Each of our member cores plays an important role in the research and educational missions of their respective institutions. The Focus Session will have selected presentations from Stem Cell COREdinate members and our sponsors. These presentations will cover a number of different areas of expertise including stem cell characterization, gene editing and disease modeling. This session will benefit stem cell researchers who are just starting to use pluripotent stem cell tools in their own laboratories and experienced researchers who are seeking to expand their toolbox. These presentations from the COREdinate members will cover a variety of topics that will have direct impact on improving workflow, establishing new technology and advancing existing methodology.

4:00 PM – 4:05 PM **Tenneille E. Ludwig,** *WiCell, USA*
WELCOME AND OVERVIEW

4:05 PM – 4:20 PM **Laurent David,** *Universite de Nantes, France*
UNRAVELING HALLMARK SUITABILITY FOR STAGING PRE- AND POST-IMPLANTATION STEM CELL MODELS REVEALS MEDIA-SPECIFIC FEATURES

4:20 PM – 4:32 PM **Camille Tempier Lemey,** *STEMCELL Technologies, Inc., France*
CLINICAL APPLICATION OF AUTOLOGOUS IPSC-DERIVED CARDIAC CELLS IN PATIENTS IN UNIVENTRICULAR CONGENITAL HEART DISEASE

4:32 PM – 4:47 PM **Dmitry Ovchinnikov,** *The Florey / University of Melbourne, Australia*
CHARACTERIZATION STRATEGIES FOR GENE-EDITED CELL LINES: REVEALING THE UNINTENDED AND OFTEN OVERLOOKED GENOMIC CHANGES

4:47 PM – 5:02 PM **Grazia Iannello,** *Columbia University, USA*
TISSUE-SPECIFIC X-CHROMOSOME INACTIVATION SKEWING AFFECTS IPSC REPROGRAMMING IN SOME NEURODEVELOPMENTAL DISORDERS

5:02 PM – 5:14 PM **Sarah Perez Munoz,** *Thermo Fisher Scientific, Spain*
IPSC-DERIVED BETA CELL SPHEROIDS DEVELOPED USING MRNA FOR TREATING DIABETES

5:14 PM – 5:29 PM **Sebastian Diecke,** *Max Delbruck Center for Molecular Medicine, Germany*
AUTOMATION OF STEM CELL LABORATORIES: LESSONS LEARNED

5:29 PM – 5:30 PM **Tenneille E. Ludwig,** *WiCell, USA*
CLOSING AND THANK YOU

THURSDAY, 11 JULY | 8:15 AM – 9:45 AM

STRATEGIES FOR THE DEVELOPMENT OF ALLOGENIC IPSC-DERIVED CELL THERAPIES

Organized by: Evotec

Hall Y7-12, Level 2

iPSCs can serve as starting material for generating potentially limitless amounts of cells for therapeutic applications, especially when focusing on allogenic, off-the-shelf approaches in regenerative and anti-tumor medicine. This session emphasizes distinct strategies for different categories of therapeutic cells, such as mature cells derived from organoids, cell clusters, and single-cell populations. Predictive and efficient functional assays both for cellular maturation and immune-evasion are essential to determine the chances of product success.

8:15 AM – 8:30 AM	**Audrey Holtzinger,** *Evotec, Germany* **Matthias Austen,** *Evotec, Germany* **WELCOME AND OVERVIEW**
8:30 AM – 8:55 AM	**Nico Lachmann,** *Medizinische Hochschule Hannover, Germany* **HARNESSING THE THERAPEUTIC POTENTIAL OF IPSC-DERIVED IMMUNE CELLS TO TREAT DISEASES OF THE LUNG AND BEYOND**
8:55 AM – 9:20 AM	**Lorenzo Piemonti,** *Vita-Salute San Raffaele University, Italy* **STRATEGIES FOR IMPROVING BETA CELL REPLACEMENT WITH INSULIN-PRODUCING CELLS FROM PLURIPOTENT STEM CELLS**
9:20 AM – 9:45 AM	**Marius Ader,** *Technische University Dresden / CRTD, Germany* **TRANSPLANTATION OF PHOTORECEPTORS ISOLATED FROM HUMAN IPSC-DERIVED RETINAL ORGANOIDS INTO MOUSE MODELS OF RETINAL DEGENERATION**

FRIDAY, 12 JULY | 8:15 AM – 9:45 AM

PROGRESSING CELL THERAPIES TO CLINIC: UNDERSTANDING THE CELLULAR DRUG PRODUCT

Organized by: Novo Nordisk A/S

Hall Y1-6, Level 2

There are many challenges in moving an academic discovery towards clinical application. A major hurdle to overcome is how to understand and characterize the composition and behavior of the cellular drug product. Technologies, methodologies, and the level of detail required for academic publication do not always match those required for large scale manufacturing, or by regulators for clinical trial approval and, ultimately, the granting of marketing authorization.

In this Focus Session, we will address issues such as scale up, prevention of off-target differentiation, in vitro prediction of function, and in vivo proof of engraftment and viability. An expert academic and industry faculty will discuss these issues, the techniques that currently exist to address them, and the innovation challenges facing the field in order to close the technological gaps that exist in these areas.

8:15 AM – 8:20 AM	**Charis Segertiz-Walko,** *Novo Nordisk A/S, Denmark* **WELCOME AND INTRODUCTION**
8:20 AM – 8:40 AM	**Timothy Kieffer,** *University of British Columbia, Canada* **OPTIMISING THE SAFETY & PURITY OF CELLULAR DRUG PRODUCT**
8:40 AM – 9:00 AM	**Melissa H. Little,** *Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Denmark, and Murdoch Children's Research Institute, Australia* **LINKING THE IN VITRO AND IN VIVO FUNCTION OF REGENERATIVE CELL THERAPIES**
9:00 AM – 9:20 AM	**Catherine Priest,** *Neurona Therapeutics, USA* **ASSESSMENT OF CELL ENGRAFTMENT AND VIABILITY AFTER TRANSPLANTATION**
9:20 AM – 9:40 AM	**Charis Segertiz-Walko,** *Novo Nordisk A/S, Denmark* **PANEL DISSCUSSION: WHAT TECHNOLOGICAL INNOVATION IS REQUIRED TO EXPEDITE CLINICAL TRANSLATION?**
9:40 AM – 9:45 AM	**Brendan Jones,** *Novo Nordisk A/S, Denmark* **WRAP-UP AND CLOSE**

REALIZING THE POTENTIAL OF PSC-DERIVED THERAPIES: FROM RESEARCH TO CLINICAL TRANSLATION

Organized by: *BlueRock Therapeutics*

Hall Y7-12, Level 2

Despite their immense potential for treating a wide range of diseases characterized by irreversible cell loss and high unmet medical needs, the broad clinical application of PSC-based stem cell therapies faces major obstacles. These hurdles include technical limitations, high costs, as well as challenges related to poor cell survival and engraftment. The purpose of this session is to provide an update on the ongoing efforts within both industry and academia aimed at overcoming significant barriers hindering the widespread adoption of PSC-based stem cell therapies in the clinic.

8:15 AM – 8:25 AM **Sandra Milista,** *BlueRock Therapeutics, USA*
WELCOME AND OVERVIEW

8:25 AM – 8:45 AM **Wolfram Zimmermann,** *University Medical Center Göttingen and Repairon GmbH, Germany*
TISSUE-ENGINEERED HEART REPAIR FROM BENCH TO BED

8:45 AM – 9:05 AM **Mark Kotter,** *bit.bio, UK*
CODING CELLS FOR NOVEL CURES

9:05 AM – 9:25 AM **Christine Günther,** *Evotec, Germany*
FOCUS DIABETES: THE PATH OF IPSC-DERIVED BETA CELLS TO CLINICAL APPLICATION

9:25 AM – 9:45 AM **Lorenz Studer,** *BlueRock Therapeutics and Center for Stem Cell Biology at Memorial-Sloan Kettering Cancer Center, USA*
TITLE NOT AVAILABLE AT TIME OF PUBLISHING

FRIDAY, 12 JULY | 1:30 PM – 3:00 PM

STRATEGIES FOR GENE AND CELL-BASED THERAPIES IN EUROPE

Organized by: *Berlin Institute of Health (BIH) at Charité Berlin*

Hall Y7-12, Level 2

In this focus session, we will explore the opportunities and challenges associated with the development of stem cell-based therapies within the broader context of gene and cell-based therapies. The session will kick off with an introductory talk by Giulio Cossu, who will highlight the obstacles encountered in the translational process and the complexities of establishing a sustainable framework for delivering these therapies to patients, particularly those with rare diseases. Participants will be introduced to two distinct cases demonstrating how Advanced Therapy Medicinal Products (ATMPs) can reach patients, despite commercialization hurdles.

Moreover, the session will delve into various strategies adopted across Europe to support the advancement of gene and cell therapy. We will examine the German national strategy for gene and cell therapy, the initiative by French INSERM PEPR Biotherapies and Bioproduction for innovative therapies, and the efforts of the UK Catapult for Cell and Gene Therapy. A panel discussion will provide insights into how these approaches address the promising opportunities and challenges in the field.

This focus session aims to provide a comprehensive overview of the current landscape and future directions in stem cell-based therapy development, emphasizing collaborative and innovative strategies to navigate the existing hurdles.

1:30 PM – 1:50 PM **Giulio Cossu,** *Ospedale San Raffaele, Italy*
CHALLENGES AND OPPORTUNITIES OF (STEM) CELL- AND GENE-BASED THERAPIES IN THE EUROPEAN ECOSYSTEM AND POST-MARKETING DIFFICULTIES

1:50 PM – 2:10 PM **Stefano Benvenuti,** *Fondazione Telethon, Italy*
ENSURING ACCESS TO LIFE-SAVING GENE THERAPY FOR ULTRA-RARE DISEASES: A NOT-FOR-PROFIT MODEL

2:10 PM – 2:30 PM **Claire Booth,** *UCL Great Ormond Street Institute of Child Health, UK*
ACCESS TO EFFECTIVE GENE THERAPIES FOR RARE DISEASES - THE AGORA INITIATIVE

2:30 PM – 3:00 PM **Moderator: Daniel Besser,** *Berlin Institute of Health/German Stem Cell Network, Germany*
Christopher Baum, *Berlin Institute of Health at Charité, Germany*
Cecile Martinat, *INSERM, France*
Jacqueline Barry, *Cell and Gene Therapy Catapult, UK*
PANEL DISCUSSION: EUROPEAN STRATEGIES OF GENE AND CELL-BASED THERAPIES

SATURDAY, 13 JULY | 8:15 AM – 9:45 AM

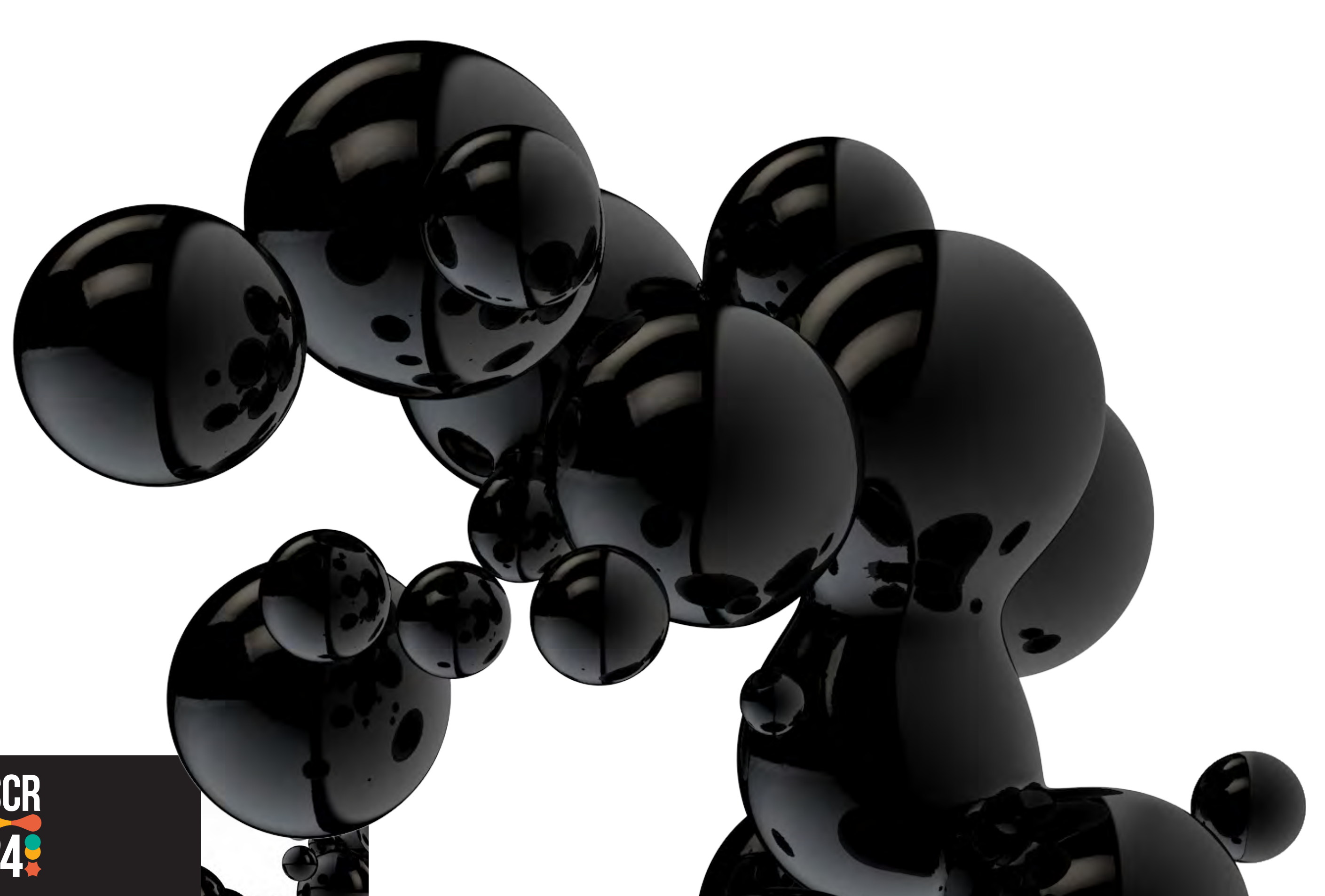
INSIGHTS FROM REGULATORS: LESSONS LEARNED FROM THE ISSCR'S REGULATORY LIAISON MEETINGS

Organized by: ISSCR Industry Subcommittee

Hall G1, Level 2

Human Pluripotent Stem Cell (hPSC)-derived cell therapies are now being investigated in clinical trials. Despite 26 years of rigorous basic science with hPSCs, navigating the regulatory landscape for the clinical translation of PSC-derived cell therapies remains challenging due to the complexities of cellular drug products and limited experiences reviewing and approving them. As the leading stem cell society, the ISSCR is in a unique position to share its scientific expertise with global regulators and work with agencies to facilitate improved future regulatory processes for stem cell-based therapies. In this ISSCR Industry Focus Session, the Society shares important insights and feedback gleaned from its liaison meetings with regulatory agencies with our community of scientists to ameliorate their chances of IND approvals and inform the development of effective and safe new therapies.

8:15 AM – 8:17 AM	**Jennifer Moody,** *Danaher, Canada* **WELCOME AND OPENING REMARKS**
8:17 AM – 8:37 AM	**Tenneille E. Ludwig,** *WiCell, USA* **RECOMMENDATIONS ON PHASE-APPROPRIATE GMP COMPLIANCE**
8:37 AM – 8:57 AM	**Jacqueline Barry,** *Cell and Gene Therapy Catapult, UK* **REGULATORY FEEDBACK ON GTP COMPLIANCE**
8:57 AM – 9:17 AM	**Nissim Benvenisty,** *The Hebrew University, Israel* **REGULATORY AUTHORITY VIEWS ON GENOMIC STABILITY**
9:17 AM – 9:45 AM	**Moderator: Jennifer Moody,** *Danaher, Canada* **Tenneille E. Ludwig,** *WiCell, USA* **Jacqueline Barry,** *Cell and Gene Therapy Catapult, UK* **Nissim Benvenisty,** *The Hebrew University, Israel* **Derek J. Hei** **Kapil Bharti,** *National Eye Institute; National Center for Advancing Translational Sciences, National Institutes of Health, USA* **PANEL DISCUSSION**



INNOVATION SHOWCASES

WEDNESDAY, 10 JULY | 12:00 PM – 1:00 PM

CuSTOMIZING ORGANOIDS FOR DRUG DEVELOPMENT AND REGENERATIVE MEDICINE

Presented by: Ajinomoto Co., Inc.

Hall G2, Level 2

The rapidly evolving field of stem cell biology is reshaping the medical landscape, offering new tools to enhance human health. At the Center for Stem Cell and Organoid Medicine (CuSTOM) at Cincinnati Children's, a collaborative, cross-departmental hub of excellence, we harness breakthroughs in developmental biology and pluripotent stem cell technologies to develop three-dimensional tissue structures known as organoids. These platforms enable us to improve our understanding of human biology, model patient-specific diseases in a dish, and advance personalized medicine. However, challenges persist in realizing their full potential and practical applications.

To bridge this gap, CuSTOM Accelerator (CA) was established in 2019, with a mission to translate innovations into actionable solutions, fostering synergies between academia and industry to drive the development of organoid-based drug discovery platforms and therapeutics for tissue regeneration and organ replacement. In this talk, I will elucidate our strategy for overcoming key challenges in organoid technology translation, with a keen focus on scalability, robustness, and in situ monitoring and characterization. Highlighting two pivotal organ models—the liver and intestine—I will unveil our pioneering efforts in developing fully automated AI-empowered organoid-based platforms for high-throughput drug assessment. Additionally, I will offer insights into our journey towards translating human organoids from bench to bedside, including our efforts on the establishment of cGMP-compliant scalable manufacturing of organoids in matrix-free suspension culture.

PRESENTERS:
Magdalena Kasendra, *Cincinnati Children's Hospital Medical Center, CuSTOM, USA*
Shuhei Wakimoto, *Ajinomoto Co., Inc., Japan*

TRANSFORMING hiPSC DIFFERENTIATION BY INCREASING EFFICIENCY AND FIDELITY FOR NPCS, HSCS, AND LPCS

Presented by: Cell Microsystems

Hall G1, Level 2

Unlocking the full potential of patient-derived and genetically modified human induced pluripotent stem cells (hiPSCs) for disease modeling requires precise differentiation protocols. Despite the availability of various protocols and kits, the technical intricacies of hiPSC differentiation often lead to inefficiencies and reproducibility challenges. We aim to address these hurdles by leveraging CellRaft® Technology, offering solutions for hiPSC differentiation workflows.

What you will learn:

- How to enhance efficiency in hiPSC differentiation
- How to automate the monitoring and isolation of neural progenitor cells (NPCs), ensuring high fidelity differentiation
- How to improve hematopoietic progenitor cell (HSC) differentiation, leading to enhanced colony survival and yield
- How to utilize technology to streamline differentiation by accurately purifying populations, increasing differentiation accuracy

Overall, our findings underscore the significance of automating manual steps in hiPSC differentiation, highlighting how image-based monitoring, phenotypic selection, and isolation can enhance efficiency and fidelity, thereby expediting the development of relevant disease models.

PRESENTER:
Jessica Hartman, *Cell Microsystems, USA*

STEM CELLS IN LOW EARTH ORBIT: THE NEXT FRONTIER

Presented by: ISS National Laboratory and Sanford Stem Cell Institute at University of California - San Diego

Hall 4, Entrance Level

The "Stem Cells in Low Earth Orbit: The Next Frontier" at the ISSCR Conference aims to explore the groundbreaking intersection of stem cell research and the unique environment of low Earth orbit (LEO). This panel brings together leading experts to discuss the latest advancements, challenges, and prospects of conducting stem cell research onboard the International Space Station (ISS). Attendees will gain insights into how microgravity and the extreme space environment can influence stem cell behavior and the potential implications for regenerative medicine and biomanufacturing.

Panel Objectives:

1. Highlight Innovations: Showcase recent innovations from stem cell research conducted in LEO and their potential applications for regenerative medicine and beyond.
2. Discuss Challenges: Address the scientific and logistical challenges of conducting stem cell research in space and potential solutions.
3. Future Prospects: Explore the future of stem cell research in space, including opportunities for collaboration to accelerate the translation of emerging technologies for applications on Earth.
4. Engage with Experts: Provide an interactive platform for attendees to engage with leading scientists and researchers in the field.

PRESENTERS:
Michael Roberts, *ISS National Lab, USA*
Meghan Everett, *NASA, USA*
Catriona Jamieson, *Sanford Stem Cell Institute UCSD, USA*
Valentina Fossati, *New York Stem Cell Foundation, USA*
Jeanne Loring, *National Stem Cell Foundation, USA*
Arun Sharma, *Cedar-Sinai, USA*

THE FUTURE OF CELL CULTURE: EMPOWERING RESEARCHERS TO MAKE KEY DECISIONS SOONER, ACHIEVE MILESTONES FASTER, AND GET TO CLINIC EARLIER—WITH LOWER ATTRITION RATES

Presented by: *Molecular Devices*

Hall Y7–12, Level 2

The majority of drugs fail in the later stages of the drug development pipeline and in clinical trials because of insufficient predictivity of cell models used to screen drug candidates. Organoids show great promise as a game-changer in disease modeling and drug screening since they better resemble tissue structure and functionality and show more predictive response to drugs. However, challenges associated with using organoids, such as assay complexity, reproducibility, and the ability to scale up have limited their widespread adoption as a primary screening method in drug discovery.

To alleviate the bottlenecks that come with labor-intensive manual protocols, we developed the CellXpress.ai™ Automated Cell Culture System. This instrument automates the entire 3D organoid or 2D cell culture workflow: providing media exchange, plating, passaging, organoid monitoring, end-point assay execution, and complex image analysis. It contains functional components including an automated imager, liquid handler, and incubator, connected by AI- powered software. The development of cell cultures is monitored by periodic imaging and analysis, which can trigger automatic decisions to initiate passaging, end-point assays, or troubleshooting steps. We will present the results from the automation of several commonly used 3D organoid protocols, as well as 2D assays.

PRESENTER:
Felix Spira, *Molecular Devices, Austria*

GENETIC WHACK-A-MOLE: BATTLING INSTABILITIES IN iPSCS

Presented by: *Pluristyx, Inc.*

Hall X4–9, Level 1

With the ability to differentiate into all body tissue types and the potential for commercial scale manufacture, human induced Pluripotent Stem Cells (iPSCs) are an ideal starting material for the next generation of cellular therapeutics. However, inconsistency in the culture process can predispose cells to genetic abnormalities that can influence growth rate and differentiation efficiency. Persistence of these genetic alternations in the final product can introduce a safety risk to patients receiving these life altering therapies. Detecting genetic abnormalities is difficult, as no single assay can cover all potential alterations and may be at low levels that are below the detection limit of some assays. A combination of testing modalities at frequent and predetermined intervals can cover the most common genetic alterations and limit downstream risk. Similarly, culture strategies can be implemented to minimize the rate of de novo mutations and prevent abnormal colonies from overtaking genetically normal variants. This presentation will discuss the challenges of maintaining genetic integrity during the commercial manufacture of iPSCs and propose practical approaches to ensuring that clinical iPSCs are free of mutations for product development.

PRESENTER:
Brian Hawkins, *Pluristyx, Inc., USA*

WEDNESDAY, 10 JULY | 12:00 PM – 12:25 PM

ISSCR STANDARDS IN ACTION: ADVANCEMENTS IN CELL LINE GENERATION AND ORGANOID INNOVATION

Presented by: *STEMCELL Technologies, Inc.*

Hall Y1-6, Level 2

Join us for an insightful session on our latest advancements in cell line generation, featuring the SCTi003-A and SCTi004-A healthy control iPSC lines. These cell lines represent a significant step forward in the field, aligning with and advancing beyond the established ISSCR guidelines for stem cell research. Our presentation will focus on how these lines are shaping the future of stem cell research, including their central role in various applications and contribution to setting new benchmarks in research quality and ethical standards. We will spotlight iPSCdirect™, our efficient, ready-to-use, singularized iPSC product. Additionally, we will showcase the development of various differentiated types and organoids, including the launch of live, experiment-ready midbrain organoids, designed for immediate application upon delivery to your laboratory. Explore how these cutting-edge technologies are revolutionizing disease modeling, drug discovery, and more, while upholding our commitment to advancing research quality and ethical integrity.

PRESENTER:
Andrew Gaffney, *STEMCELL Technologies Inc., Canada*

WEDNESDAY, 10 JULY | 12:25 PM – 1:00 PM

IMPROVING THE GENETIC STABILITY OF SINGLE-CELL-PASSAGED HUMAN PLURIPOTENT STEM CELL CULTURES USING eTeSR™

Presented by: *STEMCELL Technologies, Inc.*

Hall Y1-6, Level 2

In this talk, we'll discuss new genetic stability data on cultures maintained in eTeSR™, a novel human pluripotent stem cell (hPSC) maintenance medium, specifically developed to support routine single-cell passaging. The study comprises over 250 SNP microarray samples collected from clones derived using three hPSC lines and maintained for 20 weeks in four media conditions. The study shows that clones maintained in eTeSR™ acquire fewer de novo cytogenetic changes compared to two alternative, commercially available maintenance media. This improvement in genetic stability can be attributed to the absence of 20q11 gains in eTeSR™-maintained cultures, a recurrent abnormality that has been well-documented in hPSC cultures. This study provides a better understanding of culture-acquired genetic aberrations in hPSCs and demonstrates that innovative media formulations such as eTeSR™ can address major challenges in the hPSC field.

PRESENTER:
Adam Hirst, *STEMCELL Technologies Inc., UK*

UNLOCKING THE POWER OF DETERMINISTIC CELL PROGRAMMING IN BIOMEDICAL RESEARCH AND DRUG DISCOVERY

Presented by: *bit.bio*

Hall G2, Level 2

The session is split into 3 parts.
1) Transcription factor-mediated cell programming. Roger Pedersen (Stanford University) will discuss the paradigm shift achieved using transcription factor-mediated cell programming to alter pluripotent stem cell fate. He will detail how transcription factor-based programming impacts reproducibility and scalability and dramatically improves stem cell utility in research and future therapeutic applications.

2) Unravelling Alzheimer's disease: Insights into pathogenesis, promising therapies, and the potential of stem cells. Matthias Pawlowski (University of Münster) will explore genetic, protein misfolding, and neuroinflammation roles in the pathogenesis of Alzheimer's disease, alongside promising treatment strategies including small molecule inhibitors and immunotherapies as well as research on pluripotent stem cells as a transformative approach for advanced disease modelling and drug development.

3) hiPSC-derived cell models for functional genomics and neural network formation studies. Sejla Salic-Hainzl (bit.bio) will present on the use of human iPSC-derived cells in functional genomics and drug candidate characterisation. She will discuss the integration of CRISPR-Cas9 technologies with these cells, exploring their potential for disease modelling, target identification and validation. Additionally, she will showcase data on co-cultured neural cells forming functional networks, highlighting their importance in understanding disease mechanisms and developing targeted treatments.

PRESENTERS:
Roger Pedersen, *Stanford University, USA*
Matthias Pawlowski, *University of Münster, Germany*
Sejla Salic-Hainzl, *bit.bio, Austria*

STEM CELLS: FROM RESEARCH TO MANUFACTURING AND CLINICAL APPLICATIONS

Presented by: *Corning Life Sciences*

Hall 3, Entrance Level

Corning has been committed to stem cell research for decades, developing the necessary tools that allow you to advance groundbreaking research in the field. Whether your stem cell research requires advanced cell culture surfaces, state-of-the-art vessels, nutrient-rich media, or innovative closed system solutions, look to Corning products to ensure cell viability and reproducibility, and streamline regulatory compliance in your lab. From isolation to analysis, Corning is committed to supporting cutting-edge innovation across the spectrum of stem cell research. Nicolas Andre, Scientific Manager at Corning Life Sciences, will show case examples of how Corning technologies enabled stem cells research and development of new models.

Lucienne Vonk, Xintela CSO, will present Xintela's journey going from an idea in the lab to preclinical studies, GMP manufacturing and clinical studies. Xintela develops medical products in stem cell therapy based on the Company's cell surface marker integrin α10β1. The stem cell marker is used to select and quality-assure the patent-protected stem cell product XSTEM®, which is in clinical development for treatment of knee osteoarthritis and difficult-to-heal leg ulcers. The company produces XSTEM for the clinical studies in its GMP-approved manufacturing facility.

PRESENTERS:
Lucienne Vonk, *Corning Life Sciences, Netherlands*
Nicolas Andre, *Xintela, Sweden*

ADVANCED FUNCTIONAL CHARACTERIZATION OF iPSC-DERIVED IN VITRO MODELS IN DISEASE MODELLING AND ARTIFICIAL INTELLIGENCE

Presented by: *MaxWell Biosystems*

Hall 4, Entrance Level

Two-dimensional (2D) and three-dimensional (3D) cell cultures, designed to mimic in vivo conditions to varying extents, particularly when derived from human induced pluripotent stem cells (iPSCs), serve as a valuable substitute for conventional animal models. These cellular models not only provide a crucial avenue in disease modeling but also offer significant opportunities in artificial intelligence. Our guest speakers will explore innovative applications and methodologies of iPSC-derived neural cultures for modeling neurodegeneration and showcasing the computational capabilities of 3D biological neural networks. Following the seminar, we will engage in an interactive Q&A session to shed light on diverse perspectives regarding the future of iPSC in vitro models.

PRESENTERS:
Feng Guo, *Indiana University, USA*
Marian Hruska-Plochan, *University of Zurich, Switzerland*

INNOVATION ACROSS PLURIPOTENT STEM CELL RESEARCH: FROM REPROGRAMMING TO MANUFACTURING AND ORGANOID IMAGING

Presented by: *Miltenyi Biotec B.V. & Co. KG*

Hall Y1-6, Entrance Level

In the first part of the talk, Sebastian Knöbel, PhD, Senior R&D Manager at Miltenyi Biotec, will guide us through a comprehensive array of solutions that cover the whole journey of pluripotent stem cell (PSC) research from bench to bedside. These include product developments for mRNA-based reprogramming, pluripotent stem cell expansion, differentiation, and characterization. With a focus on PSC workflows, he will showcase how these developments can pave the way for manufacturing in the closed CliniMACS Prodigy® Adherent Cell Culture.

Afterwards, we will have the pleasure of hearing from Stephan Werk, Instrument Sales Specialist Imaging Business, who will introduce light sheet imaging through the lens of the UltraMicroscope Blaze™. Delving further into the topic, he will unveil light sheet imaging capabilities in visualizing organoids, organs, and organisms.
In addition, he will discuss the in-depth analysis of organoids regarding morphology, cellular composition and architecture, made possible by the UltraMicroscope Blaze. He'll also discuss leveraging

in-depth phenotyping to refine cell culture conditions and quality control measures.

PRESENTERS:
Sebastian Knöbel, *Miltenyi Biotec, Germany*
Stephan Werk, *Miltenyi Biotec, Germany*

USING HUMAN PLURIPOTENT STEM CELL-DERIVED NEURAL ORGANOIDS FOR DISEASE MODELING

Presented by: STEMCELL Technologies, Inc.

Hall G1, Level 2

The human brain is a complex system, and neither traditional 2D tissue culture techniques nor animal models can fully recapitulate the complexity necessary for understanding neural pathologies. In contrast, cutting-edge culture models such as human neural organoids contain diverse tissue-specific cell types—progenitors, neurons, and glial cells—thereby offering enhanced physiological relevance. Here, we will introduce the STEMdiff™ neural organoid portfolio, which can generate unguided or guided neural organoids from human pluripotent stem cells (hPSCs) with high efficiency. We will showcase the generation of unguided cerebral organoids for modeling microcephaly and epilepsy, and how to generate guided spinal cord organoids for modeling Amyotrophic Lateral Sclerosis. This presentation will feature our latest state-of-the-art product: Human iPSC-Derived Midbrain Organoids, which are shipped fully differentiated and ready for immediate use. We will showcase the quality of these organoids and their use in a variety of applications, such as studying Parkinson's disease and neuroinflammation.

PRESENTER:
Jinyuan Wang, *STEMCELL Technologies Inc., Canada*

INNOVATION SHOWCASE - THERMO FISHER SCIENTIFIC

Presented by: Thermo Fisher Scientific

Hall X4–9, Level 1

Innovation Showcase details not available at time of publishing.

THURSDAY, 11 JULY | 12:00 PM – 12:30 PM

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

Presented by: FUJIFILM

Hall Y7–12, Level 2

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

PRESENTER:
Ilyas Singeç, *Fujifilm Cellular Dynamics, Inc., USA*

THURSDAY, 11 JULY | 12:30 PM – 1:00 PM

STRATEGIES AND SOLUTIONS FOR ACCELERATING DRUG DISCOVERY AND DEVELOPMENT IN ATMPS AND BIOPHARMA

Presented by: FUJIFILM

Hall Y7–12, Level 2

The concept and development of advanced therapies and innovative biopharmaceutical products face many challenges. In the identification and assessment of novel molecules and therapeutic strategies lack of reproducibility of pre-clinical test methods, costs and time are factors that developers have to factor in to maximize the success of a pipeline. Concurrently, in the optimization of the manufacturing processes for early clinical development, the understanding of the impact of critical raw materials choices in the attributes of the drug product, while keeping scalability and quality in sight, is key to assure manufacturability and a seamless transition to late stage clinical and commercial development phases. Fujifilm offers developers a range of services and products which assist developers in tackling these challenges early on. Together with the expanding manufacturing capacity and expertise of our CDMOs, Fujifilm aims at being a complete solution provider and partner to accelerate the way to market of innovative therapies.

PRESENTER:
Gonçalo Regalo, *FUJIFILM Portugal S.A., Portugal*

THURSDAY, 11 JULY | 6:00 PM – 6:30 PM

REVOLUTIONIZING BRAIN ORGANOID FUNCTIONAL SCREENING: UNVEILING THE POWER OF 3D MICROCHIP TECHNOLOGY FOR ENHANCED LIFE SCIENCES INSIGHTS

Presented by: 3Brain AG

Hall Y7-12, Level 2

Human-induced Pluripotent Stem Cell (hiPSC)-derived brain organoids offer invaluable insights into human brain development and disease mechanisms. However, existing technologies struggle to fully capture their intricate 3D functionality.

Accura-3D represents a groundbreaking microchip-based plate featuring thousands of ultrathin penetrating electrodes designed to record the inner layers of organoids. This innovation enables

a non-destructive, label-free electrical recording method, akin to a "functional microscope": simply retrieve your sample from the incubator, acquire data while visualizing activity in real-time and return it. Fast and easy, it's perfect for lengthy maturation protocols, kinetic studies, or examining organoid dynamics at high resolution.

Furthermore, the design of Accura-3D facilitates the creation of microfluidic channels beneath the sample, enhancing oxygenation and compound delivery.

Powered by our advanced CorePlate™ technology, Accura-3D allows simultaneous recording from 4096 electrodes, enabling the study of network activity at single-cell resolution. This yields data at exceptional spatiotemporal resolution, markedly improving data quality and reducing experimental variability. Consequently, researchers can conduct in-depth analyses of their samples, extract functional connectivity maps, study local field potentials, and calculate over 100 different activity metrics.

At 3Brain, we are dedicated to providing researchers with the most advanced tools for advancing brain organoid research.

PRESENTER:
Sercan Deniz, *3Brain AG, Switzerland*

Biolaminin® TECHNOLOGY: SUPPORTING STANDARDIZATION FOR TRANSLATIONAL SUCCESS

Presented by: BioLamina

Hall G2, Level 2

BioLamina can support scientists throughout their cell therapy development process– from concept to commercialized therapy. Our invited speakers will share their stories of translation success. It will be introduced and moderated by Dr. Graham, from BioLamina.

Dr. Hawkins will will focus on the development and manufacture of genetically stable, clinical-grade iPSC lines from regulatory-appropriate donor starting material.

Dr. Gaskell will share how Rinri Therapeutics has undertaken the journey from academic process to GMP translation. She will outline the fundamentals to building a control strategy to underpin translational success.

Finally, Dr. Eidhof will talk about how Defined culture conditions robustly maintain human stem cell pluripotency via tightly controlled Ca2+ signaling.

PRESENTERS:
Evan L. Graham, *BioLamina, USA*
Terri Gaskell, *Rinri Therapeutics Ltd., UK*
Brian Hawkins, *Pluristyx Inc., USA*
Ilse Eidhof, *Lund University and Karolinska Institutet, Stockholm, Sweden*

STEM CELLS FOR SPECIES DE-EXTINCTION AND CONSERVATION

Presented by: Colossal Biosciences

Hall Y1–6, Level 2

Colossal is a breakthrough bioscience and genetic engineering company that builds radical new technologies to advance the field of genomics. Colossal creates disruptive technologies for extinct species restoration, critically endangered species protection and the repopulation of critical ecosystems that support the continuation of life on Earth. The company is the first to apply CRISPR technology for the purposes of species de-extinction, beginning with the woolly mammoth, Tasmanian tiger, and dodo. Colossal is accepting humanity's duty to restore Earth to a healthier state, while also solving for the future economies and biological necessities of the human condition through cutting-edge science and technologies.

In this presentation we will discuss Colossal Bioscience's recent work reprogramming iPSCs of multiple species, including the Asian Elephant. The reprogramming of these species required novel reprogramming protocols and tools that may be of interest to the broader stem cell community attending ISSCR.

PRESENTER:
Evan Appleton, *Colossal Biosciences, USA*

ENABLING iPSC INNOVATION: EXPLORE EBiSC'S CELLS, SCIENCE, AND DATA

Presented by: European Bank for Induced Pluripotent Stem Cells (EBiSC)

Hall G1, Level 2

Unlock the vast potential of human induced pluripotent stem cell (iPSC) research with the European Bank for iPSCs (EBiSC). Whether you're an experienced researcher or embarking on your first project, EBiSC offers a centralized, not-for-profit repository designed to democratize access to high quality iPSC lines.

With over 950 iPSC lines covering 40+ diseases, healthy controls, isogenic variants and genetically modified 'tool' iPSC lines (e.g. gene reporters and inducible transgenes), EBiSC provides a comprehensive catalogue to support diverse research needs. Additionally, EBiSC provides pre-differentiated neurons to simplify use of iPSC-neurons across diverse applications.

EBiSC prioritizes transparency and collaboration, offering an openly accessible cell line catalogue with detailed datasets on donor demographics, reprogramming methods, and cell line performance. Managed access to genetic and clinical data ensures GDPR compliance whilst still fostering innovation and collaboration. For those seeking to support open science, EBiSC offers the opportunity for deposition of iPSC lines, allowing researchers to contribute to future R&D while retaining legal rights for use.

Join leading EBiSC scientists as they share insights, scientific developments, and an infrastructure to enable iPSC research at industry standards.

PRESENTERS:
Rachel Steeg, *Fraunhofer UK Research Ltd, UK*
Julia Neubauer, *Fraunhofer-IBMT, Germany*
Jeanette Wihan, *Fraunhofer-IBMT, Germany*
Ralf Kettenhofen, *Fraunhofer-IBMT, Germany*

SYNTHETIC PEPTIDE-BASED GROWTH FACTOR ALTERNATIVE AND THEIR APPLICATION

Presented by: PeptiGrowth Inc.

Hall X4–9, Level 1

Conventional growth factors and cytokines used in the manufacturing of regenerative medicine and cell therapy products are facing various challenges such as lot-to-lot quality variations, potential contamination with biological impurities, low stability, and high manufacturing cost. PeptiGrowth Inc. has been working on the development of a series of synthetic peptides that have better qualities, activities and functions than conventional growth factors and cytokines, and that can address and solve all these challenges. These peptides are totally chemically synthesized and animal component-free. PeptiGrowth was established in April 2020 aiming to thoroughly solve these problems and to support the development of industry growth. The alternative peptide for HGF, BDNF, Noggin, VEGF, Wnt3a, EGF, TPO have been already launched in the market and some of their application examples to cell culture models are planned to be introduced in this presentation.

PRESENTER:
Robert Brownlee, *PeptiGrowth Inc., Japan*

EMPOWERING CANCER STUDIES: REVOLUTIONIZING CANCER RESEARCH WITH A UNIVERSAL APPROACH TO ISOLATING STEM CELLS FROM TUMOR BIOPSIES

Presented by: PromoCell GmbH

Hall 4, Entrance Level

Tumors comprise various cell types, with only a small portion being cancer stem cells (CSCs) driving malignancy. Identifying CSCs is challenging due to the lack of specific markers and suitable culture methods. Traditional systems favor non-tumorigenic cells, leading to CSC loss. Mouse models aid less malignant tumor cultures, but they're costly and induce changes. Direct isolation of patient-specific tumor cells in defined culture is preferred. PromoCell's new culture system, the Primary Cancer Culture System, offers universal CSC isolation from patient samples or xenografts. It selectively supports malignant cell traits, preserving original tumor diversity. Unlike traditional media, it depletes benign cells, ensuring CSC enrichment. This system is universally applicable to various CSC types and tumor stages without reliance on uncertain markers. It avoids cytotoxic agents in animal-free environments and is cost-effective. It can enrich CSCs in established cell lines or deplete non-cancerous cells from primary cultures, aiding biomarker identification. Overall, the Primary Cancer Culture System offers a reliable and versatile method for CSC isolation and culture.

PRESENTER:
Alexander Trampe, *PromoCell GmbH, Germany*

ADVANCING CELL THERAPIES BY HARNESSING THE POWER OF STEM CELL BIOLOGY & BIOPHYSICS USING THE C-Stem™ TECHNOLOGY PLATFORM

Presented by: TreeFrog Therapeutics

Hall 3, Entrance Level

TreeFrog Therapeutics is an R&D biotech advancing a pipeline of cell therapies based on a proprietary technology platform, C-Stem™ that overcomes several of the major challenges in cell therapy development - producing safe, high-quality, cell therapies at scale. C-Stem™ is the world's first GMP-compliant cell encapsulation device capable of generating over 1,000 capsules per second. It enables the seeding of up to 10-liter bioreactors and delivers 15 billion cells in a single batch run.

This presentation is the opportunity to learn how TreeFrog crossed the frontiers of biophysics and stem cell biology to invent the GMP-compliant C-Stem™ technology platform and to understand its potential through the presentation of the pre-clinical results achieved to date in their lead program in Parkinson's Disease. The program is on track for a first-in-human trial in 2026 and is already ready for commercial scale.

PRESENTERS:
Maxime Feyeux, *TreeFrog Therapeutics, France*
Joffrey Mianne, *TreeFrog Therapeutics, France*
Clément Rieu, *TreeFrog Therapeutics, France*

FRIDAY, 12 JULY | 12:00 PM – 1:00 PM

HIGH-RESOLUTION GENOME INTEGRITY ASSESSMENT IN STEM CELL THERAPY DEVELOPMENT WITH OPTICAL GENOME MAPPING

Presented by: Bionano

Hall G2, Level 2

This session will focus on the critical role of optical genome mapping (OGM) in assessing the genome integrity and off-target events in cells engineered for therapy development, specifically within the context of stem cell research. The presentation will begin with an introduction by Alicia Bertolotti from Bionano, who will highlight how OGM provides a high resolution, genome-wide, sensitive, and reproducible workflow that can be applied in cell and gene therapy applications. Following the introduction, Dr. Wanda Gerding from the Department of Human Genetics and Lucia Gallego Villarejo from the Department of Molecular Biochemistry at Ruhr-University of Bochum will present findings from their recent publication. Their study leverages the CRISPR/Cas9 gene-editing technology in human induced pluripotent stem cells (hiPSCs) to create cerebral organoids. They found that while the edited hiPSCs retained their pluripotency and could still form organoids without significant phenotypic changes, optical genome mapping revealed various genomic alterations like chromosomal copy number variations. Professor Emeritus Dr. Jeanne Loring from the Scripps Research Institute will then share her expertise on iPSC culture and genome engineering. Her talk will focus on the use of OGM to assess the genomic stability and safety of iPSCs—crucial for their use in disease modeling, drug testing, and potentially therapeutic

applications. Overall, this session highlights the necessity of using high-resolution, unbiased genome-wide analysis workflow of OGM to assess the safety and efficacy of gene-edited models, propelling forward the field of cell and gene therapy research.

PRESENTERS:
Alicia Bertolotti, *Bionano*
Wanda Gerding, *Ruhr-University of Bochum, Germany*
Jeanne Loring, *Scripps Research Institute, USA*

ORGANOIDS: GROW THEM – GLOW THEM. INCREASE YOUR CELL CULTURE CONSISTENCY AND GET THE MOST OUT OF YOUR PRECIOUS SAMPLES WITH BIO-TECHNE REAGENTS

Presented by: *Bio-Techne*

Hall G1, Level 2

As the landscape of organoid research continues to evolve, we explore real-world applications in disease modeling and developmental biology.

Robert Opitz, Institute of Experimental Endocrinology, will discuss using hiPSC-derived cerebral organoids as a model to study the regulatory role of thyroid hormones (TH) during early human cortex development. His team applied single-cell RNA sequencing and RNAscope™ in situ hybridization to identify TH-induced changes in specific neuronal cell types and spatial expression patterns of genes regulating cortical neurogenesis, capturing these changes with high spatial resolution.

Kai Kretzschmar, Julius-Maximilians University, will present on using organoid technology to analyze the cellular and molecular biology of oral epithelia in both steady and disease states. The complex stem cell niches and structural heterogeneity of the oral cavity have left it underexplored compared to skin and gut epithelia.

Generating robust organoid cultures relies on creating consistent and reproducible conditions. Through the provision of high-quality reagents and innovative technologies for spatial biology and automated protein analysis, Bio-Techne enables researchers to increase their culture consistency and get the most out of their precious samples.

Join this Innovation Showcase to learn more about these advancements in organoid research and get recommendations for achieving reproducible culture conditions.

PRESENTERS:
Kai Kretzschmar, *Julius-Maximilians-Universität Würzburg, Germany*
Robert Optiz, *Charité Berlin, Germany*
Simon Sumer, *Bio-Techne, Germany*

KEY REQUIREMENTS FOR EFFICIENT AND LINEAR SCALE-UP OF SHEAR SENSITIVE CELL THERAPY PRODUCTS USING THE VERTICAL-WHEEL BIOREACTOR

Presented by: *PBS Biotech Inc.*

Hall Y7-12, Level 2

Pluripotent stem cells (PSCs) offer promising potential for life-saving therapies, but their clinical adoption faces challenges due to inadequate scalable production processes. Key process hurdles include understanding bioreactor mixing, medium exchange, gas transfer, and cell harvest. Developing reliable methods to scale up manufacturing processes is crucial for robust and reproducible production of clinically relevant lot sizes. Our systematic process development has identified the following key requirements to overcome these challenges: versatile bioreactors with well-characterized hydrodynamics, efficient and scalable MX methods, well characterized gas transfer in large-scale bioreactors, and scalable, low-shear methods for cell harvest, wash, and concentration. The Vertical-Wheel bioreactor-based platform enables scalable production of shear-sensitive PSCs and PSC derived products through planar seed train expansion and scalable 3D expansion/differentiation phases. We successfully scale production from 0.1L to 15L, generating clinically relevant quantities of various cell types (PSCs, PSC derivatives, MSCs, and other primary cells) and growth modalities (microcarriers, aggregates, and single cells). By proactively addressing scale-dependent challenges, we have established reliable large-scale processes for shear-sensitive cell therapy production, facilitating their transition from research to clinical use and enabling widespread access for the population.

PRESENTERS:
Omokhowa Agbojo, *PBS Biotech Inc., USA*
Sunghoon Jung, *PBS Biotech Inc., USA*

THINKING OUTSIDE THE DOME: VERSATILE CULTURE METHODS FROM TISSUE-SPECIFIC STEM CELLS

Presented by: *STEMCELL Technologies, Inc.*

Hall Y1–6, Level 2

Organoids and organotypic cultures are revolutionizing our capability to model tissues in vitro by leveraging the biological capacity of tissue-specific stem cells to generate models that closely mimic the intracellular and intercellular phenomena observed in vivo. These cultures have consequently proven valuable in diverse applications from developmental biology to evaluating antiviral effects and the toxicity of novel drugs. In addition to biological fidelity, technical characteristics such as scalability, access to both apical and basolateral surfaces, automatability, and the ability to incorporate cells from different functional lineages can be critical for being able to use stem cell-based cell cultures in impactful applications. This presentation describes novel protocols and tools, including suspension culture, culture and co-culture at the air-liquid interface, apical-out and other matrix-free methods, and variability-reducing cultureware, and reviews the benefits these adaptations have for automation, culture scale-up, increasing reproducibility and better enabling experimental measurements, including imaging.

PRESENTERS:
Nina Quiskamp, *STEMCELL Technologies Inc., Canada*
Philipp Kramer, *STEMCELL Technologies Inc., Canada*

LARGE SCALE ENGINEERING EFFORTS IN HUMAN iPSCS TO DECIPHER MOLECULAR AND CELLULAR CHANGES IN DISEASE

Presented by: The Jackson Laboratory

Hall 3, Entrance Level

Human induced pluripotent stem cells (hiPSCs) and genome engineering technologies have become powerful in vitro tools to model and study various genetic conditions. In this session, Prof. Bill Skarnes, a recognized leader in stem cell genome engineering and Director of Cellular Engineering at the Jackson Laboratory for Genomic Medicine, will present on 1) the efforts undertaken that led to the identification of KOLF2.1J as a suitable reference hiPSC line, 2) provide updates on the generation of hundreds of variants in KOLF2.1J using high-throughput precision editing as part of the NIH-funded iPSC Neurodegenerative Disease Initiative (iNDI), and 3) introduce the MorPhiC project that aims to develop a catalog of molecular and cellular phenotypes for null alleles for every human gene. In the second half of this session, Dr. Camille Januel, from the Chan Zuckerberg Biohub San Francisco, will discuss her efforts using CRISPR technology to tag organelles with the aim of studying organelle dynamics in various hiPSC-derived cell types. This platform will enable the detailed examination of organelles via live cell imaging and proteomics to better understand cellular impacts of disease-associated mutations.

PRESENTERS:
William C. Skarnes, *The Jackson Laboratory, USA*
Camille Januel, *Chan Zuckerberg Biohub San Francisco, USA*

FRIDAY 12 JULY | 12:00 PM – 12:30 PM

CAREER PATHS IN STEM CELLS AND LEO

Presented by: ISS National Laboratory and Sanford Stem Cell Institute at University of California - San Diego

Hall 4, Entrance Level

The "Career Paths in Stem Cells and LEO" panel at the ISSCR Conference is designed to highlight the contributions and challenges faced by early-career researchers and postdocs in the field of stem cell research conducted in low Earth orbit (LEO). This 30-minute session will feature young scientists and postdoctoral researchers who are at the forefront of this exciting area of research. The panel aims to provide insights into their innovative work, discuss the unique challenges of conducting research in space, and explore opportunities for career development.

Panel Objectives:

1. Highlight Contributions: Showcase the innovative research being conducted by students, postdoctoral researchers, and early-career scientists in stem cell research in LEO.
2. Discuss Challenges: Address the specific challenges faced by early-career researchers working in space-based science and potential strategies to overcome them.
3. Explore Opportunities: Discuss future opportunities for young researchers in stem cell research and space science, including potential collaborations and funding sources.
4. Provide Insights: Offer practical advice and insights on career development in this niche field.

PRESENTERS:
Davide Marotta, *ISS National Lab, USA*
Kriti Kalpana, *New York Stem Cell Foundation, USA*
Jessica Pham, *UCSD, USA*
Pinar Mesci, *Axiom Space, USA*
Livia Luz, *UCSD, USA*

FRIDAY, 12 JULY | 6:00 PM – 6:30 PM

CYTOTRONICS PIXEL: ELECTRICAL IMAGING BASED LIVE CELL CHARACTERIZATION FROM STEM CELLS TO PHENOTYPIC DISEASE MODELS

Presented by: CytoTronics, Inc.

Hall Y1–6, Level 2

CytoTronics' Pixel introduces a revolutionary method for monitoring cell activity, utilizing label-free, non-invasive live cell electrical imaging, thereby surpassing traditional optical imaging techniques. The platform uses a high-density electrode array with single cell resolution (12.5 µm) to capture over 20 functional and morphological parameters, including tissue barrier integrity, cell-surface attachment, cell flatness, and motility through unique field-based impedance measurements. To complement, electrophysiological recordings, combined with the ability to electrically stimulate cells, enables functional assessments of electrogenic cells, such as cardiomyocytes and neurons. Measurements can be taken at intervals ranging from minutes to hours, creating "electrical heat maps" and time-lapsed videos revealing the end-to-end journey of an experiment. Cell features can be assessed at the well level generating a population average, or spatial data can be used to evaluate single-cell behavior and assess heterogeneity in cells and their responses. Further insights into kinetics are derived from time-domain analyses. Assay development, initially conducted in a single plate, can seamlessly scale up to a multi-plate format without compromising time resolution or readout quality. The Pixel represents a groundbreaking tool for characterizing in vitro disease models and streamlining phenotypic screening for therapeutic interventions.

PRESENTER:
Shalaka Chitale, *CytoTronics, Inc., USA*

FRIDAY 12 JULY | 6:00 PM – 7:00 PM

STEM CELL RESEARCH IN SPACE

Presented by: The Stem Cell Podcast

Hall 4, Entrance Level

Join the Stem Cell Podcast for a live show, where hosts Drs. Daylon James and Arun Sharma will discuss research taking place at the International Space Station (ISS). Experts from the ISS will discuss the opportunities and challenges of working with stem cells in a microgravity environment, and what this could mean for the future of stem cell-based therapies.

HOSTS:
Daylon James, *Weill Cornell Medical College, USA*
Arun Sharma, *Cedars-Sinai Medical Center Regenerative Medicine Institute, USA*

GUESTS:
Catriona Jamieson, *University of California, San Diego, USA*
Davide Marotta, *International Space Station, USA*

ON-DEMAND ONLY

This Innovation Showcase will be available to view during the on-demand period following the meeting.

ERC INFO SESSION

Presented by: European Research Council Executive Agency (ERCEA)

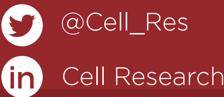
The ERC, set up by the European Union in 2007, is an European funding organization for excellent frontier research. It funds creative researchers of any nationality and age, to run projects based across Europe, in any field of research. The ERC offers 4 core grant schemes: Starting Grants, Consolidator Grants, Advanced Grants and Synergy Grants. With its additional Proof of Concept Grant scheme, the ERC helps grantees to explore the innovation potential of their ideas or research results.

The overall ERC budget from 2021 to 2027 is about €16 billion. To date, the ERC funded more than 12 000 projects and evaluated more than 100 000 research proposals.

In this presentation, the ERCEA representative will go through the ERC's funding schemes as well as provide answers to practical questions such as:

- How can the ERC support research careers?
- What are the main features of the ERC's funding schemes?
- What are the selection criteria?
- How does the selection process take place?
- What are the changes introduced in 2024?

PRESENTER:
Giuliana Gagliardi, *European Research Council Executive Agency, Belgium*



Cell Research

Cell Discovery

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

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

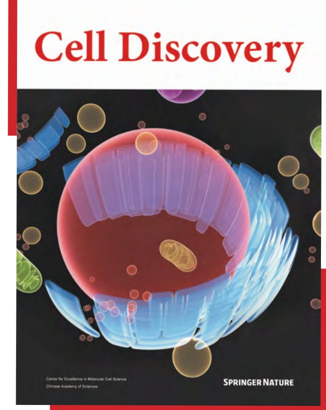
Cell Research is a premium international life science journal with a broad scope in basic molecular and cell biology. The journal publishes original research results that are of unusual significance or broad conceptual or technical advances in all areas of life sciences, as well as authoritative reviews and sharply focused research highlights. The journal aims to provide a highly visible platform for the publishing of best research in the field, alternative to venues such as Cell, Nature, and Science.

www.nature.com/cr

Editor-in-Chief: Dangsheng Li

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

www.nature.com/celldisc



Featured Papers

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

Single-cell RNA sequencing reveals the developmental program underlying proximal–distal patterning of the human lung at the embryonic stage
Cell Research (2023) 33:421–433; https://doi.org/10.1038/s41422-023-00802-6

Dynamic nucleosome organization after fertilization reveals regulatory factors for mouse zygotic genome activation
Cell Research (2022) 32:801–813; https://doi.org/10.1038/s41422-022-00652-8

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

Gut microbiota drives macrophage-dependent self-renewal of intestinal stem cells via niche enteric serotonergic neurons
Cell Research (2022) 32:555-569; https://doi.org/10.1038/s41422-022-00645-7

SPRINGER NATURE

EXHIBIT HALL THEATER

The ISSCR 2024 Exhibit Hall Theater is located next to the Meet-up Hub in the center of Exhibit & Poster Hall, Hall H, Entrance Level in the CCH – Congress Center Hamburg.

WEDNESDAY, 10 JULY

5:40 PM – 5:55 PM

HUMAN PLURIPOTENT STEM CELL (HPSC) PLATFORMS FOR TARGET DISCOVERY AND THERAPEUTIC DEVELOPMENT

Presented by: AstraZeneca

Exhibit Hall Theater Talk details not available at time of publishing.

6:00 PM – 6:15 PM

STREAMLINE YOUR RESEARCH: THE ADVANTAGES OF OUR COMPREHENSIVE GENOMIC INTEGRITY TESTING, CELL AUTHENTICATION, AND MYCOPLASMA DETECTION SOLUTIONS

Presented by: Stem Genomics

Researchers face significant challenges when working with human stem cells, including genomic abnormalities, cell line authentication issues, and bacterial contamination. These factors not only compromise the safety and reliability of research results, but also affect the overall reputation of the field. In response to these concerns, the ISSCR has issued guidelines aimed at mitigating these risks, as outlined in the "Standards for the Use of Human Stem Cells in Research", published in June 2023.

To address these challenges, we offer a comprehensive solution. Our one-stop shop provides fast genomic integrity testing, cell line authentication, and mycoplasma detection services throughout the cell culture lifecycle.

Our 3-in-1 offering includes:

- The iCS-digital™ range, a digital PCR-based karyotyping assay that detects recurrent abnormalities in human stem cell lines (hPSCs, hMSCs and other stem cell types).
- STR (Short Tandem Repeat) testing is used to verify the identity of your cell line.
- The Myco-digital test, specifically designed to target several mycoplasma genomes.

Our fast, standard service delivers results in as little as 3 days and we provide comprehensive yet simple reports that can be easily understood. In summary, our one-stop shop solution offers unparalleled convenience, quality, and support for scientists. Experience the difference today and unlock the full potential of your research.

PRESENTER:
Reda Zenagui, *Stem Genomics, France*

6:20 PM – 6:35 PM

ANALYSIS, IMAGING, AND SORTING OF SPHEROIDS, ORGANOIDS, AND 3D CELL CLUSTERS ON THE COPAS VISION

Presented by: Union Biometrica, Inc.

Large particle flow cytometers from Union Biometrica provide automation for the analysis and dispensing of intact cell clusters. Cells growing in clusters communicate with each other and behave differently than cells grown as monolayers or in suspension. Many cell types will naturally form cell clusters when given the opportunity. These organoids and spheroids are believed to more closely recapitulate a normal physiological state. Research using stem cell clusters, organoids, tumor spheres and other types of 3D cultures are important biological systems for the discovery of signals responsible for normal development as well as the abnormal disease states. The COPAS Vision instrument can characterize these sample types with measurements typical of flow cytometry, like size, optical density, and fluorescence. In addition, the COPAS Vision collects brightfield images of the cell clusters during analysis. The COPAS Vision instrument provides automation for unbiased analysis, handling of large numbers of cell clusters, and dispensing of these sample types in a multiwell plate format. This approach can be used to characterize populations of organoids and organoid bodies of various types. Dispensing to wells of multiwell plates provides an approach to using these 3D cultures in large scale biological assays and screens.

PRESENTER:
Rock Pulak, *Union Biometrica, Inc., USA*

6:40 PM – 6:55 PM

FROM R&D TO MANUFACTURING: THE CELL AS A PRODUCT

Presented by: Eppendorf

Cell and gene therapies represent groundbreaking advancements in personalized medicine and regenerative therapies, employing "living" medications derived from genes, tissues, or cells to combat various diseases. Within this innovative domain, the progress in the development of cell therapies necessities in the need of high quantities and qualities of cells manufactured through precisely monitored and traceable bioprocesses.

As the industry moves more and more in the direction of allogenic cell therapies, single-use stirred-tank bioreactors have emerged as the tool of choice for the scalable production required in the transition from autologous to allogeneic cell therapies. This paradigm shift underscores a future where the scalability and control afforded by cutting-edge bioprocessing technologies are central to harnessing the full potential of cell therapies, marking a significant milestone in the journey from laboratory research to robust manufacturing frameworks.

In this talk, we will highlight the importance of process understanding and control, the implementation of automation and digital solutions significantly improve process performance.

PRESENTER:
Philipp Nold, *Eppendorf SE, Germany*

7:00 PM – 7:15 PM

INNOVATIVE scFAST-seq TECHNOLOGY: ACCESSING ANALYSIS FROM MUTATION, REGULATION TO EXPRESSION

Presented by: Beijing Seekgene Biosciences Co., LTD

Single-cell RNA sequencing (scRNA-seq) is pivotal for exploring cellular heterogeneity, but current methods have limitations. They rely on oligo-dT primers, leading to poor detection of non-polyadenylated transcripts and bias towards RNA ends. To overcome these challenges, we introduce Single Cell Full-length RNA Sequence Transcriptome-seq (scFAST-seq), an innovative, rapid, and cost-effective method. scFAST-seq combines semi-random priming, efficient reverse transcription, and rRNA removal, yielding full-length RNA libraries for up to 12,000 cells in 8 hours. It excels in detecting non-polyadenylated transcripts, covers longer transcript lengths, and identifies more splice junctions. scFAST-seq also shines in non-coding transcript discovery. When coupled with targeted region enrichment, it can detect somatic mutations and tumor cell status. In summary, scFAST-seq outperforms 3' scRNA-seq, offering sensitivity, affordability, and enhanced capabilities crucial for studying cellular heterogeneity and advancing precision medicine.

PRESENTER:
Yunica Liu, *Beijing SeekGene BioSciences Co., Ltd, China*

7:20 PM – 7:35 PM

BIOMANUFACTURING IN LOW EARTH ORBIT: ACCELERATING BREAKTHROUGHS IN REGENERATIVE MEDICINE

Presented by: Axiom Space

Exhibit Hall Theater Talk details not available at time of publishing.

THURSDAY, 11 JULY

3:40 PM – 3:55 PM

MOVING iPSC BASED CGT INTO A GMP SETTING

Presented by: CCRM

CCRM is a not-for-profit regenerative medicine innovation incubator spearheading technology commercialization and clinical translation with a strong focus on induced pluripotent stem cells (iPSC)-based therapies. iPSC-based therapies offer advantages in their potential to address clinical applicability and scalable manufacturing to meet patient demand. As the number of iPSC-based therapies in clinical development is increasing, the industry is seeing significant advancement following decades of the industry's iPSC development efforts. Despite these noteworthy strides, there are still many existing dilemmas to address for sustained progress and commercial viability. CCRM has spent the last 10 years tackling both manufacturing and commercialization challenges in iPSC to produce GMP platform programs to broadly enable iPSC therapy companies. This talk will describe CCRMs platform program and touch on crucial elements impacting efficient and effective clinical translation of these cell therapies. The talk will explore key areas such as material access and readiness, operational intricacies, technological innovations, and standardization for iPSC reprogramming, cell banking, scale-up, gene editing and differentiation all through a manufacturing lens.

PRESENTER:
Lise Munsie, *CCRM, Canada*

4:00 PM – 4:15 PM

UNVEILING VERLOTM: THE FUTURE OF IMAGE-GUIDED CELL SORTING

Presented by: NanoCellect Biomedical, Inc.

This presentation introduces the VERLO™ Image-Guided Cell Sorter, a novel product from NanoCellect. VERLO integrates advanced image-guidance technology with cell sorting, enhancing precision and efficiency. The system captures high-resolution images of individual cells, providing spatial information such as cell morphology and marker localization. Enhanced resolution imaging capabilities allow for the visualization and analysis of subcellular structures and spatial variations in brightfield, darkfield, and fluorescent images. VERLO's gating strategy incorporates imaging features to define cell phenotypes, increasing the precision of cell sorting. The system combines low-pressure microfluidics with single-cell image acquisition to measure a multitude of features from cell images, generating comprehensive multivariate datasets. Applications of VERLO include label-free cell structure analysis, investigation of cell-cell interactions, study of nuclear translocation, and cell organelle staining. This presentation will delve into the technological details and potential applications of the VERLO, allowing researchers to study cells in their physiologically relevant state in downstream processes.

PRESENTER:
Rea Dabelic, *NanoCellect, USA*

4:20 PM – 4:35 PM

SCALABLE HUMAN IPSC-TO-3D BIOPRINTING PIPELINE: SUCCESSFUL LARGE-SCALE PRODUCTION USING AUTOMATED BIOREACTOR SYSTEMS

Presented by: Sartorius Stedim Biotech GmbH

Human induced pluripotent stem cells (hiPSCs) are pivotal in advancing tissue engineering, particularly for transplantation therapy and disease modeling. A sustainable approach to organ-scale tissue engineering demands the production of billions of human cells for bioprinting, especially wholly cellular bioinks. However, scalability challenges in conventional 2D cell culture methods, such as cost, space, and handling constraints, present significant hurdles. To address these issues, we optimized and developed a robust, scalable pipeline to produce hiPSC aggregates (hAs) at 1L scale using an automated stirred-tank bioreactor system for bioprinting applications. These pluripotent aggregates were subsequently differentiated into derivatives of the three germ layers, including cardiac, vascular, cortical, and intestinal organoids. The aggregates were successfully compacted into wholly cellular bioinks for rheological analysis and 3D bioprinting. The 3D bioprinted tissues exhibited high post-printing viability and the potential for vascular and neuronal differentiation, highlighting a promising pathway for billion cell-scale organ engineering. Our next objective is to further expand this process by implementing a 10L scale

bioreactor system to expand and differentiate the cells to enhance cell yield and process efficiency.

PRESENTER:
Maya Fuerstenau-Sharp, *Sartorius Stedim Biotech GmbH, Germany*

4:40 PM – 4:55 PM

CRACKING THE CODE: ACCELERATED DIRECTED DIFFERENTIATION OF HIGH PURITY NEURONS AND NEURAL CREST DERIVATIVES FROM ANY HIPSC LINE

Presented by: Anatomic Incorporated

Anatomic Incorporated's rapid, directed differentiation platform facilitates the manufacture of high-purity sensory neurons, motor neurons, melanocytes, Schwann cell precursors, and spinal dorsal horn neurons from any human induced pluripotent stem cell (hiPSC) line within just 7 to 9 days. These breakthroughs in manufacturing efficiency are due to precision-engineered protocols that use exclusively growth factors and small molecules, without the need for transcription factor overexpression. This allows for the first time efficient, scaled-out manufacturing of any of our cell types from any pluripotent stem cell line, enabling donor-specific disease modeling. This technology is available in the form of differentiation kits, off-the-shelf human cells, or tailored differentiation services.

Our sensory neurons express druggable pain targets and functionally respond to key reference compounds, making them invaluable for pain pathway studies. Our motor neurons, invaluable for the study of ALS, demonstrate robust functionality in electrophysiological assays. Our melanocytes exhibit characteristic pigmentation and gene expression profiles, ideal for investigating skin disorders and cosmetic applications. Our Schwann cell precursors provide the only scalable model for peripheral myelination in conjunction with our neuronal cell types. And finally, our dorsal horn population provide the first-ever humanized in vitro model for central pain mechanisms, including central sensitization.

PRESENTER:
Patrick Walsh, *Anatomic Incorporated, USA*

5:00 PM – 5:15 PM

STREAMLINING CELL THERAPY MANUFACTURING WITH ACROBIOSYSTEMS AS YOUR GMP RAW MATERIAL SUPPLIER

Presented by: ACROBiosystems

Qualifying GMP or cGMP (current Good Manufacturing Practice) raw materials is a responsibility that falls upon cell therapy manufacturers. Finding a good supplier that can support the transition to clinical manufacturing is crucial in regulated manufacturing. As an expert in protein manufacturing, our stringent quality control and regulatory support enables us to offer industry leading GMP proteins for ancillary use. From our perspective, we see numerous considerations in selecting a GMP raw material supplier begins long before entering clinical trials. Early adoption of GMP raw materials can significantly streamline regulatory approval. By establishing robust quality control systems and documentation practices early on, researchers can avoid costly and time-consuming revalidation studies when formal GMP compliance becomes necessary. Additionally, utilizing premium, pre-GMP compliant materials can minimize the burden during transition. These materials often come with established quality control data, simplifying integration into GMP workflows. Our approach is to provide raw materials and solutions that help expedite the regulatory process and pave the way for smoother clinical trials for cell and gene therapies from discovery to the clinic.

PRESENTER:
Anil Kumar, *ACROBiosystems, Switzerland*

5:20 PM – 5:35 PM

SOLUTIONS FOR SINGLE CELL AND ORGANOID SORTING AND ISOLATION

Presented by: Cellenion

Cellenion offers solutions and technologies for controlled cell dispensing with applications in the fields of single cell and single organoids isolation. Our systems allow high throughput, image-based automated dispensing onto any substrates of choice. Together with a range of dedicated consumables, the solutions enable miniaturization of sample preparation protocols on the same instrument before downstream analyses. With no dead volumes and outstanding recovery rates, Cellenion's platforms offer unique capacities for applications including stem cell research, single-cell omics, rare cells, cell line development, microbiology, drug screening and 3D cell model development. Information about Cellenion is available at www.cellenion.com.

PRESENTER:
Fabiana Izaguirre, *Cellenion, France*

FRIDAY, 12 JULY

3:40 PM – 3:55 PM

PROFILING AND PROGRAMMING IN VITRO HUMAN NEURONAL DIVERSITY AT SINGLE-CELL RESOLUTION

Presented by: Parse Biosciences

Human neurons programmed through transcription factor (TF) overexpression model neuronal differentiation and neurological diseases. However, programming specific neuron types remains challenging. Here, we modulate developmental signaling pathways combined with TF overexpression to explore the spectrum of neuron subtypes generated from pluripotent stem cells. We screened 480 morphogen signaling modulations coupled with NGN2 or ASCL1/DLX2 induction using a multiplexed single-cell transcriptomic readout. Analysis of 700,000 cells identified diverse excitatory and inhibitory neurons patterned along the anterior-posterior and dorsal-ventral axes of neural tube development. We inferred signaling and TF interaction networks guiding differentiation of forebrain, midbrain, hindbrain, spinal cord, peripheral sympathetic and sensory neurons. Our approach provides a strategy for cell subtype programming and to investigate how cooperative signaling drives neuronal fate.

PRESENTER:
Hsiu-Chuan Lin, *ETH Zürich, Switzerland*

4:00 PM – 4:15 PM

BEYOND ACADEMIA - SHOWCASING SCIENCE CAREERS WITH SCISMIC

Presented by: Scismic

We've all seen the graph of people that start a science degree and how many stay within academia. While the data may seem disheartening, what the graph doesn't show us are the myriad of career stories about the people that left academia and used their scientific superpowers to continue to make an impact on science and society beyond academia.

In this talk, we'll share some science career stories, and showcase how Scismic's machine-learning powered platform can help uncover the range of alternative research careers that are out there, waiting for you to unleash your creativity and know how on overcoming a range of challenges that we face as a society.

PRESENTER:
Suze Kundu, *Scismic, UK*

4:20 PM – 4:35 PM

NUVISAN - THE SCIENCE CRO

Presented by: NUVIASN ICB GmbH

NUVISAN Innovation Campus Berlin (ICB) GmbH is an Australian-owned, European-based CRO and your go-to partner for all your therapeutic development needs. Our expertise and capabilities span the entire pharmaceutical discovery pipeline from target identification and validation through to phase 3 clinical trials. Experts from our four main functions serve your project to streamline drug development. With flexible entry points, we thrive by working collaboratively with you to achieve both scientific rigor and yield the best possible outcome.

In our presentation, we will give you a brief introduction to the company, an overview of our extensive capabilities (including our unique access to compound libraries not available elsewhere) and examples of how we can work with you to leverage human iPSCs in your drug discovery journey. We also look forward to meeting and sharing more details with you at our booth.

PRESENTER:
Norman Liaw, *Nuvisan ICB GmbH, Germany*

4:40 PM – 4:55 PM

PIONEERING THE FUTURE OF ADVANCED THERAPY AND TARGETED DELIVERY

Presented by: SmartCella

Exhibit Hall Theater Talk details not available at time of publishing.

PRESENTER:
Ricardo Baptista, *SmartCella, Sweden*

CAREER EXPLORATION

FRIDAY, 12 JULY | 3:45 PM – 5:45 PM

Sponsored By: Bayer AG and BlueRock Therapeutics

Career Exploration presentations will take place in the Exhibit Hall Theater and will feature short, 5-15 min presentations from companies seeking to recruit from ISSCR's talented community.

The Exhibit Hall Theater is located next to the Meet-up Hub in the center of the Exhibit & Poster Hall, Hall H, Entrance Level in the CCH – Congress Center Hamburg.

5:00 PM – 5:15 PM **CAREER EXPLORATION WITH BLUEROCK THERAPUTICS**

5:17 PM – 5:27 PM **CAREER EXPLORATION WITH STEMCELL TECHNOLOGIES**

5:29 PM – 5:34 PM **CAREER EXPLORATION WITH THE EUROPEAN RESEARCH COUNCIL (ERC)**

EXHIBIT HALL PUB CRAWL

THURSDAY, 11 JULY | 3:00 PM – 6:00 PM

New this year, the ISSCR will host an "Exhibit Hall Pub Crawl" from 3:00 PM – 6:00 PM on Thursday, 11 July. Enjoy a complimentary beverage or snack from participating exhibitors as you connect with exhibitors, colleagues, and friends!

Participating Exhibitors:

- Axion BioSystems at Booth #1202
- MCRI iPSC Gene Editing and Derivation Facility at Booth #1210
- PBS Biotech at Booth #503
- Society for Laboratory Automation and Screening (SLAS) at Booth #1206

WEDNESDAY, 10 JULY

PLENARY I: PRESIDENTIAL SYMPOSIUM

Sponsored by: Bayer AG and BlueRock Therapeutics
9:30 AM – 11:30 AM
Hall 1, Level 2

9:50 AM – 10:15 AM
ORGANELLAR HETEROGENEITY IN STEM CELL DIFFERENTIATION AND REPROGRAMMING

Goetz, Magdalena, Masserdotti, Giacomo and Merino, Florencia
Physiological Genomics, Ludwig-Maximilian University of Munich (LMU), Germany

Organelles such as centrosomes, nucleoli or mitochondria perform well-known common functions in all cell types. I will discuss their surprisingly large degree of different composition in the context of development, disease and direct reprogramming. For example, the centrosome of human neural stem cells differs by more than half of its proteome from the one in neurons. Such cell type-specific composition also explains why some ubiquitous proteins have organ-specific defects, when mutated, as they are only at a specific organelle in specific cell types. I will explain this for the splicing protein PRPF6 that plays specific roles at the centrosome in neural stem cells. In the context of this I will also discuss unpublished data on the role of neural stem cells in a disease previously consider largely a cell migration disorder. Finally, I will turn to organellar heterogeneity in direct neuronal reprogramming and discuss the role of mitochondria heterogeneity in this process and how to overcome hurdles in this conversion process due to late change of the mitochondrial proteome to a neuronal identity. These data highlight the importance of distinct composition of organelles in a highly cell type-specific manner in development, disease and repair.

Keywords: neural stem cells, neurogenesis, reprogramming

10:15 AM – 10:40 AM
SENSORY PERCEPTION IN DEFINING IMMUNE POTENTIAL: A ROLE BEYOND ITS SENSES

Mukherjee, Tina, Naik, Meghashree, Chatterjee, Nabhonil, G. Aravindhan and Malik, Mansi
Institute for Stem Cell Science and Regenerative Medicine (inStem), India

Our past work has alluded to sensory control of immunity in Drosophila, where our findings elucidated the influence of environmental odor perception in the development of a competent repertoire of blood-progenitor cells. The findings put forth a neuro/immune cross-talk in hematopoiesis, and revealed the impact of environmental odor detection and their sensing modules as determinants of defining immune potential of the animal. Taking forward our observations, we have embarked on an exploration to address the influence of odor based immune priming across systems. My talk will share some of our very recent and unpublished findings on how odors influence mosquito immunity. Given both Anopheles and Aedes, are potent vectors for many parasitic and viral infections, the implications of odor sensing is central to their blood-feeding and vector potential. Our current findings reveal an interesting insight into the implications of sensing human volatiles on their internal physiology and unveils how odors might have led to the emergence of their vector competency. From flies to mosquitoes, the use of model system has lent us with an edge to uncover newer principles and my talk will highlight the sensory routes underlying immune potential.

Keywords: odor, immunity, drosophila, mosquito, vector competency

10:40 AM – 11:05 AM
UNLOCKING THE MYSTERIES OF INCRNA XIST: A JOURNEY OF CONSTANT DISCOVERY

Plath, Kathrin
Biological Chemistry, University of California Los Angeles School of Medicine, USA

Abstract not available at the time of publishing.

11:05 AM – 11:30 AM
CELLS, TISSUES & ORGANS: ASSEMBLING THE HUMAN CELL ATLAS

Teichmann, Sarah
Cellular Genetics, Wellcome Sanger Institute, UK

The 37 trillion cells of the human body have a remarkable array of specialized functions,and must cooperate and collaborate in time and space to construct a functioning human. Harnessing cutting-edge single cell genomics and spatial technologies, my lab has been attempting to understand this cellular diversity, how it is generated during development and how it goes wrong in disease. My talk will illustrate how cell atlasing in three spatial dimensions and across developmental time can accelerate our understanding of how functioning tissues and organs are formed in the body.

Keywords: genomics, spatial technologies, cell atlasing

PLENARY II: NEW TECHNOLOGIES TO ENGINEER AND PHENOTYPE STEM CELL SYSTEMS

1:30 PM – 3:35 PM
Hall 1, Level 2

1:35 PM – 1:55 PM
MOLECULAR BIOGRAPHY OF TUMOR EVOLUTION AND NORMAL HEMTOPOIESIS

Weissman, Jonathan
Biology, Whitehead Institute for Biomedical Research, Howard Hughes Medical Institute (HHMI), Massachusetts Institute of Technology (MIT), USA

Cancer progression is characterized by rare, transient events, which are nonetheless highly consequential to disease etiology and mortality. Detailed cell phylogenies can recount the history and chronology of these critical events including tumor evolution and

metastasis. We have applied our Cas9-based lineage tracer in two setting: (1) the study of metastatic spread in a lung cancer xenograft mouse model revealing the underlying rates, routes, and drivers of metastasis. (2) the study of tumor evolution in a mouse model of non-small cell lung cancer in which an oncogenic Kras mutation and homozygous loss of the P53 tumor suppressor gene is initiated sporadically in the adult mouse. Finally, I will present our recent efforts to exploit somatic accumulation of mutation in mitochondrial DNA as a natural lineage tracing system and our application of this system to the study of human hematopoiesis. The human blood system is maintained through the differentiation and massive amplification of a limited number of long-lived hematopoietic stem cells (HSCs). Perturbations to this process underlie diverse diseases, but the clonal contributions to human hematopoiesis and how this changes with age remain incompletely understood. While recent insights have emerged from barcoding studies in model systems, simultaneous detection of cell states and phylogenies from natural barcodes in humans has been challenging. We have developed a single-cell lineage tracing system based on deep detection of naturally-occurring mitochondrial DNA (mtDNA) mutations with simultaneous readout of transcriptional states and chromatin accessibility. We use this system to define the clonal architecture of HSCs and map the physiological state and output of clones. We uncover functional heterogeneity in HSC clones, which is stable over months and manifests as differences in total HSC output as well as biases toward the production of different mature cell types. We also find that the diversity of HSC clones decreases dramatically with age leading to an oligoclonal structure with multiple distinct clonal expansions. Our study thus provides the first clonally-resolved and cell-state aware atlas of human hematopoiesis at single-cell resolution revealing an unappreciated functional diversity of human HSC clones.

Keywords: hematopoiesis, cancer evolution, lineage tracing, single cell

1:55 PM – 2:15 PM
MODELING SINGLE-CELL DYNAMICS ACROSS MODALITIES, TIME AND SPACE

Theis, Fabian
Computational Health Center, Helmholtz Zentrum München, Germany

Modeling single-cell dynamics across modalities, time and space Single-cell technologies are revolutionizing our understanding of cellular dynamics across biological processes, with exciting impact in our understanding of cell decisions for example in development. However, analyzing and interpreting these data poses computational and conceptual challenges, in particular with recent developments regarding spatio-temporal profiling and lineage tracing. Here, I will discuss AI-based approaches for studying single-cell dynamics and fate decisions across molecular modalities, time, and space, and under perturbations such as drugs of CRISPR knockouts. After a brief review of pseudotemporal ordering and RNA velocity, I will show how optimal transport can be used consistently across biological applications, including temporal, spatial, and spatio-temporal single cell problems, such as aligning multi-modal single-cell data across space and time. Finally I will discuss CellRank and a recent extension beyond RNA velocity to learn dynamics based on any pseudotime, developmental potential, real-time information, and metabolic labeling data. I will finish with an outlook towards generative AI and foundation models and their potential impact in single cell genomics.

Keywords: generative AI, foundation models, single-cell genomics

2:15 PM – 2:35 PM
TOWARD A HOLISTIC AND QUANTITATIVE STEM CELL STATE LANDSCAPE

Rafelski, Susanne[1] and Theriot, Julie A.[2]
[1]Allen Institute for Cell Science, USA, [2]Department of Biology and Howard Hughes Medical Institute, University of Washington, USA

The Allen Institute for Cell Science aims to understand the principles by which human induced pluripotent stem cells (hiPSCs) establish and maintain robust dynamic localization of cellular structures, and how they transition between states during differentiation and disease. Single-cell imaging and analytics are advancing at a breakneck pace via the collection of large-scale, systematic cell image datasets and the application of quantitative image-based data science methods. This is, therefore, a key moment in the arc of biological research to develop methods and analyses that integrate the spatiotemporal observables of the physical structure and organization of the cell with molecular observables, and to update the concept of a holistic cell state. We propose a conceptual framework for holistic cell states and state transitions that is practical and useful and enables integrative analyses and modeling across many data types. We are developing computational approaches to quantify cell organization and cell function within this framework in undifferentiated hiPSCs, differentiated endothelial cells and beyond. We are also exploring appropriate experimental, computational, and theoretical frameworks to test hypotheses within the holistic cell state framework with a focus on our current model system for state transitions being an induced early differentiation EMT along the mesodermal lineage. Along the way we have had to develop image analysis, visual analysis, data analysis, and simulation tools, which we release openly and, in some cases, develop further for greater community accessibility and useability.

Keywords: hiPSC, microscopy imaging, cell organization, cell states

2:35 PM – 3:00 PM
THE JOHN MCNEISH MEMORIAL LECTURE: ENGINEERING NEXT-GENERATION TUMOROIDS FOR PRECISION MEDICINE

Lutolf, Matthias P.
Institute of Human Biology (IHB) F. Hoffmann-La Roche, 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 briefly discuss some of our recent efforts in developing next-generation organoids that are assembled by guiding cell-intrinsic self-patterning through engineered stem cell microenvironments. I will then give some examples of how we are using these technologies to build next-generation patient-based tumor models for precision medicine.

Keywords: organoids, patterning, bioengineering, organoids-on-a-chip, tumoroids, precision medicine

3:03 PM – 3:33 PM
ISSCR 2024 OUTSTANDING YOUNG INVESTIGATOR AWARD PRESENTATION: THE CURIOUS CASES OF PLURIPOTENT STEM CELL ADADPTIONS

Wu, Jun
Department of Molecular Biology, University of Texas Southwestern Medical Center, USA

Pluripotent stem cells (PSCs) harbor the extraordinary ability to self-renew and differentiate into nearly any cell type within an adult body. Over recent decades, the field of PSC research has experienced a renaissance of technological innovation that continually stretches the horizons of what's possible. This includes developing novel culture conditions to maintain diverse states of pluripotency in vitro, the generation of induced pluripotent stem cells (iPSCs), the development of sophisticated in vitro differentiation protocols, and the pioneering of models that mimic early embryos and organs. Such advancements not only propel our understanding of mammalian development forward but also hold the promise to redefine regenerative medicine. PSCs are distinguished not just by their generative potential but by their unparalleled plasticity, allowing them to navigate and adapt to "foreign" environments in ways that challenge their inherent biological limits. These adaptations, although artificial in nature, provide windows into the molecular, cellular, and developmental principles of mammalian biology that remain elusive to traditional scientific inquiry. In my presentation, I will delve into two intriguing instances of PSC adaptations. Through these "curious" adaptations, we can develop novel tools and methodologies, broadening our understanding of the natural world in ways previously unimagined.

Keywords: pluripotent stem cells, inter-species chimeras, mitochondria

THURSDAY, 11 JULY

TRACK: Disease Modeling and Drug Discovery (DMDD)

ADVANCING IN VITRO MODELS

Sponsored by: AstraZeneca
8:15 AM – 9:45 AM
Hall 3, Entrance Level

8:20 AM – 8:40 AM
ENHANCING MATURATION OF STEM CELL-DERIVED CARDIOMYOCYTES

Elliott, David
Stem Cell Medicine, Murdoch Children's Research Institute, Australia

Human pluripotent stem cell (PSC)-derived cardiomyocytes are emerging as a powerful platform for cardiovascular drug discovery and regenerative medicine. However, PSC-derived cardiomyocytes are typically immature, which limits their capacity to predict human biology and disease mechanisms. Here, I will discuss recent research from our laboratory defining mechanisms controlling cardiomyocyte maturation during postnatal development with implications for cardiac disease modelling, drug discovery and regenerative medicine.

Keywords: cardiomyocytes, cardiovascular, regenerative medicine

8:40 AM – 8:50 AM
MALIGNANT PLEURAL MESOTHELIOMA ORGANOIDS ENABLE PERSONALIZED MEDICINE FOR A HIGHLY HETEROGENEOUS DISEASE

Gehart, Helmuth[1], Rossell, Carla[1], Meerang, Mayura[2], Barkmann, Florian[3], NDiaye, Daba[1], Boeva, Valentina[3] and Schmitt-Opitz, Isabelle[2]
[1]D-BIOL, ETH Zürich, Switzerland, [2]Thoracic Surgery, University Hospital Zurich, Switzerland, [3]D-INFK, ETH Zürich, Switzerland

Malignant Pleural Mesothelioma (MPM) is an aggressive cancer of the pleura primarily caused by exposure to asbestos and related minerals in the environment. Despite the high phenotypic heterogeneity of the disease, MPM patients face almost universally poor prognosis with overall 5-year survival rates of less than 10%. In absence of more personalized treatment options, most patients receive Platinum-based doublet chemotherapy with limited success. However, the high patient-to-patient heterogeneity in MPM suggests a high potential for more personalized treatment approaches. However, we currently lack a patient-derived, expandable culture system to develop, validate and match personalized treatment options with patients. In this study, we aimed to close this gap and developed an expandable, defined, 3-dimensional, patient-derived culture system for MPM that maintained tumor heterogeneity on inter- and intra-patient level. We demonstrated that MPM tumoroids could be established across the spectrum of the disease and maintained molecular features of their tumor of origin. We showed that intra-tumor heterogeneity of MPM was primarily driven by sub-clonal CNV variability, which was also correctly maintained in derived tumoroid cultures. By performing the first high-throughput drug screening in MPM, we uncovered new vulnerabilities of MPM tumors among 3200 FDA-approved drugs. Strikingly, the majority of hits were highly patient-specific, which corroborated the urgent need for personalized treatment of the disease. Finally, we demonstrated how MPM-tumoroids could be applied for personalized medicine in clinically relevant timeframes to identify the most promising treatment strategy for individual patients.

Funding Source: This project was funded within the framework of the Sinergia program of the SNSF.

Keywords: cancer, organoid, personalized medicine

8:50 AM – 9:00 AM
MICROENVIRONMENT-MEDIATED MECHANISMS DRIVING TARGETABLE LEUKAEMIA DORMANCY

Pal, Deepali
School of Cell and Molecular Medicine, University of Bristol, UK

Cancer dormancy and treatment resistance remain key unmet clinical challenges in acute lymphoblastic leukaemia (ALL). Biology-driven therapeutics targeting malignant dormancy are urgently needed. This highlights the significance of human cell-based, precision oncology models. The leukaemia bone marrow (BM) niche is dynamic and evolves to preferentially aid survival of leukaemia over haematopoietic cells. However, druggable mechanisms driving niche-mediated dormancy remain unexplored. My group has developed a chemically defined, human-BM-like extracellular matrix, and human induced pluripotent stem cell (hIPSC)-based immune-responsive organoids, to enable ex vivo survival and growth of patient-derived ALL cells. We explore leukaemia dormant and cycling patterns and reveal key differences between osteoblast (OB)-primed versus mesenchymal stem cell (MSC)-primed

ALL. We find that unlike MSC, OB cells support a slow cycling, potentially dormant ALL population. Moreover, dexamethasone treatment-induced ALL dormancy, is a key characteristic of OB-primed ALL. We find that OB-ALL co-cultures produce higher levels of secreted collagen than MSC-ALL co-cultures. In contrast, tunnelling nanotubules (TNT) are formed between ALL and MSC under dexamethasone treatment pressure, and no TNT formation is evident between ALL and OB. Moreover, we reveal reduction in both MSC-ALL TNT formation and dormant OB-primed ALL following treatment with an FDA-approved CDH2 antagonist, ADH-1. ADH-1 treatment in vivo successfully decreased Ki67+ ALL tumour burden. Ultimately, we incorporate hiPSC monocyte derived macrophage into BM-ALL-organoids and show ADH-1-dexamethasone combination in an immune-responsive context to retain efficacy in eliminating OB-primed dormant ALL populations. In summary, we provide proof-of-concept data to discover targetable mechanisms driving niche-mediated cancer dormancy. These insights will enable beginning of investigations into niche-driven therapeutics to be developed within an immune-responsive, precision oncology context. In addition, we have been developing advanced scalable platforms, including 3D-bioprinted drug combination screens and arrayed CRISPR screens, to accelerate treatment discovery in haematological malignancies.

Funding Source: The NC3Rs CCLG

Keywords: leukaemia niche, leukaemia dormancy, hIPSC-derived-niche

9:00 AM – 9:10 AM

FROM CELLS TO CURES: HIPSC-DERIVED INNER EAR ORGANOIDS AND RNA THERARPY TO RESOLVE GENETIC HEARING LOSS

Fousert, Esther[1], Van Den Boogaard, Winnie[2], Van Der Valk, Wouter[2], Lucassen, Amy[2], de Groot, John[1], van Benthem, Peter Paul[1], Kremer, Hannie[3], de Vrieze, Erik[3], Van Wijk, Erwin[3] and Locher, Heiko[2]

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Genetic hearing loss impacts millions worldwide, yet effective treatments remain unavailable, leaving patients reliant on technological aids such as hearing aids or cochlear implants. One major obstacle in therapy development is the lack of representative in vitro models of the human inner ear capable of mimicking genetic inner ear diseases and facilitating treatment validation. In this study, we present a novel approach to address this challenge. We differentiated human induced pluripotent stem cells (hiPSCs) derived from patients with genetic hearing diseases into 3D self-organizing inner ear organoids. Specifically, we focused on two genes associated with significant auditory impairments: USH2A, hereditary deaf-blindness, and COCH, implicated in late-onset genetic hearing loss, the latter presenting a window for intervention. We successfully generated disease-specific inner ear organoids by growing patient hiPSCs through precise modulation with small molecules and growth factors at distinct intervals. With immunohistochemistry we showed the presence of organ-specific cell structures within both USH2A- and COCH-inner ear organoids, including otic vesicles, hair cells and peri-otic mesenchymal cells. We compared the disease-specific inner ear organoids with healthy inner ear organoids through molecular and structural analyses and confirmed the presence of mutant transcripts in the patient-derived inner ear organoids. Moving beyond characterization, we demonstrate the clinical relevance of the model by countering the disease phenotype with antisense oligonucleotides (ASOs) in vitro. ASOs can specifically target and modify RNA transcripts and slow down or halt genetic disease progression. We applied ASOs to late-stage disease-specific inner ear organoids via gymnotic delivery and observed its effect on mutant transcript expression through PCR analysis following ASO therapy. This study underscores the potential of human inner ear organoids as a platform for modelling genetic inner ear diseases and evaluating potential therapeutic interventions. Our findings offer promising avenues for increasing treatment options for individuals affected by genetic hearing loss, offering hope for improved outcomes and quality of life.

Funding Source: This research is funded by the Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW), which is supported by a Novo Nordisk Foundation grant, number NNF21CC0073729.

Keywords: inner ear organoids, disease modelling of genetic hearing loss, RNA therapeutics

9:10 AM – 9:20 AM

ELECTRICAL IMAGING: LIVE CELL CHARACTERIZATION FROM STEM CELL BIOLOGY TO PHENOTYPIC DISEASE MODELS

Chitale, Shalaka, Abbott, Jeffrey and Wu, Vince (Wenxuan)

CytoTronics Incorporated, USA

The emphasis on developing in vitro disease models to support improved drug discovery highlights the necessity for more sophisticated assay readouts. CytoTronics' Pixel electrical imaging platform addresses this gap by providing non-invasive, label-free, live cell, multiparametric readouts. The platform uses a high-density electrode array with single cell resolution (12.5 µm) to capture over 20 functional and morphological parameters, including tissue barrier integrity, cell-surface attachment, cell flatness, and motility through unique field-based impedance measurements. To complement, electrophysiological recordings enable functional assessments of electrogenic cells, such as cardiomyocytes and neurons. Measurements can be taken at intervals ranging from minutes to hours, creating "electrical heat maps" and time-lapsed videos revealing the end-to-end journey of an experiment. Cell features can be assessed at the well level generating a population average, or spatial data can be used to evaluate single-cell behavior and assess heterogeneity in cells and their responses. Further insights into kinetics are derived from time-domain analyses. Assay development, initially conducted in a single plate, can seamlessly scale up to a multi-plate format without compromising time resolution or readout quality. Here, we showcase the capability of utilizing high-dimensional morphological and functional readouts to accurately distinguish pluripotent cells from differentiating cells with a high level of sensitivity. Moreover, we employ iPSC-derived cardiac lineage cell lines to discriminate among heterogeneous cell populations and monitor functional changes in individual populations. The integration of morphological and functional readouts positions the system as a valuable tool for distinguishing disease phenotypes and facilitating phenotypic screening for therapeutic interventions. The versatility of our platform renders

it applicable across diverse biological domains and through all stages of stem cell culture and assay optimization. By seamlessly integrating with established methods, our platform extends the horizon of cellular analysis, enabling researchers to uncover previously hidden dimensions of cellular behavior.

Keywords: high-throughput, live-cell characterization, phenotypic disease models

9:20 AM – 9:40 AM

BUILDING ARCHITECTURE AND COMPLEXITY IN TISSUE-DERIVED LIVER ORGANOIDS

Huch, Meritxell[1], Dowbaj, Anna[2], Sljukic, Aleksandra[1] and Niksic, Armin[1]
[1]Max Planck Institute of Molecular Cell Biology & Genetics (MPI-CBG), Germany, [2]Meritxell Huch Laboratory, Max Planck Institute of Molecular Cell Biology and Genetics, Germany

Modelling liver disease has been hampered by the lack of culture systems that recapitulate disease progression in vitro. In vitro 3D cultures are emerging as novel systems to study development, organogenesis, stem cell behavior and disease ex-vivo. We have developed organoid cultures from healthy and diseased, human and mouse, adult and embryonic tissues for a range of organs including stomach, liver and pancreas. Here, I will focus on our liver organoid work which has allowed, for the first time, the expansion of liver tissue for months in culture, thus defying the established Hayflick limit. However, the cellular composition and tissue architecture of the mammalian liver is remarkably complex, and current tissue-derived organoid models fail to capture this complexity in vitro. By co-culturing liver ductal epithelial organoids and portal mesenchyme we have recently recapitulated the native epithelial -mesenchymal interactions and found that heterotypic cellular interactions between stromal and epithelial cells dictate the behavior of the epithelia, thus reconciling the apparent dichotomy between a pro-regenerative and a pro-quiescent stromal niche. Now, we have expanded on these findings and describe a next generation organoid model composed of adult hepatocytes, cholangiocytes and liver mesenchymal cells that reconstructs the architecture of the periportal liver lobule and is fully functional; they consistently drain bile acid from the bile canaliculi of hepatocytes into the lumen of bile ducts. Strikingly, manipulation of the system allows modelling biliary fibrosis in vitro. Together, we demonstrate that increasing complexity and recapitulating tissue architecture in periportal liver assembloids provides a framework to gain novel biological understanding of the complexity and dynamics of liver physiology and disease.

Keywords: liver, organoids

TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)

AGING AND METABOLIC REGULATION OF TISSUE STEM CELLS

Sponsored by: Stem Cell Reports
8:15 AM – 9:45 AM
Hall Y1-6, Level 2

8:20 AM – 8:40 AM

INVESTIGATION OF THE MECHANISMS OF AGING- AND CANCER-RESISTANCE IN THE LONGEST-LIVED RODENT, THE NAKED MOLE-RAT

Miura, Kyoko
Faculty of Life Sciences, Kumamoto University, Japan

The naked mole-rat (NMR) is the longest-lived rodent and is remarkably resistant to cancer; its maximum lifespan exceeds 37 years, and spontaneous carcinogenesis has rarely been observed. In recent years, the NMR has become an attractive model in various research fields, especially in aging and cancer studies. We have previously identified several mechanisms that contribute to the NMR's resistance to carcinogenesis and its delayed aging. We generated iPS cells from the NMR and demonstrated their unique resistance to tumorigenesis due to species-specific activation of the tumor suppressor ARF and a loss-of-function mutation in the oncogene ERAS. NMR neural stem cells (NSCs) were more resistant to gamma-irradiation than mouse NSCs. Recently, we performed two types of in vivo chemical carcinogenesis induction in NMRs and found that NMR tissues exhibited remarkable resistance to carcinogenic insults through a dampened inflammatory response due to an inability to induce necroptosis caused by loss-of-function mutations in the RIPK3 and MLKL genes. Upon induction of cellular senescence, we found that NMR fibroblasts progressively underwent cell death through activation of the INK4a-RB pathway and unique regulation of serotonin metabolism. This process may serve as "natural senolysis," preventing the accumulation of senescent cells in their tissues. In this symposium, I will present and discuss our findings focusing on the unique regulation of cell death and cellular senescence in this longest-lived rodent.

Keywords: naked mole-rat, cancer, iPS cell, aging

8:40 AM – 8:50 AM

INTRACELLULAR IRON OVERLOAD REWIRES HSC METABOLISM BY IMPAIRING MITOCHONDRIAL FITNESS

Sighinolfi, Silvia[1], Aprile, Annamaria[1], Cassina, Laura[2], Beretta, Stefano[1], Storto, Mariangela[1], Boletta, Alessandra[2], Merelli, Ivan[1] and Ferrari, Giuliana[1]
[1]San Raffaele-Telethon Institute for Gene Therapy, Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) San Raffaele Scientific Institute, Italy, [2]Division of Genetics and Cell Biology, Scientific Institute for Research, Hospitalization and Healthcare (IRCCS) San Raffaele Scientific Institute, Italy

Mitochondrial activity and metabolism control hematopoietic stem cell (HSC) function and fate. Glycolysis preserves HSC quiescence and self-renewal, whereas high rates of glycolysis, oxidative phosphorylation (OXPHOS) and fatty acid oxidation (FAO) drive HSC differentiation. However, little is known about the extrinsic factors regulating HSC metabolism. Iron exerts fundamental roles within the cell but its impact on HSC metabolism is still undetermined. To explore which metabolic pathways are triggered by intracellular iron, we exploited the murine models of β-thalassemia and sickle cell disease, the most common monogenic disorders worldwide characterized by chronic iron overload (IO). In both models, we and other groups previously demonstrated an impaired function of HSCs due to persistence into altered bone marrow (BM) niche. IO HSCs accumulate iron in mitochondria, which correlates with 2-fold increase in ROS content. As a result, mitochondria are impaired, with low mass and mitochondrial membrane potential (MMP). Moreover, in vitro inhibition of OXPHOS did not lower ATP in IO HSCs, suggesting that their metabolism is not OXPHOS-dependent. These data, along with a reduced expression of mitochondrial biogenesis and mitophagy genes, indicate an accumulation of dysfunctional mitochondria in IO HSCs. Further, we proved that iron has a direct effect on the metabolic programs regulating HSC function, as shown

by decreased MMP and OXPHOS in HSCs from wt mice treated with iron dextran in vivo. We found a positive enrichment of glycolytic genes, as Tpi1, Gapdh and Pklr, and a 1.4-fold higher glucose uptake in IO HSCs, indicating increased glycolytic dependency to compensate for reduced OXPHOS. In vivo reduction of iron and ROS rescued mitochondrial dysfunction and more importantly restored the quiescence and self-renewal of IO HSCs, as shown by superior chimerism in secondary transplantation of HSCs from treated IO mice in lethally irradiated recipients. We provided the first demonstration that iron has an active role as extrinsic regulator of HSC metabolism, since abnormal levels can cause oxidative stress which in turn impairs mitochondrial function. Targeting iron or ROS might represent a promising strategy to preserve HSC function, which is particularly important in clinical conditions associated to IO.

Keywords: metabolism, iron overload, hematopoietic stem cell

8:50 AM – 9:00 AM

LONG LIVE THE QUEEN - UNDERSTANDING METABOLISM AND LIFESPAN IN EUSOCIAL SUPER AGERS WITH INDUCED PLURIPOTENT STEM CELLS

Bayerl, Jonathan[1], Pavlovic, Bryan[2], Bernard, Julia[1], Villeda, Saul[3], Holmes, Melissa[4], Dey, Siddharth[5], Finley, Lydia[6], Pollen, Alex[2] and Laird, Diana J.[1]

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A species that defies the evolutionary correlation between lifespan and metabolism is the naked mole-rat (NMR). This mouse-sized eusocial mammal is celebrated for its exceptional and robust 3 decades of lifespan. Similar to ants, NMRs live in colonies with social role specialization, where one queen reproduces while other females remain prepubertal by social suppression. An epigenetic basis for lifespan and reproductive capacity in NMRs is suggested by the substantially increased lifespan of queens compared to genetically-related subordinates and the potential for reproductive activation of subordinates upon queen removal. A stem cell-based model would help to establish the NMR as a robust and unique high-throughput system to interrogate the epigenetic foundations of eusociality and longevity. We devised a novel NMR reprogramming platform and created a collection of bona fide induced pluripotent stem cells (iPSCs) spanning the entire age and the socio-reproductive spectrum -- a “colony in a dish”. The duration of NMR reprogramming is exceedingly long and implies de-accelerated developmental timing (heterochrony), reminiscent of the prolonged 2-week NMR pre-implantation period. We found that primary fibroblasts from queens had discrete phenotypes compared to subordinates: slower growth kinetics, decreased senescence, lower migratory behavior, reduced efficiency of reprogramming and higher frequency of transgene silencing. Persistence of these phenotypes in iPSCs and their differentiated cells indicates that epigenetic memory from the source animal is retained even through reprogramming. The observed queen cellular phenotypes point to de-accelerated cell cycling, quiescence, and epigenetic resilience as strategies for longevity. Global profiling of transcriptome, DNA methylome and metabolites of parental fibroblasts and their derived iPSCs revealed increased dependence of queens on oxidative phosphorylation and other differences discriminating social castes. Based on these data, we propose that crosstalk between metabolism and epigenetic regulators enforces phenotypic states in NMR castes during early development (iPSCs) and adulthood (fibroblasts). Understanding the triggers and basis of this state switch would provide insights into heterochrony, eusociality and aging.

Funding Source: This project is supported by an EMBO postdoctoral fellowship, a PBBR Independent Postdoctoral Fellow Research Award (Sandler Program for Breakthrough Biomedical Research), the Chan Zuckerberg Biohub and the W.M. Keck foundation.

Keywords: naked mole-rat, iPSCs and epigenetic memory, fertility and aging

9:00 AM – 9:10 AM

INDUCIBLE 3D MODELING OF HUMAN BRAIN AGING RECAPITULATES HALLMARKS OF AGING AND IDENTIFIES DISTINCT TRANSCRIPTOMIC SIGNATURES

Gabassi, Elisa[1], Campagnol, Sara[1], Fellner, Lisa[1], Ulz, Julia-Anna[1], Lindlbauer, Theresa[1], Günther, Katharina[1], Grill, Nina[1], Arnst, Nikita[2], Salti, Ahmad[3], Esk, Christopher[4] and Edenhofer, Frank[1]

[1]Genomics, Stem Cell Biology and Regenerative Medicine, University of Innsbruck, Austria, [2]Department of Biomedical Sciences, University of Padova, Italy, [3]University Clinic for Ophthalmology and Optometry, Johannes Kepler University Linz, Austria, [4]University of Innsbruck, Austria

Aging is a complex biological process characterized by the gradual accumulation of molecular and cellular damage over a lifespan and particularly represents a critical factor for functional decline in the human brain. As a matter of fact, the study of the human aged brain faces challenges due to restricted access to patient material. While models derived from induced pluripotent stem cells (iPSCs) would offer a valuable tool for investigating various aspects of human diseases and physiological processes, iPSC-type reprogramming results in the loss of age-related signatures and limits the ability to faithfully recapitulate late-onset conditions in vitro. In this study, we present a novel engineered human iPSCs line that stably and consistently overexpresses Progerin in a Doxycycline (DOX)-inducible manner. We subsequently exploited differentiation into neural lineages, in particular focusing on 3D cortical organoids, to study different aging phenotypes. We found that Progerin overexpression in organoids induces significant key cellular hallmarks of aging, including nuclear lamina aberrations, a 40% reduction in H3K9me3-marked heterochromatin, a two-fold increase in double-strand DNA breaks indicated by γH2Ax and p53BP1, and elevated senescence-associated β-galactosidase activity. Transcriptome-wide analysis revealed a distinctive age-associated gene expression profile with 1,366 dysregulated genes, partially mirroring alterations in neuronal genes previously reported in post-mortem tissue from aged individuals. These include dysregulation of age-associated pathways, such as DNA repair and epigenetic modifications, while also providing novel insights into previously unexplored aging-related transcriptomic profiles. Our results suggest that Progerin overexpression is a proxy for inducing aging in neuronal lineages, allowing for the dissection of early aging events. We anticipate that our system holds promise for further exploration of mechanisms underlying

age-related changes in the human brain and for in vitro modelling of neurodegenerative diseases.

Keywords: human brain aging, inducible aging model, progerin-overexpressing iPSCs

9:10 AM – 9:20 AM

RECONSTITUTION OF A SOFT BONE MARROW ORGANOID FOR HEMATOPOIETIC STEM CELL REJUVENATION

Yue, Rui
School of Life Sciences and Technology, Tongji University, China

Hematopoietic stem cell (HSC) self-renewal and aging are tightly regulated by paracrine factors from the bone marrow niche. However, whether HSC rejuvenation could be achieved by engineering a bone marrow organoid ex vivo remains unknown. Here, we show that matrix stiffness fine-tunes HSC niche factor expression by bone marrow stromal cells (BMSCs). Increased stiffness activates Yap/Taz signaling to promote BMSC expansion upon 2D culture, which is largely reversed by 3D culture in soft gelatin methacrylate (GelMA) hydrogels. Notably, 3D co-culture with BMSCs promotes HSC maintenance and lymphopoiesis, reverses aging hallmarks of HSCs, and restores their long-term multilineage reconstitution capacity. In situ atomic force microscopy analysis reveals that mouse bone marrow stiffens with age, which correlates with a compromised HSC niche, suggesting that bone marrow stiffening is a novel hallmark of hematopoietic aging. To test whether human hematopoietic stem/progenitor cells (HSPCs) could be maintained or rejuvenated by the same strategy, we first show that 3D culture of human BMSCs in GelMA hydrogel significantly up-regulates a panel of HSC niche factors as compared to 2D culture. Next, we perform 3D co-culture of human BMSCs and cord blood HSPCs, and find that the frequency and colony-forming activity of cord blood HSPCs are significantly higher than 2D cultures. Long-term multilineage reconstitution analyses confirm that cord blood HSPCs are maintained after 3D co-culture. Finally, we perform 3D co-culture of human BMSCs and aged bone marrow HSPCs, and show that it promotes lymphopoiesis, reverses aging hallmarks of HSPCs, and significantly restores their multilineage reconstitution capacity. Taken together, our study highlights biomechanical regulation of the HSC niche by BMSCs, which could be harnessed to engineer a soft bone marrow organoid for HSC maintenance and rejuvenation.

Keywords: hematopoietic stem cells, aging, rejuvenation

9:20 AM – 9:40 AM

ROLE OF CIRCADIAN RHYTHMS IN SYSTEMIC SYNCHRONISATION OF TISSUE FUNCTION: IMPACT IN AGING

Aznar Benitah, Salvador
Institute for Research in Biomedicine (IRB Barcelona), Spain

Our body´s circadian clock allows cells to "know" the time of the day and to function according to it. This incredible mechanism ensures that all tissues function in a synchronized manner, which is essential for remaining healthy. Importantly, our clock progressively fails as we age, significantly contributing to neural, heart, and muscle degeneration, obesity, arthritis, loss of vision, infections, and cancer. Within the brain, a region known as the suprachiasmatic nuclei detects changes in light and communicates this information to all tissues in our body, which then communicate between each other to perform their daily functions in a concerted manner. How does this communication network happen? Why it is lost during aging? How does the misalignment of clocks of different tissues contribute to age-related pathologies? In a collaborative effort of several labs we are mapping all systemic nodes that govern clock communication between the central clock in the brain and tissues, and between peripheral tissues, and determine targetable nodes for anti-aging efforts. We have generated different mouse models in which we can restore the clock in any tissue of choice, or combinations of thereof. I will present data obtained from these models that is allowing us to obtain an atlas of the connections that ensure a coherent daily physiology, and of the critical clock nodes that "fail" during aging and that can be targeted to promote a healthier aging.

Keywords: aging, circadian rhythms, physiology, systemic communication

EMERGING NEW THERAPIES

Sponsored by: Healios K.K.
8:15 AM – 9:45 AM
Hall Z, Level 3

8:20 AM – 8:40 AM

A PERSONALIZED iPSC-BASED THERAPY FOR RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA DELIVERED VIA CELL SUSPENSION: PRE-CLINICAL DEVELOPMENT

Bilousova, Ganna
Dermatology, University of Colorado Anschutz Medical Campus, USA

Epidermolysis bullosa (EB) encompasses a subset of genetic skin disorders characterized by severe blistering of the skin. Some of the variants of EB sentence those afflicted to a life of disability and even early death. This is especially true for severe autosomal recessive dystrophic EB (RDEB), which is caused by mutations in the COL7A1 gene, encoding Type VII Collagen. Induced pluripotent stem cells (iPSCs) offer a promising avenue for treating skin disorders such as RDEB. In a clinical scenario, skin cells can be biopsied from a patient suffering from RDEB and then reprogrammed into iPSCs. The iPSCs can then be grown outside the body, genetically corrected, differentiated into new skin stem cells, and administered back to the same patient as an autograft. To date, we have addressed all major challenges in developing this iPSC-based therapy for RDEB and have started adapting our protocols to clinical manufacturing in preparation for filing an Investigational New Drug application with the Food and Drug Administration in the United States. Among major challenges that we have recently addressed is inconsistent differentiation of iPSCs into high-quality iPSC-derived keratinocytes (iKs) and fibroblasts (iFs). To address the inconsistency of iPSC differentiation into skin cells, we now differentiate iPSCs into iKs and iFs via a human skin organoid approach. Thus far, we have generated four genetically corrected RDEB iPSC lines using our patented combined gene editing and reprogramming approach. We have also differentiated these iPSC lines into iKCs and iFBs using our modified organoid-based differentiation procedure. Finally, we have successfully reconstituted the corrected human skin on a mouse model by delivering these genetically corrected RDEB iPSC-derived cells as a suspension in a fibrin-based gel. Our organoid-based differentiation protocol will now allow us to manufacture both genetically corrected RDEB iKs and iFs in one differentiation procedure. In conclusion, if successful and proven to be safe in a clinical trial for RDEB, the iPSC-based therapy could then be easily expanded to monogenic diseases affecting internal organs, where

the difficulty in monitoring adverse effects of an iPSC-based therapy would make them unlikely first targets.

Keywords: skin, induced pluripotent stem cells, cell therapy, organoids, RDEB

8:40 AM – 8:50 AM
TRANSPLANTATION OF ACTH-SECRETING HUMAN PLURIPOTENT STEM CELL (HPSC)-DERIVED PITUITARY CELLS

Kondo, Tatsuma[1], Suga, Hidetaka[2], Taga, Shiori[3], Arima, Hiroshi[2] and Saito, Ryuta[4]
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This study aimed to develop an innovative therapeutic approach for hypopituitarism, a disorder resulting from various hormonal imbalances that lead to diverse symptoms. In particular, the potential life-threatening adrenal crisis caused by lowered ACTH levels is critical. Although the current treatment involves hormone replacement therapy (HRT), its inability to adequately mimic the body's finely tuned hormone fluctuations contributes to a higher risk of sudden death compared with healthy individuals. The goal is to create pituitary hormone-producing cells that respond to the environment similar to the human body, offering a more effective treatment than current HRT. In the clinical application of human pluripotent stem cell (hPSC)-derived pituitary cells, our research group achieved a 100% success rate in generating pituitary–hypothalamus organoids (POs), including ACTH-producing cells from human embryonic stem cells (hESCs). To demonstrate proof of concept for these products, we transplanted pituitary organoids (POs) into the subcutaneous site of mice in which the pituitary gland had been removed (a mouse model of pituitary insufficiency). The transplanted cells were viable for more than six months and increased blood ACTH levels, and the transplantation group showed improved survival compared with the sham surgery group. Based on the results of this research, we created hypopituitary crab-eating macaques and performed the world's first subcutaneous transplantation of human ES cell-derived pituitary organoids using immunosuppressive drugs. The transplanted cells were viable for over a month and increased blood ACTH levels. We successfully transplanted pituitary organoids into primates using immunosuppressive drugs and have taken a step toward the practical application of regenerative medicine for patients with impaired pituitary function. In the future, we will perform subcutaneous cell transplantation in humans to realize regenerative medicine for the pituitary gland.

Funding Source: The Japan Agency for Medical Research and Development (AMED) (grants JP22ek0109524, Japan), Sumitomo Pharma Co., Ltd., Sumitomo Chemical Co., Ltd.

Keywords: pituitary gland, regenerative medicine, cell therapy

8:50 AM – 9:00 AM
BIOENGINEERING AND IN VIVO ASSESSMENT OF 3D BIOPRINTED HUMAN CARDIAC CONDUITS

Bliley, Jacqueline, Ashraf, Faaz, Stang, Maria, Behre, Annie, Dikyol, Caner and Feinberg, Adam
Department of Biomedical Engineering, Carnegie Mellon University, USA

Single ventricle disease (SVD) is a severe congenital heart defect where one of the ventricles forms improperly leading to an impaired ability of the heart to pump fluid. Current treatment approaches require a staged surgical palliation and culminates with a vascular graft known as the Fontan conduit that connects the inferior vena cava directly to the pulmonary arteries. This approach has enabled survival of SVD patients, but leads to significant co-morbidities including elevated central venous pressures, liver fibrosis and ultimately, single ventricle failure. A bioengineered pump in the form of a contractile Fontan conduit could serve the role of the absent ventricle, but few tissue engineering approaches can concurrently build a complex human tissue pump incorporating valves that would be capable assisting with the contractions of the single ventricle. Here, we use Freeform Reversible Embedding of Suspended Hydrogels (FRESH) 3D bioprinting to create a contractile tubular pump composed of (i) collagen and (ii) embryonic stem cell derived cardiomyocytes and primary fibroblasts. These bioprinted pumps demonstrated linear action potential propagation and were able to generate luminal pressures to displace fluorescent beads in vitro. Bi-leaflet valves were also bioprinted within the tube lumen to increase unidirectional pumping and it was demonstrated that tubular pumps could increase pressure within the lumen sufficient to open the valve. Bioprinted pumps were then implanted in the inferior vena cava of mice and demonstrated extensive vascular in-growth and contractility at 6 months post-implantation. This work demonstrates that bioprinted pumps can be fabricated in vitro and then implanted in vivo where they survive and display contractile function over time. Ongoing work is focused on improving pump design (decreasing tubular wall thickness and/or incorporating chamber-like structures) to increase pumping capacity. Long-term, we will be evaluating these bioprinted contractile conduits in larger animal models as we progress towards a right ventricle-like pump for the single ventricle patient, which may not only be applicable SVD but also to other diseases where right ventricular function is impaired.

Funding Source: This work was funded by the Additional Ventures Cures Collaborative the Dowd Fellowship, and the Carnegie Mellon Presidential Fellowship.

Keywords: 3D bioprinting, cardiac tissue engineering, engineered heart muscle

9:00 AM – 9:10 AM
ATTIL12-T CELL THERAPY FOR SIMULTANEOUSLY DISRUPTING STROMA/TUMORS AND INDUCTION OF ENDOGENOUS TCR-T CELLS

Li, Shulin[1], Dotti, Gianpietro[2], Gorlick, Richard[1], Hu, Jiemiao[1], Mahadeo, Kris[3] and Shpall, Elizabeth[4]
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The anticancer effectiveness of both adoptive T-cell transfer and interleukin-12 (IL12) therapy has been demonstrated in clinical settings, but these promising results have been tempered by prominent challenges, including cytokine release syndrome (CRS), trapping the infused T cells in stromal tissues, and poor activity against heterogeneous solid tumors. To address these challenges, we created a novel type of IL12, a cell membrane–anchored and

tumor-targeted IL12, with which to modify T cells. Surprisingly, this modification transforms the biological roles of both IL12 and CAR-T cells. Using T cells expanded from peripheral blood, we modified T cells (including CAR-T cells, TILs, and TCR-T cells) with a membrane-anchored and cell surface vimentin (CSV)–targeted IL12. Infusion of the modified T cells eliminated inflammatory cytokine such as IL6 induction in peripheral tissue, which often occurs with CAR-T cell infusion or IL12-associated injection, thereby eliminating these treatment-associated CRS in treated mice. Of note, the infused T cells not only did not become trapped in tumor stromal tissues but also broke down the stromal tissues (collagen, fibronectin, and cancer-associated fibroblasts) to engage directly with tumor cells, causing remarkable antitumor efficacy in human and mouse large solid tumor models. Thus, these modified T cells are a dual tumor- and stromal cell–targeted therapy for tumors. The underlying mechanism will also be discussed in this meeting.

Keywords: IL12, T cell, stroma

9:10 AM – 9:20 AM

BIOENGINEERING HUMAN HEART VALVE TISSUE FOR CELLULAR REPAIR USING HUMAN PLURIPOTENT STEM CELLS

Voges, Holly K.[1], Durrant-Whyte, Jessica[1], See, Michael[1], Parker, Benjamin[2], Bibby, Kaitlyn[1], Keen, Ellen[1], Rossello, Fernando[1], Ramialison, Mirana[1], Porrello, Enzo[1] and Hidalgo, Alejandro[1]
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Heart valve disease is a rising cause of global cardiovascular mortality that has a projected disease burden expected to reach 4.5 million people in 2030. Heart valves are a critical internal structure that facilitate unidirectional blood flow which is important for maintaining cardiac output. In disease, heart valve tissue undergoes pathological remodelling that is characterised by thickened leaflets, fibrosis and calcification. Currently, end stage heart valve disease is treated surgically to replace damaged tissue with prosthetic material. Biological prosthetics rely on animal pericardium which has different composition and fibre organisation to human heart valve tissue. To date there is no description of a precision-made pluripotent stem cell-derived valve tissue to overcome limitations and shortcomings of animal valve prosthetics. To this end, we have developed a novel protocol to differentiate heart valve interstitial cells from human pluripotent stem cells that mimics the cell identity and extracellular matrix composition of native valve leaflets. We've performed detailed single cell RNA-sequencing and proteomic assessment of differentiated cells and 3-dimensional tissues made using our previously described tissue engineering approaches. In addition, we have determined the physical properties of engineered valve tissues using uniaxial stretch testing. Further, we have demonstrated the utility of the tissues through the absence of calcification following in vivo subcutaneous implantation. Together, this study describes progress towards a stem cell-derived cellular therapy to treat patients with heart valve disease.

Funding Source: The Novo Nordisk Foundation Center for Stem Cell Medicine, reNEW, is supported by a Novo Nordisk Foundation grant number NNF21CC0073729.

Keywords: heart valve, tissue engineering, valve organoid

9:20 AM – 9:40 AM

CELL BASED THERAPY AGAINST LIVER DISEASES, WHAT'S NEW?

Vallier, Ludovic
Berlin Institute of Health at Charite, Germany

Diseases targeting the liver are life threatening, with chronic disorders resulting in life-long treatment, a significant reduction in the quality of life, and progression to hepatocellular carcinoma, a form of cancer with very poor prognosis. Liver transplantation remains the only treatment for acute liver failure and end-stage chronic liver disease. However, transplantation does not represent an ideal treatment as it entails high risk of surgical complications, indefinite immunosuppression associated with severe side effects, and organ dysfunction. More importantly, the number of organ donors remains constant while the demand for liver transplantation has more than doubled in 10 years. Thus, only a limited number of patients can benefit from this therapy and 23% of people die while on the transplantation waiting list. Cell therapy using hepatocytes have been proposed as an alternative for organ transplantation. However, this approach has been limited since adult primary hepatocytes can't be grown in vitro. Human induced Pluriptotent Stem Cells (hiPSCs) could provide an alternative source of liver cells for clinical applications. However, several challenges need to be addressed before clinical applications including the development of culture conditions compatible with GMP requirements, large scale production method, and protocol of differentiation allowing the generation of cells with mature hepatic functions. Here, we describe our recent progress in addressing these limitations through the development of a 3D Bioengineered Liver (BioLive) with sufficient hepatic function to alleviate life threatening liver diseases.

Keywords: human pluripotent stem cells, organoids, liver, hepatocytes, cell based therapy

IMAGING STEM CELL SYSTEMS ACROSS SCALES

8:15 AM – 9:45 AM
Hall G1, Level 2

8:20 AM – 8:40 AM

ILLUMINATING MECHANISMS OF EARLY MOUSE DEVELOPMENT THROUGH ADAPTIVE LIVE-IMAGING

McDole, Kate
Cell Biology, Medical Research Council (MRC) Laboratory of Molecular Biology, UK

Organ systems are complex, three-dimensional structures built for highly specialized tasks, yet arise from a relatively simple, uniform population of cells. Despite this initial simplicity, our knowledge of how early organ systems develop and the role that physical forces play in sculpting these complex tissue structures is extremely limited. Likewise, how dynamic physical environments influence cell fate or behavior is unclear. We use the mouse embryo to investigate these fundamental problems in development. As mammalian embryos are highly sensitive, visualizing their development has been notoriously difficult. We have developed an advanced, adaptive light-sheet microscope to gently and comprehensively image mouse embryo development at single-cell resolution over a course of days. With this system and computational tools, we can track individual cells and analyze patterns of divisions, as well as build dynamic cell fate maps and computational models. We are

able to describe not only the morphogenesis of complex three-dimensional structures such as the formation of the early heart or neural tube, but also follow the migration of specific cell types such as primordial germ cells. PGCs are specified far from their final destination and must travel through diverse tissue environments in the embryo. The dramatic embryo-wide structural changes that occur throughout this journey present significant challenges to studying this migration. Our high-resolution and dynamic imaging approaches provide new insights into the expansive and historically inaccessible journey of PGCs during mouse embryogenesis.

Keywords: mouse development, morphogenesis, light-sheet microscopy

8:40 AM – 8:50 AM
POLYTOPE: A NOVEL EPITOPE BARCODING SYSTEM FOR ENDOGENOUS FATE-MAPPING VIA MULTIPLEXED IMAGING

Postrach, Daniel[1], Frank, Larissa[1], Pritchard, Colin[2], Rodewald, Hans-Reimer[1] and van Rheenen, Jacco[3]
[1]Cellular Immunology, German Cancer Research Center, Germany, [2]Transgenic Core Facility, Mouse Clinic for Cancer and Aging (MCCA), Netherlands Cancer Institute, Netherlands, [3]Division of Molecular Pathology, Netherlands Cancer Institute, Netherlands

Tracing the fate of individual cells and their progeny remains a challenging task. While recently developed DNA barcoding improved in terms of resolution and complexity up to hundreds of thousands of distinct barcodes, imaging-based systems still lack behind. On the other hand, imaging-based fate-mapping tools provide a simple spatial readout, which is difficult to achieve with DNA-based barcoding. Here, we introduce a new epitope barcoding system named 'Polytope', capable of generating 512 unique color-codes. Polytope consists of nine distinct epitope tag cassettes (such as FLAG, HA, …), which are flanked by loxP sites, allowing random excision upon Cre activity (akin to Polylox), thereby generating individual color-codes. These codes are detectable through multiplexed immuno-staining and can be analysed via subsequent image analysis. Moreover, we engineered a knock-in Polytope mouse model, offering the capability for endogenous barcoding of stem cell systems within living organisms in a non-invasive manner. Using Polytope, we generated hundreds of distinct color-codes in vivo and traced the fate of embryonic progenitor cells up until adulthood. Together, Polytope presents an adoptable imaging-based fate-mapping system for high-resolution tracing of clones in the spatial context.

Keywords: fate-mapping, lineage-tracing, barcoding

8:50 AM – 9:00 AM
RECORDING AND RECONSTRUCTING CELLULAR HISTORIES IN DIFFERENTIATING PLURIPOTENT STEM CELLS

Chadly, Duncan M.[1], Frieda, Kirsten[2], Gui, Chen[3], Klock, Leslie[1], Hadas, Ron[1], Horns, Felix[1], Tran, Martin[1], Sui, Margaret[1], Takei, Yodai[1], Bouckaert, Remco[4], Cai, Long[1], Lois, Carlos[1] and Elowitz, Michael[1]
[1]Biology and Biological Engineering, Caltech, USA, [2]Spatial Genomics, USA, [3]Palo Alto Veterans Institute for Research, USA, [4]School of Computer Science, University of Auckland, New Zealand

Dividing and differentiating cells form exquisitely organized structures across every facet of multicellular life. If we could measure the complete history of cells as they divide, change transcriptional state, and move spatially, we could address critical questions about stem cell differentiation and the onset of disease. However, determining cellular ontologies is challenging except in rare cases where continual optical access is possible. Base editing technology enables the generation of stochastic, heritable mutations into genomic DNA while cells grow and divide. Comparing mutation patterns between cells allows reconstruction of their lineage relationships, in a manner analogous to evolutionary phylogenetic reconstruction. Here, we present "baseMEMOIR", a high-density phylogenetic recording system that uses this principle to enable detailed lineage reconstruction over long time scales. We introduce a highly multiplexed, genomically dispersed set of editable targets into mouse embryonic stem cells that can be read out by imaging in situ. This system preserves spatial organization of cells and is compatible with downstream transcriptional measurements. Bayesian phylogenetic reconstruction methods enable us to combine lineage and phenotypic information, recovering the temporal histories of ancestral cells in differentiating mESC colonies. These methods enable analysis of temporal dynamics in diverse biological systems.

Funding Source: NSF GRFP (2139433, D.C.); NIH (T32 GM07616, D.C.; R01 MH116508, M.B.E.; F31EY033220, M.T.); Paul G. Allen Frontiers Group (UWSC10142, M.B.E.); Burroughs Wellcome Fund CASI (1018146, K.F.); M.B.E. is an HHMI Investigator

Keywords: lineage tracing, microscopic imaging, pluripotent stem cells

9:00 AM – 9:10 AM
A SYSTEMS VIEW OF CELLULAR STATE HETEROGENEITY IN HUMAN PLURIPOTENT STEM CELLS

Pfaendler, Ramon, Hanimann, Jacob, Vogt, Sarah, Lee, Sohyon, Wegmann, Rebekka, Mena, Julien and Snijder, Berend
Department of Biology - Institute of Molecular Systems Biology, ETH Zürich, Switzerland

Early human embryogenesis relies on cellular fate transitions of pluripotent stem cells orchestrated by various signalling pathways and spatio-temporal dynamics. Recent advances improved our understanding of the gene regulatory programs underlying these processes, but the determinants governing cellular state heterogeneity of pluripotent stem cells at the single-cell level remain incompletely understood and quantified. Here, we investigate the molecular and morphological plasticity of induced pluripotent stem cells (iPSCs) upon drug perturbations using high-content imaging, computer vision, and high-throughput molecular profiling. Using a novel self-supervised deep learning approach, we comprehensively quantify the single-cell morphological heterogeneity of iPSCs across diverse drug mode-of-actions, which groups iPSCs in distinct morphological subgroups with varying degrees of pluripotency. In addition, we perform multiplexed transcriptomics and high-throughput proteomics across 31 perturbation conditions in iPSCs derived from 4 healthy donors, revealing condition-specific expression dynamics of key proteins and transcripts regulating pluripotency and early differentiation. Association of this multimodal molecular data with iPSC morphological states links iPSC morphologies to different cellular fate trajectories. Globally, this suggests that upon different signalling cues, iPSCs navigate an intricate path between simultaneously changing cellular morphology and fate. Overall, our study provides insights into how morphological states shape cellular fate commitment in a cellular system characterised by maximal developmental plasticity.

Funding Source: We gratefully acknowledge funding from the Swiss National Science Foundation (PP00P3_163961 and PP00P3_194809) and the ETH Zurich (ETH-28 20-1).

Keywords: cellular state heterogeneity, high-content imaging, multi-omics

9:10 AM – 9:20 AM

TRACKING AND MITIGATING IMPRINT ERASURE DURING INDUCTION OF NAÏVE HUMAN PLURIPOTENCY

Fischer, Laura[1], Meyer, Brittany[1], Reyes, Monica[2], Zemke, Joseph[1], Harrison, Jessica[3], Jueppner, Harald[2], Dietmann, Sabine[4] and Theunissen, Thorold[1]

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Naïve human pluripotent stem cells (hPSCs) model the pre-implantation epiblast. However, parent-specific epigenetic marks (imprints) are eroded in naïve hPSCs, which represents an important deviation from the epiblast in vivo. Imprints regulate gene expression and are essential for controlling embryo size, placental growth, and neural development. In addition, dysregulation of imprinted gene expression can manifest itself clinically as intellectual disability, behavioral abnormalities, and an increased risk of certain cancers. To track the dynamics of imprint erasure during primed-to-naïve resetting in real time, we established a dual-colored fluorescent reporter at both alleles of the imprinted SNRPN locus. We found that during resetting, SNRPN expression became biallelic in most naïve cells and biallelic SNRPN expression was irreversible upon differentiation. Importantly, this live-cell reporter enabled us to evaluate chemical and genetic strategies to mitigate imprint erasure. Removal of ERK inhibition during naïve resetting prevented imprint erasure, but failed to induce a bona fide naïve identity. In contrast, decreasing the level of ERK inhibition delayed the overall loss of imprinting in naïve hPSCs. We also evaluated the impact of various maternal effect genes with suspected imprint-protective activity and found that overexpression of the KRAB zinc finger protein ZFP57 protected a subset of imprints during naïve resetting. Overall, imprint reporter activity allowed us to predict global DNA methylation levels in experimental conditions, serving as an efficient alternative to whole-genome sequencing. This work has generated a versatile tool for tracking both locus-specific imprinting and global DNA methylation levels at single-cell resolution, which is valuable for enhancing epigenetic stability during human pluripotent state transitions.

Funding Source: NIH Director's New Innovator Award (DP2 GM137418), Shipley Foundation Program for Innovation in Stem Cell Science, Edward Mallinckrodt, Jr. Foundation Grant, WU Children's Discovery Institute, Covey Graduate Student Fellowship

Keywords: imprinting, naïve pluripotency, DNA methylation

9:20 AM – 9:40 AM

HIGHLY MULTIPLEXED IMAGING OF IN SITU TUMOR ECOSYSTEMS TOWARDS PRECISION MEDICINE

Bodenmiller, Bernd

University of Zurich and ETH Zurich, Switzerland

Cancer is a tissue disease. Heterogeneous cancer cells and normal stromal and immune cells form a dynamic ecosystem that evolves to support tumor expansion and ultimately tumor spread. The heterogeneity of this dynamic system is the main obstacle in our attempts to treat and heal the disease. The study of the tumor ecosystem and its cell-to-cell communications is thus essential to enable an understanding of tumor biology, to define new biomarkers to improve patient care, and ultimately to infer for each patient a tailored therapeutic rout. To study and understand the workings of the tumor ecosystem, highly multiplexed image information of tumor tissues is essential. Such multiplexed images will reveal which cell types are present in a tumor, their functional state, and which cell-cell interactions are present. To enable multiplexed tissue imaging, we developed imaging mass cytometry (IMC). IMC currently allows to visualize over 50 antibodies and DNA probes simultaneously on tissues with subcellular resolution. To exploit multiplexed tissue imaging data for research and translation to patients, we have validated hundreds of antibodies, developed multiple computational toolboxes (histocat, cytomapper, steinbock) and introduced novel concepts to describe tissues (cellular neighborhoods, communities and motives). Application of IMC to large patient cohorts of revealed novel spatial biomarkers of disease progression and whether patients might benefit from immunotherapy. Application in an observational clinical trial showed clear clinical usefulness and already indicates benefit for patients.

Keywords: highly multiplexed imaging, precision medicine, imaging mass cytometry

TRACK: Pluripotency and Development (PD)

INTEGRATED STEM CELL MODELS OF EARLY EMBRYO DEVELOPMENT

Sponsored by: Stem Cell Reports

8:15 AM – 9:45 AM

Hall 4, Entrance Level

8:20 AM – 8:40 AM

ADJUSTING MAMMALIAN DEVELOPMENTAL TIMING

Bulut-Karslioglu, Aydan

Max Planck Institute for Molecular Genetics, Germany

Dormancy is an essential biological process for the propagation of life forms through generations and stressful conditions. Early embryos of many mammals are preservable for weeks to months within the uterus in a dormant state called diapause, which can be induced in vitro through mTOR inhibition. Whether the evolutionary response to diapause is conserved in humans is not known. Here I will summarize our recent efforts in understanding the mechanisms of this biological process and its relevance to human biology.

Keywords: dormancy, blastoid, timing

8:40 AM – 8:50 AM

COMPLETE HUMAN PERI-GASTRULATION STEM CELL DERIVED EMBRYO MODELS WITH ENHANCED DEVELOPMENTAL POTENTIAL AND EFFICIENCY

Oldak, Bernardo, Comar, Mehmet Yunus and Hanna, Jacob

Molecular Genetics, Weizmann Institute of Science, Israel

Studying the post-implantation and peri-gastrulation stages of human development have been a challenge for the scientific community due to ethical and technical limitations with obtaining and utilizing such samples for experimental research. Recently, we have reported a system that demonstrates the capability of

human (HENSM) naïve stem cells without genetic modifications to be primed to the three extraembryonic lineages present in the peri-implantation embryo: induction of trophectoderm (TE) alone and co-induction of primitive endoderm (PrE) and extraembryonic mesoderm (ExEM) cells. Furthermore, the co-aggregation of these lineages with naïve PSCs allowed after 8 days the formation of whole structured embryo models that mimic human development up to day 14 post-fertilization. As the efficiency reported for validated day 14-like human SEMs was below 1% and the most developed SEMs did not proceed through gastrulation, here I described our ability to overcome critical obstacles that underlie the latter limitations. This includes (i) improving of quality and high purity of the PrE induction with ability to contribute specifically to the yolk sac structure through a novel induction regimen, (ii) our new ability to separately induce pure ExEM cells from naïve PSCs that can functionally facilitate remodelling of the chorionic space. which represents one of the main hallmarks of day 14 stage (iii) devising new aggregation platform and culture conditions that facilitate the expansion and contribution of cytotrophoblast cells to the aggregates to the point of colocalization with extra embryonic mesoderm for further formation of the primary villi (iv) incorporating static and dynamic whole embryo culture platforms. Collectively, these new modifications and additions to the human SEM protocol mentioned above, facilitate the progression of our human SEMs towards and through gastrulation and with significantly higher efficiencies. This system will likely enable grasping key developmental processes in human gastrulation within the context of a more harmonized embryo-like structure, that incorporates all expected lineages in a more robust and high-quality embryo model system that reflects more advanced complete developmental models and stages than previously achieved.

Keywords: human peri-gastrulation development, integrated human embryo models, stem cell derived embryo models

8:50 AM – 9:00 AM

A SIGNALLING RHEOSTAT CONTROLS CHROMOSOME SEGREGATION FIDELITY DURING EARLY LINEAGE SPECIFICATION AND NEUROGENESIS BY MODULATING REPLICATIVE STRESS

de Jaime-Soguero, Anchel[1], Hattemer, Janina[1], Haas, Alexander[2], Bufe, Anja[1], Di Marco, Barbara[3], Böhly, Nicolas[2], Landry, Jonathan[4], Schoell, Brigitte[5], Rosa, Viviane[6], Villacorta, Laura[4], Baskan, Yagmur[1], Androulaki, Stefania[1], Trapp, Marleen[7], Das, Biswajit[8], Benes, Vladimir[4], Shahbazi, Marta[6], Jauch, Anna[5], Engel, Ulrike[9], Patrizi, Annarita[7], Sotillo, Rocio[10], Bageritz, Josephine[1], Alfonso, Julieta[3], Bastians, Holger[2] and Acebron, Sergio[1]
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The development and homeostasis of organisms rely on the correct replication, maintenance and segregation of their genetic blueprints. How these intracellular processes are monitored across generations of different human cellular lineages, and why the spatio-temporal distribution of mosaicism varies during development remain unknown. Here, we identify several lineage specification signals that regulate chromosome segregation fidelity in both human and mouse pluripotent stem cells. Through epistatic analyses, we find that that WNT, BMP and FGF form a signalling "rheostat" upstream of ATM that monitors replication fork velocity, origin firing and DNA damage during S-phase in pluripotency, which in turn controls spindle polymerisation dynamics and faithful chromosome segregation in the following mitosis. Cell signalling control of chromosome segregation fidelity declines together with ATM activity after pluripotency exit and specification into the three human germ layers, or further differentiation into meso– and endoderm lineages, but re-emerges during neuronal lineage specification. In particular, we reveal that a tug-of-war between FGF and WNT signalling in neural progenitor cells results in DNA damage and chromosome missegregation during cortical neurogenesis, which could provide a rationale for the high levels of mosaicism in the human brain. Our results highlight a moonlighting role of morphogens, patterning signals and growth factors in genome maintenance during pluripotency and lineage specification, which could have important implications for our understanding on how mutations and aneuploidy arise during human development and disease.

Keywords: pluripotency and lineage specification, morphogens and patterning signals, genome stability and DNA replication stress

9:00 AM – 9:10 AM

METABOLIC REWIRING UNDERPINS HUMAN TROPHOBLAST INDUCTION

Van Nerum, Karlien[1], Wenzel, Anne[1], Argemi Muntadas, Lidia[2], Kafkia, Eleni[1], Lavro, Viktoria[1], Roelofsen, Annina[1], Drews, Antar[1], Bages Arnal, Sandra[1], Zhao, Cheng[3], di Sanzo, Simone[4], Völker-Albert, Moritz[4], Petropoulos, Sophie[3], Moritz, Thomas[2] and Zylicz, Jan[1]
[1]ReNEW, Novo Nordisk Foundation Center for Stem Cell Medicine, University of Copenhagen, Denmark, [2]CMBR, Novo Nordisk Foundation Center for Basic Metabolic Research, University of Copenhagen, Denmark, [3]Department of Clinical Sciences, Intervention and Technology, Karolinska Institutet, Sweden, [4]EpiQMAx GmbH, Germany

Early human development is driven by a sequence of molecularly interconnected transcriptional, epigenetic, and metabolic changes. Certain metabolites function as signalling molecules affecting the activity of chromatin modifying enzymes. It remains unclear, how such non-canonical function of metabolism coordinates specific cell-state changes especially in early development. Here we uncover the occurrence of a significant metabolic rewiring, which takes place when naive human embryonic stem cells (nESC) are induced towards human trophoblast stem cells (hiTSC). In vivo transcriptomic data further confirmed that metabolic rewiring likely takes place in the nascent trophectoderm (TE). We show that the intracellular level of a specific metabolite is an important regulator of TE fate acquisition. Indeed, a metabolic treatment of nESC increases their competence towards TE-like cells during hiTSC induction. Moreover, metabolite supplementation also increased the robustness of blastoid polarisation, marking the first step of TE induction. Surprisingly, the treatment does not affect global histone methylation levels in nESC, but rather leads to decreased H3K27ac and weakening of the pluripotency network. Further functional

assays confirmed that both reduced histone acetyltransferase activity and increased levels of a specific metabolite promote nESC competence towards the TE-lineage but not extraembryonic mesoderm. We propose that this metabolite regulates pluripotency through deacetylation, thus creating a positive feedback loop promoting the induction of TE fate.

Keywords: early human development, metabolism and epigenetic interplay, cell fate acquisition

9:10 AM – 9:20 AM

ESSENTIAL FUNCTION OF AN HOMINOID-SPECIFIC TRANSPOSON IN HUMAN PREIMPLANTATION DEVELOPMENT

Fueyo, Raquel and Wysocka, Joanna

Chemical and Systems Biology, Stanford University, USA

Preimplantation development spans the time between fertilization and the blastocyst invasion of the uterine wall. Despite seemingly morphological conservation, preimplantation development diverges among mammalian species in terms of gene expression patterns, timing, and precise regulation of pathways involved in lineage specification. Much of our understanding of early mammalian development comes from studies in mouse embryos. However, performing similar experiments in humans is limited by the scarcity of human embryos and the ethical and technical challenges of their functional manipulation. Recent progress in the 3D models of human preimplantation embryos, the so-called blastoids, offers unique opportunities for functional studies of human-specific features of early development. One key feature of preimplantation development is the widespread activation of endogenous retroviruses (ERVs) also known as LTR retrotransposons for their Long Terminal Repeat regulatory elements. ERVs are DNA remnants of past exogenous retroviral infections that occurred in the germline and subsequently became fixed in the population. ERVs comprise over 8% of the human genome and are largely species- or clade-specific. Furthermore, due to an intrinsic regulatory capacity of the LTRs, they are often coopted for novel cis-regulatory functions as enhancers or alternative promoters, thus diversifying the cis-regulatory control of gene expression in a species-specific manner. We have previously reported that a hominoid-specific ERV called HERVK is transcriptionally active during human preimplantation development from the 8-cell to the blastocyst stages and that its LTR elements, named LTR5Hs, function as long-range enhancers in pluripotent cells. We have now pioneered genetic and epigenetic functional manipulation of HERVK in human blastoids and assessed its impact on blastoid formation as a proxy for understanding its role in the human blastocyst. Our work has uncovered the essentiality of HERVK during human blastoid formation and its influence on transcriptome diversification, epiblast identity, and lineage specification. Altogether our results shed light on human-specific aspects of early embryogenesis and reveal a potential non-neutral contribution of ERVs to mammalian cis-regulatory networks.

Keywords: blastoids, endogenous retrovirus, pluripotency

9:20 AM – 9:40 AM

A COMPREHENSIVE HUMAN EMBRYOGENESIS REFERENCE TOOL USING SINGLE-CELL RNASEQUENCING DATA

Petropoulos, Sophie[1], Zhao, Cheng[2], Plaza Reyes, Alvaro[3], Schell, John P.[4], Weltner, Jere[5], Ortega, Nicolas[2], Zheng, Yi[6], Bjorklund, Asa[7], Baque, Laura[7], Sokka, Joonas[5], Trokovic, Ras[5], Cox, Brian[8], Rossant, Janet[9], Fu, Jianping[10] and Lanner, Fredrik[4]

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Stem cell-based embryo models provide unprecedented experimental resources for investigating early human development. The effectiveness of these models depends on how accurately they replicate the molecular, cellular, and structural characteristics of in vivo embryos. To validate human embryo models, researchers have turned to single-cell RNA sequencing for unbiased transcriptional profiling. However, a comprehensive dataset of human embryo single-cell RNA data, which could serve to evaluate human embryo models, is currently unavailable. We have now developed such a reference by integrating six previously published human datasets that cover developmental stages ranging from the zygote to the gastrula. Lineage annotations have been compared and validated using both human and non-human primate datasets. Utilizing a stabilized UMAP, we have created a web-based tool where researchers can project their own datasets onto the reference dataset and annotate them with predicted cell identities. This reference tool has been employed to examine several recent human embryo models, revealing the potential for misannotation in the absence of relevant references. We hope this tool will facilitate development of more refined systems to study early human embryogenesis and benchmark these against the human embryo.

Keywords: embyro, single-cell RNA, human, reference map

TRACK: Pluripotency and Development (PD)

PLENARY III: EXPLORING THE BASIC PRINCIPLES OF DEVELOPMENT USING STEM CELLS

10:00 AM – 11:45 AM

Hall 1, Level 2

10:20 AM – 10:40 AM

INVESTIGATING THE MYSTERY OF HUMAN TROPHECTODERM EXPANSION FOR IMPLANTATION

Nichols, Jennifer[1], Corujo-Simon, Elena[2], Bates, Lawrence[2], Yanagida, Ayaka[3] and Jones, Kenneth[4]

[1]MRC Human Genetics Unit, University of Edinburgh, UK, [2]College of Medicine and Veterinary Medicine, UK, [3]University of Tokyo Institute of Medical Science, Japan, [4]University of Cambridge, UK

Mammalian embryos implant in the uterus as blastocysts, comprising an inner cell mass that segregates into epiblast and hypoblast, surrounded by trophectoderm, confined to the polar region by expansion of the blastocyst cavity. The mode of implantation varies significantly between species. Murine embryos are cushioned within decidual swellings until the onset of organogenesis, whereas human blastocysts rapidly attach to the uterine wall via polar trophectoderm. From our licenced bank of human embryos left over from IVF programmes from several assisted conception clinics, we observed that polar trophectoderm becomes multi-layered soon after cavitation, a possible prerequisite for rapid uterine invasion to secure the developing embryo. Using

sequential contrasting fluorescent labelling of outer cells, applied one day apart, we discovered that at least the majority of internal trophectoderm arises primarily by inward displacement from the polar trophectoderm. If allowed to develop until late day 7, the expected time of implantation, some embryos acquire vastly enlarged inner masses, accompanied by reduction of the blastocoel and stretching of the remaining mural trophectoderm. Human mural trophectoderm has been reported to undergo mitosis to supply the polar region, in contrast to the mechanism used by the mouse. We cannot determine if this phenotype arises because the embryos were cultured beyond their optimal implantation time, or if they were already defective. In our hands, around 30% of thawed blastocysts exhibit more severe trophoblast overgrowth, becoming solid spheres by D7. We hypothesise that embryos destined to acquire this abnormality, if transferred to the uterus, could cause early pregnancy losses, or formation of hydatidiform moles. We are characterising this phenotype in donated embryos and modelling it in stem cell-based ‘blastoids’. The goal is to develop culture regimes to recognise non-invasively the onset of trophoblast overgrowth, and ultimately to eliminate this aberrant phenotype from embryos destined for transfer.

Keywords: blastocyst, trophectoderm, human

10:40 AM – 11:00 AM
EPIGENETIC MECHANISMS OF CELLULAR PLASTICITY AND REPROGRAMMING TO TOTIPOTENCY

Torres-Padilla, Maria Elena
Helmholtz Zentrum München, Germany

Totipotency is a fundamental cellular feature. In mammals, the terminally differentiated sperm and oocyte fuse to create a totipotent zygote upon fertilisation. The mechanisms underlying the epigenetic reprogramming towards totipotency are not fully understood and the molecular features of totipotent cells remain scarce. Embryonic cells of the early embryo remain totipotent only for a restricted time window. During this time, embryonic cells are characterised by an atypical chromatin structure and reactivation of specific families of retrotransposons. To address how the expression of these elements is regulated during the transition between totipotent and pluripotent states, we first examined histone modifications and chromatin structure in early mouse embryos. Based on this analysis, we have begun to decipher key molecular regulators of repetitive elements in the embryo and how heterochromatin first forms at repeats during this reprogramming process in vitro and in vivo. We will present our latest results that reveal a new role for chromatin integrity in promoting epigenetic reprogramming and sustaining molecular features of totipotent cells in vivo. In addition, we will discuss the potential conservation of these findings across mammals beyond the mouse model.

Keywords: totipotency, epigenetics, reprogramming, mouse embryo, early development, cellular plasticity

11:00 AM – 11:20 AM
THE MECHANISMS AND EVOLUTION UNDERLYING PLURIPOTENT STEM CELLS ACROSS ANIMALS

Srivastava, Mansi
Organismic and Evolutionary Biology, Harvard University, USA

Wound repair and regeneration are fundamental features of animal biology. In humans and other vertebrates, virtually all wounds can be healed yet only some will result in regeneration (e.g., liver in humans, limbs in axolotls). Strikingly, many invertebrate species (e.g. cnidarians, acoels, planarian flatworms) undergo whole-body regeneration, replacing any missing cell type. A major correlate of the difference in regenerative capacity between invertebrates and vertebrates is the presence of pluripotent stem cells in adult animals. Many regenerative invertebrates harbor adult pluripotent stem cells (aPSCs) that can differentiate into any cell type. While pluripotent cells are present in vertebrate embryos, these cells are absent in adult animals. Studies of embryonic stem cells (ESC) and induced pluripotent stem cells (iPSCs) have uncovered mechanisms of pluripotency in early embryos and in cell culture, yet major gaps in knowledge remain. It is unknown which mechanisms enable an embryo to form pluripotent cells that can be retained into adulthood, and which mechanisms regulate pluripotent cells in vivo in adult animals. Studies of regenerative invertebrates are needed to answer these central questions about pluripotent cells. I will discuss how my laboratory applies a diversity of approaches including functional genomics, single-cell RNA-sequencing, and transgenesis in the acoel worm Hofstenia miamia to address these questions.

Keywords: pluripotent stem cell, regeneration, invertebrate, acoel

11:20 AM – 11:45 AM
THE ANNE MCLAREN MEMORIAL LECTURE: PLURIPOTENT STEM CELL MODELS OF GASTRULATION: DRAWING LINES

Martinez Arias, Alfonso
MELIS, Universitat Pompeu Fabra Barcelona, Spain

Gastrulation is the process whereby the mass of cells that results from fertilization is shaped into the body plan of an organism. The 14 day rule points to the initiation of this process in humans as the moment at which a human embryo requires legal protection. Anne mcLaren played a key role in this statement by famously drawing a line at that moment. Over the last few years, advances in reproductive and developmental biology have led to the consideration of extending this rule to postgastrulation stages However, an alternative to study gastrulation has emerged from the realization of the self organizing abilities of Pluripotent Stem Cells. I will discuss these models, their strengths and weaknesses as well as the ethical considerations that they deserve.

Keywords: gastrulation, pluripotent stem cells, gastruloids, stembryo, models, mouse, human

TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)

PLENARY IV: TISSUE ARCHITECTURE AND STEM CELL FUNCTION IN HEALTH AND DISEASE

Sponsored by: Stem Cell Reports
1:30 PM – 3:00 PM
Hall 1, Level 2

1:35 PM – 1:55 PM
REGENERATION OF HEALTHY AND MALIGNANT HAEMATOPOIESIS: SIMILAR SIDES OF TWO VERY DIFFERENT COINS

Lo Celso, Cristina
Department of Life Sciences, Imperial College London, UK

Haematopoietic stem cells (HSCs) maintain the turnover of all blood cells, involving the generation of billions and trillions of new cells every day in mice and humans. While mostly quiescent, various

stresses induce HSCs to increase proliferation and differentiation to cope with increased demand for differentiated progeny. These responses have vastly been associated with loss of functional HSCs. Over the last few years my group has focussed on understanding the mechanisms leading to HSC damage during acute, severe infection, using natural rodent malaria models. In particular we have focussed on the role of the bone marrow microenvironment in mediating such damage and as a potential therapeutic target to safeguard HSC numbers and function. More recently, we started exploring mechanisms of regeneration. Leukaemia is cancer of the blood, developing in the bone marrow and overtaking healthy haematopoiesis. Acute myeloid leukaemia (AML) is the prime example of a stem cell-based cancer and is particularly difficult to treat due to the ability of leukaemia stem cells (LSCs) to evade therapeutic interventions. Similarly to healthy HSCs, LSCs are affected by inflammatory stimuli, and we have recently focussed on understanding how heterogeneity in the response to interferon may provide mechanisms of LSC survival and, eventually, AML relapse following inflammation-inducing therapies such as chemotherapy and immunotherapy.

Keywords: haematopoiesis, leukaemia, inflammation

1:55 PM – 2:15 PM

STEM CELL AGING: LOCAL AND SYSTEMIC EFFECTS

Jasper, Heinrich
Regenerative Medicine, Genentech, USA

In aging and diseased tissues, regeneration and regenerative therapies are limited by stem cell dysfunction and unfavorable tissue environments. We study stem cells and tissue repair in barrier epithelia and the retina of Drosophila and mice to explore the causes and consequences of age-related regenerative dysfunction. These studies have led to the discovery of interventions targeting age-related inflammation, stem cell proliferation, stem cell metabolism, innate immune responses, and the commensal microbiota as strategies to enhance regeneration and extend lifespan. I will discuss these strategies and provide perspectives for the development of targeted interventions to improve tissue function in the elderly. We have recently discovered a role for Ptk7 in regulating intestinal stem cell migration during regenerative responses. In Drosophila, we find that the N-terminal domain of Ptk7 is shed from enteroendocrine cells in response to tissue damage. This secreted form of Ptk7 promotes non-canonical Wnt signaling in intestinal stem cells, inducing cell migration towards the site of injury. We have now observed a similar mechanism in mice and find that this mechanism is conserved and contributes to stem cell dysfunction in older animals, where Ptk7 is released by senescent cells. We propose that senescent cell accumulation in aging tissues thus results in perturbation of intestinal stem cell differentiation and function. I will discuss this work and recent insight at the conference.

Keywords: intestinal stem cells, airway, aging

2:15 PM – 2:35 PM

REGULATION AND DIVERSITY OF ADULT NEURAL STEM CELLS

Doetsch, Fiona
Biozentrum, University of Basel, Switzerland

Neural stem cells reside in specialized niches in the adult mammalian brain. Adult neural stem cells in the ventricular-subventricular zone form a mosaic of spatially distinct pools that generate different types of neurons and glia. Adult neural stem cells dynamically integrate intrinsic and extrinsic signals to either maintain the quiescent state or to become activated to divide and give rise to progeny. I will present our recent findings highlighting the importance of adult neural stem cell heterogeneity, and the key roles of physiological states and long-range signals in the regulation of regionally distinct pools of adult neural stem cells, for on-demand adaptive brain plasticity.

Keywords: neural stem cells, niche, physiology

2:35 PM – 3:00 PM

ERNEST MCCULLOCH MEMORIAL LECTURE: MEMORIES FOR BETTER OR FOR WORSE: HOW TISSUE STEM CELLS COPE WITH AND REMEMBER STRESSFUL SITUATIONS

Fuchs, Elaine
Laboratory of Mammalian Cell Biology and Development, HHMI, The Rockefeller University, USA

The skin epithelium is our barrier to the outside world. As such it is subject to a barrage of external assaults, including pathogens, allergens, wounds and carcinogens. To cope with these stresses, the body surface must be rejuvenated by epithelial stem cells, able to self-renew long term and differentiate to make and maintain the barrier. The skin epithelium must also be able to sense and respond quickly to injury in order to fuel rapid tissue regeneration. The regulatory circuitry governing this balancing act must be intricately regulated in normal homeostasis, and then transiently altered to cope with injury responses. In dissecting at a molecular level how stem cell interactions with their microenvironments differ in homeostasis, wound repair and inflammation, we discovered that skin stem cells retain long-lasting memories of stressful encounters. In using high throughput genetic and genomic approaches, we dissected the underlying mechanisms involved. We learned that tucked inside the nucleus of the stem cell are hundreds of non-genetic ('epigenetic') changes in the chromatin that help a stem cell remember and recall memories of particular experiences. The mechanisms involved bear strong resemblance to those involved in brain memories, and suggest that many, perhaps all, of our tissues may have cells that can acquire, maintain and recall memories. In my presentation, I'll discuss our work and go over the implications for whole body fitness and disease.

Keywords: skin epithelium, inflammation and wound repair, epigenetics

FRIDAY, 12 JULY

GENE THERAPIES

8:15 AM – 9:45 AM
Hall G1, Level 2

8:20 AM – 8:40 AM

ENGINEERING NEURAL CELL FATES BY IN VIVO LINEAGE REPROGRAMMING

Berninger, Benedikt[1], Marichal, Nicolás[2], Péron, Sophie[3], Beltrán Arranz, Ana[2], Cooper, Alexis[1], Shi, Youran[2], Leaman, Sydney[2], Schuurmans, Carol[4], Guillemot, François[5] and Khan, Adil[2]

[1]Centre for Developmental Neurobiology, King's College London, UK, [2]King's College London, UK, [3]Institute of Physiological Chemistry, Germany, [4]Sunnybrook Research Institute, Canada, [5]The Francis Crick Institute, UK

Direct lineage reprogramming of glia into neurons emerges as an innovative strategy towards experimental brain repair. We are currently exploring the possibility of converting glia of the early postnatal cerebral cortex into induced neurons. Towards this we found that a phospho-site mutant variant of Achaete-scute complex like-1 (Ascl1), here referred to as Ascl1SA6, exerts a markedly enhanced neurogenic reprogramming activity as compared to wildtype Ascl1. Retrovirus-driven expression of Ascl1SA6 (in combination with Bcl2) induced conversion of a large proportion of the virus-targeted astrocytes of postnatal day 5 mouse cerebral cortex into neurons, many of which expressed the calcium-binding protein parvalbumin and exhibited action potential discharge in the range of fast-spiking interneurons (>100Hz). Two-photon live imaging revealed that initial conversion of astrocytes into induced neurons occurs surprisingly fast, followed by integration into cortical circuits as determined by in vivo live calcium imaging as well as electrophysiology. Accordingly, single cell sequencing corroborated rapid rewiring of gene expression programmes. Intriguingly, distinct reprogramming factor combinations (Ascl1/Bcl2; Ascl1SA6/Bcl2; Ascl1SA6/Dlx2) elicited substantially diverging downstream gene expression programmes indicating that these factors could regulate non-overlapping modules of interneuron identity which could be exploited for circuit repair.

Keywords: neurogenesis, brain repair, cerebral cortex

8:40 AM – 8:50 AM

LENTIVIRAL VECTOR MEDIATED IN VIVO GENE TRANSFER INTO HEMATOPOIETIC STEM AND PROGENITOR CELLS FOR THE TREATMENT OF FANCONI ANEMIA

Milani, Michela[1], Fabiano, Anna[1], Perez-Rodriguez, Marta[2], Zonari, Erika[1], Volpin, Monica[1], Basso-Ricci, Luca[1], Quaranta, Pamela[1], Seffin, Luca[1], Russo, Fabio[1], Biffi, Mauro[1], Montini, Eugenio[1], Scala, Serena[1], Bueren, Juan[2], Rio, Paula[2], Aiuti, Alessandro[1], Cantore, Alessio[1] and Naldini, Luigi[1]
[1]San Raffaele Telethon Institute for Gene Therapy, IRCCS San Raffaele Hospital, Italy, [2]Division of Hematopoietic Innovative Therapies, CIEMAT/CIBERER, Spain

Lentiviral vector (LV) mediated ex vivo gene therapy in hematopoietic stem and progenitor cells (HSPC) fulfilled the promise of a cure for a number of genetic diseases. However, collection and ex vivo manipulation of HSPC and the risks associated with patient conditioning and transplant still pose challenges to broad access to HSPC gene therapy. These hurdles might be overcome by an in vivo approach. To investigate the feasibility of this approach, we studied HSPC biodistribution in newborn or adult mice and discovered a unique window of opportunity in the formers due to early post-natal persistence of the hepatic fetal hematopoietic niche and extensive trafficking of HSC to the bone marrow (BM). Indeed, we were able to successfully target bona fide HSC by intravenous (i.v.) administration of GFP-LV to newborn mice. We obtained stable life-long GFP expression in up to 10% of all blood lineages, paralleled by a comparable expression in HSPC harvested from the BM, which could engraft long-term in busulfan-conditioned mice. LV integration site analysis confirmed common origin of different hematopoietic lineages from multiple clones. As a paradigmatic disease model to test this approach we chose Fanconi anemia (FA), a rare genetic disorder belonging to the DNA repair deficiency syndromes. We administered i.v. FANCA-LV to FA newborn mice and showed progressive increase of LV-positive cells in treated mice throughout growth and homeostasis of the hematopoietic system, suggesting selective advantage of the corrected cells over the non-corrected ones, coupled with progressive normalization of white blood cell and lymphocyte counts. To mimic the BM failure observed in FA patients, LV-treated FANCA mice were challenged with Mitomycin C (MMC), a DNA cross-linking agent causing death of non-corrected cells. Remarkably, we observed a significant expansion of corrected cells after two doses of MMC, reaching up to 100% in MMC challenged mice with prompt recovery of blood parameters after MMC challenging only in LV-treated mice. Our work shows efficacy and safety of in vivo gene transfer into HSPC in newborn mice, life-long maintenance of transgene expression and, as we also documented high numbers of circulating HSPCs early post-natal in humans, set the basis for possible clinical translation of this approach for FA.

Keywords: gene therapy, hematopoietic stem cells, Fanconi anemia

8:50 AM – 9:00 AM

TESTING LENTIVIRAL VECTORS ENCODING FOR CHIMERIC HUMAN GALC ENZYMES TO REFINE HEMATOPOIETIC STEM CELL GENE THERAPY FOR GLOBOID CELL LEUKODYSTROPHY

Ricca, Alessandra[1], Valeri, Erika[1], Cascino, Federica[1], Picciotti, Ilaria[1], Freschi, Marta[2], Unali, Giulia[3], Morena, Francesco[4], Martino, Sabata[4], Kajaste-Rudnitski, Anna[1] and Gritti, Angela[1]
[1]San Raffaele Telethon Institute for Gene Therapy, San Raffaele Hospital, Italy, [2]Gene Therapy Program, Dana-Farber/Boston Children's Cancer and Blood Disorder Center, USA, [3]The National Emerging Infectious Diseases Laboratories, University of Boston, USA, [4]Chemistry, Biology, and Biotechnology, University of Perugia, Italy

Globoid cell leukodystrophy (GLD) is a fatal lysosomal storage disease caused by the deficiency of the beta-galactosylceramidase (GALC) enzyme, resulting in severe central and peripheral nervous system dysfunction. The difficulty in achieving supranormal levels of GALC activity in affected tissues limits the clinical exploitation of gene therapy (GT) approaches. Chimeric GALC enzymes with enhanced secretion and increased capability to cross the blood-brain barrier may potentiate the bioavailability of GALC and overcome the limitations of current experimental GT strategies. We designed and tested the safety and efficacy of lentiviral (LV) constructs encoding for engineered chimeric human GALC enzymes in CD34+ hematopoietic stem and progenitor cells (HSPCs) and in neural cells generated from GLD patient-derived induced pluripotent stem cells (hiPSCs), the closest human in vitro models of effector and target cells, respectively, in HSPC GT approaches. Safe overexpression of transgenic mRNA in LV-transduced human cells correlated with supranormal GALC activity. HSPCs and hiPSC-derived neural progeny secreted the chimeric GALC enzymes more efficiently than the unmodified counterpart. Importantly, GLD patient-derived neurons/glial cells recaptured the chimeric GALC enzymes proficiently, achieving physiological GALC levels upon cross-correction. LV-transduced CD34+ HSPCs engrafted in immunodeficient NSG mice, up to 20% of human cells in peripheral blood at eight weeks after transplantation. Notably, we measured enhanced GALC activity in the sera of mice receiving CD34+ HSPCs expressing the chimeric human GALC enzyme as compared to the unmodified counterpart, suggesting enhanced secretion and

circulation of the chimeric GALC enzyme in the bloodstream. These data support the rationale of testing the safety and functional advantage of chimeric GALC enzymes in ex vivo HSPC GT approaches in GLD mouse models. Improving GALC bioavailability may reduce the need for GALC overexpression in effector cells, simplifying the development of clinical protocols and refining their safety profile.

Funding Source: Giovani ricercatori 2019-12369357, Ministry of Health, Italy

Keywords: gene therapy, hematopoietic stem and progenitor cells, neural cells derived from globoid cell leukodystrophy IPSCs

9:00 AM – 9:10 AM

COMBINED CELLULAR AND GENE THERAPY TO TREAT PRIMARY CILIARY DYSKINESIA

Bourdais, Carine[1], Nadaud, Marion[2], Coeur, Agathe[1], Foisset, Florent[1], Ahmed, Engi[2], Vachier, Isabelle[2], Bourdin, Arnaud[2], Assou, Saïd[1] and De Vos, John[1]

[1]IRMB, Université de Montpellier, INSERM, CHU Montpellier, France, [2]Department of Respiratory Diseases, CHU Montpellier, INSERM, France

Primary Ciliary Dyskinesia (PCD) is a genetic disease caused by mutations that alter cilia beating, including in the respiratory airways, resulting in impaired mucus clearance and severe morbidity as well as increased mortality. We hypothesized that we could restore bronchial ciliary beating with genetically corrected iPSC differentiated into air-liquid interface bronchial epithelium model (iALI) for autologous cell therapy. We already shown that corrected cells generated from a PCD patient IPS cell line can be differentiated in iALI with functional ciliary beating. The aim of the project now is to assess the engraftment ability of the corrected cells and the repair of the pathological model after engraftment. Different issues have to be considered: the characterization of competent cells for bronchial engraftment, the study of different strategy for previous erosion of the bronchial epithelium and the assessment of the ciliary beating recovery to assure bronchial repair. We use a GFP-iPSC cell line generated in the lab to engraft on the corresponding control cell line and mutated cell line differentiated in iALI to answer these issues. Our results suggest that lung progenitors at the ventralized anterior foregut endoderm stage could be the most efficient cells for engraftment. Their self-renewal ability and their capacity to differentiate in the different cell type spectrum of the bronchial epithelium are promising for the development of a long term and efficient therapy. Concerning the bronchial erosion, we considered it necessary to promote cell engraftment because of the barrier function of the intact bronchial epithelium and the lack of selection advantage from the corrected cells. Different strategies, chemical or enzymatic, seem to provide good results but we need to assess the safety of each of them for in-vivo application. Finally, several experimental conditions allowed to observe GFP engrafted cells expressing cilia, suggesting that the grafted progenitors differentiated in ciliated cells. Functional recovery still needs to be confirmed. Next step of the project is to develop the therapy for in-vivo application, assessing the safety and efficiency of the graft in immunodeficient mini-pig model.

Keywords: cell therapy, bronchial conditioning, progenitors and stem cells

9:10 AM – 9:20 AM

OPTIMIZATION OF A GMP-COMPATIBLE GENE EDITING METHODOLOGY TO GENERATE HUMAN INDUCED PLURIPOTENT STEM CELLS WITH ENHANCED FEATURES FOR THERAPEUTIC APPLICATIONS

Berger, Thomas[1], Gamerschlag, Anna[2], Huehne, Melanie[2] and Greber, Boris[2]

[1]Research and Development, Catalent Cell and Gene Therapy, Germany, [2]Research and Development, Catalent Duesseldorf GmbH, Germany

Human induced pluripotent stem cells (iPSCs) are gaining increased significance in cell therapy. However, rejection of therapeutic iPSC-derived effector cells by the immune system poses a major limitation to its application. Rejection is primarily caused by the polymorphic structure of human leukocyte antigen (HLA) genes leading to numerous variants of major histocompatibility complex receptors in the human population and preventing successful cell transplantation. While autologous cell therapies allow for cell transplantation without the risk of immune rejection, they are expensive and time-consuming, both major hurdles for effective and accessible treatments. HLA-homozygous iPSCs offer one solution to this problem, as they provide increased compatibility within the human population and may thus favor Off-the-Shelf cell therapy. Still, complete compatibility can even not accomplished with HLA-homozygous cells. An alternative approach is the targeted genetic manipulation to cloak cells from the immune system. While this approach bears risks, combining the technology with appropriate safety measures may allow for gene editing to generate universal donor cells for allogeneic cell therapies. Genetic manipulation of iPSCs, in particular the knock-in generation, tends to be complicated and inefficient. Moreover, the simultaneous manipulation of multiple genomic loci requires high efficiencies. To address this, while avoiding labor-intensive workflows or complex equipment, we optimized gene editing using both Cas9 and Cas12a ribonucleoprotein complexes. The approach allows knock-outs of one or two genes at once at efficiencies around 90% or 50%, respectively, or knock-ins of transgenes at above 40 % efficiency, while avoiding cell sorting or antibiotic selection or the use of viral particles. Using a DNA recombination-enhancing molecule, knock-in efficiencies can reach between 60-80%. We exemplify these advances by creating and characterizing a universal donor iPSC line depleted of HLA class I and II and carrying a CD47 knock-in while retaining genomic integrity, pluripotency, and differentiation capabilities. This improved methodology will form a flexible platform for custom gene editing and providing GMP-compliant iPSCs with enhanced features.

Keywords: gene editing, iPSC, knock-In

9:20 AM – 9:40 AM

GENE THERAPY FOR FOCAL REFRACTORY EPILEPSY

Kullmann, Dimitri

UCL Queen Square Institute of Neurology, University College London, UK

Pharmacoresistant focal epilepsy affects approximately 1 in 500 individuals, and surgical options are limited by the risk of permanent neurological deficit. Focal epilepsy has numerous aetiologies, and so correction of an underlying molecular lesion is rarely feasible. Instead, gene therapies in development have generally targeted the mechanisms underlying excitation or inhibition, taking

advantage of the ability of viral vectors to restrict treatment to the epileptogenic brain area and bias expression to specific neuronal populations. I shall describe several gene therapies delivered by intra-parenchymal injection in rodent models of different epilepsies including a malformation of cortical development. Overexpression of the potassium channel Kv1.1 leads to a constitutive reduction of neuronal excitability and neurotransmitter release, and is safe and effective. Chemogenetics using muscarinic DREADDs allows the therapy to be adjusted, or even used on demand. Such controllable gene therapy has potential advantages in cases where the seizure focus overlaps with eloquent brain areas. I shall also describe two closed-loop gene therapies, which inhibit neurons in seizure foci in response to pathological activity. One such therapy is based on the expression of a glutamate-gated chloride channel, which inhibits neurons in response to increases in extracellular glutamate such as occur in seizures. Another closed-loop therapy is based on the overexpression of Kv1.1 under the control of an activity-dependent promoter derived from the immediate early gene cFos. These different gene therapy strategies have complementary advantages that make them suitable for progression to the clinic to treat different patient populations. A first in human trial in patients who are suitable for surgical resection potentially offers the ability to resect the treated brain area in the event of therapeutic failure, which is not feasible for gene therapies for most other CNS disorders.

Keywords: seizure, AAV, neuron

INTEGRATIVE SINGLE CELL OMICS

Sponsored by: Stem Cell Reports
8:15 AM – 9:45 AM
Hall Z, Level 3

8:20 AM – 8:40 AM

UNDERSTANDING HUMAN BRAIN ORGANOID DEVELOPMENT WITH INTEGRATIVE MULTI-MODAL SINGLE-CELL TECHNOLOGIES

Treutlein, Barbara
Department of Biosystems Science and Engineering, ETH Zürich, Switzerland

Pluripotent stem cell derived organoids are exciting, complex in vitro models to study human organ development. Integrative, multi-modal single-cell technologies are needed to understand the mechanisms underlying fate specification during human organoid development. In my talk, I will present our efforts to develop and use single-cell technologies combined with genetic and environmental perturbations to dissect the mechanisms underlying patterning and fate specification during human organoid development with a focus on brain and vasculature. Further, I will highlight our attempts to further improve organoid development and maturation by introducing missing lineages. Together, our work highlights the power of single-cell and organoid technologies to understand cell fate and state specification during human organ development.

Keywords: single-cell multiomics, human brain organoids, spatial omics, computational biology

8:40 AM – 8:50 AM

CEREBRAL ORGANOIDS DISPLAY DYNAMIC CLONAL GROWTH WITH LINEAGE REPLENISHMENT

Esk, Christopher[1], Lindenhofer, Dominik[2], Haendeler, Simon[3], Littleboy, Jamie[2], Brunet Avalos, Clarisse[4], Naas, Julia[3], Pflug, Florian[3], van de Ven, Eline[2], Reumann, Daniel[2], Baffet, Alexandre[4], von Haeseler, Arndt[3] and Knoblich, Juergen[2]
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Neurogenesis varies between species but is a tightly regulated process of neural stem cells generating differentiated cells in well-defined numbers to form species specific brain sizes. Neural stem cells divide in two phases, first symmetrically expanding the progenitor pool in a logarithmic manner, followed by asymmetric cell divisions generating one progenitor and one division-restricted daughter cell resulting in near linear growth. Transition between those modes varies between species and individual neural progenitors, resulting in differentially sized progenitor clones. Imaging-based lineage tracing in mice allows for lineage analysis at high cellular resolution but systematic approaches to analyze clonal behavior in an entire tissue are currently lacking. Here we implement whole-tissue lineage tracing by genomic DNA barcoding in 3D human cerebral organoids and show that individual progenitor clones produce progeny on a vastly variable scale. We find that these variations in lineage size distribution are driven by a subpopulation of lineages that retain symmetrically dividing cells. We further show that progenitor division modes are tunable to tissue needs. Chemical ablation or genetic fate restriction by knockout of TP53, ASPM or PAX6 in half of cerebral organoids' cells is completely compensated for by unaffected lineages producing additional progeny to compensate for induced cell loss or fate restriction resulting in normal sized organoids. This data reveals adaptive plasticity of stem cells in a human developing 3D tissue dependent on tissue needs to ensure normal development.

Keywords: neural development, brain organoids, lineage tracing

8:50 AM – 9:00 AM

BEYOND CURRENT MULTI-MODAL ANALYSES OF SINGLE CELLS: HIGH-RESOLUTION MASS SPECTROMETRY UNRAVELS PROTEIN DYNAMICS IN STEM CELL MODELS

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Multi-modal analysis of pluripotent stem cells (PSCs) during early embryonic development is crucial for gaining mechanistic insights into cell identity and differentiation. Pluripotency encompasses various phases, from its initial establishment to the eventual exit from this state. PSCs cultured under conditions promoting constant MAPK/ERK and GSK3β activity (serum + LIF) have been extensively characterized by single cell multi-omic approaches, providing intricate insights into the heterogeneity of this culture model with cells ranging from a 2-cell like state to almost differentiated states. However, sequencing-based techniques that measure the transcriptome or chromatin accessibility fall short in capturing the full spectrum of phenotypic protein dynamics. To address this, we developed a highly sensitive single cell proteomics (scProteomics) workflow by leveraging recent developments on the cellenONE, Evosep One and Orbitrap Astral mass spectrometry instruments. This innovative approach was first applied to mouse PSCs cultured under serum + LIF conditions and sorted for high-to-low levels of key pluripotency factors and second to early differentiation

models starting from ground state PSCs. Our workflow enabled the quantification of over 4,000 proteins from single cells, revealing significant cellular heterogeneity at the protein level and identifying differential regulation for key pluripotency regulators. Our results demonstrate that scProteomics offers a highly reproducible method for identifying cell identities, delivering insights beyond those achievable with current single-cell techniques. This approach is poised to become invaluable in the stem cell field, which increasingly depends on single-cell-based phenotyping to understand normal and perturbed cell states in both research and clinical settings.

Keywords: single cell proteomics, pluripotent stem cells, mass spectrometry

9:00 AM – 9:10 AM

INVESTIGATION LINEAGE FATE DECISIONS IN INTESTINAL EPITHELIUM USING THE DCM-TIME MACHINE

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Homeostasis is maintained by tightly controlled gene regulatory networks. Changes in gene and regulator activity in these networks are difficult to track in real time. Commonly used techniques often depend on in silico predictions. To circumvent this, we recently introduced a system which enables whole genome cell state tracing, the DCM time machine (DCM-TM). DCM-TM utilizes the bacterial methylase DCM fused to subunit B of RNA polymerase 2 to add a methylation label to active gene bodies and enhancers at induction of the fusion gene. The methylation label is propagated during cell division. We generated differentiation maps from intestinal stem cells (ISC) towards enterocytes, indicating rapid and simultaneous activation of enhancers and nearby genes. In this study, we elaborate on the secretory/absorptive lineage fate decisions within the small intestine. We followed enterocyte and tuft differentiation back in time by generating DCM methylation profiles (DMP) at multiple time points post induction of the DCM-TM. By combining these enhancer and gene associated DMPs with single cell RNA- and ChIP-sequencing data we characterized the dynamics of cell signaling, transcription factor network and chromatin changes from ISC differentiation towards enterocytes and Tuft cells, defining common and distinct mechanisms in cell type specific gene activation. In future studies we will apply DCM-TM to study gene regulation in homeostasis and regeneration, not only in the small intestine but a plethora of organs and tissues. This will provide valuable insights into the regulatory networks underlying the fine balance between health and disease.

Keywords: intestinal epithelium, DCM-time machine, lineage fate decisions

9:10 AM – 9:20 AM

HIGH-THROUGHPUT SINGLE-CELL PROFILING OF DNA METHYLATION ALLOWS TRANSGENE-FREE TRACKING OF CLONAL DYNAMICS IN HEMATOPOIESIS

Singh, Indranil[1], Scherer, Michael[2], Szu-Tu, Chelsea[2], Rühle, Julia[2], Frömel, Robert[2], Beneyto-Calabuig, Sergi[2], Rodriguez-Fraticelli, Alejo[1] and Velten, Lars[2]

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Tracing lineage histories and molecular states of cells has the potential for unravelling fundamental questions in developmental biology. Existing lineage-recording models, such as lentiviral barcoding, Cas9-based mouse lines, and fluorescent reporters have provided critical insights into the dynamics of stem cells. However, these technologies require advanced transgenesis, limiting their wide adoption and precluding their use in banked human samples. We address this critical gap by introducing EPI-Clone, a novel method that leverages targeted single-cell DNA methylation profiling of hundreds of CpGs in tens of thousands of cells with a CpG dropout rate of only ~7%. Here, we show that measuring DNA methylation at the single-cell level reveals joint information about cellular differentiation states and clonal identity in unsupervised manner. We find that CpGs associated with cellular differentiation are enriched for enhancer elements, while clone-specific CpGs preferentially reside in heterochromatic and late-replicating regions. Furthermore, by leveraging our high-resolution map of murine hematopoiesis, we were able to characterize the functional behavior of individual stem cell clones, including lineage biases. Finally, we show that the method can be applied for natural and non-invasive clone tracking in native hematopoiesis, including mature tissue immune cells. In sum, EPI-Clone offers a means to explore the phylogenetic and epigenetic features of cell ontogeny and to investigate otherwise invisible cellular states during cellular differentiation. This work opens new avenues for understanding and utilizing epigenomic information in the context of cell-fate choices, with significant promise for clinical applications.

Keywords: DNA methylation, lineage tracing, hematopoiesis

9:20 AM – 9:40 AM

OLIGODENDROGLIA IN DEVELOPMENT AND MULTIPLE SCLEROSIS: INSIGHTS FROM SINGLE-CELL AND SPATIAL OMICS

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Oligodendroglia (OLG) mediate myelination of neurons, a process that allows efficient electrical impulse transmission in the central nervous system. An autoimmune response in multiple sclerosis (MS) leads to OLG cell death, loss of myelin and neuropathology. Using single cell transcriptomics, we have previously identified disease-specific OLG populations in the EAE mouse model of MS and in human MS brain archival tissue, characterized by the expression of immune genes. By assessing chromatin accessibility and the transcriptome simultaneously at the single cell level at different stages of the disease course, we found that immune genes exhibit a primed chromatin state in mouse and human OLG in a non-disease context, compatible with rapid transitions to immune-competent states in MS. We found dynamic and distinct transcriptomic and epigenomic responses of OLG subpopulations to the evolving environment in EAE mouse model of MS. While single-cell genomics are powerful for investigating disease-specific cellular states, these methods involve isolating the tissue under study from its niche, leading to a loss of spatial information. Such information is essential for determining cell-to-cell communication in disease niches. We have applied in situ sequencing to investigate disease evolution in MS at a spatial level, both in the EAE mouse model of MS and in human post-mortem MS samples. We annotated disease neighborhoods during lesion evolution and found centrifugal propagation of active lesions. We demonstrated that disease-

associated (DA)-glia arise independently of lesions and are dynamically induced and resolved over the disease course. We have also applied dBIT-Seq, a ligation-based method for deterministic barcoding in tissue, to probe different histone modifications and chromatin accessibility in the mouse brain tissue sections, either in an unimodal or simultaneously with transcriptomics. This spatial epigenome–transcriptome co-profiling has allowed us to identify cellular lineage progression and epigenomic priming events that precede transcription during development with spatial resolution. We are currently applying these methods to disease paradigms in MS, to uncover how transitions to pathological cellular states occur at epigenomic and transcriptomic levels.

Keywords: single-cell omics, spatial omics, brain

TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)

MECHANOBIOLOGY OF STEM CELLS AND TISSUES

8:15 AM – 9:45 AM
Hall G2, Level 2

8:20 AM – 8:40 AM

A MITOCHONDRIAL MECHANOTRANSDUCTION SIGNALING PATHWAY COORDINATES CELL FATE DIFFERENTIATION IN RESPONSE TO FORCES

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Tissue-scale architecture and mechanical properties instruct cell behavior in physiological and diseased conditions, but our understanding of the underlying mechanisms remains fragmentary. I will discuss new data indicating that ECM stiffness, spatial confinements, and applied forces including stretching of the mouse skin regulate mitochondrial dynamics. Mechanistically, actomyosin tension promotes phosphorylation of a DRP1 receptor, limiting the recruitment of DRP1 at mitochondria, peri-mitochondrial F-actin formation, and mitochondrial fission. Strikingly, mitochondrial fission is also a general mechanotransduction mechanism. Indeed we found that fission is required and sufficient to regulate three transcription factors of broad relevance to control cell proliferation, lipogenesis, antioxidant metabolism, chemotherapy resistance, and adipocyte differentiation in response to mechanical cues. This extends to the mouse liver, where DRP1 regulates hepatocyte proliferation and identity. We propose that mitochondria fulfill a unifying signaling function by which the mechanical tissue microenvironment coordinates complementary cell functions.

Keywords: mechanobiology, mitochondrial fission, signaling, metabolism, cell fate determination

8:40 AM – 8:50 AM

UNRAVELING THE INTERPLAY BETWEEN CARDIAC MECHANOBIOLOGY AND METABOLIC REGULATION IN STEM CELL MODELS

Savorè, Giulia[1], Sorge, Matteo[1], Becca, Silvia[1], Nattenberg, Gabrielle[2], Sniadecki, Nathan[2], Brancaccio, Mara[1] and Bertero, Alessandro[1]
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Cardiovascular disease is the leading cause of death worldwide. The heart does not normally regenerate but could be coaxed to do so through cell or gene therapy. A complementary approach would be to tune the cardiac hypertrophic response to prevent maladaptive remodeling. The cardioprotective protein Melusin may enable these goals, but — having been studied only in mouse models — its translational relevance is unclear. Melusin is a muscle-specific chaperone that participates in mechanosensing downstream of integrins, promoting cardiomyocyte physiological hypertrophy and protecting from apoptosis. We recently found that Melusin also limits lipid metabolism to prevent reactive oxygen species (ROS) damage. It is an intriguing possibility that Melusin bridges mechanosensing and metabolic regulation. Since ROS limit postnatal cardiac proliferation, this mechanism could also regulate heart development and regeneration. To mechanistically test this hypothesis in a human relevant system, we established and characterized human induced pluripotent stem cell (hiPSC)-derived 2D and 3D cardiac models of Melusin loss- and gain-of-function, as well as fluorescent reporters of Melusin localization. In monolayer hiPSC-derived cardiomyocytes (hiPSC-CMs), Melusin knock-out (KO) via CRISPR/Cas9 augments ROS damage and sensitizes cells to the cardiotoxic drug doxorubicin. hiPSC-CMs transduced with AAV6 to overexpress Melusin develop an opposite phenotype. This is molecularly explained by an inhibitory interaction between Melusin and the mitochondrial trifunctional protein (MTP), demonstrated by proximity ligation assays, enzymatic assessment of MTP activity, and oxygen consumption rate analyses. Super-resolution localization of a HaloTag-Melusin knock-in identifies dynamic relocalization of Melusin between mitochondria, sarcomeric A bands, and the nucleus. In cardiac organoids, Melusin KO results in smaller chambers, which is associated to a modulation of cardiomyocyte cell cycle. Lastly, three-dimensional engineered heart tissues (3D-EHTs) from Melusin KO cells develop less contractile force. Our work shows that Melusin is cardioprotective in human stem cell models, paving the way to translational applications leveraging its ability to control mechanosensing and metabolism.

Funding Source: National Heart, Lung and Blood Institute of the National Institutes of Health R01 HL149734

Keywords: mechanobiology, metabolism, cardiac biology

8:50 AM – 9:00 AM

FORCE INITIATES MITOCHONDRIAL REMODELING NECESSARY FOR HEMATOPOIETIC STEM CELL FATE

Wenzel, Pamela L., Horton, Paulina, Dumbali, Sandeep and Moore, Travis
Integrative Biology and Pharmacology, University of Texas Health Science Center at Houston, USA

Transplantation of hematopoietic stem cells (HSCs) is curative for many patients with bone marrow failure and blood malignancies, yet two-thirds of these patients have no suitable donor. This unmet need has driven enterprising efforts to identify cues that dictate HSC fate such that alternative sources can be produced in culture. Our research shows that blood flow in the embryonic vasculature drives remodeling of mitochondrial machinery that endows endothelial precursors with an HSC fate. We leveraged fluidics and a cardiac-mutant mouse model to examine a continuum of hematopoietic specification wherein specific effects of fluid shear stress could be isolated. Using single-cell methodologies in RNA-seq, protein synthesis, and microscopy, we show that the physical forces associated with arterial blood flow are critical for mitochondrial assembly, cristae formation, and energy-generating capacity as cells commit to a hematopoietic fate. Force triggers transcriptional

activation of genes encoding mitochondrial ribosomes, mitochondrial protein import complexes, and electron transport chain proteins, but also induces anabolic processes that precede transcription. Shear stress directly stimulates PI3K-Akt signaling to post-translationally modify the mTORC1 effectors S6K and 4E-BP1 that dictate translation initiation and elongation of peptides required for mitochondrial capacity. We find via transplantation that HSC activity resides strictly within high mitochondrial membrane potential populations, supporting the key role that both biophysical force and mitochondria play in dictating HSC fate in the mid-gestation embryo. Although in vitro specification of HSCs remains elusive, our study could provide clues to a flow-sensitive molecular mechanism essential for maturation of mitochondrial machinery that could be leveraged for generation of HSCs in culture.

Funding Source: Grants to P.L.W. from the American Society of Hematology Scholar Award and National Institutes of Health (K01DK092365, R01DK111599) supported this work.

Keywords: mechanobiology, mitochondria, hematopoietic stem cells

9:00 AM – 9:10 AM
PROCR+ CHONDROPROGENITORS SENSE MECHANICAL STIMULI TO GOVERN ARTICULAR CARTILAGE MAINTENANCE AND REGENERATION

Zhu, Qiaoling and Yue, Rui
College of Life Science and Technology, Tongji University, China

Protein C receptor (Procr) has been identified as an adult stem cell marker across multiple tissues. However, whether Procr labels skeletal stem/progenitors in long bones remains unknown. Here, we profiled articular cartilage from healthy and osteoarthritic (OA) mouse knee joints by single-cell RNA sequencing (scRNA-seq), and identified a significant augmentation of Procr+ cells in the superficial articular cartilage after OA. By genetic lineage tracing using Procr-CreER mice, we confirmed that Procr+ cells are predominantly distributed in the superficial layer of tibial, but not femoral, articular cartilage and meniscus, which generate chondrocytes during postnatal knee joint development. Interestingly, mechanical overload by forced running caused a significant increase of Procr+ cells in both the tibial and femoral articular cartilage, while mechanical unloading by tail suspension led to a significant reduction of Procr+ cells in the tibial articular cartilage, suggesting that Procr+ cells are a mechanical sensitive chondroprogenitor population. Consistent with this, post-traumatic OA induced by destabilization of the medial meniscus also expanded Procr+ cells on the femoral side to repair articular injury, while genetic ablation of Procr+ cells accelerated OA progression. Mechanistically, pharmacological inhibition or genetic deletion of the pivotal mechanosensor Piezo1 significantly blunted the ability of Procr+ cells to regenerate articular cartilage, which exacerbated OA symptoms. In contrast, intra-articular administration of Piezo1 agonist showed therapeutic effects against OA. scRNA-seq analysis revealed that CD105 enriches articular Procr+ cells. Procr+CD105+ cells showed enriched CFU-F and multilineage differentiation potential in vitro, and robust osteochondrogenic capacity after renal transplantation in vivo. Orthotopic transplantation of Procr+CD105+ cells in micro-fractured knee joints also showed improved cartilage repair. Taken together, we discovered a mechanosensitive chondroprogenitor population indispensable for articular cartilage maintenance and regeneration, which could be utilized for next-generation stem cell therapy to treat OA in the near future.

Funding Source: This work was supported by grants from the National Key R&D Program of China (2022YFA1103200) and National Natural Science Foundation of China (91749124, 81772389, 82070108).

Keywords: Procr, articular progenitor cells, mechanobiology

9:10 AM – 9:20 AM
TISSUE-SCALE MECHANICS CONTROL STEM CELL FATE AND POSITIONING DURING EPITHELIAL DEVELOPMENT

Villeneuve, Clementine[1], Azote, Somiealo[2], Lawson-Keister, Elisabeth[2], Kruse, Kai[3], Wirtz, Lisa[4], Rübsam, Matthias[5], Bazzi, Hisham[4], Niessen, Carien[5], Manning, Lisa[3] and Wickström, Sara[1]
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The development and maintenance of a functional tissue and organs require synchronized regulation of cell state transitions and dynamic spatial positioning of specific cell states. During embryogenesis, the skin epidermis gradually transitions from a single stem cell (SC) layer to a multilayered stratified epithelium through coordinated differentiation and upward movement of cells. However, what mechanisms trigger initial fate commitment and how cell fate transition and positioning are coordinated during development remain poorly understood. We show, using single cell transcriptomics, embryo live imaging, mechanical testing and 3D vertex modelling, that during early phases of stratification, multilayering occurs independently of cell fate specification, driven by high proliferative activity and a fluid-like tissue state. Subsequently, as the connective tissue matures and cell density increases, the tissue gradually solidifies and the stem cell compartment separates from the suprabasal differentiated compartment through high interfacial tension. This mechanical phase transition coincides with emergence of a committed stem cell population, characterized by altered cell state but stem-like adhesive and mechanical properties. In a second transition, the committed cells undergo a cytoskeletal and adhesion molecule switch, likely facilitating upward movement of the differentiated cell. Interestingly, the early fate commitment of basal stem cell is triggered by Notch signaling, reported to be modulated by cell geometry. Collectively, this work suggests two, mechanically distinct phases of epithelial barrier formation: (1) rapid growth-driven development of a first suprabasal layer and (2) mechanical separation of stem cell and suprabasal compartments requiring a Notch signaling-dependent early fate commitment to facilitate the transition of differentiated cells across this mechanical barrier to the upper layers.

Funding Source: This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No [101032331]

Keywords: skin stratification, tissue mechanics, notch signaling

9:20 AM – 9:40 AM

P53-MEDIATED STEM CELL COMPETITION: INSIGHTS INTO MECHANISMS OF CLONAL DOMINANCE

Piddini, Eugenia

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TP53 Mutations confer clonal advantage in several tissues contributing to tumorigenesis. It has traditionally been proposed that heightened resistance to apoptosis/cell cycle arrest can account for clonal advantage. P53 mediated clonal dominance has also been observed in cultured embryonic stem (ES) cells, though it is not clear how this is established. I will discuss our recent unpublished work demonstrating that differences in p53 activity lead to cell competition in human embryonic stem cells. This results in the elimination of wild-type stem cells by hES-P53KO cells. We suggest that this is responsible for the observed selective advantage and clonal dominance of p53 mutant cells in cultures of ES and iPS cells. I will present our characterization of p53 induced cell competition and our insight into the mechanisms that lead p53 mutant cells to eliminate wild-type cells, including data indicating that this type of competition may be mechanically induced by differential sensitivity to compaction in high-density cultures. Identifying the mechanisms by which p53 confers resistance to cell compaction could lead to novel actionable targets to prevent the expansion of p53 mutant stem cells in cancerous and pre-cancerous lesions.

Keywords: P53, cell competition, embryonic stem cells

TRACK: Pluripotency and Development (PD)

NON-INTEGRATED STEM CELL MODELS OF EARLY EMBRYO DEVELOPMENT

8:15 AM – 9:45 AM

Hall 3, Entrance Level

8:20 AM – 8:40 AM

NAIVE HUMAN PSCS MODEL PRE- TO POST-IMPLANTATION DEVELOPMENT

Takashima, Yasuhiro

CiRA, Kyoto University, Japan

We aim to understand early human development by focusing on the pre-implantation to post-implantation stages. To achieve our objective, our group has established a series of methods and human cells that correspond to human peri-implantation embryos. The blastocyst contains three cell types, epiblast, hypoblast, and trophectoderm. We successfully induced hypoblast and trophectoderm from naive human pluripotent stem cells (PSCs), which share features with pre-implantation embryos. In this presentation, I will present in vitro lineage specifications for human extraembryonic lineages from naive human PSCs and in vitro development using naive PSCs together with hypoblast-like cells and trophectoderm-like cells during peri-implantation.

Keywords: human pluripotent stem cells, stem cell models, early development

8:40 AM – 8:50 AM

PERI-GASTRULATION PATTERNING OF THE HUMAN EMBRYONIC DISC DOES NOT REQUIRE AN EPITHELIAL TO MESENCHYMAL TRANSITION

Arabpour, Auriana[1], Jacobson, Elsie[2], DiRusso, Jonathan[1], Pham, Thi Xuan Ai[3], Sparrow, Megan[1], Agranonik, Nicole[1], Hwang, Youngsun[1], Wu, Qiu Ya[1], Pasque, Vincent[3], Plath, Kathrin[2] and Clark, Amander[1]

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Human stem cell-based embryo models (SCBEMs) are important research tools that can facilitate our understanding of early human embryo development. These tools could also be used in the future to understand infertility, early pregnancy loss or environmental effects on early embryo development which could lead to public health interventions aimed at improving reproductive and child health outcomes. In the current study, we utilized a Geltrex-incorporated Medium Overlay (GiMO) model in the chemically defined media (E8) to promote a predicted and ordered series of differentiation events. Time-lapse imaging over the first 72-hours of GiMO reveals the formation of disc-like structures, that develop a cavity and initiate an epithelial to mesenchymal transition (EMT) followed by the expansion of a mesenchymal population. Using single cell RNA-Seq, our data demonstrates that these events are associated with the specification of amniotic ectoderm-like cells (AMELCs), primordial germ cell-like cells (PGCLCs), primitive-streak-like cells (PS-like cells), mesoderm-like cells (MeLCs) and endoderm-like cells. Thus, the GiMO model represents a non-integrated peri-gastrulation model of human embryo development. To spatially position the specification of major embryonic lineages relative to the EMT event, we performed immunofluorescence and time-lapse imaging. Using a TFAP2A-tdTomato human embryonic stem cell line reporter, our data demonstrates that within the first 24 hours of GiMO, a subpopulation of CDH1+ disc cells repress NANOG and up-regulate the lineage marker TFAP2A. Next, TFAP2C/SOX17/NANOG+ PGCLCs and GATA6+ MeLCs are specified within the CDH1+ discs. Following EMT, specified PGCLCs down-regulate CDH1 and migrate out of epithelial discs along with GATA6+ MeLCs and a small portion of SOX17+ endoderm-like cells. Blocking BMP4 in the first 24 hours of GiMO leads to loss of TFAP2A, and failure of the disc cells to differentiate into PGCLCs and MeLCs. In contrast, blocking EMT does not affect lineage patterning in the disc, but does prevent the expansion of GATA6+ mesoderm. In summary, the GiMO model successfully recapitulates key peri-gastrulating events that take place in the posterior developing human embryo and reveals that EMT is not necessary for the specification of PGCLCs or MeLCs.

Keywords: human stem cell- based, non-integrated embryo model, peri-gastrulation

8:50 AM – 9:00 AM

METABOLIC AND LIPIDOMIC REMODELLING INSTRUCT EARLY MAMMALIAN EMBRYO DEVELOPMENT

Zhang, Jin[1], Li, Da[2], Shui, Guanghou[3], Zhao, Jing[4] and Zhang, Ling[4]

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During early mammalian embryogenesis, changes in cell growth and proliferation depend on strict genetic and metabolic instructions. However, our understanding of metabolic reprogramming and its influence on epigenetic regulation in early embryo development remains elusive. Here we first show a comprehensive metabolomics profiling of key stages in mouse early development and the two-cell and blastocyst embryos, and we reconstructed the metabolic landscape through the transition from totipotency to pluripotency. Our integrated metabolomics and transcriptomics analysis shows that while two-cell embryos favour methionine, polyamine and glutathione metabolism and stay in a more reductive state, blastocyst embryos have higher metabolites related to the mitochondrial tricarboxylic acid cycle, and present a more oxidative state. Together, our data demonstrate dynamic and interconnected metabolic, transcriptional and epigenetic network remodelling during early mouse embryo development. Secondly, lipids are indispensable for energy storage, membrane structure and cell signalling. However, dynamic changes in various categories of endogenous lipids in mammalian early embryonic development have not been systematically characterized. Here we comprehensively investigated the dynamic lipid landscape during mouse and human early embryo development. Lipid signatures of different developmental stages are distinct, particularly for the phospholipid classes. We highlight that the high degree of phospholipid unsaturation is a conserved feature as embryos develop to the blastocyst stage. Moreover, we show that lipid desaturases such as SCD1 are required for in vitro blastocyst development and blastocyst implantation. One of the mechanisms is through the regulation of unsaturated fatty-acid-mediated fluidity of the plasma membrane and apical proteins and the establishment of apical–basal polarity during development of the eight-cell embryo to the blastocyst. Overall, our study provides an invaluable resource about the remodelling of the endogenous lipidome in mammalian preimplantation embryo development and mechanistic insights into the regulation of embryogenesis and implantation by lipid unsaturation.

Keywords: early embryo development, metabolomics, lipidomics

9:00 AM – 9:10 AM

REGULATIVE DEVELOPMENT IN THE PREIMPLANTATION EMBRYO: A ROLE FOR OCT4 IN PLASTICITY MAINTENANCE IN THE MOUSE PRIMITIVE ENDODERM

Linneberg-Agerholm, Madeleine[1], Sell, Annika Charlotte[1], Redó-Riveiro, Alba[1], Perera, Marta[1], Proks, Martin[1], Knudsen, Teresa Emmilie[2], Barral, Antonio[3], Manzanares, Miguel[3] and Brickman, Joshua M.[1]
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Mammalian blastocyst formation involves the specification of trophectoderm followed by the differentiation of the inner cell mass into either embryonic epiblast or extra-embryonic primitive endoderm. During this time, the embryo maintains a window of plasticity and can redirect its cellular fate when challenged experimentally. In this context, we found that the primitive endoderm alone was sufficient to regenerate a complete blastocyst and continue normal postimplantation development. Using an in vitro culture system for blastocyst-stage primitive endoderm, we identify a population similar to the early primitive endoderm in vivo that exhibits a similar degree of embryonic and extra-embryonic potency, forming three dimensional spheroid structures that model epiblast-primitive endoderm interactions in vitro. Lineage commitment in the early primitive endoderm is suppressed by LIF/JAK/STAT signalling, collaborating with OCT4 and the residual expression of other key pluripotency-related transcription factors to safeguard an enhancer landscape that enables multi-lineage differentiation. Our observations support the notion that transcription factor persistence underlies plasticity in regulative development and highlights the importance of the primitive endoderm in perturbed preimplantation development.

Funding Source: Lundbeck Foundation (R198-2015-412 and R286-2018-1534), Independent Research Fund Denmark (DFF-8020-00100B), Danish National Research Foundation (DNRF116) and Novo Nordisk Foundation (NNF17CC0027852 and NNF21CC0073729).

Keywords: plasticity, primitive endoderm, OCT4

9:10 AM – 9:20 AM

SELF-ORGANIZED, PERI-GASTRULATION HUMAN EMBRYO MODEL WITH TRILAMINAR EMBRYONIC DISC-, AMNION-, AND YOLK SAC-LIKE STRUCTURES

Kim, Yung Su[1], Sun, Shiyu[1], Zheng, Yi[2], Kobayashi, Norio[1], Xu, Yanhong[3], Zhai, Jinglei[3], Wang, Hongmei[3] and Fu, Jianping[4]
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Despite its importance in human development, gastrulation remains difficult to study, due to both technical and ethical challenges. Stem cell-based embryo models, including those recapitulating different aspects of pre- and peri-gastrulation human development, are emerging as promising experimental tools to study human embryogenesis. However, it remains unclear whether existing three-dimensional human embryo models can faithfully mimic the development of the trilaminar embryonic disc structure, a hallmark of human gastrulation. Even so, there remains significant ethical challenges, since most existing pre- and peri-gastrulation human embryo models are designed to follow natural developmental programs and some of them are considered as integrated models. There are ongoing discussions about the regulations of these human embryo models following those for natural human embryos. In this study, we report a transgene-free human embryo model derived solely from primed human pluripotent stem cells (hPSCs) that recapitulates different aspects of peri-gastrulation human development, including formation of trilaminar embryonic layers situated between dorsal amnion and ventral secondary yolk sac. This embryo model is thus termed the peri-gastrulation trilaminar embryonic disc (PTED) embryoid. Cell lineage identities in PTED embryoids are validated based on both immunostaining for lineage markers and benchmarking against in vivo human and monkey gastrula at the transcriptomic level. Comparative transcriptome and experimental analysis further reveal the importance of lipid metabolism in extraembryonic endoderm differentiation from hPSCs. Furthermore, primary hematopoiesis and blood cell generation in PTED embryoids are investigated. Our data further support that in PTED embryoids, embryonic and extraembryonic mesoderm cells, as well as embryonic and extraembryonic endoderm cells, share common progenitors that emerge during

peri-gastrulation development. Together, the PTED embryoid provides a promising and ethically less challenging experimental tool to study self-organizing properties of peri-gastrulation human development, shedding light on complex cellular events involved in early human embryogenesis.

Funding Source: Michigan-Cambridge Collaboration Initiative, the University of Michigan Mcubed Fund, and the Mid-career Biosciences Faculty Achievement Recognition Award from the University of Michigan.

Keywords: human gastrulation, embryo model, trilaminar embryonic disc

9:20 AM – 9:40 AM

MODELING POST-IMPLANTATION HUMAN EMBRYOGENESIS TO YOLK SAC BLOOD EMERGENCE

Ebrahimkhani, Mo R.
Department of Pathology, Pittsburgh Liver Research Center, McGowan Institute for Regenerative Medicine, University of Pittsburgh, USA

The implantation of human embryos initiates a critical developmental phase encompassing pivotal events like body axis and germ layer formation and hematopoietic system emergence. Studying early post-implantation stages of human development faces technical and ethical hurdles. We introduce heX-embryoids, a genetically inducible embryo model showcasing self-organizing peri/post-implantation cellular programs. They exhibit the formation of key structures like the amniotic cavity and bilaminar disc, as well as the generation of body axes. Additionally, heX-embryoids feature multilineage yolk sac morphogenesis with distinct waves of hematopoiesis including such as erythroid, myeloid , NK and lymphoid -like cells. Highly scalable, they transition from 2D to 3D, enhancing reproducibility. The model offers new avenues for studying early human development, developmental toxicology, and regenerative therapies.

Keywords: human embryogenesis, embryoids, stem cells, yolk sac, blood, hematopoiesis, endoderm, mesoderm

TRACK: Disease Modeling and Drug Discoveries (DMDD)

STEM CELLS FOR PERSONALIZED MEDICINE

Sponsored by: Mytos
8:15 AM – 9:45 AM
Hall 4, Entrance Level

8:20 AM – 8:40 AM
IDENTIFYING NEW MECHANISMS AND THERAPEUTIC OPPORTUNITIES FOR CARDIOMYOPATHY

van Rooij, Eva
Hubrecht Institute, Netherlands

Arrhythmogenic cardiomyopathy (ACM) is a progressive biventricular disease with a prevalence of 1:2000 to 1:5000 for which there is currently no cure. With disease progression, fibrofatty replacement of the myocardium becomes evident, consequently exacerbating life threating ventricular arrhythmias and sudden cardiac death. Approximately 50% of patients diagnosed with ACM carry one or more mutations in genes encoding desmosomal proteins most commonly in Plakophilin-2 (PKP2). Even though the genetic basis is fairly well defined, mechanisms by which the remodeling and subsequent dysfunction occur currently remain to be resolved. Our lab has used technologies like iPS cell cultures and CRISPR/Cas9 to generate human relevant models to study disease related mechanisms and to allow us to test the benefit of novel interventions. In doing so were able to show that point mutations in PKP2 are sufficient to cause a reduction in desmosomal and adherens junction proteins, which in time leads to disarray of the intercalated discs in areas of active fibrotic remodeling and cardiac dysfunction. Adeno-associated virus (AAV)-mediated supplementation of PKP2 resulted in the restoration of the desmosomal proteins and consequently an improvement in contractile function in 2 and 3D models of PKP2 mutant iPS-cardiomyocytes and Pkp2 mutant knock-in mice. These data indicate the therapeutic benefit of PKP2 restoration in human relevant pre-clinical models of ACM and support the clinical exploration of using PKP2 gene therapy in patients suffering from cardiomyopathy driven by PKP2 haploinsufficiency. Together these data show the relevance of human relevant disease models and underscore the potential of using gene therapy as a strategy to improve the quality of life for patients suffering from genetic cardiomyopathy.

Keywords: genetic cardiomyopathy iPSC EHM gene therapy

8:40 AM – 8:50 AM
PROGRAMMING AGE IN HUMAN STEM CELL MODELS OF NEURODEGENERATIVE DISEASE

Saurat, Nathalie[1], Minotti, Andrew[1], Zhang, Chao[2], Cornacchia, Daniella[1], Sikder, Trisha[1], Rahman, Maliha[1], Betel, Doron[3] and Studer, Lorenz[1]
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Aging dramatically affects the incidence of late-onset diseases. However, cellular age is reset during reprogramming posing a major technical challenge to modelling neurodegenerative diseases using pluripotent stem cell derived neurons. To address this challenge and test whether cellular age can contribute to disease progression it is critical to identify methods to both measure and manipulate age in iPSC-derived neurons. To identify tissue specific drivers of cellular age, we used a two-pronged approach. First, we established a novel whole-genome CRISPR screening platform that allowed us to perform a screen for candidate age-inducers in human neurons. Using this strategy, we identified neddylation as a regulator of neuronal age. Second, we developed a novel RNAseq-based method of scoring age based on human primary tissues and used this to perform an in-silico screen for aging regulators in the L1000 perturbagen dataset. We experimentally validated the top candidates and showed that regulators of cellular age can trigger different subsets of canonical aging hallmarks. Critically, we were able to apply our novel aging inducing strategies to accelerate the acquisition of late-onset phenotypes in human pluripotent stem cell models of Alzheimer's disease and Parkinson's disease. This acts as a proof of principle that programming age into stem cell models of disease can enable the study of late onset neurodegenerative disease phenotypes in vitro. Our work further offers a template for identifying additional age-regulators across cell types and disease states.

Keywords: aging, neurodegeneration, Alzheimer's

8:50 AM – 9:00 AM

GENE THERAPY INDUCES PIGMENTATION IN INDUCED PLURIPOTENT STEM CELLS DERIVED RETINAL PIGMENT EPITHELIUM FROM OCA1A PATIENTS AND ALBINO RAT EYE

George, Aman[1], Leigh, Arnold[1], Selzer, Evan[1], Pfister, Tyler[1], DeYoung, Charles[1], Villasmil, Rafael[2], Abu-Asab, Mones[2], Hiriyana, Suja[3], Hwang, Philsang[3], Maminishkis, Arvydas[4], Li, Tiansen[3], Bharti, Kapil[4] and Brooks, Brian[5]

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Oculocutaneous albinism type 1A (OCA1A) is caused due to mutations in TYROSINASE gene and results in pigmentation defects of the skin, hair, and eyes. OCA1A is associated with abnormal development of the fovea, a retina structure important for high-acuity and central vision. It is still unknown how the lack of pigmentation in retinal pigment epithelium (RPE) and choroid affects the neighboring neural retina during development. OCA1A is the most severe and prevalent form of albinism and currently no treatment is available. We provide proof-of-principle of an effective gene therapy-based strategy for future human application in OCA1A patients. Here we show that a AAV based TYROSINASE gene delivery under the control of human BESTROPHIN promoter VMD2, can be successfully employed to induce pigmentation in human RPE monolayer tissue, derived from OCA1A patients, via induced pluripotent stem cells. One-time treatment for 48 hours, was able to induce pigmentation that was sustained for one year post treatment with varying efficiency among three biologically different OCA1A RPE monolayer, tested in vitro. The increased pigmentation was further confirmed by transmission electron microscopy where significantly increased number of mature and pigmented melanosomes were observed in AAV treated RPE as opposed to untreated RPE. This increased pigmentation was achieved without significantly compromising the RPE monolayer tissue integrity, apical-basal polarization, cellular morphology, and functionally relevant gene expression pattern. This human RPE specific construct was able to induce pigmentation in albino rat RPE and choroid when delivered via suprachoroidal injection into the eyes. Our strategy can be employed to not only induce pigmentation, but also efficiently deliver other target genes, without significantly compromising monolayer tissue integrity and viability of human RPE, a prime gene therapy target tissue for many degenerative disorders affecting vision.

Funding Source: NIH Intramural

Keywords: albinism gene-therapy, eye retinal pigment epithelium, melanosome pigment

9:00 AM – 9:10 AM

HIGH-THROUGHPUT NEURAL CONNECTIVITY MAPPING IN HUMAN BRAIN ORGANOIDS

Vertesy, Abel[1], Doleschall, Balint[1], Najm, Ramsey[1], Li, Chong[1], Burkard, Thomas[2], Novatchkova, Maria[3], Ben-Simon, Yoav[4] and Knoblich, Jürgen[1]

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The human brain represents a complex network of ~80 billion neurons, which changes with age and environment, and is vulnerable to perturbations. To understand how neural networks form and why they change in disease, we need to determine connectivity, gene expression, and genotype in the same cell. Current single-neuron connectivity mapping methods cannot cover these modalities, nor are they scalable to 10's or 100's of conditions. To overcome these limitations in scale and transcriptional information, we have developed a 'connectomics-by-sequencing' method combining barcoded, retrograde transsynaptic rabies tracing with single-cell RNA sequencing to map thousands of synaptic networks with their transcriptomes. We then applied our new method to human cortical organoids, which allow scalable, accessible, and sophisticated 3D human disease modeling. With our data, we described the connectivity preferences of different classes of neurons, and linked connectivity to gene expression. We identified the connectivity patterns of thousands of neurons across different ages, cell lines, and disease conditions. We identified a stage of organoid development with drastic changes in network composition. Investigating the most mature organoids, we found that a fixed network stoichiometry exists for excitatory neurons, but not for interneurons. This means that, within conditions, we find a fixed cell type ratio in networks, independent of tissue composition. Finally, we applied our method to Tuberous Sclerosis Complex (TSC), a neurodevelopmental disorder where cell fate defects cause severe intractable childhood epilepsy. With multiple complementary methods, we showed that our previously established disease model also recapitulates changes in network activity. We can now distinguish healthy and diseased network types, and we linked altered connectivity to transcriptional state. Our data have the potential to explain neurodevelopmental disorders on the cortical circuit level, identifying the most affected neuronal subtypes and synaptic connections which can provide a basis for potential therapeutic intervention.

Funding Source: A.V. received funding from Postdoctoral Fellowships of Marie Skł.Curie Actions (898231) and EMBO (ALTF 1112-2019), J.A.K.from the Austria's FWF (F 7804-B, P 35680, P 35369) and European Research Council (695642 and 874769).

Keywords: connectomics, brain organoids, neurodevelopmental disorders

9:10 AM – 9:20 AM

RESTORING DELETED IN LIVER CANCER 1 (DLC1) ISOFORM 1 EXPRESSION IS A MORE EFFECTIVE GENE THERAPY FOR SPINAL MUSCULAR ATROPHY

Shi, Tianyuan[1], Chang, Hanlin[1], Huang, Zhihao[2], Liao, Baoshan[3], Lo, Su Hao[4], Xiong, Wenjun[3], Liu, Jessica Aijia[5], Cheung, Martin[1] and Chan, Sophelia Hoi Shan[6]

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Spinal muscular atrophy (SMA) is a neuromuscular disease caused by the loss of the ubiquitously expressed survival motor neuron (SMN) protein, resulting in the selective degeneration of spinal motor neurons (MNs). While current SMN-enhancing therapies have

shown promise in reducing disease severity, they do not reverse motor axon degeneration, leading to limited locomotor recovery. Additionally, the mechanism underlying the specific loss of MNs remains unknown. A previous report identified Deleted in Liver Cancer 1 (DLC1) as the most down-regulated gene in MNs derived from a SMA patient but its precise roles in MN development and SMA pathogenesis are unknown. Here, we found that among five isoforms in humans, DLC1 isoform 1 (DLC1-i1) is predominantly expressed in MN lineage compared to other neuronal subtypes, and its reduced expression was detected in MNs derived from SMA patients' urine-derived induced pluripotent stem cells (UiPSCs). Functional studies revealed the crucial role of DLC1-i1 in human motor axon outgrowth and MN survival. Mass spectrometry and RNA immunoprecipitation analysis identified many RNA binding proteins associated with DLC1-i1 that are crucial for axonal mRNA transport to facilitate axon growth. The single-cell transcriptomic analysis confirmed a marked reduction of DLC1-i1 expression in neuromuscular organoids (NMOs) derived from SMA patients' UiPSCs. These NMOs showed defective formation of neuromuscular junctions (NMJs) and increased cell death, which can be recapitulated by DLC1-i1 knockdown in wild-type NMOs. Overexpression of DLC1-i1 restores NMJ formation and cell survival in SMA NMOs. Moreover, we detected reduced DLC1-i1 expression in the lumbar spinal cord of SMA mice, indicating conservation of dysregulated DLC1-i1 expression in both SMA mice and patients MNs. Postnatal knockout of DLC1 partly recapitulated SMA phenotypes, highlighting the importance of DLC1-i1 in MN development and SMA pathogenesis. Importantly, gene therapy with AAV PhP.eB-DLC1-i1 was more effective than SMN in improving the lifespan and locomotor activity of SMA mice. Altogether, our findings reveal that the loss of MN-specific DLC1-i1 expression partly mediates the neuromuscular defects in SMA and DLC1-i1 is a promising candidate for gene therapy to enhance the efficacy of SMA treatment.

Funding Source: Research Grants Council and the University Grants Council of HK (GRF_17114619, 17102420, R7018-23), URC Seed Fund for Collaborative Research 2022/2023, Liu Po Shan/Dr Vincent Liu Endowment Fund for Motor Neurone Disease 2021-2022.

Keywords: spinal muscular atrophy, motor neuron, DLC1 isoform 1

9:20 AM – 9:40 AM

INTESTINAL ORGANOIDS FOR CYSTIC FIBROSIS PRECISION MEDICINE

Beekman, Jeffrey
University Medical Center Utrecht, Netherlands

Patient-derived primary adult stem cell cultures hold great promise for precision medicine applications. Here, we report progress on the use of fluid secretion phenotypes of patient-derived 3D intestinal organoids for clinical applications in the context of cystic fibrosis. Cystic fibrosis is a rare genetic disease caused by potentially more than 2000 variants in the CFTR gene. The majority of CFTR variants remain uncharacterised, which impact the ability to inform on individual disease progression and therapeutic benefit. Luminal fluid secretion phenotypes in intestinal organoids are strongly dependent on CFTR function, and can be used to estimate individual CFTR function, and the ability of drugs to modify CFTR function. I will discuss the performance of intestinal organoid fluid secretion assays of large collections of patient-derived organoids for prediction of individual disease and therapeutic benefit, and the development of new cystic fibrosis drugs for people with rare variants of CFTR who currently remain in large need for new CFTR function increasing treatments. Our data demonstrates that fluid secretion phenotypes of patient-derived intestinal organoids can be implemented at a European scale for the functional characterisation of CFTR variants in the context of multiple clinical applications.

Keywords: intestinal organoids, precision medicine, cystic fibrosis

TRACK: Disease Modeling and Drug Discovery (DMDD)

PLENARY V: ORGANOID MODELS OF DISEASE

Sponsored by: Stem Cell Network
10:00 AM – 11:25 AM
Hall 1, Level 2

10:05 AM – 10:25 AM

LESSONS FROM ORGANOIDS TO STUDY TISSUE REGENERATION AND DISEASE

Lee, Joo-Hyeon
University of Cambridge, UK

Organoids have become indispensable tools in various research fields, transforming preclinical models with their ability to culture tissues directly from patients and induce pathogenesis for disease modeling. We previously developed 3D organoid co-culture models from mouse lung tissues, which recapitulate stem-niche interactions for lung regeneration. Additionally, we recently created cell type-specific organoids from healthy and diseased human lung tissues, which exhibit cellular features of tissue origins, in defined conditions. In this presentation, we will explore the fidelity of in vitro models to their tissue sources, their representation of diverse patient populations, and their ability to capture patient-specific nuances. We will also discuss the impact of altered tissue mechanics in lung diseases and strategies to target these changes in vitro for innovative therapeutic approaches.

Keywords: organoids, tissue regeneration, disease modeling

10:25 AM – 10:45 AM

MICROENVIRONMENTAL REGULATION OF VASCULAR FATE, ASSEMBLY, AND FUNCTION

Gerecht, Sharon
Duke University, USA

Vascular differentiation, morphogenesis, and eventual homeostasis occur in a complex and dynamic milieu. Using engineering approaches, we recapitulate aspects of the developing or diseased tissue in vitro to understand how the surrounding milieu regulates fate and tissue assembly and function. We focus on the extracellular matrix, which provides critical support for vascular cell adhesion, proliferation, migration, and morphogenesis. Additionally, we study hypoxia, a critical factor promoting vascularization during embryonic development, injury, and tumor growth. In this talk, I will present our recent efforts to understand how these physicochemical cues and downstream signaling pathways impact vascular fate, assembly, and function, leading to fundamental knowledge and future therapeutics.

Keywords: matrix, hypoxia, tissue engineering

10:45 AM – 11:05 AM

EXTRACELLULAR MORPHOGENS AND GENOMIC VARIATION INSTRUCT CELL TYPE SPECIFICATION PROGRAMS IN HUMAN PLURIPOTENT CELLS

Vaccarino, Flora M.[1], Scuderi, Soraya[2], Kang, Taeyun[2], Jourdon, Alexandre[2], Yang, Liang[2], Wu, Feinan[2], Nelson, Alex[2], Anderson, George[2], Mariani, Jessica[2], Tomasini, Livia[2], Abyzov, Alexej[3] and Levchenko, Andre[2]
[1]Child Study Center, Yale University, USA, [2]Yale University, USA, [3]Mayo Clinic, USA

Neuronal subtype specification in the vertebrate neural tube is thought to be a consequence of embryonic pattern formation, however the extent to which embryonic patterning is cell intrinsic or dictated by the microenvironment is debated. Distinct neuronal subtypes are generated in a precise spatial order from progenitor cells according to their location along the anterior-posterior and dorsal-ventral axes. To understand the sufficiency of this dual patterning in the determination of cellular diversity in human brain development, we designed a mesofluidic device to expose spheres of human induced pluripotent stem cells (iPSC) to concomitant orthogonal gradients of a posteriorizing and a ventralizing morphogen, activating WNT and sonic hedgehog (SHH) signaling, respectively. We demonstrate that this dual gradient specifies organoids into different regional identities. Using projection of organoids single cell transcriptomes on a fetal human brain atlas, we demonstrate that device-patterned organoids generate the major neuronal lineages of the forebrain, midbrain, and hindbrain. We relate the production of these neuronal lineages to the activation of defined genetic and molecular programs triggered by morphogens crosstalk. Applying this method to human iPSC lines from six different genetic backgrounds revealed substantial differences in patterning response, suggesting that interindividual genomic variation has a drastic impact on brain lineages formation during brain development. We conclude that both cell-extrinsic factors and cell-intrinsic genomic variations guide and modify neural patterning in human development.

Keywords: pluripotent stem cells, morphogens, patterning

11:05 AM – 11:25 AM
UNDERSTANDING OF HUMAN ORGAN FUNCTION AND DISEASE USING ORGANOID TECHNOLOGY

Sato, Toshiro
Keio University, Japan

Advancements in sequencing technology have propelled rapid progress in genomic research on human diseases. However, a fundamental question persists: how do genomic abnormalities manifest as clinically observed disease phenotypes? Traditionally, this correlation has been explored using mouse gene engineering models in biomedical research. However, the complicated nature of human diseases, often involving multiple genetic variants and environmental exposures, poses challenges for in vitro disease recapitulation. In recent years, organoid culture technology and CRISPR-Cas9 genome editing have emerged as promising tools to overcome these limitations. Organoid technology facilitates the culture of tissue stem cells in an environment closely resembling the in vivo state, utilizing niche factors supporting tissue stem cell maintenance. Initially developed for mouse intestinal epithelium, this technique has been successfully adapted to various organs across multiple species and applied in culturing both normal and diseased human tissues, thereby enabling the observation of their biological behavior. Furthermore, the integration of genome editing technology allows for the introduction of disease-related gene abnormalities into normal tissue cells, establishing a novel research methodology for studying genotype-phenotype correlations using human tissue cells, which is distinct from conventional genetically modified mouse models. Through this integrated approach, leveraging disease tissue models and genome-edited organoids, human disease research has entered a new phase. In my talk, I will showcase the latest research findings from the development of organoid technology and the investigation of diseased tissues.

Keywords: organoid, Wnt, tissue stem cells

TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)

MAINTENANCE AND REGENERATION OF TISSUE ARCHITECTURE

1:30 PM – 3:00 PM
Hall Y1-6, Level 2

1:35 PM – 1:55 PM
RETURN TO HOME-OSTASIS – THE MECHANISM TO RESOLVE INJURY RESPONSE OF THE INTESTINE

Koo, Bon-Kyoung
Institute of Molecular Biotechnology (IMBA), Austria and Center for Genome Engineering, Institute for Basic Science, Korea

Intestinal stem cells (ISCs) are highly vulnerable to damage, being in a constant state of proliferation. Reserve stem cells repair the intestinal epithelium following damage-induced ablation of ISCs. Here, we report that an epigenetic regulator restores homeostasis of the intestinal epithelium after initial damage-induced repair. In *Phf16*$^{-/Y}$ mice, revival stem cells (revSCs) showed defects in exiting the regenerative state and intestinal crypt regeneration failed, even though revSCs were still induced in response to tissue damage, as observed by single-cell RNA-sequencing. Analysis of *Phf16*$^{-/Y}$ intestinal organoids by RNA-sequencing and ATAC-sequencing revealed that PHF16 restores homeostasis of the intestinal epithelium by inducing RAR/RXR target genes through HBO1-mediated histone H3K14 acetylation, while at the same time counteracting YAP/TAZ activity by ubiquitination of CDC73. Together, our findings demonstrate the importance of timely suppression of regenerative activity by PHF16 for the restoration of gut homeostasis after acute tissue injury.

1:55 PM – 2:05 PM
A CELL SIZE HOMEOSTASIS MECHANISM AUTONOMOUSLY DETERMINES THE TIMING OF THE G1/S TRANSITION FOR MAMMALIAN STEM CELLS IN VIVO

Xie, Shicong[1], Zhang, Shuyuan[1], de Medeiros, Gustavo[2], Liberali, Prisca[2] and Skotheim, Jan[1]
[1]Biology, Stanford University, USA, [2]Liberali Group, Friedrich Miescher Institute for Biomedical Research, Switzerland

In adult tissues, heterogeneity in stem cell cycle progression underlies the spatiotemporal dynamics of when and where tissues regenerate and turn over. We show that cell size homeostasis, which couples cell cycle progression to cell growth, is the predominant mechanism that governs the heterogeneity of stem cell cycle timing. Using week-long intravital imaging of intrafollicular epidermal stem cells and 3D reconstruction of cell growth trajectory, we resolved skin

stem cell growth in vivo at single cell resolution within a living mouse. We find that the coupling of G1/S transition to cell size accounts for the majority of the heterogeneity of cell cycle timing, irrespective of varying features of the stem cell microenvironment. We also show that ectopically disrupting the tissue microenvironment does not change the quantitative way in which cell size and G1/S transition are coupled. Lastly, we find that deletion of the retinoblastoma protein RB and its homolog RBL1 leads to the ablation this autonomous cell size homeostasis in vivo. This work identifies that the RB pathway encodes a cell size homeostasis mechanism that operates autonomously in the adult skin to determine skin stem cell cycle dynamics.

Funding Source: NIGMS RO1 NIGMS R35 NIGMS K99 CZ Biohub Investigator fund

Keywords: tissue homeostasis, cell cycle progression, epidermal stem cells

2:05 PM – 2:15 PM

SPATIAL TRANSCRIPTOMICS REVEAL ASYMMETRIC CELLULAR RESPONSES TO INJURY IN THE REGENERATING SPINY MOUSE (ACOMYS) EAR

Bartscherer, Kerstin[1], van Beijnum, Henriette[2], Koopmans, Tim[2], Tomasso, Antonio[2], Bakkers, Jeroen[2], Alemany, Anna[3] and Berezikov, Eugene[4]

[1]Biology, Osnabrueck University, Germany, [2]Hubrecht Institute, Netherlands, [3]Department of Anatomy and Embryology, Leiden University Medical Centre, Netherlands, [4]European Research Institute for the Biology of Ageing, University of Groningen, Netherlands

In contrast to other mammals, the spiny mouse (Acomys) regenerates skin and ear tissue, which includes hair follicles, glands and cartilage, in a scar-free manner. Interestingly, ear punch regeneration is asymmetric with a regeneration blastema only forming at the proximal side of the wound. Here, we show that cues infiltrating the ear from the proximal side are required for normal regeneration and use spatially resolved transcriptomics (Tomo-seq) to understand the molecular and cellular events underlying this process. Analysing gene expression across the ear and comparing expression modules between proximal and distal wound sides, we identify asymmetric gene expression patterns and pinpoint regenerative processes in space and time. Moreover, using a comparative approach with non-regenerative rodents (Mus, Meriones) we strengthen a hypothesis in which particularities in the injury-induced immune response may be one of the crucial determinants for why spiny mice regenerate while their relatives do not.

Funding Source: ERC-2016-StG 716894-IniReg

Keywords: regeneration, spiny mouse, spatial transcriptomics

2:15 PM – 2:25 PM

OVERARCHING SINGLE-CELL MAP AND STEM CELL LANDSCAPE OF THE MOUSE ENDOCRINE PITUITARY ACROSS KEY TIME POINTS OF LIFE IN HEALTH AND DISEASE

Vankelecom, Hugo[1], De Vriendt, Silke[1], Abaylı, Berkehür[1], Hermans, Florian[2] and Laporte, Emma[1]

[1]Development and Regeneration, KU Leuven, Belgium, [2]Cardiology and Organ Systems, Biomedical Research Institute, Hasselt University, Belgium

The pituitary represents the core gland of the endocrine system, governing vital processes such as body growth, metabolism, sexual development, reproduction, stress and immunity. To perform this key role, the gland houses various hormonal cell types as well as stem cells. Despite their convincing assignment almost 20 years ago, the stem cell population remains enigmatic regarding molecular identity, cellular complexity, stem cell niche regulatory circuit and functional role. To fill these important gaps, we have built a comprehensive single-cell (sc) transcriptomic atlas of the mouse endocrine pituitary across key time points of life covering neonatal maturation, young-adult homeostasis and progressive aging, in both healthy and diseased (damage, tumor) conditions. We show the strong applicability of this new atlas to unravel pituitary (patho)biology by focusing on the still enigmatic stem cells and performing proof-of-principle inquiries into their molecular phenotype, cellular complexity and regulatory interactions with other cell types to unravel the tissue's stem cell niche. In addition, we functionally interrogated these molecular findings using our pituitary stem cell organoid model. Several growth factor pathways were pinpointed to regulate pituitary stem cell behavior. Moreover, our exploration reinforced that aging is associated with increasing inflammatory/immune nature of the pituitary stem cells. Finally, we touched upon the translatability of our mouse pituitary map-based findings to humans and observed specific commonalities. In summary, we composed an overarching mouse endocrine-pituitary sc transcriptomic atlas which provides a powerful tool to gain deep insight into the pituitary cells' molecular and functional landscape, especially into the cellular complexities and regulatory networks of the puzzling pituitary stem cell compartment across postnatal life. A thorough understanding of the pituitary (stem) cells is not only essential to fully grasp the biology of this central endocrine organ, but also to gain insight into its burdening disorders, which eventually may lead to the identification of therapeutic possibilities. The atlas will be made publicly available in an easily manageable form to accelerate basic and translational pituitary research.

Funding Source: This work was supported by grants from the KU Leuven Research Fund and from the Fund for Scientific Research Flanders (FWO).

Keywords: pituitary stem cells, single-cell transcriptomics, pituitary aging

2:25 PM – 2:35 PM

VITAMIN A RESOLVES LINEAGE PLASTICITY TO ORCHESTRATE STEM CELL LINEAGE CHOICES

Tierney, Matthew and Fuchs, Elaine

Mammalian Cell Biology and Development, The Rockefeller University, USA

Lineage plasticity – a state of dual fate expression – is required to release stem cells from their niche constraints and redirect them to tissue compartments where they are most needed. Here, we found that without resolving lineage plasticity, skin stem cells cannot effectively generate each lineage in vitro nor regrow hair and repair wounded epidermis in vivo. A small molecule screen unearthed retinoic acid as a critical regulator. Combining high-throughput approaches, cell culture and in vivo mouse genetics, we dissected its roles in tissue regeneration. We found that retinoic acid is made locally in hair follicle stem cell niches, where its levels determine identity and usage. Our findings have therapeutic implications for hair growth as well as chronic wounds and cancers where lineage plasticity is unresolved.

Keywords: hair follicle stem cells, cellular plasticity, wound repair

2:35 PM – 2:55 PM
GENE REGULATORY MECHANISMS OF TISSUE REGENERATION IN ZEBRAFISH

Poss, Kenneth
Duke Regeneration Center, Duke University Medical Center, USA

Abstract not available at time of publishing.

NOVEL APPROACHES TO PROGRAM AND PERTURB CELL FATE

1:30 PM – 3:00 PM
Hall 4, Entrance Level

1:35 PM – 1:55 PM
A COMBINATORIAL TRANSCRIPTION FACTOR SCREENING PLATFORM FOR IMMUNE CELL REPROGRAMMING

Pereira, Filipe
Lund Stem Cell Center, Wallenberg Centre for Molecular Medicine, Lund University, Sweden

The direct cell fate reprogramming of immune cells offers enormous potential for regenerative medicine and immunotherapy but is limited by the identification of cell type and cell state-specific instructive transcription factor (TF) networks. Here, we develop REPROcode, a combinatorial platform to experimentally screen TF combinations for immune cell reprogramming at the single cell level. We first generated a immune-restricted TF library through an aggregated ranking method based on single-cell gene expression data. Next, we developed a screening approach that combines single-cell mRNA sequencing with TF barcoding to enable the identification of potent combinations for direct reprogramming. We validated the efficacy of our screening method by inducing cDC1 reprogramming with 9 barcoded TFs with opposing effects on reprogramming. Reassuringly, successfully reprogrammed cells harbored the highest frequency of PU.1, IRF8 and BATF3 combination, which was previously shown to induce cDC1-like cells from fibroblasts or tumor cells. Measuring TF barcode expression in single cells uncovered the optimal TF stoichiometry required for successful reprogramming and identified GATA2 as a synergistic TF that improved fidelity of cDC1 reprogramming. Additionally, we demonstrated the scalability of the approach by employing a even-distributed library of 42 TFs using both droplet and microwell single-cell sequencing techniques. Finally, we utilized REPROcode with 48 TFs enriched cDC1, cDC2, and pDC lineages, enabling the induction of diverse dendritic cell identities and states dependent on the combination of TFs received. Collectively, the REPROcode platform advances our foundational knowledge of immune cell transcriptional networks. We lay the groundwork for inducing immune cell identities and functional states that control discrete modules of the immune response significantly advancing the development of targeted immunotherapeutic strategies.

Keywords: combinatorial perturbation, cellular reprogramming, single cell screening, transcription factor, dendritic cells

1:55 PM – 2:05 PM
VALIDATED GENOMIC SAFE HARBOUR LOCI & LANDING-PAD CASSETTES ENABLE EASY INTEGRATION AND STABLE TRANSGENE EXPRESSION IN HUMAN PLURIPOTENT STEM CELLS AND DIFFERENTIATED PROGENY

Autio, Matias Ilmari[1], Bin Amin, Talal[2], Ding, Shirley[3], Do, Dang Vinh[2], Foo, Roger[4], Lee, Mick[4], Motakis, Efthymios[4], Perrin, Arnaud[2], Tan, Joanna[2], Tan, Wei Xuan[3], Teo, Adrian[3], Tiang, Zenia[4] and Wang, Jiaxu[2]
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Stable expression of transgenes is essential in both therapeutic and research applications. Traditionally, transgene integration has been accomplished via viral vectors in a semi-random fashion, but with inherent integration site biases linked to the type of virus used. The randomly integrated transgenes may undergo silencing and more concerningly, can also lead to dysregulation of endogenous genes that may give rise to malignant transformation of cells. Genomic safe harbour (GSH) loci have been suggested as safe sites for transgene integration. Criteria proposed for a putative universal GSH include a set distance from coding and non-coding genes, with added separation from known oncogenes and miRNAs, and no disruption of transcriptional units or ultra-conserved regions. To date, several sites in the human genome have been used for directed integration; however, none of these pass scrutiny as bona fide GSH. Here, we conducted a computational analysis to filter sites that meet criteria for GSH loci. In addition to the safety criteria, we identified regions that reside in active chromosomal compartments in many human cell and tissue types. Our analysis yielded a final list of 25 unique putative GSH that are predicted to be accessible in multiple cell types. We used human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs) as well as their differentiated progeny to validate stable transgene expression and minimal disruption of the native transcriptome in three of the putative GSH sites in vitro. Furthermore, we generated hESC and iPSC lines with constitutive landing pad expression constructs targeted into the three different GSH. For high efficiency integration of transgenes, we optimised the Bxbl-recombinase and other reagents to reach approximately 20% integration of a payload without selection. The generated landing pad human pluripotent cell lines and recombination reagents allow for easy targeted expression of genes of interest in the pluripotent cell state or in cells differentiated to the cell type of interest. We also demonstrate the integration of more complex payload cassettes that enable e.g. inducible expression or reporter function from the GSH. With further testing the validated GSH may potentially enable expression of therapeutic genes in a cell therapy setting.

Funding Source: Biomedical Research Council (1610851033) and Agency for Science Technology and Research (202D8020), Singapore

Keywords: genomic safe harbour, recombinase mediated cassette exchange, pluripotent stem cell

2:05 PM – 2:15 PM
BASE EDITING IN HUMAN EMBRYOS ENABLES KNOCKDOWN OF PCSK9 WITHOUT DETRIMENTAL CHROMOSOMAL CHANGES

Jerabek, Stepan[1], Kim, Jimin[1], Kulmann, Marcos[2], Robles, Alex[3], Sung, Julie[1], Marin, Diego[4], Xu, Jia[4], Costa, Bruna[5], Hwang, Gue-Ho[6], Jung, Chanju[6], Dolezal, Michal[7], Quinn, Peter[8], Pichova, Iva[7], Woo, Jae Sung[9], Bae, Sangsu[6], Treff, Nathan[4] and Egli, Dieter[1]
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Nearly all diseases have a genetic component, and the genome received at conception is thus key to human health. Better knowledge about mechanisms protecting the genome after DNA damage in early human embryos will be relevant for comprehension of the origin of de novo mutations and for future efforts to prevent genetic disorders. Genome editing tools enable the introduction of a defined lesion at an intended genomic site and the analysis of DNA repair outcomes. Previously, our laboratory found that CRISPR/Cas9-induced DNA double-strand breaks (DSBs) at the EYS locus lead to common chromosomal abnormalities in human embryos. Here, we detected segmental aneuploidies following CRISPR/Cas9 cleavage at other genes (MYBPC3, CCR5, and HBG), broadening the risks of on-target DNA DSBs in human embryos using this technology. Newer genome editing tools, such as base editing and prime editing, introduce nicks rather than DSBs. We focused on base editing of two therapeutically relevant genes (PCSK9 and HBG) and injected the editing tool into human zygotes either as RNA or purified protein. Sequencing analysis of DNA from single blastomeres revealed multiplex on-target editing efficiency higher than 80%, with few undesired editing byproducts. Using single nucleotide polymorphism arrays, we demonstrated that base editing does not cause segmental chromosome changes detrimental to further development. We derived the first embryonic stem cell (ESC) lines from base-edited blastocyst-stage embryos and used them for the assessment of editing at potential off-target sites. We also delivered the base editor into MII oocytes during intracytoplasmic sperm injection to determine the kinetics of base editing and the prevalence of genetic mosaicism. Overall, this work establishes new understandings of DNA repair in the early human embryo, emphasizes the risks and potential of germline genome editing, and shapes future discussions on the ethics of germline gene therapy.

Funding Source: IOCB Tech Foundation

Keywords: human embryo, base editing, DNA repair

2:15 PM – 2:25 PM

UNCOVERING REGULATORS OF DEGREES OF CELLULAR PLASTICITY BY DIRECT REPROGRAMMING

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Developmental specification entails the sequential generation of stem cells, progenitors and somatic cell identities. The limited understanding of how these different degrees of plasticity are established and modified hinders the clinical applicability of regenerative medicine approaches. Here, we employed direct cell reprogramming to uncover molecular drivers that define degrees of cellular plasticity, allowing or restricting the interconversion between cellular identities with different potencies. Hence, we implemented CRISPR/Cas9 perturbation screenings coupled with three different reprogramming systems directed to pluripotency (pluripotent stem cells, iPSCs), multipotency (hematopoietic stem and progenitor cells, iHSPCs) and unipotency (dendritic cells, iDCs). Using human dermal fibroblasts from several donors, we optimized the efficient silencing with a sgRNA library targeting 1,345 genes encoding for chromatin and RNA regulators. We generated iDC, iHSPCs and iPSCs by expressing combinations of reprogramming-inducing transcription factors and sorted successful reprogrammed and non-reprogrammed cell populations. Through deep sequencing, we mapped sgRNA abundance and identified the candidate genes acting as barriers and facilitators of each conversion. For the DC reprogramming, we identified 130 barriers and 62 facilitators that were significantly represented across all donors. For HSPC reprogramming, we found 71 barriers and 92 facilitators. When overlapping these results, we found 10 barriers and 3 facilitators that were shared among both reprogramming systems. These genes include the chromatin remodeling factor RB Binding Protein-4 (RBBP4) and the Splicing Factor 3B subunit 6 (SF3B6) as the main shared barriers. Conversely, Protein Polybromo-1 (PBRM1), involved in nucleosome remodeling, emerged as the top common facilitator. Our work provides a perturbation overlay approach among several reprogramming systems to uncover genes associated with the regulation of the degrees of plasticity, for deeper exploration and extrapolation to regeneration or cancer initiation events. Overall, this study delves into the principles of plasticity and reveals avenues for interrogating complex processes that establish competence to generate cellular identities.

Keywords: cellular reprogramming, cell plasticity, CRISPR/Cas9

2:25 PM – 2:35 PM

A CRISPR SCREEN COMBINED WITH SINGLE-CELL TRANSCRIPTOMICS IN HUMAN PLURIPOTENT STEM CELLS DEFINES THE HIERARCHY OF TRANSCRIPTION FACTORS GOVERNING PLURIPOTENCY AND DIFFERENTIATION

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Human pluripotent stem cells (hPSCs) are defined by their ability to give rise to the three embryonic germ layers, together with a limitless propagation potential in culture, making them highly attractive for medicinal and research applications. We have previously defined the essentialome of hPSCs through a genome-wide CRISPR screen in haploid cells, which serve as an ideal platform for genetic screens. This analysis led to the identification of the transcription factors (TF) necessary for the growth of hPSCs. Nevertheless, the role of each TF in maintaining pluripotency and the hierarchy between those TFs is still obscure. We have thus integrated data from our genome-wide screen with results from tissue-specific expression, identifying over 40 transcription factors enriched in expression and essential for growth in hPSCs. Interestingly, the TF list included genes that are well implicated in the pluripotency network, together with novel TFs with an unknown role in hPSCs. To understand the functionality of these TFs, we targeted them with a pooled CRISPR library in haploid hPSCs, and performed single cell RNA-seq, obtaining each cell's perturbation label and transcriptome. Indeed, we observed that most of these TFs form a remarkably interconnected regulatory network, in agreement with their essentiality and increased expression in hPSCs. Importantly, we were able to dissect TF modules that control different cellular processes and developmental programs, including

some TF that serve as gatekeepers, regulating mesendodermal or neuroectodermal fate. We further show that while different TFs have a set of genes they regulate exclusively, many genes are regulated by multiple TF, revealing feed-forward loops which may help to balance between pluripotency maintainance and a robust response to a strong differentiation signal. Finally, to understand whether the same TF network functions similarly between different pluripotency states, we repeat the perturbation under the naïve ground state. In summary, this analysis enabled the construction of an extended network for human pluripotency. This network does not only shed new light on early human developmental principles but can hopefully be better manipulated in the future to enhance the use of hPSCs for disease modelling or cell therapy.

Keywords: human pluripotent stem cells, pluripotency, single cell CRISPR screen

2:35 PM – 2:55 PM

IDENTIFYING NOVEL FACTORS THAT AFFECT CELLULAR REPROGRAMMING BY USING THE GENETIC MODEL ORGANISM C. ELEGANS

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We use the nematode C. elegans as a powerful model organism for in vivo studies of cell fate reprogramming. Focusing on transcription factor-induced direct reprogramming, we previously identified evolutionarily conserved factors that limit cell identity conversion by transcription factors (TFs). Systematic investigation of cell fate maintenance by applying whole-genome genetic screening identified several factors that block TF-induced direct reprogramming. These factors are involved in chromatin, metabolism, proteostasis, and other cellular processes, including small RNA pathways. Notably, previous studies and ongoing research support the notion that many identified factors in C. elegans have analogous functions in human cells with regard to impacting cellular reprogramming. I will report on recent findings, including the identification of a highly conserved isocitrate-dehydrogenase as an impediment to direct reprogramming in living animals. Depletion of this mitochondrial enzyme allows TF-induced conversion of germ cells into neurons in worms. Furthermore, we developed a novel direct reprogramming phenomenon, allowing us to study extensive morphological changes during direct reprogramming in vivo. In particular, we observe the remarkable generation of an intestinal lumen by a single cell. Additionally, our novel reprogramming system allowed the identification of a small RNA pathway, which is required for cellular conversion. Overall, I will present that the genetic model organism C. elegans is a powerful in vivo system for identifying uncharted implications of molecular processes in cellular reprogramming, which may also be highly relevant in reprogramming human cells.

Keywords: direct reprogramming, C. elegans, genetics

PSC-BASED CELL THERAPIES

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Hall 3, Entrance Level

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AUTOLOGOUS 3D ENGINEERED TISSUES FOR THERAPEUTIC APPLICATIONS

Harel Adar, Tamar
Matricelf, Israel

Spinal Cord Injury (SCI) affects hundreds of thousands of individuals worldwide annually, resulting in substantial disabilities and immense economic and social burden. Unfortunately, despite extensive research efforts, an effective curative solution remains elusive. The emergence of tissue engineering technologies holds promise for ameliorating SCI patients' devastating condition. Ongoing advancements often rely on synthetic materials or allogeneic cells which may lead to immunogenic complications culminating in inflammation and transplant rejection. This highlights the critical need for safe and efficacious alternatives for the treatment of SCI. At Matricelf we developed an innovative platform merging stem cell science with tissue engineering technologies. Our platform utilizes induced pluripotent stem cells (iPSCs) derived from the patient's blood. These iPSCs are differentiated within an Extracellular Matrix scaffold crafted from the patient's omentum (intra-abdominal fatty tissue) forming a fully autologous, functional 3D neural tissue, personalized for each SCI patient. The neural tissue prominently expresses key neuronal markers at both the gene and protein levels. These markers include microtubule elements, neurofilaments, motor neuron-specific indicators, synaptic markers, and cholinergic neuron markers. Moreover, we have observed the emergence of extensive electrical activity within the neural tissue using a high-density microelectrode array. Spontaneous and synchronized firing patterns were detected, suggesting the successful establishment of functional neural networks within the 3D architecture of the engineered tissue. Feasibility in vivo study in a chronic hemi-section SCI mouse model shows promising efficacy results, emphasizing the potential of the engineered neural tissue to regenerate an injured spinal cord. Furthermore, preliminary safety results in rats demonstrated no evidence of teratoma formation. Next, we are looking to prove safety and efficacy in definitive animal studies which will pave the way to a phase I/IIa safety and feasibility clinical trial in humans. This innovative technology holds great promise to become a life-changing solution through personalized autologous tissue transplantation, offering new hope for those affected by SCI.

Keywords: autologous, spinal cord injury, iPSCs

1:55 PM – 2:05 PM

CO-GRAFT OF DOPAMINE PROGENITORS AND SUPPORTING CELLS TO ENHANCE CELL-BASED THERAPY FOR PARKINSON'S DISEASE

Sozzi, Edoardo[1], Garcia Garrote, Maria[1], Mudannayake, Janitha[1], Åkerblom, Malin[1], Mattsson, Bengt[1], Nilsson, Fredrik[1], Galeotti, Greta[2], Ramos Passarello, German[1], Corsi, Sara[1], Habekost, Mette[1], Scaramuzza, Linda[2], Besusso, Dario[2], Bjorklund, Anders[1], Storm, Petter[1], Cattaneo, Elena[2], Fiorenzano, Alessandro[1] and Parmar, Malin[1]
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Parkinson´s Disease (PD) is one of the most common neurodegenerative disorders, characterized by the loss of midbrain dopaminergic (DA) neurons in the substantia nigra, with consequent depletion of DA in the striatum and the rise of motor symptoms. Transplantation of midbrain DA progenitors derived from human pluripotent stem cells is currently being explored in, and developed for, clinical trials, aiming to replace neurons lost in the disease and thereby restore DA neurotransmission in the striatum. It is interesting though, that within these fully functional grafts, only a small proportion of cells are mature DA neurons. The reason for this graft diversification and the role of other cell types in the graft remains to be determined. In this study, we assess potential function and support for the development and maturation of the therapeutic DA neurons by other cell types performing co-grafting experiments. We co-transplanted different cell types, including glial, striatal, and ventral forebrain progenitors together with DA progenitors into the striatum of 6-OHDA lesioned nude rats. Histological analysis has shown that co-grafting of DA and forebrain progenitors together results in a higher yield of TH+ neurons and more extensive innervation of the striatum, compared to grafting DA progenitors alone. Single-nuclei RNA sequencing of the co-grafts revealed a variety of cell types in the graft, including multiple DAergic and interneuron subtypes, astrocytes, and glial progenitors. Moreover, we showed that the interaction with specific cell types influence DA neuron maturation and specification towards distinct subtypes. Finally, we used molecular barcoding to investigate the lineage relationships between cell of origin and graft populations. Overall, this study sheds light on the role of graft composition on DA neuron development and maturation and paves the path for a more refined and effective product for cell replacement therapy for PD.

Keywords: cell-replacement therapy, Parkinson's disease, dopaminergic neurons

2:05 PM – 2:15 PM

LARGE-SCALE LIVE-CELL QUANTITATIVE LABEL-FREE IMAGING OF INDIVIDUAL IPSC FOR MONITORING PLURIPOTENCY

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The ability to quantitatively image induced pluripotent stem cells (iPSC) to monitor their state of pluripotency and differentiation is important for establishing better metrics for pluripotency, and to assure consistency and efficiency in human iPSC manufacturing. We have developed an imaging and image analysis pipeline that allows tens of thousands of individual iPSC and their progeny to be segmented and tracked for over 24h in phase contrast microscopy. The AI U-Net model for this analysis is trained with tens of thousands of cells identified through automated segmentation of fluorescent nuclei. This obviates the need for manual annotation and provides access to the large diversity of cells within an isogenic population. Our AI pipeline allows us to accurately segment cells in phase contrast imaging (F1 score ~0.96), providing reliable, real-time, cell counts as the culture expands. The reproducibility and generalizability of the algorithm is evidenced by similar results when applied to different iPSC cell samples, and by applying the algorithm to different pluripotent cell lines. By acquiring phase contrast images every two minutes we identify mitotic events and allows cells and their progeny to be tracked for long times. The algorithm detects approximately 80% of mitotic events compared to manual annotation. Cell count and mitosis rate are two criteria by which cell cultures can be evaluated in real time for quantitatively assessing their response to culture conditions. We are now using this imaging and analysis pipeline to examine a mouse embryonic stem cell line that expresses different fluorophores for the transcription factors Sox2 and Nanog. The relative expression of these two transcription factors will provide information about the state of the regulatory network that controls pluripotency in the population. The variation in expression of these transcription factors in individual cells and their progeny provides a more complex criteria for comparison of cell lines and their response to culture conditions. The resulting 2-dimensional potential energy landscape indicates how these network components interact to control and regulate the state of pluripotency.

Keywords: label free quantitative live-cell imaging, long-time tracking of iPSC and progeny, pluripotency regulation

2:15 PM – 2:25 PM

ENGINEERED IPSC-DERIVED MACROPHAGES EVADE HOST-VERSUS-GRAFT ALLOREACTIVITY AND ENHANCE T CELL CYTOTOXICITY TO TRIPLE NEGATIVE BREAST AND OVARIAN CANCER CELLS IN VITRO

Hay, Ian[1], Aibel, Claire[1], Angel, Matthew[2], Blatchford, Abigail[1] and Rohde, Christopher[2]
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Despite profound clinical success in B-cell lymphoma and multiple myeloma, chimeric antigen receptor T (CAR T) cell therapies have not translated to solid tumors, which comprise 90% of cancer cases worldwide. A key barrier for CAR T therapy in solid tumors is the immunologically cold microenvironment of the tumor, which blocks T cells from infiltrating and killing cancer cells. Myeloid cells efficiently traffic deep into solid tumors and thus engineered monocytes and macrophages are being explored to reprogram the solid tumor microenvironment. Autologous macrophages for clinical use are limited by the maximum number of cells that can be obtained from leukapheresis and the difficulty of genetically engineering these cells using established techniques. Here we present induced pluripotent stem cell (iPSC)-derived macrophages as a platform to overcome these limitations. We generated an iPSC line with bi-allelic knockout of the beta-2-microglobulin (B2M) gene. B2M-knockout (B2M-/-) iPSCs efficiently differentiate into macrophages that do not express MHC-I molecules while maintaining expression of MHC-II, preserving their ability to present antigens to T and B cells. When co-cultured with PBMC-derived T cells, wildtype iPSC-derived macrophages, but not B2M-/- iPSC-derived macrophages, upregulate T cell early activation marker CD69 (2.52- and 0.88-fold, respectively), suggesting that the B2M-/- iPSC-derived macrophages do not cause T cell-mediated alloreactivity. B2M-/- iPSC-derived macrophages transfected with mRNA encoding the immunostimulatory cytokine IL-12 and co-cultured with PBMC-T cells showed greater cell lysis of MDA-MB-231 breast adenocarcinoma cells (12% vs 2%; p=0.01) and SK-OV-3 ovarian adenocarcinoma cells (62% vs. 33%; p=0.03) compared to mock transfected macrophages. When co-cultured with IL-12 mRNA transfected B2M-/- iPSC-derived macrophages, ROR1-CAR T cells showed greater cell lysis of MDA-MB-231 cells (46%) compared to the ROR1-CAR T cells alone (29%, p=0.001) or with mock transfected macrophages (39%, p=0.05). These results suggest that engineered iPSC-derived macrophages

may prove useful to translate CAR T therapy to treat solid tumors by delivering potent immunomodulatory proteins such as IL-12 to solid tumors while avoiding host-versus-graft alloreactivity.

Keywords: cell therapy, solid tumor immunology, mRNA engineering

2:25 PM – 2:35 PM

GENERATION OF CD4 SINGLE POSITIVE CELLS FROM IPSCS AND INVESTIGATION OF CD4/CD8 T CELL LINEAGE CHOICE

Furukawa, Yoshiki[1], Ishii, Midori[1], Goto, Ayaka[1], Kinoshita, Shintaro[1], Ando, Jun[1], Nakauchi, Hiromitsu[2] and Ando, Miki[1]
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iPSC-derived functionally rejuvenated antigen-specific cytotoxic T lymphocytes (CTL) generated from exhausted CTLs show antitumor effect towards refractory tumors. However, iPSCs always differentiate into CD8 T cells, and stable generation of CD4 single positive (SP) cells from iPSCs has never been accomplished without enforced CD4 gene transduction. Therefore, we aimed to investigate why iPSC-derived T cells (iPSC-Ts) only differentiate into CD8 T cells. We focused on adult T cell leukemia (ATL) because HTLV-1 infected CD4+ T cells clonally expand in ATL. We reprogrammed CD4+ ATL cells into iPSCs (ATL-iPSCs) and differentiated these according to our method. ATL-iPSCs successfully generated CD4 SP cells. These showed regulatory T cell phenotype and demonstrated functional suppression. To further understand CD4/CD8 T cell lineage choice, we performed single cell RNA-sequencing on ATL-iPSC-Ts (CD4-iPSC-Ts) and healthy donor-derived iPSCs (CD8-iPSC-Ts) as control. Gene expression of CD4-iPSC-Ts and CD8-iPSC-Ts was compared to identify a group of genes with significantly different expression patterns. We knocked out selected genes by CRISPR/Cas9, resulting in successful generation of CD4 SP cells. In contrast, overexpression of the genes on ATL-iPSCs led to generation of CD8 SP cells. To prove reproducibility, we next used this method on several types of antigen specific CTL-derived-iPSCs, and these resulted in generation of CD4+ SP cells which maintained the same antigen specificity. At an effector: target ratio of 40:1, the cytotoxicity of these CD4 SP cells against EBV-associated lymphoma was 49 ± 5%. Moreover, these cells secreted cytokines (IL-2, IFN-γ, TNF-α), expressed genes (TBX21, STAT1, STAT4) and surface proteins (CD107a, CD366) at high levels, showing Th1 phenotype. The discovery of key regulators for lineage selection may lead to a better understanding of CD4/CD8 T cell lineage choice and the stable generation of Th1 cells. Adding Th1 cells have been proven to enhance cytotoxicity of CTLs via enriched cytokine secretion, which could be used for future cancer immunotherapy.

Keywords: iPSC-derived CD4 T cells, CD4/CD8 T cell lineage choice, Th1 cells

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STEM CELL-DERIVED, FULLY DIFFERENTIATED ISLET CELLS FOR TYPE 1 DIABETES

Pagliuca, Felicia
Vertex Pharmaceuticals, USA

Abstract not available at the time of publishing.

Keywords: diabetes, clinical, trials

TRACK: Disease Modeling and Drug Discovery (DMDD)

THE USE OF STEM CELLS IN DISEASE MODELING I

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Hall Z, Level 3

1:35 PM – 1:55 PM

ADVANCED HUMAN IPSC-BASED PRECLINICAL MODEL FOR PARKINSON'S DISEASE WITH OPTOGENETIC ALPHA- SYNUCLEIN AGGREGATION

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Human induced pluripotent stem cells (hiPSCs) offer advantages for disease modeling and drug discovery. However, recreating innate cellular pathologies, particularly in late-onset neurodegenerative diseases with accumulated protein aggregates including Parkinson's disease (PD), has been challenging. To overcome this barrier, we developed an optogenetics-assisted α-synuclein (α-syn) aggregation induction system (OASIS) that rapidly induces α-syn aggregates and toxicity in PD hiPSC-midbrain dopaminergic neurons and midbrain organoids. Our OASIS-based primary compound screening with SH-SY5Y cells identified 5 candidates that were secondarily validated with OASIS PD hiPSC-midbrain dopaminergic neurons and midbrain organoids, leading us to finally select BAG956. Furthermore, BAG956 significantly reverses characteristic PD phenotypes in α-syn preformed fibril models in vitro and in vivo by promoting autophagic clearance of pathological α-syn aggregates. Following the FDA Modernization Act 2.0's emphasis on alternative non-animal testing methods, our OASIS can serve as an animal-free preclinical test model (newly termed "nonclinical test") for the synucleinopathy drug development.

Keywords: pluripotent stem cell, Parkinson's disease

1:55 PM – 2:05 PM

INTERSPECIES ORGANOIDS REVEAL HUMAN-SPECIFIC MOLECULAR FEATURES OF DOPAMINERGIC NEURON DEVELOPMENT AND VULNERABILITY

Nolbrant, Sara, Wallace, Jenelle, Ding, Jingwen, Schaefer, Nathan, Schmitz, Matthew, Pavlovic, Bryan and Pollen, Alex
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The human brain has evolved remarkable cognitive and social abilities over the last 6 million years, but these adaptations involved tradeoffs that may leave us more vulnerable to neurological disorders, such as Parkinson's disease. Dopaminergic (DA) neurons of the ventral midbrain (vMB) may be under particular stress in the human brain because their target regions in the striatum and cortex have disproportionately increased in size relative to the DA nuclei, and require increased functional innervation compared to other primates. We hypothesize that cell intrinsic gene regulatory changes related to cellular stress and metabolism evolved in human DA neurons in the context of this altered cellular ecology. To test this hypothesis, we developed interspecies vMB organoid models. We pooled and differentiated induced pluripotent stem cell-lines from human (n=8), chimpanzee (n=7), orangutan (n=1) and macaque (n=3) individuals into vMB progenitors and matured these into DA neurons in a 3D environment. To study divergence in gene expression and chromatin accessibility during DA neuron development, we performed single-nucleus RNA-seq and ATAC-seq analysis across

stages of midbrain neuron specification (D16) and maturation (D40-100). Single cell gene expression analysis of these cultures revealed cell type identities corresponding to the full rostral-caudal axis of the developing vMB, in both humans and chimpanzees, enabling direct cross-species comparison of gene expression and chromatin accessibility. In addition, to further unmask genetic variation in regulatory elements and gene expression related to vulnerabilities, mature vMB organoids were exposed to rotenone to induce oxidative stress in DA neurons. By combining gene expression and chromatin data we were able to identify conserved and divergent transcriptional responses and enhancer-driven gene regulatory networks related to stress response and resilience. These networks involve genes with known, as well as previously uncharacterized, roles in DA neuron stress response and vulnerability. Collectively, this study helps illuminate the genomic mechanisms underlying human neuronal specializations and vulnerability of DA neurons and could translate to a better understanding of disorders involving dysregulation or degeneration of DA neurons.

Keywords: dopamine neuron development, Parkinson's disease, brain evolution

2:05 PM – 2:15 PM

APOL1 RISK VARIANTS INDUCE PODOCYTE MITOCHONDRIAL DYSFUNCTION IN PATIENT-DERIVED KIDNEY ORGANOIDS

Song, Heein[1], Dumas, Sébastien[1], Wang, Gangqi[1], Ma, Lijun[2], Witjas, Franca[1], Van den Berg, Cathelijne[1], Rocco, Michael[2], Freedman, Barry[2], Rabelink, Ton[1] and Spijker, H.[1]
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Apolipoprotein L1 (APOL1) high-risk genotypes with two G1 and/or G2 variants cause much of the increased risk for CKD in African-Americans, especially in high interferon gamma (IFN-γ) states. Developing disease models has been challenging since APOL1 expression is restricted to higher level primates and humans. Here, novel patient-derived induced pluripotent stem cells (iPSCs) were applied to generate a kidney organoid model resembling human APOL1 nephropathy. iPSCs were generated from fibroblasts of two patients with APOL1 nephropathy homozygous for G1 and G2 risk variants (RV) and an isogenic control (G0) was created using CRISPR-Cas9 gene editing. Kidney organoids were generated, treated with IFN-γ and analyzed by means of single cell transcriptomics, immunofluorescence imaging and spatial dynamic metabolomics. APOL1 expression was induced in all genotypes up to 7 days following single dose IFN-γ treatment. Increased cell death was observed in RV podocytes at 7 days (but not 3 days) post-IFN-γ. This phenotype was rescued by treatment with Inaxaplin (Vx-147), a clinically tested small-molecule inhibitor of APOL1. Single cell transcriptomics of organoids 3 days post IFN-γ exposure showed APOL1 induction was primarily detected in podocytes, confirmed with colocalized immunolabeling of APOL1 and podocalyxin. Gene set enrichment analysis showed significantly decreased oxidative phosphorylation and increased glycolysis in RV podocytes. Furthermore, a novel subpopulation of RV podocytes characterized by a metabolic switch to glycolysis and a response to hypoxia was identified. Consistent with transcriptomic data, spatial dynamic metabolomics with glucose and glutamine isotope tracing showed that RV podocytes had higher glucose contribution in both glycolysis and the TCA cycle. As opposed to G0, maximal respiration rate upon IFN-γ treatment did not increase in isolated RV glomeruli, suggesting dissociation of TCA cycle and oxidative phosphorylation. This human organoid model indicates that early changes in APOL1 nephropathy are dominated by mitochondrial dysfunction in podocytes. This model supports further mechanistic research and testing of potential therapeutics for APOL1 nephropathy.

Keywords: apolipoprotein L1(APOL1), disease modelling, kidney organoid

2:15 PM – 2:25 PM

IDENTIFICATION OF TWIST1 AS A TRUE SYNTHETIC LETHAL TARGET OF TSC2-NULL NEURAL CREST CELLS THROUGH GENOME-WIDE CRISPR KNOCKOUT SCREEN

Camacho Magallanes, Alberto, Lian, Eric, Yockell-Lelievre, Julien, Batoff, William and Stanford, William
Regenerative Medicine, Ottawa Hospital Research Institute, Canada

Lymphangioleiomyomatosis (LAM) is a rare disease involving cystic lung destruction by invasive LAM cells. These cells harbor loss-of-function mutations in TSC2, conferring constitutive mTORC1 signalling. Rapamycin is the only clinically approved disease-modifying treatment, but its action is cytostatic, and disease progresses upon its withdrawal. The discovery of new therapeutics to eradicate LAM cells has been hampered by the difficulty in culturing primary patient cells or effectively modelling LAM in cell or animal models. Here we employed genome-wide approaches in a novel cellular model to identify the vulnerabilities of TSC2 knockout (TSC2-/-) human pluripotent stem cell lines differentiated to neural crest cells (NCC). We found that TSC2-/- NCC recapitulate many LAM phenotypes. Leveraging our NCC model, we conducted a combination of temporal RNA-seq and genome-wide CRISPR knockout screens to identify genotype-specific synthetic lethal genes in TSC2-/- NCC. Analysis of the two screens revealed the transcription factor TWIST1 as a true synthetic-lethal target, culminating in the discovery of a TWIST1 inhibitor with cytotoxic effects specific to TSC2-/- cells. Importantly, the selective cell death induced by the TWIST1 inhibitor was found to be independent of mTORC1 signaling and mediated through apoptosis. These findings provide compelling evidence supporting TWIST1 inhibitors as promising therapeutic candidates for further exploration in LAM patients.

Keywords: lymphangioleiomyomatosis, disease modeling, mTOR

2:25 PM – 2:35 PM

ASTROCYTE DIVERSITY CAPTURED IN GLIA-ENRICHED CORTICAL ORGANOID TRANSPLANTED IN MOUSE BRAIN

Wang, Meiyan[1], Zhang, Lei[1], Novak, Sammy Weiser[2], Yu, Jingting[3], Gallina, Iryna[1], Xu, Lynne[1], Lim, Christina[1], Fernandes, Sarah[1], Saxena, Monisha[1], Williams, April[3], Parylak, Sarah[1], Manor, Uri[2] and Gage, Fred[1]
[1]LOG-G, Salk Institute for Biological Studies, USA, [2]Waitt Advanced Biophotonics Core, Salk Institute for Biological Studies, USA, [3]Integrative Genomics and Bioinformatics Core, Salk Institute for Biological Studies, USA

Astrocytes, the most abundant glial cell type in the brain, are underrepresented in traditional cortical organoid models due to the delayed onset of cortical gliogenesis. Here, we introduce a novel glia-enriched cortical organoid model that exhibits accelerated astrogliogenesis. We demonstrated that induction of a gliogenic switch in a subset of progenitors enabled rapid

derivation of astroglial cells, which account for 25-31% of the cell population within eight to ten weeks of differentiation. Intracerebral transplantation of these organoids reliably generated a diverse repertoire of cortical neurons and anatomical subclasses of human astrocytes. Spatial transcriptome profiling identified layer-specific expression patterns among distinct subclasses of astrocytes within the organoid transplants. Using an in vivo acute neuroinflammation model, we identified a subpopulation of astrocytes that rapidly activates proinflammatory pathways upon cytokine stimulation. Additionally, we demonstrated that CD38 signaling plays a crucial role in mediating metabolic and mitochondrial stress in reactive astrocytes. This model provides a robust platform for investigating human astrocyte function.

Keywords: brain organoids, astrocyte, neuroinflammation

2:35 PM – 2:55 PM

THINKING BIG TO SEE SMALL: RESOLVING PROTEINOPATHY IN PATIENT DERIVED STEM CELL MODELS OF PARKINSON'S DISEASE

Gandhi, Sonia
The Francis Crick Institute and University College London, UK

Neurodegenerative diseases are incurable progressive brain disorders that are characterised by the common feature of proteinopathy: the abnormal accumulation of aggregated proteins. My laboratory's research program focusses on understanding how, where and why proteins misfold in human cells and brain, and how this affects organellar homeostasis, and function, and ultimately leads to neuronal death. We have adapted a range of single molecule and super resolution approaches to study the earliest stages of protein self assembly and aggregation in human neurons and glia, and we have described the factors that influence the kinetics of the aggregation process. We have studied the functional consequence of different protein aggregates in human patient derived iPSC derived neurons, microglia, astrocytes and oligodendrocytes, and reported mechanisms by which aggregates can induce toxicity by cell autonomous and non cell autonomous processes. Funded by Aligning Science Across Parkinson's, we are integrating single cell genomics, single molecule imaging, and spatial technologies to generate a detailed molecular and cellular map of the human Parkinson's brain. We are using this map to develop the iPSC based platform to model Parkinson's pathogenesis. Our approach models Parkinson's across different scales and modalities, integrating cellular, computational, and clinical neuroscience to understand causation and progression in Parkinson's.

Keywords: proteinopathy, iPSC, neurons

TRACK: Pluripotency and Development (PD)

TOTIPOTENCY AND GERM CELL DEVELOPMENT

1:30 PM – 3:00 PM
Hall G1, Level 2

1:35 PM – 1:55 PM

INDUCTION, REGULATION, AND APPLICATION OF HUMAN TOTIPOTENT-LIKE CELLS

Esteban, Miguel
Guangzhou Institutes of Biomedicine and Health, China

Our understanding of human totipotency is limited due to ethical concerns and the scarcity of embryos available for research. Therefore, the generation and study of human totipotent-like cells that mimic their embryonic counterparts has wide-ranging implications. Our team recently established a methodology for inducing 8-cell embryo-like cells (8CLCs) from pluripotent stem cells, mirroring the time of major zygote activation in human. In this talk, I will elaborate our systematic efforts to characterize 8CLCs and further enhance the stability of their conversion, focusing on existing roadblocks and potential solutions. This will encompass the crosstalk between signaling pathways and epigenetic modifications, along with proteomic and metabolomic profiling, and high-throughput screenings, among others. In addition, I will provide an overview of our progress in generating interspecies and monkey-monkey chimeras, as well as ongoing endeavours to produce a virtual multi-stage embryo model for studying early embryonic cell fate transitions and predicting the effects of perturbation in silico.

Keywords: totipotency, totipotent-like cells, pluripotency, pluripotent stem cells, early human development

1:55 PM – 2:05 PM

LINE1 RNA PREVENTS DEVELOPMENTAL REVERSION OF HUMAN EMBRYONIC STEM CELLS TO THE 8-CELL STATE

Ramalho-Santos, Miguel
Molecular Genetics, Lunenfeld-Tanenbaum Research Institute and University of Toronto, Canada

The family of LINE1 transposable elements underwent a massive expansion in mammalian genomes. We showed that LINE1 RNA is required for mouse development and are investigating its function in hESCs. Silencing of LINE1 using either ASOs or CRISPRi in naïve hESCs leads to a strong developmental reversion to 8C-like cells (8CLCs). Genes derepressed upon LINE1 KD are enrichment for chromosome 19, which includes key 8C genes such as TPRX1. Silencing of TPRX1 suppresses the 8C program induction in LINE1 KD hESCs. LINE1 RNA is preferentially localized to the lamina and periphery of the nucleolus. Using LAD-seq, NAD-seq and imaging, we found that 8CLCs have a distinct nucleolar morphology and a lower association of chromosome 19 and TPRX1 loci with the nucleolus relative to hESCs, suggesting a role for nucleolar dynamics in the 8CLC-hESC transition. In agreement, LINE1 KD leads to disruption of nucleolar architecture, and independent perturbations of the nucleolus induce the 8C program in hESCs. Biochemical and function data indicate that LINE1 RNA and the Polycomb Repressive Complex 2 (PRC2) complex cooperate to repress the 8C state in hESCs. We find that LINE1 RNA binds to PRC2 and that genes induced by LINE1 KD are enriched for targets of PRC2. In support of this notion, inhibition of PRC2 leads to a strong induction of the 8C program. Our recent findings point to uniquely mapped LINE1 elements that partially account for the role of LINE1 RNA in nucleolar function and 8C program repression. These data indicate that LINE1 coordinates nuclear compartmentalization and chromatin-mediated gene repression to prevent developmental reversion of hESCs towards totipotency. Our most recent results will be presented.

Keywords: human embryonic stem cells, 8 cell-like cells, chromatin

2:05 PM – 2:15 PM
PROTEIN NETWORKS UNDERLYING THE MOUSE TOTIPOTENT-LIKE STATE

Lawrence, Moyra[1], Yamakawa, Tatsuya[2], Kabata, Mio[2], Sakurai, Satoko[2], Nakajima-Koyama, May[2], Woltjen, Knut[2], Iwasaki, Mio[2] and Yamamoto, Takuya[1]
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Recent advances in stem cell biology have allowed reprogramming to the naïve pluripotent state at near 100% purity, as well as primed-to-naïve conversion at high purity. Differentiation protocols have also generated pure populations of differentiated cells from pluripotent ones. However, protocols to generate totipotent cells, corresponding to the two-cell stage of mouse embryogenesis, have lagged behind, generating totipotent cells at very poor purity. Here we describe a transcription factor overexpression, repeat element activation and small molecule inhibitor combination which can generate totipotent-like cells at 75-94% efficiency, higher than that generated by existing protocols. This highly efficient protocol allowed us to perform proteomic and phosphoproteomic studies of the totipotent-like state, allowing us to identify protein and signalling networks underlying the transition. Insights provided from this and single-cell RNA sequencing enabled us to characterise the role of translational regulation, protein degradation by the proteasome and post-translational SUMOylation in regulating the transit to the totipotent-like state. In vitro induced totipotent cells pave the way for new treatments for diseases such as Fascioscapulohumeral dystrophy, where totipotent genes are mis-expressed in adult tissue, and provide a crucial starting cell type for the differentiation of extra-embryonic tissue in vitro.

Funding Source: JSPS short-term postdoctoral fellowship (PE21019) Fusion grant (ASHBi) Program-specific researcher funding (ASHBi) Foreign/Female Researcher Employment Support Program (ASHBi)

Keywords: totipotency, cellular reprogramming, single-cell RNA sequencing

2:15 PM – 2:25 PM
MOLECULAR TIMETABLE OF LINEAGE SPECIFICATION IN HUMAN PLURIPOTENT EPIBLAST

Rostovskaya, Maria[1], Coussement, Loius[2], Ciarchi, Matteo[3], Della Rosa, Monica[4], Argelaguet, Ricard[5], Rulands, Steffen[6], Spivakov, Mikhail[4], Rugg-Gunn, Peter[1] and Reik, Wolf[5]
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Pluripotency is the ability of single cells to differentiate to any cell type of the body. In human, the major embryonic lineages originate from the pluripotent epiblast over about 2 weeks sequentially, in a specific order and at specific time points. How this timetable of lineage specification is controlled, is unknown. Previously, we established a human pluripotent stem cells (hPSC)-based model of the entire 2 week-long window of epiblast development, also called pluripotent state transition. Single-cell multiomics showed that the transition is a step-wise rather than a gradual process. As the transition occurs under constant conditions, this step-wise switch is not extrinsically-induced, but an intrinsic cell decision. We reconstructed the dynamic gene regulatory network (GRN) and interpreted it as a transcription factor (TF) cascade, ensuring directionality, timing and intrinsic decisions of the epiblast development ("transcriptional clock"). Mathematical model closely reproduced the gene expression dynamics and predicted key TFs of this genetic programme. We found that the TFs of the human GRN are expressed in a different order during the pluripotent state transition in mouse, which is much faster (2 days). Strikingly, when mouse-specific TF profile was plugged into the mathematical model of human GRN, the transition matched the mouse pace, yet leading to the human-like expression state. Therefore, this species-specific timing of the pluripotency window is not due to simple scaling but associated with reconfiguration of the GRN built of evolutionary conserved TFs. We discovered that during the pluripotent state transition hPSCs step-wise change the abilities to respond to differentiation signals inducing definitive endoderm and neuroectoderm. The emergence of these abilities recapitulated the order in which the respective lineages emerge in the embryo. Epigenetic profiling showed that the emergence of differentiation competence was associated with epigenetic priming of developmental enhancers during the transition, which also correlated with the step-wise transcriptional switches of the GRN in hPSCs. Therefore, we propose a model of transcriptional clock that establish a timetable of lineage segregation from human epiblast through epigenetic remodelling of cis-regulatory elements.

Funding Source: Medical Research Council UK (MR/V02969X/1); Biotechnology and Biological Sciences Research Council UK (BBS/E/B/000C0421, BBS/E/B/000C0422)

Keywords: pluripotent stem cells, gene regulatory network, epigenetic priming

2:25 PM – 2:35 PM
HIGHLY COOPERATIVE CHIMERIC SUPER-SOX INDUCES NAÏVE PLURIPOTENCY ACROSS SPECIES

Velychko, Sergiy[1], MacCarthy, Caitlin[2], Wu, Guangming[2], Malik, Vikas[3], Menuchin-Lasowski, Yotam[2], Velychko, Taras[2], Keshet, Gal[4], Fan, Rui[5], Bedzhov, Ivan[5], Church, George[1], Cojocaru, Vlad[2], Jauch, Ralf[6] and Schöler, Hans[2]
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Our understanding of pluripotency remains limited: iPSC generation has only been established for a few species, pluripotent stem cell lines exhibit inconsistent developmental potential, and germline transmission has only been demonstrated for mice and rats. By swapping structural elements between Sox2 and Sox17, we created a chimeric super-reprogramming factor, Sox2-17, which enhanced iPSC generation in five tested species: mice, humans, cynomolgus monkeys, cows, and pigs. The most crucial gain-of-function came from a single residue swap, alanine to valine at position 61 of the Sox2-HMG domain facing Oct4. Our computer simulations, biochemistry, and ChIP-seq experiments demonstrated that Sox2-A61V stabilizes Sox2/Oct4 dimerization on SoxOct DNA motif that controls the pluripotency fate. The point mutant markedly boosted the developmental potential of OSKM iPSCs, as evidenced by their

much-improved capacity to support the generation of healthy all-iPSC mice in tetraploid complementation experiments. Sox2/Oct4 dimer emerged as the core driver of naïve pluripotency both during development and in vitro, with the dimer levels diminishing upon priming. Transient overexpression of episomal SK (super-SOX+KLF4 cocktail) restores endogenous Sox2/Oct4 dimerization enhancing the developmental potential of existing pluripotent stem cell lines across different species. Our research provides a powerful tool for advancing iPSC technology, presents a universal approach for the naive reset across species, and addresses the long-standing question of what dictates the developmental potential or "quality" of pluripotent stem cells. By enabling the generation of high-quality naive pluripotent cells, our findings could enhance the production of tissues and organs and pave the way for precision mammalian germline engineering beyond the mouse model.

Funding Source: Max Planck Society, White Paper Project "Animal testing in the Max-Planck-Society", ERC (669168), CiM-Pilot-Project (PP-2017-13), RGC of HK (17128918, 17101120, 17106622, C7064-22G), and Innovation Technology Commission.

Keywords: naive reset, induction of pluripotency, engineered transcription factor super-SOX

2:35 PM – 2:55 PM
TITLE NOT AVAILABLE AT TIME OF PUBLISHING

Hayashi, Katsuhiko
Kyushu University, Japan

Abstract not available at the time of publishing.

SATURDAY, 13 JULY

TRACK: Somatic Stem Cells, Cancer and Regeneration (SSCCR)

CELLULAR PLASTICITY IN REGENERATION AND CANCER

8:15 AM – 9:45 AM
Hall Y7-12, Level 2

8:20 AM – 8:40 AM
TRACKING HUMAN HAEMATOPOIETIC REGENERATION (AND LOSS OF IT) AT SINGLE CELL RESOLUTION

Laurenti, Elisa, Johnson, Carys, Williams, Matthew, Sham, Kenny, Belluschi, Serena, Green, Anthony R. and Francis, Natalie
Cambridge Stem Cell Institute, Department of Hematology, University of Cambridge, UK

Production of all blood cells at steady-state and during injury relies on haematopoietic stem cells (HSCs). Functional HSCs are actively maintained in vivo in a highly regulated quiescent state, characterised by a unique molecular, metabolic and organelle network that guarantees preservation of HSC functionality. This network is physiologically broken down during the initial steps of HSC differentiation, depending on the specific blood lineage to which HSCs commit. When HSC are placed ex vivo, for purposes such as gene editing or expansion for clinical applications, this network also breaks down. HSCs become activated to enter the cell cycle and lose function. This represents a major barrier for the success of ex vivo HSC gene therapy and for the development of HSC expansion protocols suitable for clinical applications. However, a temporally resolved understanding of how HSC ex vivo activation leads to loss of HSC regenerative capacity has been lacking. In this talk, I will present the kinetics of the loss of human HSC regenerative capacity during their first ex vivo division in a clinically relevant setting. Through the integrated use of single-cell RNAseq, single-cell in vitro functional assays and limiting-dilution analysis in xenografts, we uncover that more than 50% of HSC long-term regeneration capacity is lost between 6 and 24 hours of culture, before HSCs enter the late G1 phase of the cell cycle. During this time-window, which we termed "adaptation", HSCs transiently upregulate stress response and JAK/STAT signalling target genes. Through reversible pharmacological inhibition, we demonstrate that the loss of HSC regenerative capacity ex vivo is independent of cell cycle progression but can be minimised by inhibition of JAK/STAT signalling. Collectively our data inform on the stress biology underlying loss of regeneration in HSCs and uncover new clinically relevant strategies to improve HSC function ex vivo.

Keywords: hematopoiesis, regeneration, gene therapy

8:40 AM – 8:50 AM
DIFFERENTIATED LINEAGES ARE THE CELLS-OF-ORIGIN OF COLON CANCER IN THE CONTEXT OF INFLAMMATION

Schmitt, Mark[1], Verhagen, Mathijs[2], Joosten, Rosalie[2], Välimäki, Niko[3], Sacchetti, Andrea[2], Rajamäki, Kristiina[3], Choi, Jiahn[4], Procopio, Paola[1], Silva, Sara[1], van der Steen, Berdine[5], van den Bosch, Thierry[2], Seinstra, Danielle[2], Doukas, Michail[2], Augenlicht, Leonard[4] and Aaltonen, Lauri[3]
[1]Pharmacology, University of Marburg, Germany, [2]Pathology, Erasmus MC, Netherlands, [3]Medical and Clinical Genetics, University of Helsinki, Finland, [4]Cell Biology, AECOM, USA, [5]Otorhinolaryngology and Head & Neck Surgery, Erasmus MC, Netherlands

According to conventional views, colon cancer originates from stem cells. However, inflammation, a key risk factor for colon cancer, was shown to suppress intestinal stemness. Here, we employed Paneth cells (PCs) as a model to assess the capacity of differentiated lineages to trigger tumorigenesis in the context of inflammation. PCs have previously been shown to respond to inflammation by dedifferentiating into stem-like cells to sustain the regenerative response. As such, they may represent the cells-of-origin of intestinal cancer in the context of inflammation. Indeed, targeted Apc mutations in Paneth cells resulted in multiple small intestinal tumors in the mouse upon DSS-driven inflammation. PC-specific Kras or Tp53 mutations did not result in any tumor. Compound Apc and Kras mutations in PCs resulted in a striking increase in tumor multiplicity even in the absence of the inflammatory insult. The conversion of PCs into tumor cells occurs through a "revival stem cell" (RSC) state characterized by high Clusterin (Clu) expression and Yap1 signaling. Accordingly, PC-derived murine intestinal tumors were remarkably similar to human colon cancers arising in the context of IBD. Of note, the latter was true also for a striking ~25% of sporadic (non-IBD) colon cancers. To validate these observations, we applied novel computational methods designed to predict the cell-of-origin by matching their genome-wide mutation spectrum with the epigenetic landscapes of colonic cell lineages. While the vast majority of colon cancers arising in the context of IBD were predicted to have originated from fully committed lineages such as goblet cells, a substantial fraction of sporadic (non-IBD) colon cancers shared similar non-stem origins. The latter can be explained by the low-grade, subclinical inflammation induced by western-

style dietary habits, the major colon cancer risk factor, likely to underlie the de-differentiation of secretory lineages of the colon and their acquisition of stem-like and tumor-initiating features. The chronic nature of the inflammatory insult caused by Western-style dietary habits is likely to underlie similar mechanisms in a significant proportion of sporadic colon cancers and warrants a novel stratification of the cases for improved clinical management.

Funding Source: Dutch Cancer Society no. 11407 WCRF no. 2014-1181, IIG_FULL_2022_015 NCI no. R01CA214625, R01CA229216, P30-013330 National Institute on Aging, no. P30 AG038072, 5T32AG023475-20 Academy of Finland no. 312041, 319083, 320149

Keywords: cell-of-origin of colon cancer, dedifferentiation, inflammation

8:50 AM – 9:00 AM
UNIFIED IDENTITY OF GOBLET AND PANETH CELLS AND CHROMATIN BASIS FOR INTESTINAL EPITHELIAL DIFFERENTIATION

Bhattacharya, Swarnabh[1], Tei, Guodong[2], Malagola, Ermanno[3], Singh, Pratik[1], Badarinath, Krithika[1], Storm, Elaine[4], Zhou, Qiao[5], Wang, Timothy[3], de Sauvage, Frederic[4] and Shivdasani, Ramesh[1]
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Intestinal stem cells (ISCs) generate transit-amplifying crypt progenitors that differentiate further into abundant enterocytes or fewer secretory (goblet (Gob), enteroendocrine (EE), Paneth (Pan), or tuft) cells. Together these cells execute vital functions in caloric, metabolic, and water balance and in supporting innate immunity. As epithelial cell proportions are altered in infectious and inflammatory disorders, it is important to know how the correct cell proportions are generated and maintained. Previous studies point to enterocytes as the default progeny of ISC differentiation and to Notch signaling and ATOH1 expression as drivers of secretory lineage commitment. Whereas knockout mice reveal transcription factors (TFs) Neurog3 and Pou2f3 as critical regulators of EE and tuft cell identities, respectively, no TF has been identified for Gob or Pan specification. To address this gap and to study transcriptional and chromatin dynamics in secretory lineage diversity, we examined transcriptomes and regions of accessible chromatin in fluorescence-labeled intestinal crypt secretory cells from Atoh1Cre(ERT2); R26RL-S-L-Tom mice at single-cell resolution. In contrast to EE or tuft cells, we identified Gob and Pan cells as a single default secretory entity, with highly overlapping transcriptional and chromatin profiles and no uniquely enriched TFs. Rather, in multiple mouse models the minimal differences between these morphologically and spatially distinct cells traced to distinct BMP and Wnt signaling environments along the crypt-villus axis. ATOH1-expressing primary human intestinal stem cells demonstrated efficient secretory differentiation in vitro and similarly revealed Gob and Pan cell plasticity in response to modulation of BMP and Wnt signaling. Our findings indicate that Gob and Pan cells are alternative phenotypic manifestations of the same versatile mature cell in response to different local signals arising from the subepithelial compartment and they recast the classic unitarian model, which regards Gob and Pan cells as distinct branches of the secretory lineage. Overall, this study also yields novel insights into the role of the mesenchymal niche not only in endowing intestinal stem cell properties but also in the phenotypic plasticity of mature secretory derivatives.

Keywords: cell plasticity, intestinal epigenetics, niche regulation of cell fate

9:00 AM – 9:10 AM
FROM AIRWAY BASAL CELLS TO PREINVASIVE LUNG SQUAMOUS CELL DISEASE

Gomez Lopez, Sandra[1], Przybilla, Moritz[2], Bordeu, Ignacio[3], Alhendi, Ahmed[1], Whiteman, Zoe[1], Butler, Timothy[2], Chandrasekharan, Deepak[1], Uddin, Imran[4], Durrenberger, Pascal[1], Simons, Benjamin[5], Campbell, Peter[2] and Janes, Sam[1]
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The pseudostratified epithelium lining the adult trachea and mainstem bronchi is composed of basal cells and various subpopulations of luminal cells. During homeostasis, basal cells divide to self-renew and to produce luminal cells. Epithelial cell dynamics, however, changes during repair and disease. Lung cancer is the main cause of cancer mortality worldwide. Lung squamous cell carcinoma (LUSC), the second most frequent lung cancer subtype, develops through increasingly disordered preinvasive lesions in the bronchial epithelium. We have previously shown that airway basal cells isolated from the seemingly normal human bronchial epithelium carry mutations occurring in LUSC. Here, we investigate the lineage relationship between airway basal cells and preinvasive squamous cell lung lesions. We have optimised a chemically-induced murine model of LUSC, based on the application of N-nitroso-tris-chloroethylurea (NTCU), that histologically recapitulates the stepwise progression of the disease seen in human patients. Using this model in combination with lineage tracing, whole-mount imaging, single-cell RNA sequencing (scRNA-seq) and low-input whole genome sequencing (WGS), we track basal cell trajectories following mutagen exposure, and demonstrate that preinvasive lung lesions develop from pre-existing basal cells. Through biophysical modelling, we show that carcinogen exposure leads to non-neutral competition among basal cells. Preinvasive lesions eventually emerge from a handful of highly mutated clones that colonise the bronchial tree. Our work indicates that LUSC evolves from aberrant basal cells that gradually expand beyond their niche, and uncovers mechanistic insights of the earliest stages of LUSC formation.

Funding Source: CRUK (EDDCPGM\100002 & A27437), MRC (MR/W025051/1), Royal Society (NF161172 & RP/R1/180165), UK Engineering and Physical Sciences Research Council (EP/P034616/1), FONDECYT (11230941), Wellcome Trust (219478/Z/19/Z)

Keywords: airway basal cell, cancer cell-of-origin, clonal dynamics

9:10 AM – 9:20 AM
LIVE-IMAGING REVEALS METABOLIC REWIRING IN SKIN STEM CELLS THAT DRIVE TOLERANCE TO ONCOGENIC MUTATIONS IN VIVO BY TWO DISTINCT CELL COMPETITION STRATEGIES

Hemalatha, Anupama[1], Perry, Rachel[2] and Greco, Valentina[1]
[1]Genetics, Yale School of Medicine, USA, [2]Endocrinology, Yale University, USA

Metabolic rewiring downstream of growth signals is a major driver of regulated and aberrant growth. To understand how oncogenic mutations are recognized and suppressed in the skin stem cells, we asked how metabolic states change in presence of mutant cells. We used two oncogenic mutations that employ different cell competition strategies: Wnt signaling mutant βcatGOF cells are eliminated and hence "lose" to Wild-type(WT) cells; HrasG12V mutant cells outcompete WT cells and "win". Using two techniques :1. optical redox imaging to visualize endogenous levels of NADH and FAD, adapted in vivo in skin of live mice over time and 2.13-C- glucose tracer-mass spectrometry to measure metabolic fluxes from epidermis directly, we tracked spatio-temporal changes in the metabolic states of skin stem cells as it adapted to the mutations. We discover: 1. There is a rapid redox (NADH/FAD) drop in the stem cells in response to the mutations that precede other tissue aberrancies making it one of the first observable responses to the oncogenic insult. 2. Redox ratios and their temporal dynamics are a measure of cell fitness and predicts the ability of a mutant cell to persist or get eliminated from the stem cell compartment. The βcatGOF cells that maintain low redox ratio are eliminated; and HrasG12V cells that recover their redox after a transient drop persist and expand within the skin stem cell compartment 3.The βcat and Hras mutants that are ultimately tolerated by the tissue display metabolic rewiring contrary to Warburg effect, a fundamental concept in cancer metabolism, wherein cancer cells upregulate glycolysis in favor of glucose oxidation despite the ATP deficit. Instead, we discovered that both winner and loser mutations upregulate glucose oxidation. 4. Inhibiting glucose oxidation specifically inhibits the tissue morphological changes downstream of βcat and Hras mutations and reverses the cell competition outcome such that the loser βcatGOF cells are no longer effectively eliminated and winner HrasG12V cells lose their proliferative advantage. Hence, metabolic rewiring downstream of oncogenic growth factor signaling is necessary for the aberrant phenotypes downstream of these mutations and the tissue responses that suppress/tolerate them.

Funding Source: AH is supported by the New York Stem Cell Foundation (NYSCF) Druckenmiller Fellowship.

Keywords: metabolic rewiring, skin stem cell metabolism, oncogenic tolerance

9:20 AM – 9:40 AM

CHOICES IN REGENERATION: HOW PLANARIAN STEM CELLS CHOOSE THEIR FATE

Reddien, Peter W.
Whitehead Institute, MIT, USA

Planarians are flatworms famous for their ability to regenerate any missing body part. This regeneration involves a population of pluripotent stem cells called neoblasts. Neoblasts continuously divide to replace differentiated cells throughout the body during tissue turnover and act at wound sites to generate all missing tissues. Fate choices in neoblasts involve the activation of fate-specific transcription factors (FSTFs) within these stem cells. Approximately 150 cell types exist in the adult animal, and mechanisms must exist in an adult context for neoblasts to select each of these possible fates. Generating cell-type diversity is a foundational task in both development and in adult regeneration. However, regeneration poses a number of unique challenges compared to development. First, cell-fate specification during regeneration must be tailored to the identity of unpredictable missing tissue types rather than initiating from a fixed starting point. Second, fate specification in regeneration occurs within an adult tissue contextual environment that influences progenitor division patterns and fate regulatory mechanisms. Finally, whereas amplification of cells prior to differentiation is a major challenge in development, wound sites can have ample progenitors from early time points. We investigate how these unique features are associated with mechanisms of fate choice in neoblasts that are central to the biology of renewal and regeneration. We found that fate choices are made in a highly intermingled manner spatially. These observations suggest that migratory sorting of fate-specified progenitors is the primary driver of pattern formation in planarian regeneration and that stem cell-internal processes have a major role in fate decisions.

Keywords: regeneration, cell fate, planarians

ENGINEERING APPROACHES TO DEVELOPMENTAL AND STEM CELL BIOLOGY

8:15 AM – 9:45 AM
Hall Y1-6, Level 2

8:20 AM – 8:40 AM

STEM CELL ZOO– A PLATFORM TO STUDY SPECIES-SPECIFIC DEVELOPMENT

Ebisuya, Miki
Physics of Life, TU Dresden, Germany

How different mammalian species develop with diverse timing and shapes is a fundamental question. However, comparing embryonic development across species is often challenging – embryos of many animal species are not accessible, and even when they are available, the stark differences in their respective physiological environments hinder direct comparisons. To overcome the issues, we employ a collection of pluripotent stem cells from diverse mammalian species named the "stem cell zoo", letting the stem cells differentiate into a target cell type. This way, the same cell type across different species can be compared in similar culture environments. Using the stem cell zoo approach, we have recently recapitulated the segmentation clock, namely the oscillatory gene expression during early development, of six mammalian species. The in vitro segmentation clocks uncovered several scaling and non-scaling laws of developmental tempo across species. As another application of the stem cell zoo, we have developed cultured beef, a skeletal muscle tissue with endothelial cell networks, from bovine embryonic stem cells.

Keywords: stem cell zoo, segmentation clock, cultured meat

8:40 AM – 8:50 AM

A FULLY PATTERNED HUMAN NEURAL TUBE MODEL USING MICROFLUIDIC GRADIENTS

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Human nervous system is arguably the most complex but highly organized organ. Foundation of its complexity and organization is laid down during regional patterning of the neural tube (NT), the embryonic precursor to human nervous system. Historically, studies of NT patterning have relied on animal models to uncover underlying principles. Recently, human pluripotent stem cell (hPSC)-based models of neurodevelopment, including neural organoids and bioengineered NT development models, are emerging. However, existing hPSC-based models fail to recapitulate neural patterning along both rostral-caudal (R-C) and dorsal-ventral (D-V) axes in a three-dimensional (3D) tubular geometry, a hallmark of NT development. Herein we report a hPSC-based, microfluidic NT-like structure (or µNTLS), whose development recapitulates some critical aspects of neural patterning in both brain and spinal cord (SC) regions and along both R-C and D-V axes. In addition to exhibiting patterned expression of canonical regional markers associated with both R-C and D-V patterning of the brain regions and SC, µNTLS show dynamic developments of HOX genes, neuromesodermal progenitors (NMPs), neural crest (NC) cells, and diverse secondary organizers, including the isthmic organizer, the roof plate, and the floor plate. Comparative transcriptome analyses using scRNA-seq datasets of human embryos at early organogenesis stages (CS12-16) as references support that µNTLS on Day 9 and on Day 21 show closest transcriptome similarities with human neural cells at CS12 and at CS15-16, respectively. The µNTLS was utilized for studying neuronal lineage development, revealing pre-patterning of axial identities of NC progenitors and functional roles of NMPs and caudal genes TBXT and CDX2 in SC and trunk NC development. We further developed D-V patterned, microfluidic forebrain-like structures (µFBLS) with spatially segregated dorsal and ventral regions and layered apicobasal cellular organizations that mimic human forebrain pallium and subpallium developments, respectively. Together, both µNTLS and µFBLS offer 3D lumenal tissue architectures with an in vivo-like spatiotemporal cell differentiation and organization, promising for studying human neurodevelopment and disease.

Funding Source: National Science Foundation (I-Corps 2112458 and CBET 1901718) and National Institutes of Health (R21 NS113518, R21 NS127983, R01 GM143297, R01 NS129850, R35 NS097370, RF1 MH123979, and R35 NS116843).

Keywords: neurodevelopment, neural organoids, microfluidics

8:50 AM – 9:00 AM

CORRECTING KIDNEY ORGANOID PATTERNING WITH SYNTHETIC DEVELOPMENTAL ORGANIZERS

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Human kidney organoids generated from induced pluripotent stem cells (iPSCs) establish cellular identities that resemble distinct in vivo progenitor populations, but lack the capacity to manipulate nephron-like cell identities which conduct fluid filtration. In vivo nephron progenitor cells (NPCs) commit to nephrogenic lineages in response to inductive WNT/β-catenin signaling from the adjacent ureteric epithelium (UE). The nascent nephron forms a distally positioned connecting tubule that develops a patent luminal connection with the ureteric epithelium through an unknown mechanism. We therefore addressed (1) which underlying molecular mechanism drives the distal nephrogenic program, and (2) how to mimic in vivo signaling cues to restore distal nephrogenic patterning in iPSC kidney organoids. Here we show an in vivo canonical/non-canonical WNT transcriptional boundary in the UE acts as an origin point for nephron patterning. Canonical WNTs drive β-catenin targets in the early nephron and a nascent distal progenitor program. To spatially recapitulate WNT/β-catenin signals in vitro, we introduced inducible synthetic developmental organizer (SynOrg) cells that secrete canonical WNT ligands into and pattern human kidney organoids. SynOrgs establish modular, localized β-catenin gradients that shift cell states and spatial arrangements of neighboring nephron-like structures. Affected nephrons exhibit expanded distal domains, and further transcriptomic profiling reveals an increased abundance of distal progenitors in nephroids within the WNT gradient. Morphologically, nephrons show restored polarization as their distal segments orient towards the WNT source and attempt to form luminal connections. This system offers a novel human kidney organoid platform with tunable WNT gradients to delineate β-catenin-mediated mechanisms that drive distal nephrogenic lineages required for renal function and a direct strategy for generating a drainage system in a functional artificial human kidney.

Funding Source: 1R01DK136802-01

Keywords: kidney nephron organoid, WNT β-catenin, artificial kidney

9:00 AM – 9:10 AM

A GENETIC SWITCH FOR GROWTH FACTOR-FREE STEM CELL EXPANSION AND SUBSEQUENT DIFFERENTIATION INTO SKELETAL MUSCLE

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Reproducible, efficient, and cost-effective large-scale expansion and differentiation of pluripotent stem cells (PSCs) is crucial for both biomedicine and bioproduction. Most applications rely on non-dividing differentiated cells (i.e. skeletal muscle); thus, PSCs must be expanded before differentiation. The expense involved represents a bottleneck towards democratization of and/or market competitiveness for these technologies. Growth factors account for ~95% of PSC media costs. Subsequent directed differentiation of PSC requires weeks or even months and can be poorly reproducible, imposing a second bottleneck. To overcome both limitations, we developed growth factor-independent PSCs which can be coaxed to forward program in skeletal myocytes in a week using an inexpensive media. First, we screened for factors that when constitutively expressed in human induced pluripotent stem cells (hiPSCs) would allow their growth factor-independent expansion. The best condition maintained pluripotency with no background differentiation for over 10 passages, as determined by flow cytometry, RT-qPCR, and single cell RNA sequencing (scRNA-seq). We then added a doxycycline-inducible system to drive muscle forward programming through forced transcription factor overexpression. Lastly, we combined this with silencing of the pluripotency network to maximize the efficiency and accuracy of myogenic differentiation. The resulting genetic circuit can be deployed with an all-in-one-vector and allows the derivation of highly pure derived skeletal myocytes in one week. The process is reproducible and homogeneous, as confirmed by immunofluorescence and scRNA-seq, and the resulting cells are conductive to the

manufacturing of 3D engineered muscle tissues (3D-EMTs) that respond to physiological and pathological stimuli. Lastly, the approach can be performed by growing hiPSCs and performing their initial differentiation in suspension culture, followed by cell seeding in fibrin scaffolds. This approach reduces the costs of 3D-EMT generation by ~100-fold compared to commercial kits and by ~10-fold compared to using conventional homemade cells. We anticipate that this technology will also readily translate to livestock animal PSCs to enable cost-effective large scale biomanufacturing of cultivated meat.

Funding Source: This work was supported by PON R&I Azione IV.5 - FSE REACT-EU (to S.B) and a PRIN 2022 PNRR project (CUP D53D23021960001 to A.B.).

Keywords: growth factor, forward programming, pluripotent stem cells

9:10 AM – 9:20 AM

DECIPHERING LINEAGE SPECIFICATION DURING EARLY EMBRYOGENESIS USING MULTILAYERED PROTEOMICS

Stelloo, Suzan[1], Alejo-Vinogradova, Maria Teresa[1], van Gelder, Charlotte[2], Zijlmans, Dick[1], van Oostrom, Marek[3], Valverde, Juan Manuel[4], Lamers, Lieke[1], Sobrevals Alcaraz, Paula[2], Schäfers, Tilman[5], Furlan, Cristina[6], Jansen, Pascal[1], Baltissen, Marijke[1], Sonnen, Katharina[3], Burgering, Boudewijn[2], Altelaar, Maarten[4], Vos, Harmjan[2] and Vermeulen, Michiel[1]

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Gastrulation is a critical stage in embryonic development during which the germ layers are established. The advances and increasing availability of sequencing technologies led to the identification of gene regulatory programs that control the emergence of the germ layers and its derivatives. However, proteome-based studies of early mammalian development are scarce. To overcome this, we utilized gastruloids and a multilayered mass spectrometry-based proteomics approach to investigate the global dynamics of (phospho)protein expression during gastruloid differentiation. Our findings revealed that many proteins exhibit temporal expression with unique expression profiles corresponding to the three germ layers, which we also validated using single-cell proteomics technology. Notably, detected temporal protein expression dynamics in gastruloids aligns with equivalent mouse embryo stages. Additionally, we profiled enhancer interaction landscapes using P300 proximity labeling, which revealed numerous gastruloid-specific transcription factors and chromatin remodelers. Subsequent degron-based perturbations combined with scRNA-seq identified a critical role for ZEB2 in regulating mouse and human somitogenesis. Overall, this study provides a rich resource for developmental and synthetic biology communities endeavoring to understand mammalian embryogenesis.

Funding Source: This work was supported by a VENI grant from the Netherlands Organisation for Scientific Research (NWO) and a Pluripotent Stem cells for Inherited Diseases and Embryonic Research (PSIDER) grant from Zonmw.

Keywords: gastruloids, proteomics, transcription factors

9:20 AM – 9:40 AM

MAMMALIAN SYNTHETIC BIOLOGY AND PROGRAMMABLE ORGANOIDS

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Mammalian synthetic biology has recently emerged as a field that is revolutionizing how we design and engineer biological systems for diagnostic and medical applications. In this talk, we will describe our integrated computational / experimental approach to engineering complex behavior in mammalian cells with applications to Programmable Organoids derived from hiPS cells. In our research, we apply design principles from electrical engineering and other established fields. These principles include abstraction, standardization, modularity, and computer aided design. But, we also spend considerable effort towards understanding what makes synthetic biology different from all other existing engineering disciplines by discovering new design and construction rules that are effective for this unique discipline. We will present Programmable Organoids, a new platform for drug discovery that enables rapid and effective drug screening. Based on programmed differentiation into synthetic mammalian tissues having multiple cell type architectures that are similar to human organs, Programmable Organoids mimic the response of a target organ to both positive and negative effects of drug candidates. Factors that can be non-destructively measured include cell state, viability, and function. Because they are synthetic, Programmable Organoids can host a large array of live-cell biosensors, built-in to one or more cell types, providing a rapid and realtime spatial readout of pathway-specific biomarkers including miRNAs, mRNAs, proteins, and other metabolites. Organoids programmed with both general and disease specific sensors then provide detailed information that can be used to identify candidates for further analysis. We envision a programmable common platform that can be shared among multiple drug candidates.

Keywords: mammalian, synthetic, organoids

TRACK: Disease Modeling and Drug Discovery (DMDD)

THE USE OF STEM CELLS IN DISEASE MODELING II

Sponsored by: Institute of Human Biology (IHB, Roche pRED)

8:15 AM – 9:45 AM

Hall Z, Level 3

8:20 AM – 8:40 AM

ADVANCING DISEASE MODELING AND THERAPEUTICS: KIDNEY ORGANOIDS AND ORGANOID-ON-A-CHIP

Morizane, Ryuji

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We have developed a chemically defined protocol that efficiently differentiates human pluripotent stem cells into multipotent nephron progenitor cells, capable of forming kidney organoids. These organoids exhibit nephron-like structures expressing markers of various kidney components, resembling the in vivo nephron arrangement. They also express genes associated with adult metanephric-derived kidneys, enabling the evaluation of transporter-mediated drug nephrotoxicity. By inducing repetitive injury to tubular cells, the organoids simulate interstitial fibroblast expansion, representing kidney fibrosis in vitro. Additionally, the integration of organ-on-chip technology enables vascularization and maturation of kidney organoids under flow, providing a physiological

model for polycystic kidney disease (PKD) research. In summary, these kidney organoids serve as valuable tools for studying genetic kidney disorders, as well as the mechanisms underlying acute and chronic kidney diseases.

Keywords: organoid, kidney, nephron, CKD, PKD, chip

8:40 AM – 8:50 AM

SCALED AND EFFICIENT DERIVATION OF FUNCTION ALLELES OF NEURODEVELOPMENTAL AND PSYCHIATRIC DISORDERS IN HUMAN INDUCED PLURIPOTENT STEM CELLS

Duan, Jubao[1], Zhang, Hanwen[2], Moorman, Lilia[2], McCarroll, Ada[2], Díaz De León Guerrerro, Sol[3], Zhang, Siwei[2], Gowda, Prarthana[3], Achwah, Mahmoud[3], Duhe, Alexandra[2], Sirkin, David[2], Wood, Whitney[2], Tracy, Gregory[2], Hart, Ron[3], Pato, Carlos[4], Mulle, Jennifer[5], Sanders, Alan[2] and Pang, Zhiping[3]
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Translating the genetic findings of neurodevelopmental and psychiatric disorders (NPD) into actionable disease biology will benefit from large-scale and unbiased functional studies of NPD genes. Here, leveraging the cytosine base editing (CBE) system, we developed a pipeline for clonal loss-of-function (LoF) allele mutagenesis in hiPSC by introducing premature stop-codons (iSTOP) that lead to mRNA nonsense-mediated-decay (NMD) or protein truncation. We tested the pipeline for 23 NPD genes on 3 iPSC lines and achieved highly reproducible, efficient iSTOP editing. Using RNAseq, we confirmed their pluripotency, absence of chromosomal abnormalities, and NMD. Interestingly, for three schizophrenia risk genes (SETD1A, TRIO and CUL1), we only obtained heterozygous LoF alleles, suggesting their essential roles for cell growth. We replicated the reported neural phenotypes of SHANK3-haploinsuficciency and found CUL1-LoF reduced neurite branches and synaptic puncta density. The iSTOP pipeline enables a scaled and efficient LoF mutagenesis of NPD genes, which yields an invaluable shareable resource.

Funding Source: National Institute of Mental Health (NIMH) RM1MH133065

Keywords: hiPSC, neurodevelopment disorders, loss of function (LOF)

8:50 AM – 9:00 AM

COMBINED SCREENING STRATEGIES IN INDUCED NEURONS AND MIDBRAIN ORGANOIDS UNVEIL REPURPOSABLE COMPOUNDS FOR THE TREATMENT OF LEIGH SYNDROME

Menacho, Carmen[1], Okawa, Satoshi[2], Wittich, Annika[3], Donnelly, Justin[4], Thevandavakkam, Mathuravani[4], Petersilie, Laura[5], Álvarez-Merz, Iris[5], Muñoz-Oreja, Mikel[6], Seibt, Annette[7], Distelmaier, Felix[7], Schuelke, Markus[8], Zakin, Shiri[4], Perlstein, Ethan O.[4], Spinazzola, Antonella[9], Holt, Ian J.[6], Rose, Christine R.[5], Zaliani, Andrea[3], Pless, Ole[3], Del Sol, Antonio[2] and Prigione, Alessandro[10]
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Mutations in mitochondrial complex IV assembly factor SURF1 causes Leigh syndrome (SURF1-LS), a rare untreatable neurologic disorder affecting children. SURF1-LS patients typically exhibit increased lactate in the cerebrospinal fluid and midbrain neurodegeneration. One factor hindering the development of treatments is the lack of in vivo models faithfully recapitulating this neuronal pathology. We previously demonstrated that mutations in SURF1 impair neuronal morphogenesis in induced pluripotent stem cell (iPSC)-derived neurons and cerebral organoids. As prime defect, mutations in SURF1 impeded a metabolic switch to oxidative phosphorylation at the level of neural progenitor cells (NPCs), a prerequisite for neural commitment that resulted in inefficient neurite outgrowth. Here, we aimed to discover pharmacological intervention strategies to rescue these neuronal defects. To this end, we performed two parallel drug-screening approaches: (I) a machine learning in silico screen based on single-cell transcriptomics of SURF1-mutant cerebral organoids, and (II) a yeast survival screen using a well-annotated library of 2,250 repurposable compounds. From both screens, we selected hit compounds and tested for their positive effect in neuronal morphogenesis. We used CRISPR/Cas9 engineered isogenic SURF1 mutant NPCs in which we induced neural commitment via overexpression of NGN2. On these early-induced neurons, we measured the impact of selected hit compounds on neurite outgrowth capacity using high content imaging. We identified two FDA-approved compounds with a dose-dependent pharmacological rescue. We next generated SURF1-mutant midbrain organoids, which showed key disease-specific features. Both compounds reduced the excess release of lactate into the media, increased the amount of tyrosine hydroxylase-positive dopaminergic neurons, and rescued the overall neuronal arborization. Lastly, the examination of these two drugs revealed surprising similarity in their chemical structures and docking features, suggesting that they might share their mode-of-action in the context of SURF1-LS. Altogether, we discovered two independent compounds that may act via a common molecular mechanism, and could represent effective repositionable drug strategies for children affected by LS.

Keywords: mitochondrial disease, drug-screening, midbrain organoids

9:00 AM – 9:10 AM

ATP13A2 AND POLYAMINE DEFICIENCY CAUSE EPIGENETIC REPROGRAMMING OF HUMAN ASTROCYTES TO A SENESCENT STATE TOXIC TO DOPAMINERGIC NEURONS PROMOTING JUVENILE ONSET PARKINSONS DISEASE

Blanchard, Joel, Coccia, Elena, Perez, Andrea and Sohail, Soha
Neuroscience, Icahn School of Medicine at Mount Sinai, USA

Aging is the strongest risk factor for neurodegeneration. However, our understanding of how cells in the human brain age and our ability to model the biological process of aging remains limited. Most genes that promote early onset neurodegeneration are associated with aberrant processing and degradation of proteins such as amyloid, tau, and synuclein. In contrast, loss of function (LOF) variants in ATP13A2 cause one of the earliest forms of Parkinson's disease (PD) with an age of

onset in the 20s that presents with mobility and cognitive impairments. LOF variants in ATP13A2 were recently identified to trap polyamines in the lysosome, but the mechanisms by which this promotes PD and cognitive impairments remain unknown. Using isogenic iPSC-derived cells we developed a 3D co-culture system of the mid-brain (in vitro Mid-Brain (iMid-Brain) that contains all the major cell types including dopaminergic neurons, vasculature, astrocytes, and microglia. Combinatorial genetic mixing experiments in the iMid-Brain revealed that ATP13A2 LOF in astrocytes is necessary and sufficient to induce dopaminergic neuronal death. Further analysis of astrocytes revealed that ATP13A2 LOF causes depletion of cytosolic polyamines leading to upregulation of de novo polyamine biosynthesis. We found that upregulated polyamine biosynthesis competes for S-adenosyl methionine (SAM) required for DNA and histone methylation. As a result, LOF of ATP13A2 in astrocytes decreases DNA and histone methylation, increasing chromatin accessibility. In combination with our molecular and biochemical analysis, our data show that ATP13A2 LOF induces epigenetic reprogramming of astrocytes to a senescent inflammatory state with impaired endo/lysosomal function that promotes the release of vesicles that are cytotoxic to dopaminergic neurons. Through chemical and genetic approaches, we found blocking the use of SAM in polyamine biosynthesis prevents epigenetic reprogramming of astrocytes to states that are cytotoxic to dopaminergic neurons. Collectively, our study provides mechanistic insight and new therapeutic opportunities in PD. This establishes a mechanism for polyamines in accelerated neurodegeneration and highlights the potential to leverage polyamine biology to mimic aspects of aging in vitro.

Funding Source: ASAP/MJFF, and R01NS114239

Keywords: Parkinson's disease, aging, in vitro models of the human brain

9:10 AM – 9:20 AM

A NEW IMMUNOCOMPETENT BRAIN ORGANOID MODEL TO STUDY DEMYELINATING DISEASES

Pietrogrande, Giovanni, Garawadmath, Soumya, Mar, Jessica, Wolvetang, Ernst and Zheng, Huiwen

Australian Institute for Bioengineering and Nanotechnology, The University of Queensland, Australia

We have harnessed the potential of immunocompetent brain organoids to study neurodegeneration, particularly in the context of demyelination and multiple sclerosis. By developing a novel protocol, these organoids now intrinsically generate various neuronal types, myelinating oligodendrocytes, microglia, and astrocytes (MOLBOs), effectively representing a complete model of the human brain. By treating the organoids with lysolecithin to induce demyelination, we gain valuable insights into the relationship between this process, inflammatory responses of microglia, and alterations in neuronal activity, ultimately leading to neuronal degeneration. Our groundbreaking approach allows us to examine the intricate dynamics between demyelination, inflammation, and neuronal activity within the brain organoids. With microglia serving as key players in neurodegenerative processes, we can now assess their role in real time and the impact on neuronal function. This comprehensive brain organoid model opens new avenues for understanding neurodegenerative diseases and identifying potential therapeutic targets. Adopting this advanced model, we plan to uncover critical mechanisms underlying neurodegeneration and facilitate the development of innovative treatments to combat these debilitating conditions and promote remyelination.

Funding Source: Perpetual's IMPACT Philanthropy MS Australia European Leukodystrophy Association (ELA) National Health and Medical Research Council (NHMRC) Australia

Keywords: brain organoids, demyelination, neuroinflammation

9:20 AM – 9:40 AM

FUNCTION OF RISK GENES FOR BRAIN DISORDERS IN NEURODEVELOPMENT

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Schizophrenia (SCZ) is a highly heritable neurodevelopmental disorder with a ~1% worldwide prevalence. Recent large-scale exome sequencing data identified rare coding variants in 10 genes which confer substantial risk for SCZ, and SETD1A gene is the top one among the 10 genes identified. SETD1A encodes for a component of a histone methyltransferase complex that produces mono-, di-, and trimethylated histone 3 at lysine 4 (H3K4), a mark that on a genome-wide scale is broadly associated with transcriptional regulation and epigenetic tagging of promoter and enhancer sequences. The biological effects of reduced SETD1A levels on gene expression and cellular function in human brain development remain unclear. We have developed a robust protocol for generation of hippocampal dentate granule cell (DGC)-like neurons from human induced pluripotent stem cells (hiPSCs) and generated heterozygous SETD1A mutant hiPSC lines under four genetic backgrounds targeting diverse exons (exon 2, 4 or 16) by CRISPR/Cas9 technology. We have identified defects in transcriptional and functional deficits across different genetic backgrounds. Our study provides new insight into a potential mechanistic link between rare SCZ risk variants and synaptic dysfunction.

Keywords: schizophrenia, iPSCs, hippocampal neurons, synapse

TRACK: Pluripotency and Development (PD)

TISSUE AND ORGAN DEVELOPMENT

8:15 AM – 9:45 AM

Hall 4, Entrance Level

8:20 AM – 8:40 AM

ORGANOID MODELS TO DECIPHER PANCREAS DEVELOPMENT

Grapin-Botton, Anne

Max Planck Institute of Molecular Cell Biology and Genetics, Germany

During development, multiple organs form fluid-filled cavities of different shapes. We investigated the mechanisms controlling lumen formation and shape using mice as well as mouse pancreas organoids. In vivo the pancreas is a branched organ with internal tubes surrounded by pancreas progenitors during development and ductal cells in the adult. At the tip of the branches, acinar cells secrete digestive enzymes. Endocrine cells form from progenitors and the architecture of the ducts affects their ability to produce endocrine cells. We used pancreas organoids to study the formation of the ductal lumen in the pancreas and what controls their shape and their ability to form networks. Moreover, to attempt to understand human pancreas development, as a complement to investigations in mice and with mouse pancreas organoids, we established 3D (three-dimensional) culture conditions that enable the efficient expansion, differentiation and morphogenesis of pancreatic progenitors isolated from human fetuses or produced from human pluripotent stem cells (hPSCs). Using this system

that we benchmarked to fetal pancreata we performed a high content imaging screen for small molecules affecting organoid cell composition and morphogenesis. We developed an image analysis pipeline and identified compounds affecting lumen size and shape, pancreas progenitor identity as well as expansion.

Keywords: organoids, pancreas, screening

8:40 AM – 8:50 AM

MACROPHAGES REGULATE PROGENITOR CELL DIFFERENTIATION DURING HEPATOBILIARY DEVELOPMENT AND LIVER REGENERATION

Goessling, Wolfram[1], Schwartz, Arkadi[2] and Penkofflidbeck, Nadia[2]
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Liver development is regulated by well-described signaling pathways. It is unknown, however, whether immune cells are involved to form the liver's complex and asymmetric structure. Here, we discover that macrophages are essential for normal vertebrate liver development. Intravital high-resolution imaging of zebrafish embryos revealed direct interaction between macrophages and the developing liver, specifically at sites of biliary tree sprouting. Surprisingly, macrophage loss caused severe biliary network impairment with reduced branching complexity, biliary secretion and altered hepatocyte polarity. Ablation of primitive macrophages in mouse embryos confirmed evolutionary conservation with impaired biliary differentiation. Importantly, chemical and genetic epistasis experiments identified TGF-β signaling as mediator of macrophage-regulated liver development. Precise temporo-spatial regulation of TNFα expression in the developing liver is the central chemoattractant: perturbations of TNFα signaling reduced macrophage density and macrophage-biliary tree interactions, causing severe biliary defects. Importantly, ablation of macrophages also led to impaired regeneration after hepatocyte ablation, indicating conserved effects of immune cells in organ differentiation and repair. Our work identifies a novel role for macrophages to affect progenitor cell differentiation into biliary epithelial cells during liver organogenesis and organ appair after injury.

Keywords: progenitor cell differentiation, immune cells in organ development, high resolution imaging

8:50 AM – 9:00 AM

DEVELOPMENTAL PATTERNING AND CELL-FATE SPECIFICATION OF THE MOUSE COLONIC EPITHELIUM

Yin, Yanbo[1], Lian, Qiuyu[2], Maimets, Martti[3], Jensen, Kim[3], Yum, Min Kyu[4] and Simons, Benjamin[2]
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The mammalian intestine transitions from a smooth tubular epithelium into a highly-ordered structure during development. Work in the mouse small intestine has found evidence for the essential role of both mechanical and biochemical cues in driving the self-organisation and patterning of the epithelium into the hallmark structures of crypts and villi during late embryonic and early postnatal development. Yet, the timing and mechanism of the formation of structures in the colon remain underexplored. Here, we focus on the origin and timing of the larger-scale epithelial folding and smaller-scale glandular organisation during colonic development; whether this organisation emerges deterministically or stochastically and whether developmental changes at different scales affect the molecular identities and fates of the cells making up the developmental epithelium. Combining quantitative imaging, fate mapping, ex-vivo live-imaging, single-cell molecular profiling and biophysical modelling in the developing mouse colon, our results show how region-specific tissue-level remodelling restricts the initiation and expansion of the glandular organization. Timelapse imaging of ex-vivo culture experiments show strong evidence for distinct symmetry-breaking mechanisms across scales in the colon when compared to the small intestine. Quantitative lineage-tracing showed characteristic statistical distributions pointing to a stochastic growth pattern for the expansion of the colon postnatally. Finally, statistical analysis of scRNAseq data show how colon regionalisation is correlated with fate decision timing, clonal composition, and molecular identity of cells in the developing epithelium. Together, these findings elucidate the physical and molecular events that drive the patterning of the colonic epithelium.

Keywords: development, colon, patterning

9:00 AM – 9:10 AM

CELL FATE REGULATION OF EXTRAEMBRYONIC CELLS IN THE GUT

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Despite a distinct developmental origin, extraembryonic cells in mice contribute to the gut endoderm and converge to match the transcriptional identity of embryonic gut cells. Notably, extraembryonic progenitors are distinguished by a non-canonical epigenetic landscape when compared to the embryonic lineage, raising the question of whether the epigenome of extraembryonic gut cells is reset to match the embryonic landscape. Moreover, it remained unknown if these extraembryonic gut cells persist throughout development and can differentiate into more specialized endodermal cell types. To address these, we developed a stable two-color lineage tracing strategy to faithfully track and characterize extraembryonic cells of the gut. We demonstrate that extraembryonic gut cells display substantial memory of their developmental origin despite their overall convergence towards embryonic programs, including clear transcriptional signatures and retention of their original DNA methylation landscape. Furthermore, we show that gut cells of extraembryonic origin undergo programmed cell death and cells of embryonic origin clear their remnants via non-professional phagocytosis by midgestation. We also identified a key regulator of the elimination process and upon mutating it, extraembryonic gut cells survive and are able to differentiate further. Our study provides insights into lineage origin-dependent transcriptional and epigenetic regulation, elucidates a selective cell clearance mechanism during mammalian organogenesis, and contributes to developing stem cell- and organoid-based models of the gut.

Keywords: organogenesis, lineage-tracing, DNA methylation

9:10 AM – 9:20 AM

LINKING CIRCADIAN RHYTHMS TO PANCREATIC BETA-CELL MATURATION

Alvarez, Juan R.[1], Montalvo Landivar, Ana[2], Gruskin, Zoe[1], Leduc, Andrew[3], Liu, Mai[4], Gao, Zihan[4], Ahn, June[1], Straubhaar, Juerg[5] and Slavov, Nikolai[6]
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How ubiquitous circadian clocks orchestrate tissue-specific outputs is not well understood. In particular, major questions remain as to how core/ancillary clock components synchronize distinct genes in distinct tissues to coordinate overall metabolism. Pancreatic β cell clocks attune insulin secretion to daily energy cycles, and desynchrony from genetic or behavioral disruptions raises type 2 diabetes risk. Here, we focus on the transcription factor BHLHE40/DEC1, an ancillary clock component induced in adult β cells. Using mice and human stem cell-derived genetic models, and single-cell transcriptomic, epigenomic, and proteomic assays, we show that DEC1 coordinates β-cell glucose responsiveness by synchronizing energy metabolism and secretory gene oscillations. Dec1-ablated mice develop lifelong hypo-insulinemic diabetes, despite normal islet formation, feeding/activity patterns, and intact circadian Clock/Bmal1 activators. DEC1, but not CLOCK/BMAL1, binds maturity-linked genes that mediate respiratory metabolism and insulin exocytosis in mouse and human, and Dec1 loss disrupts their transcription synchrony. Accordingly, mice with embryonic β-cell Dec1 ablation develop hypo-insulinemia due to poor insulin responses to glucose, as with immature fetal/neonatal islets. Thus, DEC1 links the circadian clock to acquisition of the mature β-cell phenotype, revealing a hierarchy for how the clock links to cell type-specific physiology. These findings show that synchrony of energy metabolism pathways by adult-specific clockwork is critical for physiological coordination of metabolism.

Keywords: cell maturation, circadian clocks, diabetes

9:20 AM – 9:40 AM

SKELETAL MUSCLE STEM AND NICHE CELL DYNAMICS IN PATHOLOGIES

Tajbakhsh, Shahragim
Department of Developmental and Stem Cell Biology, Pasteur Institute, France

Pathologies generating acute or chronic inflammation provoke systemic signals that can cause secondary effects in various tissues and organs. Influenza virus infects primarily the respiratory tract and not skeletal muscle, yet it induces secondary symptoms such as muscle weakness. Cancer cachexia is a wasting syndrome characterised by weight loss, resulting primarily from muscle fat wasting. Both models induce a host immune response and systemic inflammation. The impact on tissue specific quiescent stem cells remained largely unexplored. We show that quiescent muscle stem cells (MuSCs) undergo changes in properties, including a reduction in size. Gatekeepers of quiescence are downregulated, yet cell cycle entry, commitment, and differentiation are perturbed. These alterations result in delayed and compromised muscle regeneration following injury. Analysis of mesenchymal progenitors (FAPS) which are part of the MuSC niche, also showed impaired proliferation and metabolic perturbations. Intriguingly, while MuSCs are not directly exposed to the virus or the cancer cells, they exhibit an immune and stress signature. We propose that MuSCs exposed to pathology-induced systemic inflammation adopt a novel quiescent cell state that impacts their molecular and cellular properties as well as function.

Keywords: muscle stem cells, systemic inflammation, quiescence

UPDATES ON CLINICAL TRIALS

Sponsored by: Stem Cell Reports
8:15 AM – 8:45 AM
Hall 3, Entrance Level

8:20 AM – 8:40 AM

PHASE I CLINICAL TRIAL OF HUMAN ES-DERIVED DOPAMINE NEURONS GRAFTS FOR PARKINSON'S DISEASE: 18 MONTHS DATA

Tabar, Viviane[1], Henchcliffe, Claire[2], Sarva, Harini[2], Lozano, Andres[3], Kalia, Suneil[3], Kwok Hei Yu, Kenny[2], Brennan, Cameron[2], Ma, Yilong[2], Yountz, Marcus[2], Enayetallah, Ahmed[2], Stemple, Whitney[2], Abid, Nauman[2], Lampron, Antoine[2] and Fasano, Alfonso[3]
[1]Neurosurgery, Memorial Sloan Kettering Cancer Center, USA, [2]University of California Irvine, USA, [3]University of Toronto, Canada

We will present an update on data from the Phase I clinical trial of human ES-derived dopamine neuron grafts (Bemdaneprocel) up to the 18 months timepoint.

Keywords: clinical trial, human PSC, human ES cells, dopamine neurons, Parkinson's disease, grafts Parkinson disease

Clinical trial ID number: NCT04802733

8:40 AM – 8:50 AM

A PHASE I/IIA TRIAL TO TEST SAFETY AND FEASIBILITY OF AN AUTOLOGOUS IPS CELL-DERIVED RETINAL PIGMENT EPITHELIUM PATCH IN AGE-RELATED MACULAR DEGENERATION PATIENTS

Sharma, Ruchi and Bharti, Kapil
OGVFB, NEI/NIH, USA

The advanced stage of age-related macular degeneration (AMD) - geographic atrophy (GA) leads to irreversible vision loss and often manifests in people above 60 years of age. AMD is thought to initiate by the dysfunctional retinal pigment epithelium (RPE) monolayer - resulting in sub-RPE protein-rich drusen deposits. RPE sits between photoreceptors and choroidal capillaries, providing nutrients and support necessary for maintaining the homeostatic unit at the back of the eye. The GA stage is characterized by RPE atrophy, photoreceptor cell death, and the loss of the choroid-capillary bed. Currently, no treatment is available to improve vision for the late stage of GA patients. Here, we developed an autologous cell replacement therapy for treating GA patients. We used induced pluripotent stem cells (iPSC) reprogrammed from CD34+ cells isolated from PBMC collected from patients' blood. iPSCs are differentiated into pure RPE cells using a protocol developed in our lab. The RPE cells are matured on a biodegradable polylactic co-glycolic acid (PLGA) scaffold as a tissue patch for five weeks. Quality control assays confirmed the iPSC-RPE patch's purity, maturity, and

functionality. Pre-clinical studies were conducted in rats and pigs to demonstrate the safety and efficacy of the iPSC-RPE patch. Immune-compromised rats transplanted with a 0.5 mm iPSC-RPE patch showed no signs of tumor formation after nine months, confirming the safety profile. To test local safety and efficacy in a large animal model, we laser ablated the RPE monolayer in the visual streak of pig eyes and, after 48 hours, transplanted the iPSC-RPE patch. Optical coherence tomography (OCT), which measures retinal anatomy, confirmed the integration of the patch in the subretinal region. A multi-focal electroretinogram (ERG) that measures retina function showed that the retinal layers' electric response over the patch area was much higher than the lasered area without the implant. The FDA cleared this work for a Phase I/IIa clinical trial to test the safety and feasibility of an autologous iPSC-RPE patch in AMD patients with GA. The Phase I/IIa trial is ongoing at the National Eye Institute at NIH.

Keywords: iPSC-RPE, AMD, phaseI/IIa

8:50 AM – 9:00 AM
LENTIVIRAL GENE THERAPY TO CORRECT RAG1 DEFICIENCY

Ott de Bruin, Lisa[1], Pike-Overzet, Karin[2], Berghuis, Dagmar[3], van Eggermond, Marja[2], de Bruin, Sandra[2], van der Holst, Rosalie[2], de Kivit, Sander[2], Laney, Estefania[3], Ordas, Anita[2], Von Asmuth, Erik[3], van Ostaijen-Ten Dam, Monique[3], van Litsenburg, Chantal[2], Zhao, Yuxi[2], van der Stoep, Eileen[4], Tihaya, Mara[4], Zwaginga, Jaap Jan[5], Meij, Pauline[4], Staal, Frank[2] and Lankester, Arjan[3]
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Recombination activating gene (RAG)1-SCID patients completely lack circulating B and T lymphocytes due to the inability to rearrange B and T cell receptor genes, leading to an early arrest in development. Hypomorphic RAG1 mutations, with residual RAG1 activity, enable some T and/or B cell development. These patients typically suffer from severe immunodeficiency and/or autoimmunity/inflammation. Allogeneic stem cell transplantation is the established life-saving treatment for RAG1 deficiency. However, partial cure and substantial treatment-related mortality in patients lacking an HLA matched donor emphasize the need for more effective and less toxic approaches such as ex vivo gene therapy in autologous hematopoietic stem cells (HSCs). In preclinical studies including rag1 -/- mouse models we compared different constructs and demonstrated safety and efficacy of gene therapy using a SIN lentiviral (LV) vector containing codon-optimized (c.o.) RAG1 with MND promoter. Based on this, we designed a phase I/II multinational academic clinical trial where RAG1-SCID patients' mobilized HSCs are sent to our institute, genetically modified with MNDc.o.RAG1 SIN-LV and returned to the clinical sites as cryopreserved product where they are administered to the patient following busulfan-based conditioning. To date, 2 RAG1-SCID patients received this treatment. T and B cell reconstitution is encouraging, without immunoglobulin supplementation dependency, and normal vaccination responses in the first patient. Comprehensive safety monitoring has revealed no evidence of insertional mutagenesis, with a polyclonal insertion pattern and lack of clonal dominance. Gene therapy for hypomorphic RAG1 deficiency presents unique challenges distinct from those encountered in treating SCID. These challenges arise from the presence of residual T and B cells in patients before treatment, as well as the presumed, diminished selective advantage of corrected cells and the possible impact of inflammation on HSCs. Nevertheless, the MNDc.o.RAG1 SIN-LV vector proved to be effective when tested in an NSG humanized mouse model with hypomorphic RAG1 patient cells and in two different hypomorphic RAG1 mouse models. As a result, we are actively preparing a comparable trial for hypomorphic RAG1 patients, employing the same vector.

Funding Source: Partly supported by ZonMW E-RARE grant (40-419000-98-020), EU H2020 grant RECOMB (755170-2), the European Union Horizon 2020 program and reNEW, the Novo Nordisk Foundation for Stem Cell Research (NNF21CC0073729).

Keywords: lentiviral gene therapy, RAG1, immunodefiiciency

Clinical trial ID number: NCT04797260

9:00 AM – 9:20 AM
FIRST-IN-HUMAN CLINICAL TRIAL OF TRANSPLANTATION OF IPSC-DERIVED NS/PCS IN SUBACUTE COMPLETE SPINAL CORD INJURY: INTERIM REPORT

Okano, Hideyuki[1], Fujiyoshi, Kanehiro[2], Kanemura, Yonehiro[3], Kawashima, Shihoko[4], Kohyama, Jun[5], Nagoshi, Narihito[4], Nakamura, Masaya[4], Sugai, Keiko[4], Tsuji, Osahiko[4] and Yamaguchi, Ryo[6]
[1]Keio Regenerative Medical Research Center, Keio University, Japan, [2]Murayama Medical Center, Japan, [3]National Hospital Organization Osaka National Hospital, Japan, [4]Department of Orthopaedic Surgery, Keio University School of Medicine, Japan, [5]Department of Physiology, Keio University School of Medicine, Japan, [6]Sumitomo Pharma Co., Ltd., Japan

Our team has conducted the inaugural human clinical trial evaluating the transplantation of human iPSC-derived neural progenitor cells for subacute spinal cord injuries under the study "Regenerative Medicine using iPSC-derived Neural Progenitor Cells for Subacute Spinal Cord Injury (SCI)." This trial planned the transplantation of iPS cell-derived neural progenitor cells in four patients with subacute complete SCI (AIS-A), initiating the first surgery in December 2021 and achieving the target enrollment of four patients by the end of 2023. A total of four patients, with injuries ranging from C3/4 to Th10 and within 24 days post-injury, were enrolled. The study adhered to protocols approved by Japan's Ministry of Health, Labor and Welfare, and registered under the Japan Registry of Clinical Trials (jRCT number jRCTa031190228). The Neural Stem/Progenitor Cells (NS/PCs) for transplantation were produced in a Good Manufacturing Practice-grade facility, utilizing a clinical-grade, integration-free hiPSC line (Cord Blood Cells-derived YZWJs513 iPSCs) developed by CiRA. Post extensive in vitro quality checks, the long-term safety and efficacy of the transplanted cells were validated in immunodeficient NOG mouse models, with each mouse receiving one million cells.In clinical setting, after obtaining patient consent, cryopreserved cells were thawed and prepared through a meticulous process including treatment with γ-secretase inhibitors to enhance differentiation. Two million iPSC-NS/PCs in a 20µl suspension were transplanted into the injury's epicenter along with a low dose of tacrolimus. All surgical procedures were completed successfully. The trial is structured as an open-label, single-arm study, with a primary follow-up period of one year. The primary aim is to assess the safety of the hiPSC-NS/PC transplantation in

patients with subacute SCI. A secondary goal is to gather initial data on its effects on neurological functions and patient quality of life. Evaluations have measured impacts on motor and sensory functions, spasticity, and overall quality of life, with motor function changes assessed via ISNCSCI, compared against historical controls. This project marks the world's first use of human iPSC-NS/PC transplantation for spinal cord injury, with upcoming reports on follow-up data.

Funding Source: This study is supported by Grant No. 22 (18bm0204001h0006), Grant No and JP21bk0104120.and the Research Project for Practical Applications of Regenerative Medicine from AMED

Keywords: iPS cells, Neural Stem/Progenitor Cells, Spinal Cord Injury

Clinical trial ID number: UMIN000035074, jRCTa031190228

9:20 AM – 9:40 AM

HYPOIMMUNE ISLET CELLS MEDIATE INSULIN INDEPENDENCE AFTER ALLOGENEIC TRANSPLANTATION WITHOUT IMMUNOSUPPRESSION

Schrepfer, Sonja[1], Hu, Xiaomeng[2], White, Kathy[2], Young, Chi[2], Olroyd, Ari[2], Kievit, Paul[3], Connolly, Andrew[4] and Deuse, Tobias[5]
[1]Head of Hypo-immune Platform, Sana Biotechnology, USA, [2]Hypoimmune Platform, Sana Biotechnology, USA, [3]Primate Center, OHSU, USA, [4]Pathology, UCSF, USA, [5]Surgery, UCSF, USA

Treatment of type 1 diabetes mellitus (T1DM) via allogeneic donor transplant has limited success due to morbidities from immunosuppression (IS) and a gradual loss of engrafted pancreatic islet function. We report that allogeneic transplantation of engineered, primary, hypoimmune, pseudo-islets (HIP p-islets) engraft into a fully immunocompetent, diabetic non-human primate (NHP), provide stable endocrine function, and enable insulin independence without inducing any detectable immune response in the absence of IS. NHP cadaveric islet cells were engineered to disrupt function of MHC class I and II and overexpress CD47 thus rendering them hypoimmune (HIP). Diabetes was induced in the NHP with streptozotocin and daily insulin injections started to re-establish glucose control. After 78 days, NHP underwent transplantation of HIP p-islets by intramuscular injection resulting in insulin independence. As early as one week after the transplantation, the NHP's serum c-peptide level had normalized and remained stable throughout the follow-up period of 6 months. The NHP showed tightly controlled blood glucose levels for 6 months, was completely insulin-independent, and continuously healthy. Up to 6 months after HIP p-islet transplantation, PBMCs and serum were obtained for immune analyses. HIP PI showed no T cell recognition, no graft-specific antibodies, and were protected from NK cell and macrophage killing. To prove that the monkey's insulin-independence was fully dependent on the HIP p-islets graft and there was no regeneration of his endogenous islet cell population, we triggered the destruction of the HIP p-islet transplant using a CD47-targeting strategy resulting in loss of glycemic control and return to exogenous insulin dependence. These data demonstrate evidence for immune evasion of HIP p-islets, graft mediated insulin-independence of the diabetic NHP, and a potential safety strategy. In summary, this successful NHP study provides proof of concept for an upcoming clinical trial using allogeneic, HIP-edited primary islets in patients with type 1 diabetes.

Keywords: hypoimmune, type 1 diabetes, islet transplantation

Clinical trial ID number: NCT06239636

PLENARY VI: THE CLINICAL REALITY AND PROMISE OF CELL AND GENE THERAPIES

Sponsored by Healios K.K.
10:00 AM – 11:35 AM
Hall 1, Level 2

10:05 AM – 10:25 AM

A PHASE I/II CLINICAL TRIAL OF NRTX-1001 INHIBITORY INTERNEURON CELL THERAPY FOR DRUG-REFRACTORY FOCAL EPILEPSY

Priest, Catherine, Blum, David, Hixson, John, Madrid, Sheri, Lee, Seonok, Kowal, Tia, Watson, Michael, Hosford, Victoria, Feld, Brianna, Larios, Rose, Jung, Ji-Hye, Bershteyn, Marina, Maury, Yves, Fuentealba, Luis, Zhou, Robin, Parekh, Mansi, Hampel, Philip, Vogel, Alexandra, Bulfone, Alessandro, Banik, Gautam and Nicholas, Cory R.
Neurona Therapeutics, USA

GABAergic inhibitory interneuron cell therapy represents a novel therapeutic strategy for the treatment of drug-refractory focal epilepsy, and potentially other chronic neurological disorders characterized by local hyperexcitability of neural circuits. NRTX-1001 is an allogeneic cell therapy candidate comprising human pluripotent stem cell-derived post-mitotic GABAergic interneurons of a specific medial ganglionic eminence (MGE) pallial-type identity. NRTX-1001 is being evaluated for safety and efficacy in an ongoing Phase I/II (NCT05135091) open-label dose escalation trial for drug-resistant unilateral mesial temporal lobe epilepsy (MTLE). Data will be presented from the first patient cohort, who are currently up to 18 months post-NRTX-1001 administration, describing changes in seizure frequency and severity, neurocognition assessments, and the occurrence of adverse events. In addition to these latest clinical data, preclinical data will be presented characterizing the cellular composition of NRTX-1001 and the safety and efficacy of the cells in models of chronic focal epilepsy. Single cell RNA sequencing of NRTX-1001 indicates that the cells mature into somatostatin and parvalbumin lineages of MGE pallial-type interneurons, and maintain consistent fate after transplantation. Further, NRTX-1001 interneurons from multiple, independently-manufactured cell lots have disease-modifying activity across a broad range of doses in a rodent model of MTLE, leading to durable elimination of focal seizures, reduced temporal lobe sclerosis, and increased animal survival. Toxicology and biodistribution studies will also be presented. In summary, these clinical and preclinical data highlight the significant progress being made toward the use of human inhibitory interneuron cell therapy for the potential future treatment of chronic focal epilepsy.

Keywords: interneuron, cell therapy, clinical trial

10:25 AM – 10:45 AM

SALIVARY GLAND ORGANOIDS TO TREATMENT RADIOTHERAPY INDUCED XEROSTOMIA

Coppes, Robert P.
Biomedical Sciences and Radiation Oncology, University Medical Center Groningen, Netherlands

Severe hyposalivation and consequential xerostomia (dry mouth syndrome) are common, often irreversible side effects of

radiotherapy treatment for head-and-neck cancer. Symptoms include alterations in speech and taste, difficulties with mastication and deglutition, and an increased risk of developing oral infections and dental caries. Xerostomia severely hampers the quality of affected patients' lives. Currently, no successful treatment exists. The aim was to develop a stem cell therapy to treat radiation-induced hyposalivation. First, we localized the stem cells of the salivary gland in the excretory ducts using high-precision proton irradiation and subsequent stem cell-derived spheroid culturing. Indeed, sparing of this stem cell region in the parotid gland resulted in reduced levels of daytime xerostomia. Next, we developed methods to culture murine and patient-specific tissue resembling salivary gland-derived organoids (SGO). These SGOs contain all the glandular lineages and can extensively self-renew and rescue salivary gland function upon (xeno-)transplantation. Subsequently, we developed a GMP-compliant protocol for isolating and expanding human-derived salivary gland organoids derived from patient submandibular gland biopsies taken before radiotherapy treatment with an efficiency comparable to current non-GMP research-based protocols. The functionality of salivary gland-derived cells is maintained after cryopreservation, allowing the protocol to be adapted to the patient's radiotherapy treatment schedule. This presentation will show the developmental path to the first human application of autologous organoid-derived cell transplantation in head and neck cancer patients. The first preliminary results will be presented.

Keywords: organoids, xerostomia, phase I/II trail

10:45 AM – 11:05 AM

IN VIVO DIRECT REPROGRAMMING OF TUMOR CELLS TO DENDRITIC CELLS AS A NEW CANCER IMMUNOTHERAPY MODALITY

Pires, Cristiana F.[1], Ascic, Ervin[2], Akerstrom, Fritiof[1], Sreekumar Nair, Malavika[2], Rosa, André[1], Kurochin, Ilia[2], Zimmermannova, Olga[2], Catena, Xavier[1], Rotankova, Nadezhda[3], Veser, Charlotte[3], Rudnik, Michal[3], Ballocci, Tommaso[2], Schärer, Tiffany[1], Huang, Xiaoli[1], Renaud, Emilie[1], Velasco Santiago, Marta[4], Met, Özcan[4], Askmyr, David[2], Lindstedt, Malin[2], Greiff, Lennart[2], Agarkova, Irina[3], Svane, Inge Marie[4], Fiúza Rosa, Fábio[1] and Pereira, Carlos Filipe[5]

[1]Asgard Therapeutics, Sweden, [2]Lund University, Sweden, [3]InSphero, Switzerland, [4]Copenhagen University Hospital, Denmark, [5]Division of Molecular Medicine and Gene Therapy, Lund University, Sweden

Immunotherapy leads to long-term survival of cancer patients, yet generalized success has been hampered by insufficient antigen presentation and exclusion of immunogenic cells from the tumor microenvironment. Here, we present our approach to reprogram tumor cells in vivo by adenoviral delivery of the transcription factors PU.1, IRF8, and BATF3, which enabled them to present tumor antigens as type 1 conventional dendritic cells. Reprogrammed tumor cells remodeled their tumor microenvironment, recruited, and expanded polyclonal cytotoxic T cells, induced complete tumor regressions, and established systemic immunity in different mouse models. Importantly, reduced numbers of short-lived induced dendritic-like cells was sufficient to induce long-term therapeutic benefit, even in monotherapy. Delivery of the reprogramming factors to human tumor spheroids and xenografts induced their conversion to immunogenic dendritic-like cells, independently of immunosuppression, which usually limits immunotherapy efficacy. These findings provide proof-of-concept for Asgard Therapeutics' lead program AT-108, an off-the-shelf gene therapy product able to orchestrate tumor-tailored and systemic antitumor immunity. The GMP manufacturing process of AT-108 product is under development as well as safety and toxicology studies, enabling first-in-human clinical trials. AT-108 will be tested in advanced solid tumor patients refractory to standard-of-care, to demonstrate safety and provide early proof-of-mechanism in humans. Together, these studies will pave the way to a first-in-class immunotherapy based on recreating functional dendritic cells in vivo, bypassing complex ex-vivo cell manipulation and dramatically expanding patients' access to cell-based approaches.

Keywords: direct reprogramming, cancer immunotherapy, in vivo gene therapy

11:15 AM – 11:35 AM

AUTOLOGOUS IPSC-DERIVED CARDIAC CELL THERAPIES FOR PATIENTS WITH UNIVENTRICULAR CONGENITAL HEART DEFECTS

Lai, Michael

HeartWorks, USA

Congenital heart defects (CHDs) are the most common congenital disorder, as they affect approximately one percent of live births worldwide. Univentricular heart defects, which are congenital heart defects (CHDs) where only a single ventricle develops properly, affect approximately 1 in 4,000 live births worldwide and are considered among the most severe forms of CHDs. Patients with univentricular heart defects require reconstructive heart surgery early in life and lack treatment options other than heart transplantation as they age. Recent technological advancements have enabled regenerative cell therapies, from both autologous and allogenic sources, to be used in clinical trials for the treatment of both congenital and ischemic heart defects. In 2022, HeartWorks received approval to conduct the first Phase I clinical trial to deliver autologous induced pluripotent stem cell-derived cardiac lineage (iPSC-CL) cells to the patients with univentricular CHDs (NCT05647213). This Phase I trial assesses the safety and feasibility of delivering an autologous iPSC-CL therapy to a univentricular patient population with the goal of improving cardiac contractility. Ongoing product development efforts have focused on understanding the function of iPSC-CLs in both in vitro and preclinical applications to predict and optimize the efficacy of the therapy. Additionally, we are expanding characterization of patient-derived iPSCs to assess their genomic stability during the manufacturing process.

Keywords: iPSCs, CHD, clinical trial

PLENARY VII: AWARDS & KEYNOTE SESSION

1:30 PM – 3:35 PM

Hall 1, Level 2

1:52 PM – 2:22 PM

ISSCR MOMENTUM AWARD PRESENTATION: HOW THE HUMAN BRAIN BUILDS ITSELF: RECONSTRUCTING NEURODEVELOPMENT WITH STEM CELL-DERIVED ASSEMBLOIDS AND ORGANOIDS

Pașca, Sergiu

Stanford University, USA

The construction of the human nervous system involves a series of complex and largely inaccessible processes. In my talk, I will describe

efforts in my lab towards understanding the rules that govern the molecular and cellular steps underlying the assembly of the human brain and the mechanisms that lead to disease. Towards this, we have been developing approaches to generate and assemble, from multi-cellular components, human neural circuits in vitro and in living systems. We initially introduced instructive signals to derive, from pluripotent stem cells, self-organizing 3D tissue structures called regionalized brain organoids that resemble domains of the developing central nervous system. We have shown that these cultures recapitulate many features of neural development, can be derived with high reliability across dozens of cell lines and experiments, and can be maintained for years in vitro to recapitulate an intrinsic program of maturation that progresses into postnatal stages. To model complex cell-cell interactions, we developed assembloids and demonstrated their use in modeling cell migration, formation of neural circuits and disease processes. To advance maturation and circuit integration of organoids, we developed a transplantation paradigm and demonstrated that engrafted human neurons can respond to sensory stimulation in the animal and can drive reward-seeking behavior therefore enabling behavioral readouts from patient-derived cells. Lastly, I will illustrate how these methods can be combined with modern neuroscience tools to study the cellular and molecular consequences of mutations and copy number variants associated with neuropsychiatric disorders.

Funding Source: NIH, CZI, CZ BioHub, NYSCF, Wellcome LEAP

Keywords: organoids, assembloids, brain

2:25 PM – 2:55 PM

2024 ISSCR ACHIEVEMENT AWARD PRESENTATION: EXPLORING DIFFERENT CELL POPULATIONS IN HEALTHY AND DISEASED SKIN

ISSCR Achievement Award Sponsored by: Bayer AG and BlueRock Therapeutics

Watt, Fiona M.
EMBL-Heidelberg, Germany, UK

The epidermis, the outer covering of the skin, has been the subject of intense investigation for many years. Autologous sheets of cultured human epidermis have been used successfully to treat burns and other skin injuries and are an important example of cell therapy involving in vitro expanded stem cells. Numerous experiments in culture and in mouse models have provided major insights into the nature of epidermal stem cells and the local and long-range interactions that regulate their behaviour in health and disease. The advent of single-cell transcriptomics has provided an important opportunity to validate earlier conclusions based on experimental models. Currently, the integration of techniques that provide spatial information about different cell populations in the epidermis and underlying connective tissue is allowing us to design and carry out mechanistic studies.

2:55 PM – 3:30 PM

MODELLING THE HUMAN KIDNEY FOR DRUG DEVELOPMENT AND TISSUE ENGINEERING

Little, Melissa H.
Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Denmark, and Murdoch Children's Research Institute, Australia

For almost 10 years now, it has been possible to pattern human pluripotent stem cells to kidney organoids. These 3D microtissues accurately model the developing human kidney including patterning and segmenting nephrons and surrounding stroma. Using transcriptional profiling, proteomics, lineage tracing and reporter iPSC, it has been possible to show the accuracy and congruence of these models with the human fetal kidney. It has also been possible to recapitulate features of human renal disease in vitro. A remarkable achievement, there remains challenges to utility, including missing cellular components, off target patterning and quality control, maturation of nephron structures and scale up of tissues. This lecture will focus on the application of these human microtissues to the development of new therapies, including both the development of treatments for inherited kidney disease and the engineering of transplantable human tissue.

Keywords: pluripotent stem cell, kidney, organoid

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