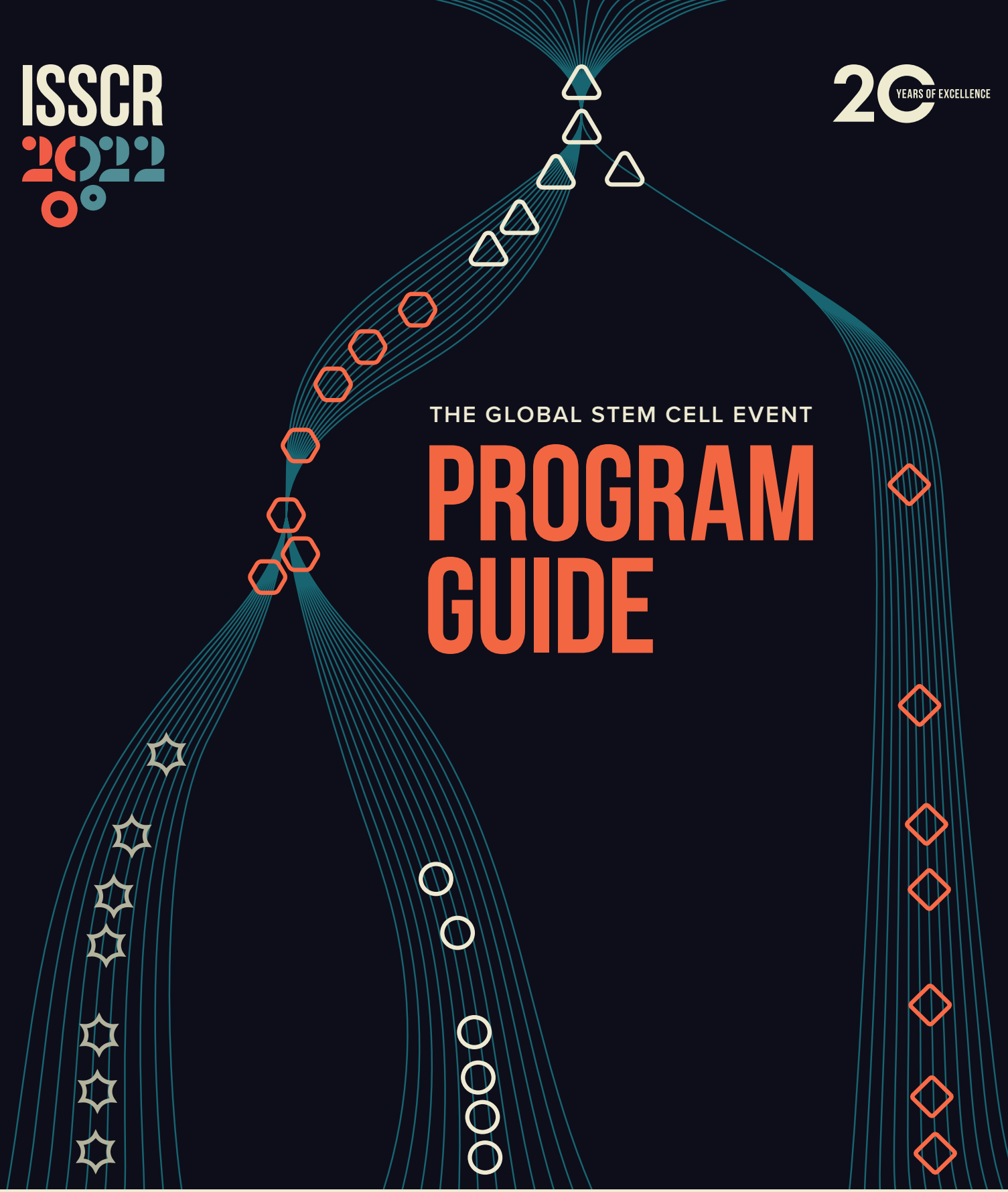
ISSCR 2022

20 YEARS OF EXCELLENCE

THE GLOBAL STEM CELL EVENT

PROGRAM GUIDE



ISSCR ANNUAL MEETING 2022

SAN FRANCISCO

15–18 JUNE 2022

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SONY

ISSCR Innovation Showcase

Sony CGX10 Cell Isolation System: An Introduction and Examples of Use in Protocols for Generating Cell Therapy Products Using Multiparametric Selection

Friday, June 17, 2022
11:30 AM – 12:30 PM PDT

Introducing the CGX10 Cell Isolation System

A next-generation cell sorting system built for GMP-compliant cell and gene therapy manufacturing workflows.

Equipped with proprietary microfluidic chip and a cabinet with built-in temperature control to maintain cell health, the CGX10 Cell Isolation System enables fully closed, high speed, high purity, multiparametric, fluorescence-based selection of target cells.

Learn more at:
www.sonybiotechnology.com/cgx10

The CGX10 Cell Isolation System and related products are intended for use by trained laboratory technicians in research, process development or manufacturing environments all related to ATMP/regenerative medicine, including cell and gene therapy. The CGX10 instrument and related products are for *ex vivo* cell separation processing only, and are not intended for therapeutic, diagnostic, or human *in vivo* applications. Any clinical application of the cells is exclusively within the responsibility of the user of the CGX10 instrument and related products. For the manufacturing and use of cells in humans, the local legislation and regulations must be followed. The CGX10 Cell Isolation System and related products are not sold as medical devices.

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ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Dear Colleagues:

It is a great pleasure to welcome all of you to the 2022 ISSCR Annual Meeting, and many of you back in person. It's only fitting to celebrate the society's 20th Anniversary, together, in a city known for innovation and leadership. This year's Annual Meeting carries forward a long tradition of bringing together the brightest minds and best research from across geographies and disciplines. Whatever your interest, you'll find it here.

The Program Committee has developed a rich and diverse program. It includes invited speakers sharing groundbreaking research, nearly 100 abstract-selected speakers, and more than 950 posters. All sessions are organized into one of five tracks, making the meeting easier to navigate, and "your people" easier to find. Look for the track icons in the program and on signage to help orient you. Better yet, if you miss a session, you can watch it on demand at ISSCR.digital.

Alongside new faces and new research, you'll find new sessions and opportunities to engage. Among them, special sessions dedicated to career development, early-career scientists, and science advocacy; a new Micro Theater on the Exhibit Floor featuring interactive presentations on techniques, technologies, and a discussion on genetic diversity in cell lines; and a robust schedule of Focus Sessions and Innovation Showcases, introducing the latest innovations driving the field forward.

A special congratulations to ISSCR's 2022 scientific award honorees, who will each deliver a talk during a plenary session: ISSCR Dr. Susan Lim Award for Outstanding Young Investigator honoree Jennifer E. Phillips-Cremins, ISSCR Momentum Award recipient Joanna Wysocka, and ISSCR Achievement Award winner Lorenz Studer. Sean Morrison, who is honored with the ISSCR Public Service Award will be recognized in our Presidential Symposium. On behalf of the ISSCR, we commend your contributions to the field.

Finally, thank you to all exhibitors and sponsors, with special thanks to co-sponsor STEMCELL Technologies. Your support and participation make the meeting possible and enriches the experience for all.

In celebration of a year of reconnection, and 20 years of excellence: welcome back.

Kind regards,

Melissa H. Little
ISSCR President

Amander Clark
Program Chair

Dear Friends and Colleagues,

I would like to welcome you to the 20th Annual Meeting of the International Society for Stem Cell Research (ISSCR) in beautiful San Francisco. STEMCELL Technologies is honored and delighted to be co-sponsoring this global stem cell event.

At this year's meeting, we are celebrating 20 years of outstanding advances to stem cell research and regenerative medicine. The annual ISSCR meeting provides an opportunity for all of us to gather and reflect on the achievements of our society and the field thus far. It is also a time to share information, debate ideas, and build relationships that will advance our collective understanding of stem cell biology and bring potential new therapies closer to reality. STEMCELL, as a company of Scientists Helping Scientists, is excited to be a part of the exchanges and collaborations that will occur over the coming days.

When I founded STEMCELL 28 years ago with a single media product for culturing hematopoietic progenitor cells, I could see the promise of the stem cell field and its need for innovative and quality products. As the field has advanced, so have we. Today, STEMCELL continues to be driven by a passion for quality, providing more than 3000 products supported by over 1700 staff. Our cell culture media, cell separation reagents, instruments, accessory products, and scientific services are now used by life science researchers in over 120 countries. Please visit us at our booth to let us know how we can continue to meet your needs.

On behalf of all of us at STEMCELL, I congratulate the ISSCR for 20 years of scientific excellence and wish you all a safe, successful, and productive conference.

Warmest regards,

Allen Eaves, **OBC MD PhD FRCPC**
President and CEO, STEMCELL Technologies
Professor Emeritus of Hematology, University of British Columbia

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GENERAL INFORMATION

ONSITE BADGE PICK UP

Pick your attendee's name badge in the registration area in the Moscone West Convention Center lobby during posted hours. Bring your confirmation email for faster badge retrieval at the Self Check-in kiosks. Name badges are required for admission to all sessions, social events, and the Exhibit & Poster Hall. Badges may be picked up during the following times:

TUESDAY, 14 JUNE	7:30 am – 6:00 pm
WEDNESDAY, 15 JUNE	7:30 am – 8:00 pm
THURSDAY, 16 JUNE	7:30 am – 6:00 pm
FRIDAY, 17 JUNE	7:30 am – 6:00 pm
SATURDAY, 18 JUNE	8:00 am – 4:00 pm

NOTE: proof of vaccination must be submitted to access the in person meeting.

VIRTUAL ASSISTANCE

Click on the 'Ask ISSCR' chat icon located on the lower right side of the screen for any questions or email ISSCRdigital@isscr.org.

ONSITE ATTENDEE ORIENTATION (IN PERSON ONLY)

Curious to find out how to best navigate through ISSCR 2022? Join us at the Moscone West Convention Center lobby for our Attendee Orientation where ISSCR staff will explain the annual meeting's highlights and facilitate attendee introductions before the meeting kicks off. There will be two scheduled Attendee Orientations:

TUESDAY, 14 JUNE	3:00 pm – 4:00 pm
WEDNESDAY, 15 JUNE	7:45 am – 8:45 am

INTERNET ACCESS

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

STEMCELL™ TECHNOLOGIES

To connect to the Wi-Fi:

Network/SSID:	ISSCR2022
Password:	stemdiff

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Still photography, screen capture, video and/or audio taping/recording of the sessions, presentations and/or posters at the ISSCR 2022 Annual Meeting is strictly prohibited. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

WHERE CAN I FIND....?

SPEAKER READY ROOM

Speakers must review their uploaded presentations at least one hour prior to session start in the Speaker Ready Room (Room 2000, Level 2) during the following times:

TUESDAY, 14 JUNE	4:00 pm – 6:00 pm
WEDNESDAY, 15 JUNE	8:00 am – 6:00 pm
THURSDAY, 16 JUNE	7:30 am – 6:00 pm
FRIDAY, 17 JUNE	7:30 am – 6:00 pm
SATURDAY, 18 JUNE	8:00 am – 5:00 pm

Plenary speakers are welcome to upload presentations in the Plenary room in the Plenary Room (Level 3) during Technical Rehearsals times:

TUESDAY, 14 JUNE	4:00 pm – 6:00 pm
WEDNESDAY, 15 JUNE	10:00 am – 12:00 pm
THURSDAY, 16 JUNE	7:30 am – 8:30 am
FRIDAY, 17 JUNE	7:30 am – 8:30 am
SATURDAY, 18 JUNE	11:00 am – 12:00 pm

MEDIA OFFICE

Credentialed members of the media may use workstations, wireless network, and a printer during posted hours in the Media Office (Room 2014, Level 2).

WEDNESDAY, 15 JUNE	11:00 am - 4:00 pm
THURSDAY, 16 JUNE	8:00 am - 12:00 pm
FRIDAY, 17 JUNE	8:00 am - 12:00 pm

COAT AND BAGGAGE CHECK

Conveniently located in the lobby of Moscone West Convention Center (next to the Exhibit & Poster Hall entrance).

TUESDAY, 14 JUNE	7:30 am – 5:30 pm
WEDNESDAY, 15 JUNE	7:30 am – 8:45 pm
THURSDAY, 16 JUNE	7:30 am – 7:30 pm
FRIDAY, 17 JUNE	7:30 am – 7:30 pm
SATURDAY, 18 JUNE	8:00 am – 6:30 pm

NURSING POD

Located on Level 2 of the Moscone West Convention Center, there is a Mamava pod for nursing mothers available throughout the meeting. These pods are private and secure with roomy bench and a place to plug in your pump.

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

SAN FRANCISCO INFORMATION DESK

Please stop by the San Francisco Information desk for information about the city, places to visit and dine. The desk is located in the lobby of the Moscone West Convention Center for limited hours.
15 - 17 June; 10:00 am - 5:00 pm each day

SMOKING

Smoking is prohibited in the Moscone West Convention Center.

LOST AND FOUND

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

PARKING

There are several public parking garages surrounding the Moscone West Convention Center. Prices will vary. Attendees are responsible for paying their own parking garage fees.

JOB OPPORTUNITIES

On the virtual platform under Directories & Networking, there will be a list of job opportunities in the Career Lab. You can contact employers through the platform to arrange a time to meet in person or on the virtual platform.

ISSCR MEETING POLICIES

CODE OF CONDUCT

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

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

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

HARASSMENT POLICY

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

RECORDING POLICY

By registering for this meeting, you agree to ISSCR's Recording Policy. The ISSCR strictly prohibits the recording (photographic, screen capture, audio and/or video), copying or downloading of scientific results from the sessions, presentations and/or posters at the ISSCR 2022 Annual Meeting. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

EMBARGO POLICY

Abstract content may not be announced, publicized, or distributed before the presentation date and time in any way including blogging and tweeting. ISSCR does permit promotion of general topics, speakers, or presentation times. This embargo policy applies to all formats of abstract publication – including abstracts in electronic version of the Annual Meeting Program Book and Abstract Book, virtual platform, Society's website(s), and other publications.

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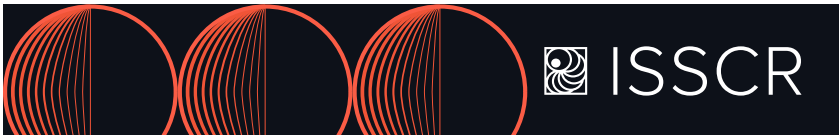

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Ulrich Martin
Zubin Master
Sandro Matosevic
Esteban Mazzoni
Philippe Menasché
Viviana Meraviglia

Jason Meyer
Sarah Millar
Gabriella Minchiotti
Guo-li Ming
Asuka Morizane
Ryuji Morizane
Samantha Morris
Megan Munsie
Alysson Muotri
Takashi Nagasawa
Christian Nefzger
Thao Nguyen
Susie Nilsson
Ryuichi Nishinakamura
Trista North
Lucy O'Brien
Michael O'Connor
Il-Hoan Oh
Steve Oh
Yohei Okada
Ryuichi Okamoto
Kenji Osafune
Pierre Osteil
Nathan Palpant
Athanasia Panopoulos
In-Hyun Park
Sangbum Park
Vincent Pasque
Duanqing Pei
Guangdun Peng
Martin Pera
Eugenia Piddini
Alessandro Prigione
Stephanie Protze
Li Qian
Pengxu Qian
Alireza Rezania
Pamela Robey
Pantelis Rompolas
Filip Roudnicky
Peter Rugg-Gunn
Holger Russ
Michel Sadelain
Mitinori Saitou
Luca Sala
Max Salick
Tomo Saric
Toshiro Sato
Kazunobu Sawamoto
Hans Schöler
Edda Schulz
Mark Shackleton
Amar Deep Sharma
Jian Shu
Robert Signer
Hans-Willem Snoeck
Evan Snyder
Hongjun Song
Berna Sozen
Lincon Stamp
Christopher Sturgeon
Jeremy Sugarman
Shigeki Sugii
Kazutoshi Takahashi
Minoru Takasato
Yasuhiro Takashima
Takanori Takebe
Nan Tang
Adrian Teo
Paul Tesar
Junya Toguchida
Mark Tomishima
Taro Toyoda
Barbara Treutlein
Alan Trounson
Leigh Turner
Tully Underhill
Achia Urbach
Ludovic vallier
Nicole Van Bergen
Sara Vasconcelos
Carlos Villaescusa
Jane Visvader
Amy Wagers
Hongmei Wang
Jianlong Wang
Sara Wickström
Rongwen Xi
Wei Xie
Yasuhiro Yamada
Nan Yang
Zheng Yin
Jessica Young
Yi Arial Zeng
Hui Zheng
Hao Zhu
Thomas Zwaka

JOIN US ON WEDNESDAY, 15 JUNE FOR THE PRESENTATION OF THE 2022 ISSCR PUBLIC SERVICE AWARD

ISSCR PUBLIC SERVICE AWARD

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

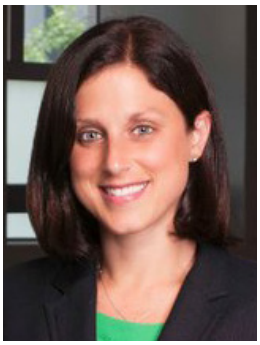
Sean J. Morrison, PhD, Director of Children's Medical Center Research Institute at UT Southwestern (CRI), USA, will receive the 2022 ISSCR Public Service Award for his leadership in identifying opportunities and challenges facing the global stem cell research community and raising the effectiveness and visibility for the ISSCR's advocacy efforts.

Dr. Morrison studies the mechanisms that regulate stem cell function and the role these mechanisms play in cancer. He completed a B.Sc. in biology and chemistry at Dalhousie University (1991), a Ph.D. in immunology at Stanford University (1996), and a postdoctoral fellowship in neurobiology at Caltech (1999). He is a Howard Hughes Medical Institute Investigator (since 2000) and Director of CRI (since 2011). At UT Southwestern he is a Professor of Pediatrics and holds the Mary McDermott Cook Chair in Pediatric Genetics and the Kathryne and Gene Bishop Distinguished Chair in Pediatric Research at CRI. He was elected to the U.S. National Academy of Medicine and the National Academy of Sciences and is a Cancer Prevention and Research Institute of Texas Scholar in Cancer Research. Dr. Morrison served as the President of ISSCR (2015-16), is founding chair of the ISSCR Public Policy Committee (since 2015), has testified before the U.S. Congress, and was a leader in the "Proposal 2" campaign that protected stem cell research in Michigan's state constitution (2008).

The award will be presented during the Presidential Symposium on Wednesday, 15 June, 12:30-2:45 PM.

JOIN US ON WEDNESDAY, 15 JUNE FOR THE PRESENTATION OF THE 2022 ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR

ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR



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

The 2022 recipient is Jennifer E. Phillips-Cremins, PhD, Associate Professor and Deans' Faculty Fellow at the University of Pennsylvania, Departments of Genetics and Bioengineering. Dr. Phillips-Cremins is a pioneer in understanding how chromatin works through long-range mechanisms to govern stem cell differentiation into neurons and neural circuits. She developed molecular and computational technologies to dissect how genomes fold at ultra-fine-scale resolution, discovering that: (i) mammalian genomes are folded hierarchically into TADs, subTADs and loops, (ii) loops/subTADs are reconfigured and functionally linked to gene expression during neural differentiation, somatic cell reprogramming, and circuit stimulation, (iii) short tandem repeat instability causes severe genome misfolding, acquisition of Megabase-scale heterochromatin domains, and pathological interchromosomal interactions. She also pioneered tools to engineer loops, catalyzing insight into the genome's structure-function relationship.

Dr. Phillips-Cremins will present the ISSCR Dr. Susan Lim Award for Outstanding Young Investigator Lecture during Plenary II on Wednesday, 15 June, 3:30-5:40 PM.

JOIN US ON FRIDAY, 17 JUNE FOR THE PRESENTATION OF THE 2022 ISSCR ACHIEVEMENT AWARD

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 2022 recipient is Lorenz Studer, MD, Memorial Sloan Kettering Cancer Center (MSK), USA. Dr. Studer has a bold goal—to make all the diverse nervous system cells from human pluripotent stem cells. Step by step, with creative thinking and dedication, he is accomplishing this goal. Dr. Studer's protocols for creating specific neural types, including cortical, midbrain dopaminergic, enteric and pain cells, are now used around the world. He brought together the team and investment to translate his groundbreaking work to develop a novel stem cell therapy for Parkinson's disease. Dr. Studer's work exemplifies the highest standard of stem cell science, creativity, and dedication needed to invent and apply stem cell research to benefit patients.

Dr. Studer will be recognized and deliver the ISSCR Achievement Award Lecture during Plenary V on Friday, 17 June, 5:15-7:20 PM.

JOIN US ON SATURDAY, 18 JUNE FOR THE PRESENTATION OF THE 2022 ISSCR MOMENTUM AWARD

ISSCR MOMENTUM AWARD

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

The 2022 recipient is Joanna Wysocka, PhD, Lorry Lokey Professor and Professor of Developmental Biology, Stanford University School of Medicine and HHMI Investigator, USA.

Dr. Wysocka's early work identified chromatin signatures of enhancers that define pluripotency, as well as those that are "poised" to become activated or repressed as cell fate emerges. In early human blastocysts, she showed that endogenous retroviruses are reactivated and regulate gene expression prior to silencing. Remarkably, she then worked with chimpanzee and human iPSCs to identify species-specific enhancers in neural crest that control facial morphogenesis. Most recently, she discovered that neural crest spontaneously dedifferentiates toward pluripotency prior to forming mesenchymal tissues of the head and neck. These contributions place her at the forefront of stem cell research and molecular development.

Dr. Wysocka will be recognized and deliver the ISSCR Momentum Award Lecture during Plenary VI on Saturday, 18 June, 12:45-2:55 PM.

CONGRATULATIONS TO THE 2022 ZHONGMEI CHEN YONG AWARD WINNERS

2022 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. These Travel Awards are given to ISSCR Trainee members who submit outstanding abstracts presented at the ISSCR Annual Meeting. Award recipients will be recognized in Plenary I on Wednesday, 15 June.

Julia Aguade Gorgorio
Rita Alves
Matias Autio
Maria Bejar
Carla Bertulfo
Sarah Bowling
Sefa Burak Çam
Sheila Castañeda
Wei-Ju Chen
Jieun Choi
Anastasia Conti
Max Friesen
Blair Gage
Christopher Gribben
Guy Haim
Peng He
Michitada Hirano
Aisha Ishaque
Vaibhao Janbandhu
Ran Jing
Julia Junghof
Kajal Kamat
Jengmin Kang
Shuntaro Kawamura
Gal Keshet
Eunjee Kim
Seong-Min Kim
Yun-Kyo Kim
Moyra Lawrence
Nitzan Letko-Khait
Hailong Liu
Nina Maenhoudt
Homa Majd
Riley McMahon
Louise A. Mesentier-Louro
Yuchuan Miao
Clara Munger
Rachel Niec
Bhav Parikh
Bruna Paulsen
Aishwarya Prakash
Andrea Carlo Rossetti
Yatsumu Saito
Roni Sarel-Gallily
Nathalie Saurat
Katie Schaukowitch
Seungmae Seo
Cleide Souza
Koji Tamai
Shoichiro Tani
Jasmin Taubenschmid-Stowers
Antonio Tomasso
Katsuhiro Tomofuji
Li-Kuang Tsai
Pallavi Varghese
Manchi Vathsalya
Rajeev Vikram
Marta Vilà-González
Li-Tzu Wang
Yuting Wang
Sam Wattrus
Thea Willis
Tianchi Xin
Ruimin Xu
Lynn Yap
Atilgan Yilmaz
Baolei Yuan
Fang Yuan

LAWRENCE GOLDSTEIN POLICY FELLOWS

Fellows receiving abstract travel awards are:

Tamra Lysaght
Kirstin Matthews

2022 ISSCR MERIT ABSTRACT AWARDS

The ISSCR recognizes outstanding abstracts with the ISSCR Merit Abstract Awards. These awards are given to ISSCR trainee members who have submitted distinguished abstracts as judged by the ISSCR 2022 abstract reviewers. Award recipients will be recognized in Plenary I on 15 June.

Louise A. Mesentier-Louro
Julia Aguade Gorgorio
Rita Alves
Giridhar Anand
Matias Autio
Maria Bejar
Carla Bertulfo
Sarah Bowling
Andrea Carlo Rosetti
Wei-Ju Chen
Gal Cleitman Blackstein
Anastasia Conti
Max Friesen
Blair Gage
Rajesh Gunage
Guy Haim
Peng He
Michitada Hirano
Aisha Ishaque
Vaibhao Janbandhu
Ran Jing
Kajal Kamat
Jengmin Kang
Eunjee Kim
Yun-Kyo Kim
Nina Maenhoudt
Homa Majd
Riley McMahon
Yuchuan Miao
Clara Munger
Mohamad Najia
Rachel Niec
Bruna Paulsen
Yatsumu Saito
Roni Sarel-Gallily
Nathalie Saurat
Katie Schaukowitch
Matthew Schmitz
Seungmae Seo
Cleide Souza
Koji Tamai
Jasmin Taubenschmid-Stowers
Antonio Tomasso
Katsuhiro Tomofuji
Yuting Wang
Samuel Wattrus
Thea Willis
Josephine Wu
Tianchi Xin
Ruimin Xu
Atilgan Yilmaz

PLENARY I: PRESIDENTIAL SYMPOSIUM

Sponsored by: Sana Biotechnology

Wednesday, 15 June 12:30 PM – 2:45 PM

Prisca Liberali, Friedrich Miescher Institute for Biomedical Research, Switzerland

Prisca Liberali is a senior group leader at the Friedrich Miescher Institute for Biomedical Research. Originally trained as a chemist, she later changed fields to become a stem cell biologist. During her postdoc, she developed single-cell methods to study cell-to-cell variability and its involvement in the emergence of complex cellular traits. She made important contributions in fields ranging from fundamental chemistry to in vivo tissue regeneration. Her laboratory focuses on decoding the design principles of tissue organization and works on the role of self-organization during collective cell behaviors, and how these are coordinated by biochemical and mechanical cues.

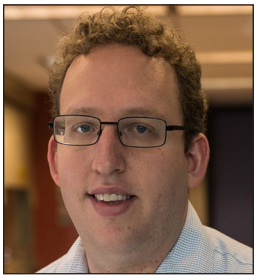
Christine L. Mummery, Leiden University Medical Center, Netherlands

Christine Mummery is Professor of Developmental Biology at Leiden University Medical Center. Mummery's research focuses on heart development and uses human pluripotent stem cells to develop disease models to understand the underlying causes and progression of heart disease and develop drugs for treatment. Mummery was founding editor-in-chief of the ISSCR journal, *Stem Cell Reports*, from its inception in 2013 through 2018. She is a member of the Royal Netherlands Academy of Science, scientific advisory board member of Sartorius and Mogrify, and was president of ISSCR (2020-2021). She has been awarded multiple prizes, including several on animal alternatives in research.

Jose Polo, The University of Adelaide, Australia

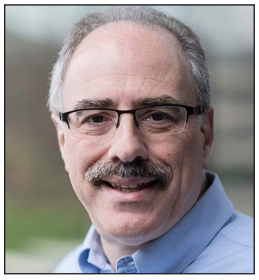
Jose Maria Polo graduated from Buenos Aires University as a Biochemist and obtained his PhD in 2008 at the Albert Einstein College of Medicine under the supervision of Prof. Ari Melnick. He then joined the laboratory of Prof. Konrad Hochedlinger at the Harvard Stem Cell Institute to work on reprogramming. In June 2011, Jose established his independent research group at Monash University. In 2016, he co-founded Mogrify, to translate reprogramming technologies into therapies. In October 2021, Jose was recruited to the University of Adelaide as the inaugural Director of the Adelaide Centre for Epigenetics and Program leader of the recently established South Australian Immunogenomics Cancer Institute to continue his work in epigenetics and its application to reprogramming, early embryogenesis and cancer.

Aryeh Warmflash, Rice University, USA



Aryeh Warmflash earned his PhD in physics from the University of Chicago. He completed postdoctoral training in the labs of Eric Siggia and Ali Brivanlou at Rockefeller University and started his lab at Rice University in 2014. His lab studies morphogen signaling dynamics and self-organized developmental patterning during mammalian gastrulation and neurulation using human embryonic stem cells as a model system.

Leonard I. Zon, Boston Children's Hospital, USA



Leonard I. Zon, is the Grousbeck Professor of Pediatric Medicine at Harvard Medical School, an Investigator at Howard Hughes Medical Institute, and the Director of the Stem Cell Program at Boston Children's Hospital. Dr. Zon is internationally recognized for his pioneering work in stem cell biology and cancer genetics and has been the preeminent figure in establishing zebrafish as an invaluable genetic model for the study of the blood and hematopoietic development.

FEATURED SPEAKERS

ERNST MCCULLOCH MEMORIAL LECTURE

Wednesday, 15 June, Plenary II

Deepak Srivastava, Gladstone Institutes, USA

Deepak Srivastava is President of Gladstone Institutes, Director of the Roddenberry Stem Cell Center, and Professor at the University of California, San Francisco. Srivastava received his B.S. from Rice University, M.D. from University of Texas, trained in pediatrics at UCSF, and in pediatric cardiology at Harvard. Srivastava's laboratory discovered genetic bases for cardiac defects and revealed complex gene networks that regulate progenitor cells to adopt a cardiac cell fate and subsequently fashion a functioning heart. He has leveraged this knowledge to reprogram fibroblasts into cardiomyocyte-like cells for regenerative purposes. Srivastava served as president of the International Society for Stem Cell Research and is a member of the National Academy of Medicine.

ANNE MCLAREN MEMORIAL LECTURE

Thursday, 16 June, Plenary III

Ruth Lehmann, Whitehead Institute, USA

Ruth Lehmann is a Member and the Director of Whitehead Institute and a Professor of Biology at MIT in Cambridge MA. Her lab studies germ cells, the only cells in the body naturally able to generate completely new organisms. The lab is interested in how germ cells become specialized and how the cytoplasmic information, including RNA-protein condensates and cellular organelles including mitochondria are passed from the egg cell to the next generation.

JOHN MCNEISH MEMORIAL LECTURE

Saturday, 18 June, Plenary VII

Masayo Takahashi, Vision Care Inc., Japan

After she received her M.D. and Ph.D. from Kyoto University, Dr. Masayo Takahashi worked as an ophthalmologist in the Kyoto University Hospital. Dr. Takahashi discovered the potential of stem cells as a tool for retina therapy when she moved to the Salk Institute, U.S. She joined RIKEN in 2006, where her team launched a pilot clinical study using first-in-human iPS cells in 2013. She started a new career as president of the start-up company; Vision Care Inc., to implement clinical therapy. Her research interests are regenerative medicine and retinal degeneration.

PATIENT ADVOCATE ADDRESS

Saturday, 18 June, PLENARY VII

Physician
Donald B. Kohn, UCLA, USA

Dr. Kohn studies the biology of blood stem cells. Over the course of 30 years of research, he has developed new clinical methods to treat genetic blood diseases using blood stem cells that have been modified to remove genetic mutations. Kohn's blood stem cell gene therapy method collects some of a patient's own blood stem cells and either adds a good copy of the defective gene or fixes the broken genes to eliminate disease-causing mutations. The patient then receives a transplant of their own corrected stem cells, which will ideally create an ongoing supply of healthy blood cells. Kohn's clinical trials for adenosine deaminase-deficient severe combined immunodeficiency (also known as ADA-SCID or bubble baby disease), an often-fatal condition where babies are born without an immune system, have cured more than 50 babies to date.

Patient Advocate
Alysia Vaccaro, Corona, California, USA

In 2012, Alysia Vaccaro's newborn daughter, Evie was diagnosed with Severe Combined Immunodeficiency (SCID). Children with SCID lack a functioning immune system so even a simple cold can be fatal. After hearing about a potential gene therapy developed by Dr. Don Kohn at UCLA, Vaccaro enrolled Evie in a clinical trial. Today, Evie is a thriving 10-year-old with a healthy immune system. Vaccaro shares a bit of Evie's journey and the impact that stem cell research has had on their family.

KEYNOTE ADDRESS

Saturday, 18 June, PLENARY VII

Priscilla Chan, Chan Zuckerberg Initiative, USA

Priscilla Chan is co-founder and co-CEO of the Chan Zuckerberg Initiative. As a pediatrician and teacher, Chan's work with patients and students in communities across the Bay Area has informed her desire to make learning more personalized, find new paths to manage and cure disease, and expand opportunity for more people. She is also the founder of The Primary School, which integrates health and education and serves children and families in East Palo Alto and the Belle Haven neighborhood in Menlo Park, California. Chan earned her BA in Biology at Harvard University and her MD at University of California, San Francisco (UCSF). She completed her pediatrics training in the UCSF/PLUS Pediatrics Residency.

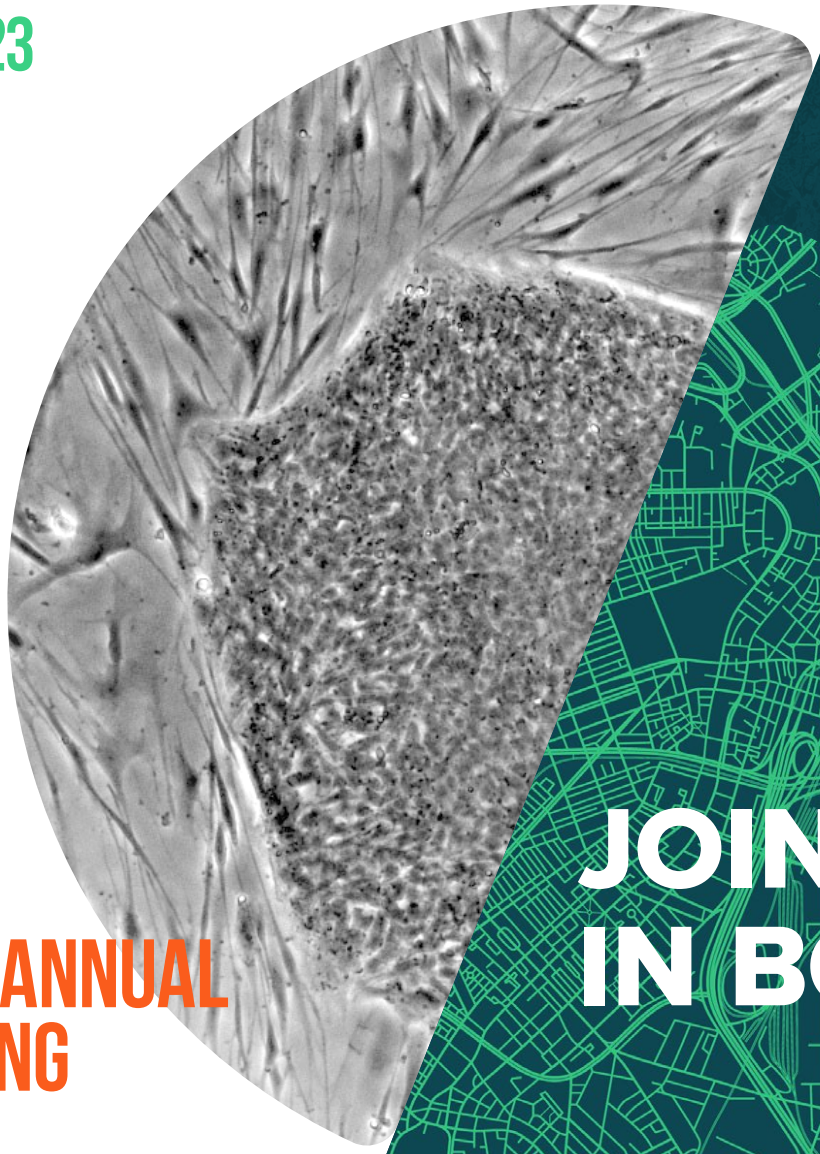
Wednesday, 15 June	
7:45 AM - 8:45 AM	Attendee Orientation
8:00 AM - 8:30 AM	Refreshment Break
8:30 AM - 11:30 AM	Focus Sessions
11:00 AM – 12:15 PM	Early Career Group Leader Luncheon
11:15 AM - 12:15 PM	Science Advocacy & Communications Seminar
12:30 PM - 2:45 PM	Plenary I
2:30 PM - 8:30 PM	Exhibit Hall Open
2:45 PM - 3:30 PM	Meet-up Hubs
2:45 PM - 3:30 PM	Refreshment Break
3:30 PM - 5:40 PM	Plenary II
5:45 PM - 8:30 PM	Opening Reception
6:15 PM - 6:30 PM	Micro Theater
6:30 PM - 7:30 PM	Poster Session I Odd
6:45 PM - 7:30 PM	Meet-up Hubs
6:45 PM - 7:00 PM	Micro Theater
7:15 PM - 7:30 PM	Micro Theater
7:30 PM - 8:30 PM	Poster Session I Even
7:45 PM - 8:00 PM	Micro Theater
8:15 PM - 8:30 PM	Micro Theater

Thursday, 16 June	
8:00 AM - 8:30 AM	Innovation Showcases
8:30 AM - 9:00 AM	Refreshment Break
9:00 AM - 10:55 AM	Plenary III
11:00 AM - 5:00 PM	Exhibit Hall Open
11:15 AM - 12:45 PM	Equity, Diversity, & Inclusion in STEM: Impact and Action Workshop
11:30 AM - 12:30 PM	Innovation Showcases
1:00 PM - 2:45 PM	Concurrent Track Sessions
3:00 PM - 4:00 PM	Poster Session II Odd
3:00 PM - 5:00 PM	Refreshment Break
3:15 PM - 3:30 PM	Micro Theater
3:45 PM - 4:00 PM	Micro Theater
3:45 PM – 4:30 PM	Meet-up Hubs
4:00 PM - 5:00 PM	Poster Session II Even
4:15 PM - 4:30 PM	Micro Theater
4:45 PM - 5:00 PM	Micro Theater
5:15 PM - 7:00 PM	Concurrent Track Sessions
7:30 PM - 9:30 PM	20th Anniversary Celebration
9:30 PM – 11:00 PM	After-Party Celebration

Friday, 17 June	
8:00 AM - 8:30 AM	Innovation Showcases
8:30 AM - 9:00 AM	Refreshment Break
9:00 AM - 10:35 AM	Plenary IV
11:00 AM - 5:00 PM	Exhibit Hall Open
11:00 AM - 11:45 PM	Meet-up Hubs
11:30 AM - 12:30 PM	Innovation Showcases
1:00 PM - 2:45 PM	Concurrent Track Sessions
3:00 PM - 4:00 PM	Poster Session III Odd
3:00 PM - 5:00 PM	Refreshment Break
3:15 PM - 3:30 PM	Micro Theater
3:45 PM - 4:00 PM	Micro Theater
4:00 PM - 5:00 PM	Poster Session III Even
4:15 PM - 5:00 PM	Micro Theater: Promoting Diversity in Stem Cell Models
5:15 PM - 7:20 PM	Plenary V

Saturday, 18 June	
8:30 AM - 9:00 AM	Refreshment Break
9:00 AM - 10:45 AM	Concurrent Track Sessions
11:00 AM - 12:20 PM	Career Panel Luncheon
12:45 PM - 2:55 PM	Plenary VI
3:00 PM - 3:30 PM	Refreshment Break
3:30 PM - 6:00 PM	Plenary VII

ISSCR23



ISSCR ANNUAL MEETING 2023

14–17 JUNE 2023
BOSTON, MA, USA

Abstracts and Registration
Open 8 December 2022

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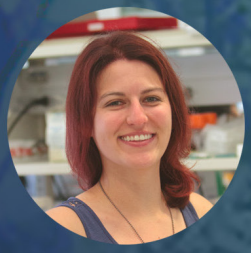
STEM CELL REPORTS

THE STEM CELL REPORT

A PODCAST WITH MARTIN PERA

EPISODE 11

WHEN ROCK STOPS THE ROLL: EXPLAINING THE AGING NEURAL STEM CELL NICHE



ELIZABETH FISHER, PHD
NEURAL STEM CELL INSTITUTE

SALLY TEMPLE, PHD
NEURAL STEM CELL INSTITUTE

XIULI ZHAO, PHD
NEURAL STEM CELL INSTITUTE

EPISODE 12

KEEPING THE IS(LETS) ON THE PRIZE: TREATING T1D WITH STEM CELL-BASED TRANSPLANTS

DOUGLAS MELTON, PHD
HARVARD UNIVERSITY

NAYARA LEITE, PHD
VERTEX PHARMACEUTICALS

Download on Apple Podcasts
or wherever you listen to your podcasts

Photo: NIH

NETWORKING & EVENTS

What better way to nurture your research and career than networking? ISSCR 2022 provides many opportunities for scientists in all stages of their careers to exchange insightful and relevant advice that helps advance their research and lab work. The ISSCR offers various avenues to help scientists foster and strengthen their professional networks.

MEET-UP HUBS

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

Early Career Scientists Networking

WEDNESDAY, 15 JUNE | 2:45 PM – 3:30 PM

The Early Career Scientist Committee will be hosting two conversations at this meet up. Early Career Group Leaders can continue the conversation from the earlier luncheon on managing your lab's research, members and projects. Trainees are welcome to meet and network with other trainees and the Early Career Scientist Committee to share your career goals and challenges and to hear from others how they are navigating their career paths, new avenues they are exploring, and how they are balancing their many priorities. Come join the conversations!

Industry Scientists Networking

WEDNESDAY, 15 JUNE | 2:45 PM – 3:30 PM

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

Computational Stem Cell Biology

WEDNESDAY, 15 JUNE | 6:45 PM – 7:30 PM

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.

Policy, Ethics, and Regulatory Issues

WEDNESDAY, 15 JUNE | 6:45 PM – 7:30 PM

Are policy, ethics, or regulatory issues impacting your research? Join us to discuss these issues with ISSCR leaders and find out about the ISSCR's advocacy program.

Finding Your Hidden Skills

THURSDAY, 16 JUNE | 11:30 AM – 12:15 PM

In examining their experiences to craft an industry resume most scientists leave a lot of relevant skills off. This is partly due to the vagueness of some job descriptions and partly due to a difference in nomenclature between STEM professions. If you would like to discover industry relevant skills you already have, then join Scismic outreach specialists at this meet-up. They will review your resume and experience to mine for valuable skills you do not have listed to improve your applications and allow hiring managers to see your full potential. *Organized by Scismic.*

STEMCELL Technologies: Careers in Biotech

THURSDAY, 16 JUNE I 11:30 AM – 12:15 PM

Have you ever wondered what it would be like to work in biotech? STEMCELL offers exciting and rewarding career paths for those with scientific training who wish to continue with a research-based career and those who are looking to support science away from the lab bench. Join us to learn about the many career opportunities at STEMCELL, ask any questions you might have, and network with STEMCELL employees and other like-minded scientists. *Organized by STEMCELL Technologies.*

Meet the Editors of *Stem Cell Reports*

THURSDAY, 16 JUNE I 3:45 PM-4:30 PM

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

German Stem Cell Network

THURSDAY, 16 JUNE I 3:45 PM – 4:30 PM

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

Stem Cell Podcast: Meet the Hosts

FRIDAY, 17 JUNE I 11:00 AM – 11:45 AM

Are you a fan of the Stem Cell Podcast? Come and meet the show's hosts, Drs. Daylon James and Arun Sharma, and learn how your research could be featured on a future episode. *Organized by STEMCELL Technologies.*

Building Relations with reNEW

FRIDAY, 17 JUNE I 11:00 AM – 11:45 AM

The Novo Nordisk Foundation Center for Stem Cell Medicine launched in January 2022 and is an international consortium of stem cell researchers with a focus on targeting their research to outcomes in drug development and advanced therapies using stem cells. Come and meet with reNEW researchers from the three nodes; Copenhagen, Leiden and Melbourne, to hear about their work and make new partnerships.

MICRO THEATER

Promoting Diversity in Stem Cell Models

FRIDAY, 17 JUNE I 4:15 PM – 5:00 PM

Join us to learn about the importance of using genetically diverse stem cell models to promote the development of inclusive regenerative medicine technologies. Together, we will discuss how the stem cell community can increase the genetic diversity of cell lines and disease models so that the resulting scientific discoveries can be used to develop targeted cures and improve health among genetically diverse groups.

CAREER LAB

Sponsored by:

BlueRock THERAPEUTICS

Interested in new career opportunities? Explore open positions in the online Career Lab and meet with fellow attendees currently hiring for academic and industry positions in stem cell science. Attendees can browse details of open positions and set up appointments to meet virtually via live video or message chat, or meet in person in San Francisco during ISSCR 2022. Open positions that match the tags in your profile will be highlighted for you.

EARLY CAREER GROUP LEADER LUNCHEON

Evolving Modes of Collaboration and Research Management

WEDNESDAY, 15 JUNE | 11:00 AM – 12:15 PM

Early-career group leaders are invited to participate in round-table discussions with the accomplished stem cell scientists who comprise the ISSCR Board of Directors.
The pandemic has posed challenges for managing people, projects, and collaborations, yet it has also propelled forward new technologies for long-distance work. The advantages of these new tools are evident: reduced travel time and increased adoption of video meetings are making interdisciplinary and international collaborations more feasible. However, the new syndrome of 'working from anywhere' also adds to the stress of having to be 'always on'. What are some strategies that help maximize the advantages and avoid the pitfalls of remote working? Come hear from both early career and seasoned group leaders on how to hack the evolving modes of collaboration and research management to make it work for you.

This session is designed for ISSCR members who are early-career research group leaders (principal investigators or junior faculty for 8 or fewer years). Advance registration required.

MODERATORS:
Valentina Greco
Yale Stem Cell Center, USA

Carolyn Sangokoya
University of California San Francisco, USA

EQUITY, DIVERSITY, AND INCLUSION WORKSHOP

Equity, Diversity, and Inclusion in STEM: Impact and Action Workshop

THURSDAY, 16 JUNE | 11:15 AM – 12:45 PM

Everyone is invited to join this interactive and introspective workshop on the power of inclusion, bringing awareness to visible and invisible diversity and discussing actionable steps to improve equity in STEM. Designed for all attendees; advance registration required.

WORKSHOP LEADER:
Joanne Kamens
The Impact Seat, and Mass Association for Women in Science, USA

Sponsored by:

CIRM CALIFORNIA'S STEM CELL AGENCY

CAREER PANEL LUNCHEON

Sponsored by:

Lonza
Cell & Gene

Molding a Multidimensional Career: Vision for the Next 20

SATURDAY, 18 JUNE | 11:00 AM – 12:20 PM

Constructing a multi-dimensional career that positions you to progress on multiple paths can be a challenge! However as the scientific landscape evolves over the next 20 years, this flexibility will become increasingly important. Join us at the 2022 ISSCR Career Panel Luncheon to engage with the experts on "Molding a Multi-dimensional Career: Vision for the Next 20". Come equip yourself with skills to explore new opportunities in both academia and industry, and seek advice on how to take the next steps in your career journey. Shaping these essential skill sets will empower you to take advantage of diverse opportunities while building your dream career. This session is designed for ISSCR trainee members (post-doctoral fellows and students). Advance registration required.

MODERATORS:

Evan L. Graham
BICO, Sweden

PANELISTS:

Kevin Eggan
BioMarin, USA

Prisca Liberali
Friedrich Miescher Institute for Biomedical Research, Switzerland

Lyndsay Morrow
Genentech, USA

Linda Vo
Third Rock Ventures, USA

SCIENCE ADVOCACY AND COMMUNICATIONS SEMINAR

Sponsored by:
AMERICANS for CURES

WEDNESDAY, 15 JUNE 11:15 AM – 12:15 PM

Scientists are often asked to explain their work to non-scientific audiences, making effective communication skills essential, particularly when translating complex concepts into lay-friendly language. Researchers need to employ a variety of tactics to build support for evidence-based science, describe progress in the field, and highlight the impact of scientific discovery worldwide. Speakers in this seminar will discuss messages that resonate with policymakers, journalists, and the public, and share insights on how to convey the value of science with less technical audiences.

11:15 AM – 11:20 PM Welcome and Topic Overview
Sean Morrison
UT Southwestern, USA

11:20 AM – 11:32 AM
Deepak Srivastava
Gladstone Institutes, USA

11:32 AM – 11:44 AM
Megan Munsie
University of Melbourne, Australia

11:44 AM – 11:56 AM
Robin Lovell-Badge
Francis Crick Institute, UK

11:56 AM – 12:10 PM Panel Discussion

12:10 PM – 12:15 PM Concluding Remarks
Sean Morrison
UT Southwestern, USA

FOCUS SESSIONS

WEDNESDAY, 15 JUNE 8:30 AM – 11:30 AM

AUTOLOGOUS iPSC-DERIVED CELL THERAPIES & ENABLING AI- AND ROBOTICS-BASED MANUFACTURING APPROACHES

Organized by: Cellino

A critical promise of induced pluripotent stem cells (iPSCs) is the ability to generate unlimited starting material for autologous, or patient-specific, stem cell-based therapies. Compared to allogeneic cell therapies, autologous cell therapies have the safety advantage of enabling transplants without requiring patients to undergo immunosuppression. However, there is currently more development in the allogeneic iPSC-derived cell therapy space than the autologous iPSC-derived cell therapy space, because of the perceived cost and complexity of manufacturing patient-specific cell therapies. In this focus session, we highlight the work of several leaders pioneering the development of autologous iPSC-derived cell therapies, as well as the importance of transitioning from the current manual processes to a more automated approach. Our goal with this session is to share relevant learnings that benefit the iPSC-derived cell therapy field at large.

8:30 – 8:35 **Marinna Madrid**, *Cellino, USA,* **Session Chair**
Welcome Remarks

8:35 – 9:00 **Ganna Bilousova,** *University of Colorado, Denver, USA*
Induced Pluripotent Stem Cell-Based Therapy for Genetic Skin Diseases

9:00 – 9:25 **Sheela Jacob,** *Vita Therapeutics, USA*
Developing an iPSC-Derived Regenerative Cell Therapy for Limb-Girdle Muscular Dystrophy 2A

9:25 – 9:50 **Yanhong Shi,** *Beckman Research Institute of City of Hope, USA*
A Human iPSC-Based Cell Therapy for Canavan Disease

9:50 – 10:15 **Rafael Carazo Salas,** *University of Bristol, UK*
Predicting 'Live' Cell Fate Dynamics in hPSCs by Deep Learning-Enhanced Morphological Profiling

10:15 – 10:40 **Kapil Bharti,** *National Eye Institute at the National Institutes of Health, USA*
iPSC-Derived RPE Cell Therapy: From Bench-to-Bedside Through Artificial Intelligence

10:40 – 11:05 **Robert Zweigerdt,** *Hannover Medical School, Germany*
High Density Manufacturing of Human Pluripotent Stem Cells

11:05 – 11:30 **Discussion Panel**
George Harb, *Cellino, USA*
Rafael Carazo Salas, *University of Bristol, UK*
Kapil Bharti, *National Eye Institute at the National Institutes of Health, USA*
Robert Zweigerdt, *Hannover Medical School, Germany*

TOWARDS BEST PRACTICES FOR PUBLIC ENGAGEMENT IN STEM CELL RESEARCH

Organized by: The ISSCR Ethics Committee

Public engagement is increasingly recognized as being integral to basic and translational research. It is especially critical in research that potentially raises ethical concerns, for example, research involving embryos, germline genome editing, stigmatized conditions, and with marginalized communities. In such research, public engagement can help to identify issues that must be addressed in order for it to be ethically sound. In addition, public engagement can help promote the appropriate implementation of research. While there have been prominent recent calls for public engagement in the emerging sciences, there is arguably little agreement about how this should be done and the best ways of doing so. However, standards for doing so have been articulated in other areas of science, especially HIV-related research. This focus session includes panelists who will describe some of the recent calls for public engagement in the emerging sciences and what might be expected from it as well those who have experience involved with public engagement in a variety of settings. A summary panel discussion will aim to identify ways that public engagement can help inform and address the ethical aspects of emerging science.

8:30 – 8:35 **Jeremy Sugarman,** *Johns Hopkins University, USA*, **Session Chair**
Welcome & Introductions

Session 1 | Calls for Engagement: Why? What is Hoped to be Achieved?

8:35 – 8:50 **Amander Clark,** *University of California, Los Angeles, USA*
Calls for Public Engagement in the ISSCR 2021 Guidelines

8:50 – 9:05 **Kazuto Kato,** *Osaka University, Japan*
International Calls for Public Engagement Regarding Human Genome Editing

9:05 – 9:20 **Michael Peluso,** *University of California, San Francisco, USA*
Engagement in Cutting Edge Translation: HIV Cure Research

Session 2 | Experiences with Engagement

9:20 – 9:35 **Robin Lovell-Badge,** *The Francis Crick Institute, UK*
Embryo Research

9:35 – 9:45 **Megan Munsie,** *Murdoch Children's Research Institute and University of Melbourne, Australia*
Stem Cells: Premature Use

9:45 – 9:55 **Kevin McCormack,** *California Institute for Regenerative Medicine (CIRM), USA*
Stem Cells: Public Outreach

9:55 – 10:05 **Raeka Aiyar,** *New York Stem Cell Foundation (NYSCF) Research Institute, USA*
Stem Cells: Advocate

10:05 – 10:15 **Nancy René**, *Patient Advocate, California Institute for Regenerative Medicine (CIRM), USA*
Stem Cells: Patient/Family Perspective

10:15 – 10:30 **Break**

10:30 – 10:50 **James Fishkin,** *Stanford University, USA*
Goals, Principles and Modalities of Public Engagement in Science

Summary and Panel Discussion

10:50 – 11:25 **Chair and All Speakers**
Panel Discussion & Questions from the Audience

BUILDING A PRODUCT, BUILDING A CAREER

Organized by: The ISSCR Subcommittee on Industry-Academic Education and Career Development

Career paths and the role and contributions of industry within the stem cell and regenerative medicine field are experiencing an unprecedented wave of change. Once-narrow career trajectories are fundamentally changing to give rise to new and flexible paths towards and within industry, providing opportunities to contribute towards the development of new technologies and products that will have meaningful impacts on scientific progress and emerging new therapies. This Focus Session, organized by the ISSCR Industry Subcommittee on Industry-Academic Education and Career Development, will explore the shifting landscape of careers in industry through the lens of those that have navigated them and spotlight how their career paths have intertwined with opportunities to shape the future of the field and enable the advancement of stem cell research and regenerative medicine.

8:30 – 8:35 **Andrew Gaffney,** *STEMCELL Technologies, Canada*, **Session Chair**
Welcome & Introduction: Building a Product, Building a Career

8:35 – 8:55 **Sandra Lubitz,** *Evotec, Germany*
Disease Modeling and Drug Discovery in Industry

8:55 – 9:15 **Brian McIntosh,** *Labcorp, USA*
Preclinical Development

9:15 – 9:35 **Ainslie Little,** *BlueRock Therapeutics, USA*
Starting a Start-Up: The Business Side of Science

9:35 – 9:45 **Break**

9:45 – 10:05 **Tenneille Ludwig,** *WiCell, USA*
Research Product Development

10:05 – 10:25 **Ricardo Baptista,** *Procella Therapeutics, Sweden*
Manufacturing Cell Therapies

10:25 – 10:45 **Yoji Sato,** *NIHS, Japan*
Regulatory Science and Ensuring the Quality and Safety of Cell Therapy Products

10:45 – 11:30 **Discussion Panel with All Speakers**
Moderator: **Andrew Gaffney,** *STEMCELL Technologies, Canada*

ACCELERATING CURES – TRANSLATING STEM CELL DISCOVERIES INTO THERAPIES

Organized by: Maryland Stem Cell Research Fund (MSCRF)

The Maryland Stem Cell Research Fund (MSCRF) is focused on identifying and fostering cutting-edge research and innovation in the field of regenerative medicine in Maryland. Our Accelerating Cures initiative promotes the transition of human stem cell-based technologies from the bench to the bedside by supporting cutting edge research from scientists at institutions and companies across Maryland. In this focus session, leading researchers from the National Institute of Health, Johns Hopkins University, and The University of Maryland will discuss groundbreaking work utilizing stem cells to advance innovative and novel therapies to patients. Talks will feature new advances in the use of pluripotent stem cells, mesenchymal stem cells and fibroblast-based approaches in the areas of musculoskeletal regeneration, neurological therapies and corneal transplants. Topics covered will include 3D printing of engineered tissues, limb regeneration, stem cell transplant and engraftment, and human cardiac xenotransplantation. In addition, top institute and industry leaders will hold a virtual panel to discuss key considerations in the commercialization and manufacturing of stem-cell therapies. Overall, MSCRF has invested over $170 million in accelerating stem cell-based research, commercialization, and cures and this session highlights some of the exciting work coming out of this collaborative stem cell community.

Two sessions are offered: In-Person and Virtual

In-Person Session

8:30 – 8:50 **Amritha Jaishankar,** *Maryland Stem Cell Research Fund, USA*, **Session Chair**
Ivy Dick, *University of Maryland, School of Medicine, USA*, **Session Chair**
Welcome and Overview

8:50 – 9:15 **Gabsang Lee,** *Johns Hopkins University, School of Medicine, USA*
Human Pluripotent Stem Cell-Derived Myogenic Progenitors Undergo Maturation to Quiescent Satellite Cells Upon Engraftment With In Vivo Therapeutic Efficacy

9:15 – 9:40 **Linda Resar,** *Johns Hopkins University, School of Medicine, USA*
HMGA1 Proteins as Epigenetic Gatekeepers of Stem Cell Function During Stress Hematopoiesis

9:40 – 10:05 **Amer Riazzuddin,** *Johns Hopkins University, School of Medicine, USA*
Pluripotent Stem Cell-Derived Corneal Endothelial Cells: An Alternative to Donor Tissue in Endothelial Keratoplasty

Break

10:15 – 10:40 **Warren Grayson,** *Johns Hopkins University, School of Medicine, USA*
Exploring Neurovascular Interactions in Musculoskeletal Tissue Regeneration

10:40 – 11:05 **John Fisher,** *University of Maryland, College Park, USA*
3D Printing Strategies for Stem Cells in Complex Engineered Tissues

11:05 – 11:30 **Luis Garza,** *Johns Hopkins University, School of Medicine, USA*
Cell Therapy to Enhance Prosthetic use in Amputees

Virtual Session

8:30 -8:45 **Curt Civin,** *University of Maryland, School of Medicine, USA*, **Session Chair**
Amritha Jaishankar, *Maryland Stem Cell Research Fund, USA*, **Session Chair**
Welcome and Overview

8:45 – 9:10 **Stuart Martin,** *University of Maryland, School of Medicine, USA*
Microfluidic Cell Tethering (TetherChip) To Improve Analysis Of Stem Cell Sphere Formation

9:10 – 9:35 **Muhammad Mohiuddin,** *University of Maryland, School of Medicine, USA*
First Pig to Human Cardiac Xenotransplantation: How We Got Here

9:35 – 10:00 **Valina Dawson,** *Johns Hopkins University, School of Medicine, USA*
Leveraging Human Brain Culture to Identify Therapeutic Targets

10:00 – 11:30 **Amritha Jaishankar,** *Maryland Stem Cell Research Fund, USA*, **Moderator**
Welcome and Overview
Panel Accelerating Cures- Translating Stem Cell Discoveries Into Therapies
Jon Rowley, *RoosterBio, USA*
Doug Falk, *Vita Therapeutics, USA*
Sashank Reddy, *LifeSprout, USA*
Murat Kalayoglu, *Cartesian Therapeutics, USA*
Kapil Bharti, *National Institutes of Health, USA*

CHALLENGES AND OPPORTUNITIES IN CELL THERAPY AND DELIVERY

Organized by: Novo Nordisk

Stem cell derived cell therapies are moving into the next era of development with a lot of novel products moving into clinic or already in early clinical trials. The field is now facing a lot of new challenges e.g. with the final cell product, cell formulation, device development, the need for immunosuppression or development of immune evasive cell lines. In this focus session we would like to shed light on some of these challenges in cell therapy development and how these are seen by different experts in the field, and the opportunities to overcome the hurdles for the generation of novel stem cell-based therapies. We will especially give examples within the development of cell therapies for T1D and Parkinson's Disease.

8:30 – 8:40 **Salka Elbøl Rasmussen,** *Cell Therapy Research and Development, Novo Nordisk, Denmark,* **Session Chair**
Welcome and Introduction

8:40 – 9:15 **Ton Rabelink,** *Leiden University Medical Center, The Netherlands*
Immunological Barriers in Stem Cell Transplantation, and Possible Ways to Deal with Them

9:15 – 9:50 **Bart O. Roep,** *Leiden University Medical Center, The Netherlands*
Immunotherapy and Beta-Cell Therapy in Type 1 Diabetes: Premise, Problems and Promise

9:50 – 10:25 **Klearchos Papas,** *University of Arizona, USA*
Designing Devices for Cell Delivery: Engineering Challenges and Solutions

10:25 – 11:00 **Mark Denham,** *Aarhus University, Denmark*
Enhanced Production of Mesencephalic Dopaminergic Neurons from Lineage-Restricted Human Undifferentiated Stem Cells

11:00 – 11:20 **Jonathan C. Niclis,** *Cell Therapy Research and Development, Novo Nordisk, Denmark*
Addressing Challenges in Neuronal Transplantation While Advancing Next Generation Therapeutics

11:20 – 11:30 **Salka Elbøl Rasmussen,** *Cell Therapy Research and Development, Novo Nordisk, Denmark*
Session Wrap-up

TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY

Organized by: Stem Cell COREdinates (COREdinates.org)
Supported by: STEMCELL Technologies and Thermo Fisher Scientific

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

8:30 – 8:35 **Wenli Yang,** *University of Pennsylvania, USA*, **Session Chair**
Welcome and Overview

8:35 – 8:50 **Laura Batlle,** *Center for Genomic Regulation, Spain*
CorEUstem Network

8:50 – 9:05 **Ting Zhou,** *Sloan Kettering Institute, USA*
Prime Editing in Human Pluripotent Stem Cells

9:05 – 9:20 **Dmitry Ovchinnikov,** *Florey Institute / University of Melbourne, Australia*
Evolving Gene Editing and Cell Functionalisation Methodologies in Human Pluripotent Stem Cells

9:20 – 9:35 **Omar Farah,** *Thermo Fisher Scientific, USA*
Stem Cell Characterizations: Normal, Abnormal and Everything In Between

9:35 – 9:50 **Brock Roberts,** *Allen Institute for Cell Science, USA*
New Stem Cell Technologies and Tools from The Allen Institute for Cell Science

9:50 – 10:05 **Kimberly Snyder,** *STEMCELL Technologies, Canada*
Consistent, Reproducible Differentiation of High-Quality hPSCs Using STEMdiff™ and TeSR™-AOF

10:05 – 10:20 **Evangelos Kiskinis,** *Northwestern University, USA*
CRISPR/CAS9 Editing in iPSCs Results in Detrimental On-Target Defects That Escape Standard Quality Controls

10:20 – 10:25 **BREAK**

10:25 – 10:30 **Laurence Daheron,** *Harvard University, USA,* **Session Chair**
Overview Disease/Therapy Topics

10:30 – 10:50 **Juan Alvarez,** *University of Pennsylvania, USA*
[Part II] Circadian Entrainment for Maturation of Stem-Cell Derived Islets

10:50 – 11:10 **Sonja Schrepfer,** *UCSF and Sana Biotechnology Inc, USA*
Protecting Islets from Immune Destruction with Hypoimmune iPSCs

11:10 – 11:30 **Barry Morse,** *Century Therapeutics, USA*
Century Therapeutics Allogeneic iPSCs-Based Therapeutic Platform and Approaches to Avoiding Alloreactivity

PUBLIC SYMPOSIUM

Organized by: California Institute for Regenerative Medicine (CIRM)

THURSDAY, 16 JUNE 3:00 PM – 4:30 PM

Moscone West Convention Center, Room 2022, Level 2

Can Regenerative Medicine Turn Back the Clock on Aging?

It is estimated that as many as 90 percent of the people who die every day die from diseases of aging such as heart disease, stroke, and cancer. Now, regenerative medicine is working to develop new therapies to address those diseases. In this special public session, CIRM will explore the impact of regenerative medicine on aging, we'll hear from experts on heart disease and stroke, and also discuss the vital role that patients and patient advocates play in helping advance this work.

Panelists

Maria T. Millan, *President and CEO of the California Institute for Regenerative Medicine*

Deepak Srivastava, *UCSF/Gladstone Institutes, USA*

S. Thomas Carmichael, *Professor, Department of Neurology, David Geffen School of Medicine at UCLA, USA*

Adrienne Shapiro, *Patient Advocate, Americans for Cures Foundation, USA*

QUALITY STANDARDS FOR STEM CELL RESEARCH

SUNDAY, 19 JUNE 8:30 AM – 1:30 PM

San Francisco Marriott Marquis, Golden Gate Ballroom A, B2 Level
Sponsored by: CIRM, STEMCELL Technologies, Synthego and WiCell

Join members of the ISSCR's Stem Cell Research Standards Task Force for a half-day meeting to learn about the initiative to develop quality standards for stem cell research to improve rigor and reproducibility. Standards set researchers up for success, ensure rigor in preclinical research, and ultimately strengthen the pipeline of therapies for patients. Separate registration required.

PROGRAM

8:30 – 8:55 AM **Morning Coffee**

8:55 AM **Welcome** (Tenneille Ludwig, WiCell, USA)

9:00 AM – 10:00 AM: ISSCR Standards Session 1

9:00 – 9:15: Presentation from working group 1: Basic Characterization Standards
Tenneille Ludwig, *WiCell, USA*

9:15 – 9:30: Q&A with working group 1 co-chairs

9:30 – 9:45: Presentation from working group 2: Standards for assaying pluripotency and undifferentiated cells, Martin Pera, *Jackson Labs, USA*

9:45 – 10:00: Q&A with working group 2 co-chairs

10:00 AM – 10:15 AM: Coffee Break

Sponsored Presentation by Matthew Hildebrandt, STEMCELL Technologies

10:15 – 10:30: Presentation from working group 3: Genomic characterization standards
Ivana Barbaric, *University of Sheffield*

10:30 – 10:45: Q&A with working group 3 co-chairs

10:45 – 11:05: Presentation from working group 4: Standards for Stem Cell-derived model systems
Christine Mummery, *Leiden University Medical Center, Netherlands*

11:05 – 11:20: Q&A with working group 4 co-chairs

11:20 – 12:00 – Panel discussion with all four working groups

12:00 PM to 1:10 PM Lunch

Sponsored Presentation by Robert Deans, Synthego

CIRM CALIFORNIA'S STEM CELL AGENCY — Gold Sponsor

STEMCELL™ TECHNOLOGIES — Gold Sponsor

SYNTHEGO — Gold Sponsor

WiCell — Bronze Sponsor

20TH ANNIVERSARY CELEBRATION

Thursday, 16 June

7:30 PM – 9:30 PM

In 2022, the ISSCR reached its milestone 20th Anniversary. To honor the field and the society, the ISSCR is celebrating two decades of achievements in stem cell research and regenerative medicine. Activities will include: live band, food and beverages, a celebration of accomplishments of the field and the ISSCR during the last 20 years.

CELEBRATION SPONSORS

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INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

2022 WORKSHOP ON CLINICAL TRANSLATION

TUESDAY, 14 JUNE, SAN FRANCISCO, USA

HOW TO MAKE CLINICALLY SUCCESSFUL CELL THERAPIES

9:00 AM – 5:20 PM

Organizing Committee
Alexander Marson, University of California, San Francisco, and David J. Gladstone Institutes, USA [chair]
Katy Rezvani, University of Texas MD Anderson Cancer Center, USA
Sonja Schrepfer, University of California, San Francisco, USA and Sana Biotechnology, USA
Linda Vo, Third Rock Ventures, USA
Juan Carlos Zuniga-Pflucker, University of Toronto, Canada

Overall theme
Genetic and Epigenetic Reprogramming of Cell States and Functions to Move Beyond Autologous T Cell Therapies

7:00 AM – 9:00 AM **Registration**

9:00 AM – 9:10 AM **Welcome and Opening Remarks: Alex Marson,** *UCSF, USA*

SESSION I: ADVANCING HEMATOPOIETIC CELL THERAPIES
Topics: iPS-derived Hematopoietic Cell Therapies

Moderator: Sonja Schrepfer

9:10 AM – 9:40 AM **Juan Carlos Zuniga-Pflucker**, *University of Toronto, Canada*

9:40 AM – 10:10 AM **Gay Crooks**, *University of California, Los Angeles, USA*

10:10 AM – 10:40 AM **Shin Kaneko**, *Centre for iPS Cell Research and Application, Kyoto University, Japan*

10:40 AM – 11:10 AM **Agnieszka Czechowicz,** *Stanford University School of Medicine, USA*

11:10 AM – 11:40 AM **Dan Kaufman**, *University of California, San Diego, USA*

11:40 AM – 12:00 PM **Panel Discussion**
(with session speakers and moderator)

12:00 PM – 1:00 PM **Lunch break**

SESSION II: CRISPR Screening, Genomic Analysis, and Synthetic Biology, Oh My! Improving Cellular Therapies
Topics: Exploring the parameters of cell therapies that make them clinically successful -- how to make them powerful

Moderator: Linda Vo

1:00 PM – 1:30 PM **Alexander Marson**, *University of California, San Francisco, and David J. Gladstone Institutes, USA*

1:30 PM – 2:00 PM **Debattama Sen**, *Massachusetts General Hospital/Harvard Medical School, USA*

2:00 PM – 2:30 PM **Yvonne Chen**, *University of California, Los Angeles, USA*

2:30 PM – 2:50 PM **Panel Discussion**
(with session speakers and moderator)

2:50 PM – 3:20 PM **Coffee break**

SESSION III: Unleashing Cells from Immune Rejection to Make Off the Shelf Therapies
Topics:

Moderator: Juan Carlos Zuniga-Pflucker

3:20 PM – 3:50 PM **Sonja Schrepfer,** *University of California, San Francisco, USA and Sana Biotechnology, USA*

3:50 PM – 4:20 PM **Akitsu Hotta,** *Centre for iPS Cell Research and Application, Kyoto University, Japan*

4:20 PM – 4:50 PM **Robert Tighe,** *TCR2 Therapeutics, Inc., Boston, USA*

4:50 PM – 5:10 PM **Panel Discussion**
(with session speakers and moderator)

5:10 PM – 5:20 PM **Closing Remarks: TBA**

TUESDAY, 14 JUNE

9:00 AM – 5:20 PM **PRE-MEETING WORKSHOP ON CLINICAL TRANSLATION** — Room 2004, Level 2
Advance registration required

3:00 PM – 4:00 PM **ATTENDEE ORIENTATION**
Advance registration required
Ground Floor next to Registration

WEDNESDAY, 15 JUNE

8:00 AM – 8:30 AM **MORNING COFFEE** — Level 2

7:45 AM – 8:45 AM **ATTENDEE ORIENTATION**
Advance registration required
Ground Floor next to Registration

8:30 AM – 11:30 AM **FOCUS SESSIONS** (see page 30 for details)

AUTOLOGOUS IPSC-DERIVED CELL THERAPIES & ENABLING AI-AND ROBOTICS-BASED MANUFACTURING APPROACHES — Room 2012, Level 2
Organized by Cellino Biotech

TOWARDS BEST PRACTICES FOR PUBLIC ENGAGEMENT IN STEM CELL RESEARCH — Room 2003, Level 2
Organized by the ISSCR Ethics Committee

BUILDING A PRODUCT, BUILDING A CAREER — Room 2001, Level 2
Organized by the ISSCR Subcommittee on Industry-Academic Education and Career Development

ACCELERATING CURES - TRANSLATING STEM CELL DISCOVERIES INTO THERAPIES — Room 2011, Level 2
Organized by Maryland Stem Cell Research Fund (MSCRF)

CHALLENGES AND OPPORTUNITIES IN CELL THERAPY AND DELIVERY — Room 2007, Level 2
Organized by Novo Nordisk

TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY — Room 2004, Level 2
Organized by Stem Cell COREdinates
Supported by Thermo Fisher Scientific and STEMCELL Technologies

11:00 AM – 12:15 PM **EARLY CAREER GROUP LEADER LUNCHEON: EVOLVING MODES OF COLLABORATION AND RESEARCH MANAGEMENT** — Room 2018, Level 2
Early career scientist event; Advance registration required

11:15 AM – 12:15 PM **SCIENCE ADVOCACY & COMMUNICATIONS SEMINAR** — Rooms 2022, Level 2
Session Sponsored by: Americans for Cures
Advance registration required

12:30 PM – 2:40 PM **PLENARY I: PRESIDENTIAL SYMPOSIUM** — Level 3
Session Sponsored by: Sana Biotechnology

Session Chair: Melissa Little
Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Denmark and Murdoch Children's Research Institute, Australia
Level 3

WEDNESDAY, 15 JUNE *(continued)*

12:30 PM – 12:35 PM **PLENARY I SPONSOR AND OPENING WELCOMES**

12:35 PM – 12:40 PM **Melissa Little**
Novo Nordisk Foundation Centre for Stem Cell Medicine (reNEW), Denmark and Murdoch Children's Research Institute, Australia

PRESIDENTIAL ADDRESS

12:40 PM – 12:45 PM **Christina Tan**
Dr. Susan Lim Endowment for Education and Research Ltd.

PRESENTATION OF ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR

12:45 PM – 12:50 PM **PRESENTATION OF ISSCR PUBLIC SERVICE AWARD**

12:50 PM – 12:55 PM **TRAVEL AWARD AND MERIT AWARD RECOGNITIONS**

12:55 PM – 1:15 PM **Leonard I. Zon**
Boston Children's Hospital, USA

STEM CELL CLONALITY AND THE NICHE, AND 20 YEARS OF A NICHE FOR STEM CELL RESEARCH - THE ISSCR

1:18 PM – 1:33 PM **Jose Polo**
The University of Adelaide, Australia

UNDERSTANDING HUMAN REPROGRAMMING: A JOURNEY FROM EPIBLAST TO TROPHOBLAST AND INTO IBLASTOIDS

1:36 PM – 1:51 PM **Aryeh Warmflash**
Rice University, USA

MODELING GASTRULATION WITH HUMAN PLURIPOTENT STEM CELLS

1:55 PM – 2:10 PM **Prisca Liberali**
Friedrich Miescher Institute for Biomedical Research, Switzerland

DECODING THE DESIGN PRINCIPLE OF TISSUE ORGANISATION

2:10 PM – 2:30 PM **Christine Mummery**
Leiden University Medical Center, Netherlands

CARDIOVASCULAR DISEASE MODELS BASED ON HUMAN PLURIPOTENT STEM CELLS

2:30 PM – 8:30 PM **EXHIBIT HALL OPEN**

2:45 PM – 3:30 PM **MEET-UP HUBS** **(See page 26 for details)**
Exhibit & Poster Hall, Ground Floor

EARLY CAREER SCIENTISTS NETWORKING
Meet-up Hub #1

INDUSTRY SCIENTISTS NETWORKING
Meet-up Hub #2

2:45 PM – 3:30 PM **REFRESHMENT BREAK**
Exhibit & Poster Hall, Ground Floor

WEDNESDAY, 15 JUNE *(continued)*

3:30 PM – 5:40 PM — **TRACK: CLINICAL APPLICATIONS (CA)** — Level 3

PLENARY II: PUSHING THE BOUNDARIES IN STEM CELL THERAPY AND REGENERATION

Session Sponsored by: T-CiRA Joint Program

Session Chairs: Malin Parmar
Lund University, Sweden
Leonard I. Zon
Boston Children's Hospital, USA

3:30 PM – 3:35 PM — **PLENARY II INTRODUCTION**

3:35 PM – 4:05 PM — **Jennifer E. Phillips-Cremins**
University of Pennsylvania, USA

ISSCR DR SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE: HIGHER-ORDER CHROMATIN ARCHITECTURE MECHANISMS ENCODING GENOME INSTABILITY IN REPEAT EXPANSION DISORDERS

4:05 PM – 4:25 PM — **Deepta Bhattacharya**
University of Arizona College of Medicine, USA

ENGINEERING PLURIPOTENT STEM CELLS TO EVADE AND PROMOTE IMMUNITY

4:25 PM – 4:45 PM — **Yvonne Chen**
University of California, Los Angeles, USA

ENGINEERING NEXT-GENERATION CAR-T CELL THERAPY FOR CANCER

4:45 PM – 5:05 PM — **Malin Parmar**
Lund University, Sweden

CAN SINGLE CELL OMICS GUIDE DEVELOPMENT OF SECOND GENERATION STEM CELL DERIVED DA NEURONS FOR CELL THERAPY IN PD?

5:05 PM – 5:30 PM — **Deepak Srivastava**
Gladstone Institutes and University of California, San Francisco, USA

ERNEST MCCULLOCH MEMORIAL LECTURE: CELLULAR REPROGRAMMING FOR REJUVENATION AND REPAIR

5:45 PM – 8:30 PM — **OPENING RECEPTION**
Exhibit & Poster Hall, Ground Floor

WEDNESDAY, 15 JUNE *(continued)*

6:15 PM – 6:30 PM **MICRO-THEATER: SONY BIOTECHNOLOGY INC.**

Aditi Singh
Sony Biotechnology Inc., USA

SONY CGX10 CELL ISOLATION SYSTEM: ENABLING GMP READY CELL THERAPY PRODUCT MANUFACTURING USING MULTIPARAMETRIC SELECTION
Exhibit Hall, Ground Floor

6:30 PM – 7:30 PM **POSTER SESSION I ODD**
Exhibit & Poster Hall, Ground Floor

6:45 PM – 7:00 PM **MICRO-THEATER: GETINGE**

George Barringer
Getinge Applikon Bioreactors, USA

IMPROVING CELL EXPANSION IN BIOREACTORS: AUTOMATED MEDIA EXCHANGE AND CELL SEPARATION STRATEGIES
Exhibit & Poster Hall, Ground Floor

6:45 PM – 7:30 PM **MEET-UP HUBS** **(See page 26 for details)**

POLICY, ETHICS, AND REGULATORY ISSUES
Meet-up Hub #1

COMPUTATIONAL STEM CELL BIOLOGY NETWORKING
Meet-up Hub #2

7:15 PM – 7:30 PM **MICRO-THEATER: SYNTHEGO**

Kevin Holden
Synthego, USA

LARGE-SCALE GENERATION OF CELL MODELS USING CRISPR FOR THE IPSC NEURODEGENERATIVE DISEASE INITIATIVE (INDI)
Exhibit & Poster Hall, Ground Floor

7:30 PM – 8:30 PM **POSTER SESSION I EVEN**
Exhibit & Poster Hall, Ground Floor

7:45 PM – 8:00 PM **MICRO-THEATER: CELL MICROSYSTEMS**

Jessica Hartman
Cell Microsystems, USA

THE CELLRAFT AIR SYSTEM: AN AUTOMATED ALL-IN-ONE SOLUTION FOR IMAGING, IDENTIFYING, AND ISOLATING STEM CELLS
Exhibit & Poster Hall, Ground Floor

8:15 PM – 8:30 PM **MICRO-THEATER: CATALENT**
Exhibit & Poster Hall, Ground Floor

Boris Greber
Catalent Cell & Gene Therapy, USA

GMP-COMPLIANT IPSC LINES AND DIFFERENTIATION WORKFLOWS FOR CELL THERAPY

THURSDAY, 16 JUNE

INNOVATION SHOWCASES (See page 101 for details)

8:00 AM – 8:30 AM — Room 2011, Level 2

ADDING A NEW DIMENSION TO IN VITRO RESEARCH: SINGLE CELL AND SPATIAL SOLUTIONS FOR ORGANOIDS*
Presented by 10x Genomics

Samantha Shelton
10x Genomics, USA

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

8:00 AM – 8:30 AM — Room 2012, Level 2

HIGH THROUGHPUT CRISPR EDITING AND GENOMIC CHARACTERIZATION
Presented by Synthego

Rebecca Nugent
Synthego, USA

8:00 AM – 8:30 AM — Room 2001, Level 2

HOW TO CHOOSE THE RIGHT NEURAL CELL CULTURE MODEL FOR YOUR RESEARCH QUESTION*
Presented by STEMCELL Technologies Inc.

Erin Knock
STEMCELL Technologies Inc, Canada

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

8:00 AM – 8:30 AM — Room 2004, Level 2

INNOVATION SHOWCASE - Agilent Technologies Inc
Presented by Agilent Technologies Inc

8:00 AM – 8:30 AM — Room 2003, Level 2

INNOVATION SHOWCASE - MAXCYTE
Presented by MaxCyte

Angelo Cardoso
Beckman Research Institute of the City of Hope, USA

8:00 AM – 8:30 AM — Room 2008, Level 2

MODELING CONTRACTILE DISEASES USING SCALABLE 3D ENGINEER MUSCLE TISSUES FOR DRUG DISCOVERY
Presented by Curi Bio

Shawn Luttrell
Curi Bio, USA
Heejoon Choi
Curi Bio, USA
Hamed Ghazizadeh
Curi Bio, USA

8:00 AM – 8:30 AM — Virtual

THE EBiSC ONE-STOP-SHOP FOR hiPSCS – HOW THE EBIS BIOBANK'S SUSTAINABLE INFRASTRUCTURE SUPPORTS YOUR RESEARCH **
Presented by European Bank for induced pluripotent Stem Cells (EBiSC)

Julia Neubauer
Fraunhofer Institute for Biomedical Engineering (IBMT), Germany

Ralf Kettenhofen
Fraunhofer Institute for Biomedical Engineering (IBMT), Germany

Andreas Kurtz
Fraunhofer Institute for Biomedical Engineering (IBMT), Germany

THURSDAY, 16 JUNE *(continued)*

Ina Meiser
Fraunhofer Institute for Biomedical Engineering (IBMT), Germany

Charlie Arber
University College London, UK

Christian Clausen
Bioneer A/S, Denmark

Eugenia Jones
Fujifilm Cellular Dynamics, Inc., USA

Juliana Laze
NYU Langone Medical Center, USA

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

8:00 AM – 8:30 AM **WHY DOES TREEFROG THERAPEUTICS LAUNCH A $100,000 RESEARCH GRANT IN THE FIELD OF STEM-CELL DERIVED CELL THERAPIES?** Room 2007, Level 2
Presented by TreeFrog Therapeutics

Maxime Feyeux
TreeFrog Therapeutics, France

8:30 AM – 9:00 AM **MORNING COFFEE** Level 3

9:00 AM – 10:55 AM **TRACK: CELLULAR IDENTITY (CI)** Level 3
PLENARY III: PROGRAMMING AND REPROGRAMMING
Session Sponsored by: BlueRock Therapeutics

Session Chairs: Nissim Benvenisty
Hebrew University, Israel

Shuibing Chen
Weill Cornell Medical College, USA

9:00 AM – 9:15 AM **ISSCR BUSINESS MEETING**

9:15 AM – 9:20 AM **PLENARY III INTRODUCTION**

9:20 AM – 9:40 AM **Douglas Melton**
Harvard University, USA

MAKING DESIGNER PANCREATIC ISLETS FROM STEM CELLS

9:40 AM – 10:00 AM **Fiona Watt**
King's College London/ EMBO, UK

EXPLORING DIFFERENTIATION AND DEDIFFERENTIATION IN MAMMALIAN EPIDERMIS

10:00 AM – 10:20 AM **Austin Smith**
University of Exeter, UK

THE PLURIPOTENCY TRANSITION

10:20 AM – 10:45 AM **Ruth Lehmann**
Whitehead Institute, USA

ANNE MCCLAREN MEMORIAL LECTURE: GUIDING GERM CELLS TOWARD IMMORTALITY

11:00 AM – 5:00 PM **EXHIBIT & POSTER HALL OPEN**

THURSDAY, 16 JUNE *(continued)*

11:15 AM – 12:45 PM — **EQUITY, DIVERSITY, AND INCLUSION IN STEM: IMPACT AND ACTION WORKSHOP** — Room 2022, Level 2
Session Sponsored by: California Institute for Regenerative Medicine (CIRM)
Advance registration required

11:30 AM – 12:15 PM — **MEET-UP HUBS** (See page 26 for details)

FINDING YOUR HIDDEN SKILLS
Session Organized by: Scismic
Meet-up Hub #1

CAREERS IN BIOTECH
Session Organized by: STEMCELL Technologies
Meet-up Hub #2

11:30 AM – 12:30 PM — **INNOVATION SHOWCASES** (See page 101 for details)

11:30 AM – 12:30 PM — **A CLOSED-SYSTEM SOLUTION DESIGNED TO GENTLY AND RAPIDLY PROCESS PSC SPHEROIDS FROM BIOREACTORS** — Room 2011, Level 2
Presented by Thermo Fisher Scientific

Michael Akenhead
Thermo Fisher Scientific, USA

11:30 AM – 12:30 PM — **ENDING DISEASE: THE STEM CELL, CAR T-CELL, AN ANTIBODY REVOLUTION IN MEDICINE - AN EXCLUSIVE SCREENING OF A POWERFUL NEW DOCUMENTARY FOR ISSCR CONFERENCE ATTENDEES **** — Virtual
Presented by Americans for Cures

Joe Gantz
Medical Revolution, USA

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

11:30 AM – 12:30 PM — **FROM CULTURE TO VISUALIZATION: EYE-OPENING SOLUTIONS FOR PLURIPOTENT STEM CELLS*** — Room 2001, Level 2
Presented by Miltenyi Biotec B.V.& Co.KG.

Kåre Kryger Vøls
Novo Nordisk A/S, Denmark
Sebastian Knöbel
Miltenyi Biotec B.V.& Co.KG., Germany

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

11:30 AM – 12:30 PM — **INNOVATION SHOWCASE – CORNING LIFE SCIENCES** — Room 2004, Level 2
Presented by Corning Life Sciences

Austin Mogen
Corning Life Sciences , USA
Rob Vries
HUB Organoid Technology (HUB), Netherlands

11:30 AM – 12:30 PM — **INNOVATIVE SOLUTIONS FOR PLURIPOTENT STEM CELL WORKFLOWS** — Room 2008, Level 2
Presented by Bio-Techne

Brittni Peterson
Bio-Techne, USA
Miriel Ho
CReATe Fertility Centre, Toronto, Canada

Mirabelle Ho
CReATe Fertility Centre, Toronto, Canada

11:30 AM – 12:30 PM **SYSTEM TO GENERATE THOUSANDS OF GMP-GRADE iPSCS PER YEAR--AND THE FUTURE IT WILL USHER** Room 2003, Level 2
Presented by I Peace Inc.

Koji Tanabe
I Peace Inc., USA
Marius Wernig
Stanford University, USA

11:30 AM – 12:30 PM **ROBUST WORKFLOWS FOR THE EXPANSION OF PLURIPOTENT STEM CELLS IN 3D SUSPENSION CULTURE*** Room 2007, Level 2
Presented by STEMCELL Technologies Inc.

Eric Jervis
STEMCELL Technologies Inc., Canada

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

11:30 AM – 12:30 PM **SUCCESS STORIES OF RELIABLE PSC DIFFERENTIATION IN 2D AND 3D CELL CULTURES** Room 2012, Level 2
Presented by BioLamina AB

Lynn Yap
Duke-NUS Medical School, Singapore
Dave Mann
Vascugen Inc, USA
Alessandro Fiorenzano
Lund University, Sweden

11:30 AM – 12:30 PM **ENDING DISEASE: THE STEM CELL, CAR T-CELL, AND ANTIBODY REVOLUTION IN MEDICINE** Virtual

An Exclusive Screening of a powerful new documentary for ISSCR Conference Attendees
by Americans for Cures

Ending Disease is a documentary film that takes the viewer through a powerful journey as it weaves human stories of patients, doctors, and scientists in the era of revolutionary new FDA-approved clinical trials for stem cell, CAR-T cell, and antibody therapies.

Granted unprecedented access to groundbreaking trials taking place at top research facilities in the United States, we follow ten clinical trials using regenerative medicine to treat brain cancer, breast cancer, leukemia, lymphoma, HIV, spinal cord injury, retinitis pigmentosa, and severe combined immunodeficiency (SCID), and witness as the patients' illnesses are profoundly transformed by these pioneering treatments.

*Available on the virtual meeting platform

1:00 PM – 2:45 PM **CONCURRENT TRACK SESSIONS**

1:00 PM – 2:45 PM **TRACK: CELLULAR IDENTITY (CI)**
CELLULAR IDENTITY TOWARDS TRANSLATIONAL MEDICINE Room 2008, Level 2
Session Sponsored by: BlueRock Therapeutics

Session Chairs: Sally Temple
Neural Stem Cell Institute, USA

Joseph Wu
Stanford University School of Medicine, USA

THURSDAY, 16 JUNE *(continued)*

1:00 PM – 1:05 PM **TOPIC OVERVIEW**

1:05 PM – 1:25 PM **Joseph Wu**
Stanford University School of Medicine, USA

STEM CELLS AND GENOMICS FOR PRECISION MEDICINE

1:25 PM – 1:35 PM **Christelle Monville**
INSERM U861-ISTEM, France

PHASE I/II OPEN-LABEL STUDY OF IMPLANTATION INTO ONE EYE OF HESC-DERIVED RPE IN PATIENTS WITH RETINITIS PIGMENTOSA DUE TO MONOGENIC MUTATION: FIRST SAFETY RESULTS

1:35 PM – 1:45 PM **Max Friesen**
Whitehead Institute for Biomedical Research, USA

A NEW PHYSIOLOGICAL MODEL OF INSULIN RESISTANCE IN HUMAN STEM CELL-DERIVED ADIPOCYTES REVEALS METABOLIC DEFECTS

1:45 PM – 1:55 PM **Niels Geijsen**
Leiden University Medical Center, Netherlands

EFFICIENT IN VIVO DELIVERY OF CRISPR/CAS9 RIBONUCLEOPROTEIN COMPLEX IN SKELETAL MUSCLE

1:55 PM – 2:05 PM **Marta Vilà-González**
University of Cambridge, UK

HIPSC-DERIVED AECS CONSTITUTE A NOVEL PLATFORM TO STUDY IONOCYTES IN A CONTEXT OF MUCOCILIARY CLEARANCE

2:05 PM – 2:15 PM **Aparna Bhaduri**
University of California, Los Angeles, USA

UNDERSTANDING CELL TYPES IN THE DEVELOPING HUMAN CORTEX

2:15 PM – 2:35 PM **Sally Temple**
Neural Stem Cell Institute, USA

RETINAL PIGMENT EPITHELIAL STEM CELLS - FROM DISCOVERY TO TRANSLATION

1:00 PM – 2:45 PM **TRACK: CLINICAL APPLICATIONS (CA)**
STEM CELL BIOENGINEERING - ENHANCING CELL FUNCTION Room 2004, Level 2
Session Sponsored by: Stem Cell Network

Session Chairs: George Daley
Harvard Medical School, USA

Darcy Wagner
Lund University, Sweden

1:00 PM – 1:05 PM **TOPIC OVERVIEW**

1:05 PM – 1:25 PM **George Daley**
Harvard University Medical School, USA

ENGINEERING BLOOD PRODUCTS FROM PLURIPOTENT STEM CELLS

THURSDAY, 16 JUNE *(continued)*

1:25 PM – 1:35 PM

Anastasia Conti
San Raffaele Telethon Institute for Gene Therapy (SR-TIGET) - San Raffaele Hospital, Italy

CELLULAR SENESCENCE AND INFLAMMATION: UNINTENDED SIDE EFFECTS OF CRISPR-CAS9 GENE EDITING IN HEMATOPOIETIC STEM AND PROGENITOR CELLS

1:35 PM – 1:45 PM

Attya Omer
IRCCS San Raffaele Scientific Institute, Italy

CHEMOTHERAPY-FREE ENGRAFTMENT OF GENE EDITED HUMAN HEMATOPOIETIC STEM CELLS LEVERAGED ON MOBILIZATION AND MRNA-BASED ENGINEERING

1:45 PM – 1:55 PM

Elad Sintov
Harvard University, USA

MECHANISMS FOR ATTAINING HYPO-IMMUNOGENICITY OF STEM CELL DERIVED PANCREATIC ISLETS BY GENE EDITING, PURSUED BY SINGLE CELL RNA SEQUENCING AND WHOLE GENOME CRISPR SCREENING

1:55 PM – 2:05 PM

Tobias Deuse
University of California, USA

THE 3 DIMENSIONS OF IMMUNE EVASION: IMMUNE EDITING MAKES CELL THERAPEUTICS ESCAPE ALL ALLOGENEIC ADOPTIVE IMMUNE CELLS, INNATE IMMUNE CELLS, AND CYTOTOXIC ANTIBODIES

2:05 PM – 2:15 PM

Kapil Bharti
National Institutes of Health, 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

2:15 PM – 2:35 PM

Darcy Wagner
Lund University, Sweden

TISSUE SPECIFIC BIOMATERIAL INKS FOR 4D+ BIOPRINTING

1:00 PM – 2:45 PM

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)
MODELING EARLY DEVELOPMENT AND DYNAMIC PROCESSES Room 2011, Level 2

Session Chairs: Cantas Alev
Kyoto University, Japan

Claire Rougeulle
Paris Diderot University, France

1:00 PM – 1:05 PM

TOPIC OVERVIEW

1:05 PM – 1:25 PM

Claire Rougeulle
Université de Paris, France

X CHROMOSOME INACTIVATION IN PRIMATES

1:25 PM – 1:35 PM

Gal Keshet
The Hebrew University, Israel

DIFFERENTIATION OF UNIPARENTAL HUMAN EMBRYONIC STEM CELLS INTO GRANULOSA CELLS REVEALS A PATERNAL CONTRIBUTION TO GONADAL DEVELOPMENT

THURSDAY, 16 JUNE *(continued)*

1:35 PM – 1:45 PM
Sajedeh Esfahani
University of Michigan, USA

EFFICIENT GENERATION OF HUMAN PRIMORDIAL GERM CELL-LIKE CELLS IN A BIOENGINEERED AMNIOGENIC NICHE.

1:45 PM – 1:55 PM
Nina Maenhoudt
Katholieke Universiteit Leuven, Belgium

A NOVEL HUMAN IMPLANTATION MODEL TO DECIPHER EMBRYO-ENDOMETRIUM INTERACTION

1:55 PM – 2:05 PM
Clara Munger
University of Cambridge, UK

MICROGEL CULTURE AND SPATIAL IDENTITY MAPPING ELUCIDATE THE SIGALING REQUIREMENTS FOR PRIMATE EPIBLAST AND AMNION FORMATION

2:05 PM – 2:15 PM
Merlin Lange
Chan Zuckerberg Biohub, USA

MULTIMODAL CELL LINEAGE TRACING REVEALS THE EXISTENCE OF MULTI GERM-LAYERS PROGENITORS DURING VERTEBRATE DEVELOPMENT.

2:15 PM – 2:35 PM
Cantas Alev
Kyoto University, Institute for the Advanced Study of Human Biology (ASHBi), Japan

TOWARDS RECONSTITUTING HUMAN SOMITOGENESIS IN VITRO

1:00 PM – 2:45 PM
TRACK: NEW TECHNOLOGIES (NT)
NEW AVATARS OF ORGANOGENESIS
Room 2012, Level 2

Session Chairs: Michael Elowitz
California Institute of Technology, USA

Valerie Weaver
University of California, San Francisco, USA

1:00 PM – 1:05 PM
TOPIC OVERVIEW

1:05 PM – 1:25 PM
Michael Elowitz
California Institute of Technology, USA

SYNTHETIC MULTISTABILITY IN MAMMALIAN CELLS

1:25 PM – 1:35 PM
Sara Howden
Murdoch Childrens Research Institute, Australia

GENOMIC LOCI FOR GENETIC ENGINEERING OF PLURIPOTENT STEM CELLS AND THEIR PROGENY

1:35 PM – 1:45 PM
Loukia Yiangou
Leiden University Medical Center, Netherlands

OPTOGENETIC REPORTERS DELIVERED AS MRNA FACILITATE REPEATABLE ACTION POTENTIAL AND CALCIUM HANDLING ASSESSMENT IN HUMAN IPSC-DERIVED CARDIOMYOCYTES

1:45 PM – 1:55 PM
Miguel Ortiz Salazar
Rice University, USA

A NOVEL MICROPATTERNED DIFFERENTIATION SYSTEM SHOWS THAT GEOMETRIC CONSTRAINT FUNDAMENTALLY CHANGES THE OUTCOME OF WNT AND FGF MEDIATED DIFFERENTIATION.

1:55 PM – 2:05 PM

Sounak Sahu
National Cancer Institute, USA

SELF-ORGANIZATION OF PLURIPOTENT MOUSE EMBRYONIC STEM CELLS TO GENERATE FUNCTIONAL MAMMARY ORGANOID

2:05 PM – 2:15 PM

Jacqueline Bliley
Carnegie Mellon University, USA

PROGRAMMED BENDING OF A 3D BIOPRINTED HEART TUBE INSPIRED BY CARDIAC MORPHOGENESIS

2:15 PM – 2:35 PM

Valerie Weaver
University of California, San Francisco, USA

MECHANICS REGULATE HUMAN EMBRYONIC STEM CELL SELF-ORGANIZATION TO SPECIFY MESODERM

THURSDAY, 16 JUNE *(continued)*

1:00 PM – 2:45 PM — **TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)** — Room 2007, Level 2

EVOLUTION OF STEM CELL FUNCTION AND TISSUE ARCHITECTURE

Session Sponsored by: Stanford Institute for Stem Cell Biology and Regenerative Medicine

Session Chairs: Miguel Concha
Universidad de Chile, Chile

Crystal Rogers
University of California, Davis, USA

1:00 PM – 1:05 PM — **TOPIC OVERVIEW**

1:05 PM – 1:25 PM — **Miguel Concha**
Universidad de Chile, Chile

A MECHANISM BASED ON MECHANICAL FORCES STEMMING FROM INCOMPLETE DELAMINATION GUIDES THE ALLOCATION OF PROGENITOR CELLS IN ZEBRAFISH

1:25 PM – 1:35 PM — **Rachel Keuls**
Baylor College of Medicine, USA

MICRORNAS AND INCREASED CHROMATIN ACCESSIBILITY EXPAND DEVELOPMENTAL POTENTIAL OF CRANIAL NEURAL CREST

1:35 PM – 1:45 PM — **Cheng Zhao**
Karolinska Institute, Sweden

REPROGRAMMED BLASTOIDS CONTAIN AMNION-LIKE CELLS BUT NOT TROPHECTODERM

1:45 PM – 1:55 PM — **Rachel Niec**
The Rockefeller University, USA

LYMPHATIC CAPILLARIES RESIDE IN THE INTESTINAL STEM CELL NICHE AND REGULATE STEM CELL ACTIVITY

1:55 PM – 2:05 PM — **Stephen Gadomski**
National Institutes of Health, USA

BONE-LINING OSTEOPROGENITORS AMPLIFY CHOLINERGIC SIGNALING IN BONE AND BONE MARROW

2:05 PM – 2:15 PM — **Mehmet Sacma**
University of Ulm, Germany

BLOOD STEM CELLS GENERATE THEIR OWN MICROENVIRONMENT

2:15 PM – 2:35 PM — **Crystal Rogers**
University of California, Davis, USA

CONSERVED AND DIVERGENT FUNCTIONS OF SOX10 IN NEURAL CREST DEVELOPMENT ACROSS SPECIES

3:00 PM – 5:00 PM — **REFRESHMENT BREAK** — Exhibit & Poster Hall, Ground Floor

3:00 PM – 4:00 PM — **POSTER SESSION II ODD** — Exhibit & Poster Hall, Ground Floor

THURSDAY, 16 JUNE *(continued)*

3:00 PM - 4:30 PM — **PUBLIC SYMPOSIUM: CAN REGENERATIVE MEDICINE TURN BACK THE CLOCK ON AGING?** — Room 2022, Level 2
Organized by: The California Institute for Regenerative Medicine (CIRM)

3:15 PM – 3:30 PM — **MICRO-THEATER: EMULATE** — Exhibit & Poster Hall, Ground Floor

3:45 PM – 4:00 PM — **MICRO-THEATER: ASPECT BIOSYSTEMS**
Erin Bedford
Aspect Biosystems, USA

BIOPRINTED TISSUE THERAPEUTICS: DEVELOPMENT THROUGH PARTNERSHIP — Exhibit & Poster Hall, Ground Floor

3:45 PM – 4:30 PM — **MEET-UP HUBS** (See page 26 for details) — Exhibit & Poster Hall, Ground Floor

MEET-THE-EDITORS OF *STEM CELL REPORTS*
Meet-up Hub #1

GERMAN STEM CELL NETWORK
Meet-up Hub #2

4:00 PM – 5:00 PM — **POSTER SESSION II EVEN** — Exhibit & Poster Hall, Ground Floor

4:15 PM – 4:30 PM — **MICRO-THEATER: STEMBIOSYS**
Travis Block
StemBioSys, Inc., USA

ACHIEVING MATURE, BIOLOGICALLY RELEVANT, SOMATIC CELL PHENOTYPES FROM IPSCs WITH CELLVO MATRICES — Exhibit & Poster Hall, Ground Floor

4:45 PM – 5:00 PM — **MICRO-THEATER: PROTEIN FLUIDICS, INC.**
Evan Cromwell
Protein Fluidics, Inc., USA

Katya Nikolov
Protein Fluidics, Inc., USA

STEM CELL & OTHER BIOMARKER IDENTIFICATION IN PATIENT-DERIVED 3D CELL MODELS USING AN AUTOMATED MICROFLUIDIC SYSTEM — Exhibit & Poster Hall, Ground Floor

5:15 PM – 7:00 PM — **CONCURRENT TRACK SESSIONS**

5:15 PM – 7:00 PM — **TRACK: CELLULAR IDENTITY (CI)** — Room 2008, Level 2
EPIGENETIC REGULATION OF STEM CELLS

Session Chairs: Eran Meshorer
Hebrew University, Israel

Kathrin Plath
David Geffen School of Medicine, UCLA, USA

5:15 PM – 5:20 PM — **TOPIC OVERVIEW**

5:20 PM – 5:40 PM — **Kathrin Plath**
University of California Los Angeles School of Medicine, USA
Title not available at time of printing

THURSDAY, 16 JUNE *(continued)*

5:40 PM – 5:50 PM
Keisuke Kaji
The University of Edinburgh, UK

B1 SINE-BINDING ZFP266 IMPEDES REPROGRAMMING THROUGH SUPPRESSION OF CHROMATIN OPENING MEDIATED BY PIONEERING FACTORS

5:50 PM – 6:00 PM
Rajesh Gunage
Boston Children's Hospital, USA

M6A EPITRANSCRIPTOME MEDIATED RNA STRESS GRANULE ASSEMBLY GOVERNS BLOOD DEVELOPMENT AND REGENERATION

6:00 PM – 6:10 PM
Katie Schaukowitch
Stanford University, USA

UNDERSTANDING THE BINDING DYNAMICS OF ASCL1 AND HES1 TRANSCRIPTION FACTORS DURING DIRECT REPROGRAMMING OF MOUSE EMBRYONIC FIBROBLASTS TO INDUCED NEURONAL (IN) CELLS

6:10 PM – 6:20 PM
Jasmin Taubenschmid-Stowers
Babraham Institute, UK

MODELLING HUMAN ZYGOTIC GENOME ACTIVATION IN 8C-LIKE CELLS IN VITRO

6:20 PM – 6:30 PM
Jengmin Kang
Stanford University, USA

THE LOSS OF HETEROCHROMATIN DURING STEM CELL AGING IS DRIVEN BY A DEPLETION OF S-ADENOSYLMETHIONINE SECONDARY TO INCREASED POLYAMINE SYNTHESIS

6:30 PM – 6:50 PM
Eran Meshorer
The Hebrew Univ of Jerusalem Inst of Life Sciences, Israel

CAPRIN1 LINKS EARLY EMBRYONIC STEM CELL DIFFERENTIATION WITH RNA METABOLISM

5:15 PM – 7:00 PM
TRACK: CLINICAL APPLICATIONS (CA) Room 2004, Level 2
BIOTECH, PHARMA AND ACADEMIA - BRINGING STEM CELLS TO PATIENTS
Session Sponsored by: Ajinomoto

Session Chairs: Melissa Carpenter
ElevateBio, USA

Carlos-Filipe Pereira
Lund University - Wallenberg Centre for Molecular Medicine, Sweden

5:15 PM – 5:20 PM
TOPIC OVERVIEW

5:20 PM – 5:40 PM
Melissa Carpenter
ElevateBio, USA

DEVELOPING PLURIPOTENT STEM CELL-DERIVED THERAPIES

5:40 PM – 5:50 PM
V. Alexandra Moser
Cedars Sinai Medical Center, USA

IPSC-DERIVED IMMUNE CELLS IMPROVE COGNITION AND NEURAL HEALTH IN AGING MICE

THURSDAY, 16 JUNE *(continued)*

5:50 PM – 6:00 PM

Stefan Irion
BlueRock Therapeutics, USA

A UNIVERSAL APPROACH TO TREAT CNS MANIFESTATIONS IN LYSOSOMAL STORAGE DISEASES USING IPSC-DERIVED MICROGLIA

6:00 PM – 6:10 PM

Michal Izrael
Kadimastem LTD, Israel

SAFETY AND EFFICACY OF FIRST-IN-HUMAN INTRATHECAL TRANSPLANTATION OF HUMAN ASTROCYTES (ASTRORX) DERIVED FROM EMBRYONIC STEM CELLS IN ALS PATIENTS: FROM BENCH TO BEDSIDE.

6:10 PM – 6:20 PM

Fei Yi
Ambys Medicines, USA

RESCUE OF A METABOLIC LIVER DISEASE MODEL BY GENETICALLY ENGINEERED HYPOIMMUNOGENIC HUMAN HEPATOCYTES

6:20 PM – 6:30 PM

Clive N. Svendsen
Cedars-Sinai, USA

A NEW TRIAL TRANSPLANTING NEURAL PROGENITORS MODIFIED TO RELEASE GDNF INTO THE MOTOR CORTEX OF PATIENTS WITH ALS

6:30 PM – 6:50 PM

Filipe Pereira
Lund University, Sweden

DEVELOPMENT OF A CANCER IMMUNOTHERAPY BASED ON DENDRITIC CELL REPROGRAMMING

5:15 PM – 7:00 PM

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD) Room 2011, Level 2

MODELING ORGANOGENESIS AND DEVELOPMENTAL DISORDERS
Session Sponsored by: NanoString Technologies

Session Chairs: Paul Gadue
Children's Hospital of Philadelphia, USA

Andrew McMahon
University of Southern California, USA

5:15 PM – 5:20 PM

TOPIC OVERVIEW

Session Chairs: Paul Gadue
Children's Hospital of Philadelphia, USA

Andrew McMahon
University of Southern California, USA

5:20 PM – 5:40 PM

Paul Gadue
Children's Hospital of Philadelphia, USA

EXAMINATION OF THE ROLE OF TBX3 AND TBX2 IN PANCREATIC BETA CELL DEVELOPMENT

5:40 PM – 5:50 PM

Seungmae Seo
Columbia University, USA

HELICASE VARIANTS ALTER THE TRAJECTORY OF NK CELL DEVELOPMENT FROM THE EARLIEST PRECURSORS

THURSDAY, 16 JUNE *(continued)*

5:50 PM – 6:00 PM
Lennart Schneider
University Medical Center, Germany

FUNCTIONAL CONNECTIVITY OF SYMPATHETIC NEURONS WITH CARDIOMYOCYTES IN A HUMAN IPSC-DERIVED INNERVATED CARDIAC MUSCLE MODEL

6:00 PM – 6:10 PM
Adriana Beltran
University of North Carolina at Chapel Hill, USA

CHARACTERIZATION OF DARK KINASES IMPLICATED IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

6:10 PM – 6:20 PM
Bruna Paulsen
Harvard University, USA

AUTISM GENES CONVERGE ON ASYNCHRONOUS DEVELOPMENT OF SHARED NEURON CLASSES

6:20 PM – 6:30 PM
Andrea Carlo Rossetti
Central Institute of Mental Health, Germany

CAPTURING THE PATHOMECHANISMS OF DIFFERENT DISEASE SEVERITIES IN A HUMAN CEREBRAL ORGANOID MODEL OF LIS1-LISSENCEPHALY

6:30 PM – 6:50 PM
Andrew McMahon
University of Southern California, USA

DEVELOPMENTAL STRATEGIZING TOWARDS KIDNEY DISEASE MODELING

5:15 PM – 7:00 PM
TRACK: NEW TECHNOLOGIES (NT) Room 2012, Level 2
PREDICTIVE MODELS OF STEM CELL BEHAVIOR

Session Chairs: Michael Stumpf
University of Melbourne, Australia

Roser Vento-Tormo
Wellcome Sanger Institute, UK

5:15 PM – 5:20 PM
TOPIC OVERVIEW

5:20 PM – 5:40 PM
Michael Stumpf
University of Melbourne, Australia

MOLECULAR NOISE AND THE ROBUSTNESS OF CELL FATE DECISION DYNAMICS

5:40 PM – 5:50 PM
Himanshu Kaul
University of Leicester, UK

VIRTUAL CELLS IN VIRTUAL MICROENVIRONMENT REVEAL HOW GRN INTERACTIONS MEDIATE TISSUE PATTERNS DURING HUMAN PLURIPOTENT STEM CELL DIFFERENTIATION

5:50 PM – 6:00 PM
Giridhar Anand
Harvard University, USA

CONTROLLED SPATIAL COUPLING OF ORGANOIDS UNCOVERS MECHANISMS OF HUMAN AXIAL ELONGATION

THURSDAY, 16 JUNE *(continued)*

6:00 PM – 6:10 PM

Daniel Aguilar Hidalgo
University of British Columbia, Canada

GROWTH CONTROL AND SCALING OF MESENDODERM IN MICRO-PATTERNED MOUSE PLURIPOTENT STEM-CELL COLONIES

6:10 PM – 6:20 PM

Yuting Wang
Stanford University, USA

A NEW SPATIAL SINGLE CELL TRANSCRIPTOMICS METHOD FOR DETECTING SIGNALING RELATIONSHIPS IN STEM CELL NICHES

6:20 PM – 6:30 PM

Brett Kagan
Cortical Labs, Australia

IN VITRO NEURONS EXHIBIT GOAL-DIRECTED LEARNING WHEN EMBODIED IN A SIMULATED GAME-WORLD: A SYSTEM FOR TESTING THE COMPUTATIONAL PROPERTIES OF SYNTHETIC NEURONS.

6:30 PM – 6:50 PM

Roser Vento-Tormo
Wellcome Sanger Institute, UK

MAPPING TISSUES IN VIVO AND IN VITRO

5:15 PM – 7:00 PM

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC) AGING AND REGENERATION Room 2007, Level 2
Session Sponsored by: UCSF Bakar Aging Research Institute

Session Chairs: Celina Juliano
University of California, Davis, USA

Emi Nishimura
Tokyo Medical and Dental University, Japan

5:15 PM – 5:20 PM

TOPIC OVERVIEW

5:20 PM – 5:40 PM

Emi Nishimura
The University of Tokyo, Japan

STEM CELL COMPETITION AND SENOLYTIC CELL ELIMINATION PROMISE AGELESS REGENERATION OF THE EPIDERMIS

5:40 PM – 5:50 PM

Ling Liu
University of California Los Angeles, USA

EXERCISE REPROGRAMS THE INFLAMMATORY LANDSCAPE OF MULTIPLE STEM CELL COMPARTMENTS DURING MAMMALIAN AGING

5:50 PM – 6:00 PM

Sarah Lloyd
Northwestern University, USA

A MOLECULAR SWITCH OF SEC-PTEFB ACTIVITY CONTROLS PROGENITOR SELF-RENEWAL VERSUS DIFFERENTIATION INITIATION

6:00 PM – 6:10 PM

John Mariani
University of Rochester, USA

AGE ASSOCIATED INDUCTION OF SENESCENT TRANSCRIPTIONAL PROGRAMS IN HUMAN GLIAL PROGENITOR CELLS

THURSDAY, 16 JUNE *(continued)*

6:10 PM – 6:20 PM

Rui Yi
Northwestern University, USA

MICRORNA-205 PROMOTES HAIR REGENERATION BY MODULATING CELL CONTRACTILITY AND MECHANOSENSITIVITY

6:20 PM – 6:30 PM

Ayelet Voskoboynik
Stanford University, USA

THE TICKING CLOCK, AN AGING STUDY OF A COLONIAL CHORDATE LINKS STEM CELL AGING TO MOLECULAR DECLINE OF CIRCADIAN REGULATION.

6:30 PM – 6:50 PM

Celina Juliano
University of California, Davis, USA

MECHANISMS OF DEVELOPMENT AND REGENERATION IN HYDRA

7:30 PM – 9:30 PM

20TH ANNIVERSARY CELEBRATION
Advance registration required
Offsite: City View at Metreon
135 4th Street, Suite 4000
San Francisco, CA

Co-Host: STEMCELL™ TECHNOLOGIES

Contributing Sponsor: SARTORIUS

Supporting Sponsors:

GLADSTONE INSTITUTES — SCIENCE OVERCOMING DISEASE; Notch THERAPEUTICS; UCSF Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research

Friends: Ajinomoto, Astellas, Axol Bioscience, bit.bio, Cedars-Sinai Boar of Governors regenerative Medicine Institute, Kuhner Shaker, Thrive Bioscience

9:30 PM – 11:00 PM

EARLY CAREER SCIENTISTS AFTER PARTY
Early Career scientist event
Offsite: City View at Metreon

FRIDAY, 17 JUNE

8:00 AM – 8:30 AM **INNOVATION SHOWCASES** **(See page 101 for details)**

8:00 AM – 8:30 AM **A SERUM-FREE, CHEMICALLY-DEFINED WORKFLOW SOLUTION FOR T CELL CULTURE AND CHARACTERIZATION** Room 2008, Level 2
Presented by BioLegend

Jessie Ni
BioLegend, USA

8:00 AM – 8:30 AM **BREAKFAST + iPSCS: FROM 2D CELL LINE DEVELOPMENT TO 3D ORGANOIDS, AUTOMATE AND SIMPLIFY COMPLEX iPSC WORKFLOWS USING THE CELLRAFT AIR® SYSTEM** Room 2003, Level 2
Presented by Cell Microsystems

Jessica Hartman
Cell Microsystems, USA

8:00 AM – 8:30 AM **INNOVATION SHOWCASE - FAST, GENTLE AND EASY SINGLE CELL SORTING: A BENCHTOP SOLUTION FOR CELL ENGINEERING** Room 2011, Level 2
Presented by Namocell Inc.

8:00 AM – 8:30 AM **SURROZEN - WNT MODULATING ANTIBODIES FOR TISSUE REGENERATION** Room 2004, Level 2
Presented by Surrozen, Inc.

Trudy Vanhove
Surrozen Inc, USA

8:00 AM – 8:30 AM **INTEGRATED iPSC AND GENOME ENGINEERING SOLUTIONS TO ADVANCE NEXT GENERATION REGENERATIVE THERAPIES** Room 2012, Level 2
Presented by ElevateBio

Austin Thiel
ElevateBio, USA
Clare Murray
Life Edit Therapeutics, UK

8:00 AM – 8:30 AM **SYNTHETIC PEPTIDE GROWTH FACTORS – FORGING THE PATH FORWARD FOR CELL THERAPY AND REGENERATIVE MEDICINE** Room 2007, Level 2
Presented by PeptiGrowth

Jes G. Kuruvilla
Mitsubishi International Food Ingredients, USA

Jiro Max Sugimoto
PeptiGrowth Inc - Mitsubishi Corporation, Japan

8:00 AM – 8:30 AM **THE EBiSC ONE-STOP-SHOP – HOW EBiSC'S OPERATIONS SUPPORT SHARING AND SAFEGUARDING OF HIPSC **** Virtual
Presented by European Bank for induced pluripotent Stem Cells (EBiSC)

Alex Ashby-Lumsden
European Collection of Authenticated Cell Culture (DH-ECACC), UK

Sabine Müller
Fraunhofer Institute for Biomedical Engineering (IBMT), Germany

Ralf Kettenhofen
Fraunhofer Institute for Biomedical Engineering (IBMT), Germany

FRIDAY, 17 JUNE *(continued)*

Andreas Kurtz
Fraunhofer Institute for Biomedical Engineering (IBMT), Germany

Zameel Cader
University of Oxford, UK

Charles Arber
University College London, UK

Eugenia Jones
Fujifilm Cellular Dynamics, Inc., USA

Minal Patel
Wellcome Trust Sanger Institute, UK

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

8:00 AM – 8:30 AM **RELIABLE IN VITRO CULTURE SOLUTIONS FOR YOUR ALVEOLAR RESEARCH*** Room 2001, Level 2
Presented by STEMCELL Technologies Inc.

Johanna Finn, PhD
STEMCELL Technologies Inc., Canada

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

8:30 AM – 9:00 AM **MORNING COFFEE** Level 3

9:00 AM – 10:35 AM **TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)**
PLENARY IV: DEFINING STEM CELLS ACROSS SPACE AND TIME
Sponsored by: Salk Institute for Biological Studies

Session Chairs: Valentina Greco
Yale University, USA

Crystal Rogers
University of California, Davis, USA

9:00 AM – 9:05 AM **PLENARY IV INTRODUCTION**

9:05 AM – 9:25 AM **Tina Mukherjee**
Institute for Stem Cell Science and Regenerative Medicine (inStem), India

AN UNDERSTANDING OF BLOOD PROGENITOR DEVELOPMENT THROUGH THE LENSES OF SENSORY PERCEPTION

9:25 AM – 9:45 AM **Sasha Mendjan**
Institute of Molecular Biotechnology (IMBA), Austria

CARDIOIDS UNRAVEL MECHANISMS OF COMPARTMENT-SPECIFIC HEART DEFECTS

9:45 AM – 10:05 AM **Tatjana Sauka-Spengler**
University of Oxford, UK

USING FUNCTIONAL GENOMICS TO DECODE GENE REGULATORY CIRCUITRY IN DEVELOPMENT

10:05 AM – 10:25 AM **Alejandro Sanchez Alvarado**
Stowers Institute for Medical Research, USA

UNDERSTANDING THE SOURCES OF REGENERATIVE CAPACITY IN ANIMALS

FRIDAY, 17 JUNE *(continued)*

11:00 AM – 11:45 AM

MEET-UP HUBS **(See page 26 for details)**
STEM CELL PODCAST: MEET THE HOSTS
Session Organized by: STEMCELL Technologies
Meet-up Hub #1

11:00 AM – 11:45 AM

BUILDING RELATIONS WITH RENEW
Meet-up Hub #2

11:00 AM – 5:00 PM

EXHIBIT & POSTER HALL OPEN

11:30 AM – 12:30 PM

INNOVATION SHOWCASES **(See page 101 for details)**

11:30 AM – 12:30 PM

ADDING THE EXTRA DIMENSION: DEVELOPING A 3D CULTURE MEDIUM AND SCALABLE BIOMANUFACTURING OF EMBRYOID BODIES TOWARDS ORGAN ENGINEERING Room 2008, Level 2
Presented by Sartorius

Sharon Daniliuc
Sartorius Stedim Biotech, Israel
Mark Skylar-Scott
Stanford University, USA
Debbie Ho
Stanford University, USA

11:30 AM – 12:30 PM

IF MICE LIE AND MONKEY'S EXAGGERATE WHAT ABOUT iPSCS?: A PANEL DISCUSSION ON ADDRESSING THE CELL PROBLEM WITHIN RESEARCH AND DRUG DISCOVERY Room 2003, Level 2
Presented by bit.bio

11:30 AM – 12:30 PM

INNOVATION SHOWCASE – EMULATE* Room 2011, Level 2
Presented by Emulate

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

11:30 AM – 12:30 PM

NEXT-GENERATION IN-VITRO ASSAYS: CHARACTERIZING THE ACTIVITY OF HUMAN IPSC-DERIVED NEURONS IN 2D AND 3D CULTURES AT HIGH RESOLUTION* Room 2001, Level 2
Presented by MaxWell Biosystems

Urs Frey
MaxWell Biosystems , Switzerland

Marie Obien
MaxWell Biosystems, Switzerland

Bruna Paulsen
Harvard University, USA

PRESENTERS (Virtual):

David Jackel
MaxWell Biosystems, Switzerland

David Pamies
University of Lausanne, Switzerland

Kenta Shimba
University of Tokyo, Japan

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

FRIDAY, 17 JUNE *(continued)*

11:30 AM – 12:30 PM — **THE HUMAN TRIAL: BEHIND EVERY BREAKTHROUGH ARE THOSE WHO RISK EVERYTHING FOR EVERYBODY ELSE** — Virtual

Presented by Americans for Cures

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

11:30 AM – 12:30 PM — **NEW ADVANCES IN INTESTINAL ORGANOID APPLICATIONS: DRUG DISCOVERY AND IMMUNOTHERAPY*** — Room 2007, Level 2

Presented by STEMCELL Technologies Inc.

Ryan Conder
STEMCELL Technologies Inc., Canada

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

11:30 AM – 12:30 PM — **PRECLINICAL STUDY OF ORGANOID BASED REGENERATIVE MEDICINE(ATORM) AND CONSIDERATION FOR FIRST-IN-HUMAN TRIALS** — Room 2004, Level 2

Presented by ORGANOIDSCIENCES

ORGANOIDSCIENCES

Kyung Jin Lee
ORGANOIDSCIENCES, Korea

11:30 AM – 12:30 PM — **SONY CGX10 CELL ISOLATION SYSTEM: AN INTRODUCTION AND EXAMPLES OF USE IN PROTOCOLS FOR GENERATING CELL THERAPY PRODUCTS USING MULTIPARAMETRIC SELECTION*** — Room 2012, Level 2

Presented by Sony Biotechnology Inc.

Aditi Singh
Sony Biotechnology Inc., USA
Manoja Eswara
CCRM, Canada

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

1:00 PM – 2:45 PM — **CONCURRENT TRACK SESSIONS**

1:00 PM – 2:45 PM — **TRACK: MODELING DEVELOPMENT AND DISEASE (MDD) MODELING DEGENERATIVE DISEASES AND CANCER** — Room 2011, Level 2

Session Sponsored by: bit.bio

Session Chairs: April Craft
Boston Children's Hospital, USA

Mina Gouti
Max Delbrück Center for Molecular Medicine, Berlin, Germany

1:00 PM – 1:05 PM — **TOPIC OVERVIEW**

1:05 PM – 1:25 PM — **Mina Gouti**
Max Delbrück Center (MDC), Germany

NEUROMUSCULAR ORGANOIDS TO STUDY HUMAN DEVELOPMENT AND DISEASE

1:25 PM – 1:35 PM — **Nadja Zeltner**
University of Georgia, USA

GENIPIN RESCUES SENSORY NEURON DEFECTS IN FAMILIAL DYSAUTONOMIA VIA CROSSLINKING OF EXTRACELLULAR MATRIX PROTEINS

FRIDAY, 17 JUNE *(continued)*

1:35 PM – 1:45 PM

Evangelos Kiskinis
Northwestern University, USA

ARTIFICIAL EXTRACELLULAR MATRIX SCAFFOLDS ENHANCE THE MATURATION AND AGING OF HUMAN STEM CELL DERIVED NEURONS AND ENABLE THE MODELING OF NEURODEGENERATIVE DISEASE PATHOLOGY

1:45 PM – 1:55 PM

Cleide Souza
The University of Sheffield, UK

DECODING NEURONAL VULNERABILITY AND RESILIENCE IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

1:55 PM – 2:05 PM

Nidhi Bhutani
Stanford University, USA

SINGLE CELL PROTEOMIC ATLAS OF CARTILAGE REVEALS MULTIPLE REGENERATIVE AND PATHOLOGICAL POPULATIONS

2:05 PM – 2:15 PM

Carla Bertulfo
Columbia University Medical Center, USA

CIRCUMVENTING INTESTINAL STEM CELL DIFFERENTIATION UPON NOTCH INHIBITION IN THE TREATMENT OF T CELL ACUTE LYMPHOBLASTIC LEUKEMIA

2:15 PM – 2:35 PM

April Craft
Boston Children's Hospital, USA

REGENERATIVE POTENTIAL AND STABILITY OF HPSC-DERIVED ARTICULAR CARTILAGE

1:00 PM – 2:45 PM

TRACK: NEW TECHNOLOGIES (NT) Room 2012, Level 2

MODELING STEM CELLS THROUGH SPACE AND TIME
Session Sponsored by: Dana-Farber Cancer Institute

Session Chairs: Daniel Wagner
University of California, San Francisco, USA

Nozomu Yachie
University of British Columbia, Canada

1:00 PM – 1:05 PM

TOPIC OVERVIEW

1:05 PM – 1:25 PM

Nozomu Yachie
University of British Columbia, Canada

TOWARDS DEVELOPMENT OF A HD VIDEO RECORDER OF THE CELL

1:25 PM – 1:35 PM

Julian Pulecio
Memorial Sloan Kettering Cancer Center, USA

ELUCIDATING THE MOLECULAR BASIS OF DEVELOPMENTAL COMPETENCE DURING HESC LINEAGE-SPECIFICATION

1:35 PM – 1:45 PM

Seth Teague
University of Michigan, USA

SINGLE CELL TRACKING SHOWS INTEGRATED BMP SIGNALING PREDICTS FATE IN HUMAN PLURIPOTENT STEM CELLS

FRIDAY, 17 JUNE *(continued)*

1:45 PM – 1:55 PM
Sophie Shen
University of Queensland, Australia

ENGINEERED BARCODE IPSCS COUPLED WITH UNSUPERVISED DATA ANALYSIS PIPELINES FOR SCALABLE ANALYSIS OF MULTI-LINEAGE CELL DIFFERENTIATION

1:55 PM – 2:05 PM
Sarah Bowling
Boston Children's Hospital, USA

HIGH RESOLUTION MAPPING OF CELL LINEAGES DURING MOUSE GASTRULATION

2:05 PM – 2:15 PM
Nisha Iyer
University of Wisconsin, USA

INVESTIGATING PHENOTYPIC DIVERSITY OF THE HUMAN POSTERIOR CNS USING STEM CELLS AND SINGLE-CELL RNA-SEQUENCING

2:15 PM – 2:35 PM
Daniel Wagner
University of California, San Francisco, USA

WHOLE EMBRYO-BARCODING FOR GENETIC INTERROGATION OF VERTEBRATE DEVELOPMENT

1:00 PM – 2:45 PM
TRACK: TISSUE STEM CELLS AND REGENERATION (TSC) Room 2007, Level 2

MOLECULAR CONTROL OF CELL FATE TRANSITIONS

Session Chairs: Dasaradhi Palakodeti
Institute for Stem Cell Science and Regenerative Medicine, India

Rosa Uribe
Rice University, USA

1:00 PM – 1:05 PM
TOPIC OVERVIEW

1:05 PM – 1:25 PM
Dasaradhi Palakodeti
Institute for Stem Cell Science and Regenerative Medicine, India

MITOCHONDRIAL STATES ARE CRITICAL TO DEFINE STEM CELL HETEROGENEITY IN PLANARIA

1:25 PM – 1:35 PM
Peng He
EMBL-EBI/Wellcome Sanger Institute, UK

A HUMAN FETAL LUNG CELL ATLAS UNCOVERS HIDDEN STATES AND KEY REGULATORS OF EPITHELIAL FATES

1:35 PM – 1:45 PM
Vaibhao Janbandhu
Victor Chang Cardiac Research Institute, Australia

HIF-1A REGULATES CARDIAC FIBROBLAST (CF)-STATE TRANSITIONS

1:45 PM – 1:55 PM
Rita Alves
Lund University, Sweden

GATA2 AT MITOSIS-TO-G1 TRANSITION IS CRITICAL FOR DEFINITIVE HEMATOPOIESIS

1:55 PM – 2:05 PM
Maria Bejar
University of Cambridge, UK

REGENERATIVE CHECKPOINTS REGULATE EPITHELIAL CELL FATE PLASTICITY IN A MODEL OF ESOPHAGEAL-TO-SKIN LINEAGE CONVERSION

FRIDAY, 17 JUNE *(continued)*

2:05 PM – 2:15 PM

Jonathan Lerner
University of Pennsylvania, USA

BASIS OF CHROMATIN SCANNING BY PIONEER TRANSCRIPTION FACTORS

2:15 PM – 2:35 PM

Rosa Uribe
Rice University, USA

IN TOTO IMAGING OF EARLY ENTERIC NERVOUS SYSTEM DEVELOPMENT REVEALS THAT RET REGULATES THE TRANSITION FROM PROLIFERATION TO DIFFERENTIATION OF ENTERIC NEURAL CREST

1:00 PM – 2:45 PM

TRACK: CELLULAR IDENTITY (CI) Room 2008, Level 2

SPHEROIDS AND ORGANOIDS
Session Sponsored by: Cell Microsystems

Session Chairs: Kunyoo Shin
Seoul National University, Korea

Jun Wu
University of Texas Southwestern Medical Center, USA

1:00 PM – 1:05 PM

TOPIC OVERVIEW

1:05 PM – 1:25 PM

Kunyoo Shin
Seoul National University, Korea

CREATION OF TISSUE ASSEMBLOIDS THAT RECAPITULATE IN VIVO TISSUE DYNAMICS AND CANCER

1:25 PM – 1:35 PM

Jessica Vanslambrouck
Murdoch Children's Research Institute, Australia

IMPROVED PROXIMAL TUBULE MATURATION AND CONTROL OF NEPHRON ALIGNMENT IN KIDNEY ORGANOIDS

1:35 PM – 1:45 PM

Shunsuke Tanigawa
Kumamoto University, Japan

GENERATION OF THE ORGANOTYPIC KIDNEY STRUCTURE SOLELY FROM PLURIPOTENT STEM CELLS

1:45 PM – 1:55 PM

Davide Marotta
The New York Stem Cell Foundation, USA

EFFECTS OF MICROGRAVITY ON HUMAN IPSC-DERIVED 3D BRAIN MODELS OF PARKINSON'S DISEASE AND MULTIPLE SCLEROSIS

1:55 PM – 2:05 PM

Ivana Matkovic Leko
Columbia University, USA

GENERATION OF PULMONARY TYPE II ALVEOLAR EPITHELIAL CELLS FROM HUMAN PLURIPOTENT STEM CELLS WITHOUT INTERMEDIATE ENRICHMENT STEPS

2:05 PM – 2:15 PM

Yuchuan Miao
Brigham and Women's Hospital, USA

RECONSTRUCTION OF HUMAN SOMITOGENESIS WITH PLURIPOTENT STEM CELLS

FRIDAY, 17 JUNE *(continued)*

2:15 PM – 2:35 PM

Jun Wu
University of Texas Southwestern Medical Center, USA

MODELING EARLY HUMAN DEVELOPMENT BY INTEGRATED STEM CELL BASED EMBRYO MODELS

1:00 PM – 2:45 PM

TRACK: CLINICAL APPLICATIONS (CA) Room 2004, Level 2
STEM CELLS - FROM DEVELOPMENT TO THERAPY
Session Sponsored by: WiCell

Session Chairs: Gordon Keller
McEwen Stem Cell Institute, University Health Network, Canada

Agnete Kirkeby
University of Copenhagen, Denmark

1:00 PM – 1:05 PM

TOPIC OVERVIEW

1:05 PM – 1:25 PM

Gordon Keller
McEwen Stem Cell Institute, University Health Network, Canada

MODELING HUMAN DEVELOPMENT FOR NEW CELL THERAPIES

1:25 PM – 1:35 PM

Hsiao-Yun Liu
Columbia University Medical Center, USA

ENGRAFTMENT OF HPSC-DERIVED LUNG PROGENITORS IN A XENO-TRANSPLANT MODEL CONDITIONED BY DE-EPITHELIALIZATION

1:35 PM – 1:45 PM

Blair Gage
McEwen Stem Cell Institute, Canada

THERAPEUTIC CORRECTION OF HEMOPHILIA A BY TRANSPLANTATION OF HPSC-DERIVED LSEC PROGENITORS

1:45 PM – 1:55 PM

Hideyuki Okano
Keio University School of Medicine, Japan

FIRST-IN-HUMAN CLINICAL TRIAL OF TRANSPLANTATION OF IPSC-DERIVED NS/PCS IN SUBACUTE COMPLETE SPINAL CORD INJURY: THE FIRST CASE

1:55 PM – 2:05 PM

Cory Nicholas
Neurona Therapeutics, USA

HUMAN INHIBITORY NEURON CELL THERAPY ENTERS PHASE I/II CLINICAL INVESTIGATION FOR CHRONIC FOCAL EPILEPSY

2:05 PM – 2:15 PM

Tamra Lysaght
Center for Biomedical Ethics, National University of Singapore, Singapore

ENCOURAGING RESPONSIBLE STEM CELL RESEARCH AND INNOVATION WITH ANTICIPATORY GOVERNANCE AND FORESIGHT

2:15 PM – 2:35 PM

Agnete Kirkeby
University of Copenhagen, Denmark

DEVELOPING A DOPAMINERGIC CELL THERAPY FOR PARKINSON'S DISEASE

FRIDAY, 17 JUNE *(continued)*

3:00 PM – 5:00 PM **REFRESHMENT BREAK**
Exhibit & Poster Hall, Ground Floor

3:00 PM – 4:00 PM **POSTER SESSION III ODD**
Exhibit & Poster Hall, Ground Floor

3:15 PM – 3:30 PM **MICRO-THEATER: CELLINK**
Wei Zhu
Allegro 3D, USA

DEVELOPING PATIENT SPECIFIC TISSUE MODELS USING A HIGH THROUGHPUT LIGHT-BASED BIOPRINTER
Exhibit & Poster Hall, Ground Floor

3:45 PM – 4:00 PM **MICRO-THEATER: EPPENDORF SE**
Philipp Nold
Eppendorf SE, Germany

FUELING AUTOMATED HIPSC PRODUCTION IN STIRRED-TANK BIOREACTORS BY EXPLOITING MULTI PROCESS PARAMETER MONITORING AND FEEDBACK-BASED PROCESS REGULATION
Exhibit & Poster Hall, Ground Floor

4:00 PM – 5:00 PM **POSTER SESSION III EVEN**
Exhibit & Poster Hall, Ground Floor

4:15 PM – 5:00 PM **MICRO-THEATER: ISSCR - PROMOTING DIVERSITY IN STEM CELL MODELS**
Exhibit & Poster Hall, Ground Floor

5:15 PM – 7:20 PM **TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)** Level 3
PLENARY V: DISENTANGLING SINGLE CELL CONTRIBUTIONS TO ORGANOGENESIS AND PATHOLOGY

Session Chairs: Shaorong Gao
Tongji University, China

Anne Grapin-Botton
Max Planck Institute of Molecular Biology and Genetics, Germany

5:15 PM – 5:20 PM **PLENARY V INTRODUCTION**

5:20 PM – 5:40 PM **Muzlifah Haniffa**
Newcastle University, UK

DECODING THE DEVELOPING HUMAN IMMUNE SYSTEM

5:40 PM – 6:00 PM **April Pyle**
University of California, Los Angeles, USA

HUMAN MYOGENESIS IN DEVELOPMENT AND DISEASE

6:00 PM – 6:20 PM **Jürgen Knoblich**
Institute of Molecular Biotechnology of the Austrian Academy of Science, Austria

GENETIC CRISPR/CAS9 SCREENING IN CEREBRAL ORGANOIDS BY SINGLE CELL TRANSCRIPTOMICS

FRIDAY, 17 JUNE *(continued)*

6:20 PM – 6:40 PM

Xiaoqun Wang
Institute of Biophysics, Chinese Academy of Science, China

VASCULARIZED HUMAN CORTICAL ORGANOIDS (VORGANOID) MODEL CORTICAL DEVELOPMENT IN VIVO

6:40 PM – 7:15 PM

Lorenz Studer
Memorial Sloan Kettering Cancer Center, NY, USA

ISSCR ACHIEVEMENT AWARD LECTURE: BEYOND FATE – MANIPULATING MATURATION AND AGE IN HPSC-DERIVED LINEAGES

SATURDAY, 18 JUNE

8:30 AM – 9:00 AM **MORNING COFFEE** Level 2

9:00 AM – 10:45 AM **CONCURRENT TRACK SESSIONS**

9:00 AM – 10:45 AM **TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)** Room 2011, Level 2

IMMUNOLOGICAL RESPONSES TO FIGHT INFECTION AND DISEASE

Session Sponsored by: Synthego

Session Chairs: Sina Bartfeld
Technische Universität Berlin, Germany

Dan Kaufman
University of California, San Diego, USA

9:00 AM – 9:05 AM **TOPIC OVERVIEW**

9:05 AM – 9:25 AM **Dan Kaufman**
University of California, San Diego, USA

IDENTIFICATION OF NOVEL REGULATORS OF NK CELL-MEDIATED ANTI-TUMOR RESPONSES

9:25 AM – 9:35 AM **Kyle Loh**
Stanford University, USA

HUMAN PLURIPOTENT STEM CELLS PROVIDE A NEW TOOLKIT TO STUDY BIOSAFETY LEVEL 4 (BSL4) VIRUSES

9:35 AM – 9:45 AM **Nadia Rajab**
University of Melbourne, Australia

BENCHMARKING AND DEVELOPING HUMAN PLURIPOTENT STEM CELL MODELS OF MACROPHAGE BIOLOGY

9:45 AM – 9:55 AM **Sharon Fleischer**
Columbia University, USA

RECAPITULATING PATIENT-SPECIFIC AUTOIMMUNE MEDIATED HEART DISEASE WITH IPSC-DERIVED ENGINEERED CARDIAC TISSUE MODELS

9:55 AM – 10:05 AM **Daniel Veronese-Paniagua**
Washington University in St. Louis, USA

UTILIZING HUMAN STEM CELL-DERIVED ISLETS AS A MODEL TO STUDY THE ROLE OF IFIH1 IN ISLET RESPONSE TO COXSACKIEVIRUS B INFECTION

10:05 AM – 10:15 AM **Andrew Khalil**
Harvard University, USA

A FULLY DEFINED HUMAN PLURIPOTENT STEM CELL-DERIVED VASCULAR MODEL ELUCIDATES MECHANISMS OF VASCULAR DYSFUNCTION CAUSED BY COVID-19

10:15 AM – 10:35 AM **Sina Bartfeld**
Technische Universität Berlin, Germany

INFECTION, INNATE IMMUNE SIGNALING AND CANCER IN THE GUT

SATURDAY, 18 JUNE *(continued)*

9:00 AM – 10:45 AM

TRACK: NEW TECHNOLOGIES (NT) Room 2012, Level 2

MANUFACTURING AND ADVANCED THERAPEUTIC PRODUCTS

Session Sponsored by: ARMI | BioFabUSA

Session Chairs: Azadeh Golipour
Avrobio, USA

Krishnendu Roy
Georgia Institute of Technology, USA

9:00 AM – 9:05 AM

TOPIC OVERVIEW

9:05 AM – 9:25 AM

Azadeh Golipour
Avrobio, USA

REDEFINING MANUFACTURING; BRINGING PERSONALIZED GENE THERAPY TO THE WORLD

9:25 AM – 9:35 AM

Kevin Ullmann
Hannover Medical School, Germany

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

9:35 AM – 9:45 AM

Kaivalya Molugu
Editas Medicine, USA

CHROMATIN MODULATION FOR EFFICIENT CRISPR-CAS9 GENE EDITING OF HUMAN PLURIPOTENT STEM CELLS

9:45 AM – 9:55 AM

Brian Coffin
Carnegie Mellon University, USA

HUMAN EMBRYOID BODY BIOINKS FOR FRESH 3D BIOPRINTING OF CONTRACTILE CARDIAC TISSUE

9:55 AM – 10:05 AM

Yao Gong
University of California, Los Angeles, USA

ACOUSTOFLUIDIC SONOPORATION GENE DELIVERY UTILIZING DNA-ENCAPSULATED SUPRAMOLECULAR NANOPARTICLES FOR GENE THERAPIES

10:05 AM – 10:15 AM

Roy Williams
Aspen Neuroscience, USA

DEVELOPMENT OF A BIOINFORMATICS-BASED TOOL, NEURITEST, FOR QUALITY CONTROL OF IPSC-DERIVED DOPAMINE NEURON PRECURSORS FOR TRANSPLANTATION

10:15 AM – 10:35 AM

Krishnendu Roy
Georgia Institute of Technology, USA

ENABLING QUALITY-BY-DESIGN (QBD)-DRIVEN MANUFACTURING OF CELL THERAPIES - THE ROLE OF DATA SCIENCE, IN/AT-LINE PROCESS AND PRODUCT ANALYTICS, AND FEEDBACK-CONTROLLED AUTOMATION

9:00 AM – 10:45 AM

TRACK: CELLULAR IDENTITY (CI) Room 2008, Level 2

PLURIPOTENT STEM CELLS

Session Sponsored by: Cellistic

Session Chairs: Nissim Benvenisty
Hebrew University, Israel

Thorold Theunissen
Washington University School of Medicine in St. Louis, USA

9:00 AM – 9:05 AM **TOPIC OVERVIEW**

9:05 AM – 9:25 AM **Nissim Benvenisty**
The Hebrew University, Israel

THE ESSENTIALOME OF HUMAN PLURIPOTENCY

9:25 AM – 9:35 AM **Wei-Ju Chen**
Academia Sinica, Taiwan

CHOLESTEROL BIOSYNTHETIC SIGNALING IN REGULATING PLURIPOTENCY AND EXTENDED PLURIPOTENCY

9:35 AM – 9:45 AM **Josephine Ferreon**
Baylor College of Medicine, USA

NANOG PRION-LIKE ASSEMBLY MEDIATES DNA BRIDGING

9:45 AM – 9:55 AM **Thorsten Boroviak**
University of Cambridge, UK

SPATIAL PROFILING OF EARLY PRIMATE GASTRULATION IN UTERO

9:55 AM – 10:05 AM **Maria Rostovskaya**
Babraham Institute, UK

AMNIOGENESIS OCCURS IN TWO INDEPENDENT WAVES IN PRIMATE EMBRYOS

10:05 AM – 10:15 AM **Silvia Santos**
Francis Crick Institute, UK

GATA3 IS AN EARLY COMMITMENT GENE IN HUMAN EMBRYONIC STEM CELL DIFFERENTIATION

10:15 AM – 10:35 AM **Thorold Theunissen**
Washington University School of Medicine in St. Louis, USA

UNDERSTANDING HUMAN PLURIPOTENT STEM CELL STATES AND THEIR APPLICATIONS

9:00 AM – 10:45 AM

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC) Room 2007, Level 2

PRINCIPLES OF TISSUE AND ORGAN REGENERATION

Session Sponsored by: Stanford Institute for Stem Cell Biology and Regenerative Medicine

Session Chairs: Hironobu Fujiwara
RIKEN Center for Biosystems Dynamics Research, Japan

Leanne Jones
University of California, San Francisco, USA

SATURDAY, 18 JUNE *(continued)*

9:00 AM – 9:05 AM **TOPIC OVERVIEW**

9:05 AM – 9:25 AM **Hironobu Fujiwara**
RIKEN Center for Biosystems Dynamics Research, Japan

TRACING THE DEVELOPMENTAL ORIGIN OF HAIR FOLLICLE STEM CELLS

9:25 AM – 9:35 AM **Antonio Tomasso**
Hubrecht Institute for Developmental Biology and Stem Cell Research, Netherlands

A MAPK/ERK-DEPENDENT MOLECULAR SWITCH ANTAGONIZES FIBROSIS AND PROMOTES REGENERATION IN SPINY MICE (ACOMYS)

9:35 AM – 9:45 AM **Laureen Hachem**
University of Toronto, Canada

GLUTAMATE ACTIVATES A PROLIFERATIVE AND ASTROGLIOGENIC PROGRAM IN EPENDYMAL STEM CELLS: IMPLICATIONS FOR REGENERATIVE THERAPEUTIC TRANSLATION

9:45 AM – 9:55 AM **Jessica Moore**
Yale School of Medicine, USA

G2 STEM CELLS ORCHESTRATE TIME-DIRECTED, LONG-RANGE COORDINATION OF CALCIUM SIGNALING DURING SKIN EPIDERMAL REGENERATION

9:55 AM – 10:05 AM **Christopher Gribben**
University of Cambridge

ACQUISITION OF CELLULAR PLASTICITY IN THE HUMAN LIVER DURING CHRONIC DISEASE PROGRESSION

10:05 AM – 10:15 AM **Yun-Kyo Kim**
Hospital for Sick Children, Canada

ABSOLUTE SCALING OF SINGLE-CELL TRANSCRIPTOMES REVEALS PERVASIVE HYPERTRANSCRIPTION IN ADULT STEM AND PROGENITOR CELLS

10:15 AM – 10:35 AM **Leanne Jones**
University of California, San Francisco, USA

METABOLIC REGULATION OF ADULT STEM CELL BEHAVIOR IN DROSOPHILA MELANOGASTER

9:00 AM – 10:45 AM **TRACK: CLINICAL APPLICATIONS (CA)** Room 2004, Level 2
PROGRAMMING AND REPROGRAMMING FOR REGENERATIVE MEDICINE
Session Sponsored by: T-CiRA Joint Program

Session Chairs: Eirini Trompouki
Institute for Research on Cancer and Aging, France

Clifford Woolf
Boston Children's Hospital, USA

9:00 AM – 9:05 AM **TOPIC OVERVIEW**

9:05 AM – 9:25 AM **Clifford Woolf**
Boston Children's Hospital, USA

EFFICIENT HUMAN SENSORY NEURON GENERATION FROM PLURIPOTENT STEM CELLS

SATURDAY, 18 JUNE *(continued)*

9:25 AM – 9:35 AM

Andrea Barabino
UDEM/Stem Axon, Canada

FIGHTING MACULAR DEGENERATION: PRECLINICAL STUDIES USING IPSC DERIVED RETINAL TISSUE IN LARGE ANIMALS

9:35 AM – 9:45 AM

Ran Jing
Harvard Medical School/Boston Children's Hospital, USA

GENERATION OF MATURE IPSC-DERIVED CAR T CELLS WITH ENHANCED ANTITUMOR ACTIVITY VIA EPIGENETIC REPROGRAMMING

9:45 AM – 9:55 AM

Elias Zambidis
The Johns Hopkins University School of Medicine, USA

FAR BEYOND JUST A WNT INHIBITOR: XAV939 GLOBALLY REPROGRAMS THE PROTEOME OF HUMAN NAÏVE STEM CELLS

9:55 AM – 10:05 AM

Sabiha Hacibekiroglu
Lunenfeld-Tanenbaum Research Institute/Sinai Health, Canada

ENGINEERED SAFE AND IMMUNE-TOLERANT RPE CELLS TOWARDS THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION

10:05 AM – 10:15 AM

Francesco Limone
Harvard Stem Cell Institute

EFFICIENT GENERATION OF LOWER INDUCED MOTOR NEURONS BY COUPLING NGN2 EXPRESSION WITH DEVELOPMENTAL CUES

10:15 AM – 10:35 AM

Eirini Trompouki
Institute for Research on Cancer and Aging, France

REPETITIVE ELEMENTS AS SIGNALS FOR DEVELOPMENTAL AND REGENERATIVE HEMATOPOIESIS

11:00 AM – 12:20 PM

CAREER PANEL LUNCHEON: MOLDING A MULTIDIMENSIONAL CAREER: VISION FOR THE NEXT 20
Room 2018, Level 2
Session Sponsored by: Lonza
Early career scientist event; Advance registration required

12:45 PM – 2:55 PM

TRACK: NEW TECHNOLOGIES (NT)
Level 3
PLENARY VI: TECHNOLOGIES THAT MODEL AND DIRECT EMERGENT CELL BEHAVIORS IN STEM CELL BIOLOGY AND REGENERATION BEHAVIORS

Session Chairs: Christine Wells
University of Melbourne, Australia

Peter Zandstra
University of British Columbia, BC, Canada

12:45 PM – 12:50 PM

PLENARY VI INTRODUCTION

12:50 PM – 1:10 PM

Alexander van Oudenaarden
Hubrecht Institute-KNAW & University Medical Center, Netherlands

SINGLE-CELL RIBOSOME PROFILING

SATURDAY, 18 JUNE *(continued)*

1:10 PM – 1:30 PM

Smita Krishnaswamy
Yale University, USA

GEOMETRIC AND TOPOLOGICAL APPROACHES TO REPRESENTATION LEARNING IN DEVELOPMENTAL DATA

1:30 PM – 1:50 PM

Gordana Vunjak-Novakovic
Columbia University, USA

ORGANS ON A CHIP PLATFORM WITH HUMAN TISSUE NICHES LINKED BY VASCULAR FLOW

1:50 PM – 2:10 PM

Satoshi Toda
Kanazawa University, Japan

PROGRAMMING MULTICELLULAR PATTERN FORMATION WITH SYNTHETIC CELL-CELL SIGNALING

2:10 PM – 2:45 PM

Joanna Wysocka
Stanford University School of Medicine, USA

ISSCR MOMENTUM AWARD LECTURE: FROM NUCLEOSOMES TO HUMAN FACES: MY JOURNEY IN STEM CELL BIOLOGY

3:00 PM – 3:30 PM **REFRESHMENT BREAK** Level 3

3:30 PM – 6:00 PM **TRACK: CLINICAL APPLICATIONS (CA)** Level 3

PLENARY VII: CELL AND GENE THERAPY IN THE CLINIC
Session Sponsored by: MaxWell Biosystems

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

Amander Clark
University of California, Los Angeles, USA

3:30 PM – 3:35 PM **PLENARY VII INTRODUCTION**

3:35 PM – 3:40 PM

Haifan Lin
Yale University School of Medicine, USA

PRESIDENT ELECT ADDRESS

3:40 PM – 3:50 PM

Physician: Donald B. Kohn
University of California, Los Angeles, USA

Patient Advocate: Alysia Vaccaro
Corona, California, USA

PATIENT ADVOCATE ADDRESS

3:50 PM – 4:10 PM

Luigi Naldini
San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) and San Raffaele University, Milan, IT, Italy

DEVELOPING NEW TRANSFORMING APPROACHES TO GENETIC ENGINEERING OF HEMATOPOIESIS TO BROADEN THE EFFICACY, FEASIBILITY AND SAFETY OF CLINICAL TRANSLATION

SATURDAY, 18 JUNE *(continued)*

4:10 PM – 4:35 PM
Masayo Takahashi
Vision Care Inc., Japan

JOHN MCNEISH MEMORIAL LECTURE: RETINAL CELL THERAPY AS A SUSTAINABLE CATEGORIZED MEDICINE

4:35 PM – 4:55 PM
Bob Valamehr
Fate Therapeutics, Inc, USA

PATH TO THE DEVELOPMENT OF IPSC-DERIVED OFF-THE-SHELF T AND NK CELLS FOR CANCER IMMUNOTHERAPY

4:55 PM – 5:15 PM
Gary Meininger
Vertex Pharmaceuticals, USA

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

5:15 PM – 5:45 PM
Priscilla Chan
Chan Zuckerberg Initiative, USA

KEYNOTE ADDRESS: BUILDING THE FUTURE OF SCIENCE

5:45 PM – 5:50 PM
POSTER AWARDS AND CLOSING

SUNDAY, 19 JUNE

8:30 AM – 1:30 PM
QUALITY STANDARDS FOR STEM CELL RESEARCH
Session Sponsored by: CIRM, STEMCELL Technologies, Synthego, and WiCell
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21 - 23 September 2022

KEYNOTE SPEAKERS

Donald Kohn, MD
UCLA, USA

Leslie Thompson, PhD
UC Irvine, USA

ISSCR BOSTON INTERNATIONAL SYMPOSIUM

Translating Pluripotent Stem Cell Discoveries to the Clinic: Preclinical, Manufacturing, and Regulatory Strategies for Success

17 - 19 November 2022

KEYNOTE SPEAKER

Peter Marks, MD, PhD
FDA Center for Biologics Evaluation and Research

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http://www.bioneer.dk
bioneer@bioneer.dk
Booth 640
Bioneer A/S is an innovative specialty CRO, creating customized research service solutions that meet your needs. We specialize in offering stem cell services, including reprogramming, CRISPR engineering and neuronal differentiation. With a team of dedicated and highly skilled employees, state-of-the-art laboratory facilities, we also offer assay development services to help bring your drug candidate to market faster.

BIOSPHERIX LTD.

25 Union Street
Parish, NY 13131 USA
http://biospherix.com/stem-cell
Booth 205
Manufacturer of hypoxia/physioxia equipment for physiologically relevant oxygen stem cell experiments. Explore options ranging from starter sets that upgrade existing CO2 incubators to advanced systems that replace traditional, non-physiologic Incubators, hoods, and BSCs. Stop by BioSpherix #205 and discover why 'Stem Cells Love #CytoCentric'. HYPOXIA / PHYSIOXIA / CONTROLLED OXYGEN and cGMP CELL PRODUCTION ENVIRONMENTS Chambers | Incubators | Glove Boxes | Cabinets | Workstations Options for: Any Budget | Any Protocol | Any Space

BIO-TECHNE

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614 McKinley Place NE
Minneapolis, MN 55413 USA
http://www.bio-techne.com
Booth 420
Bio-Techne empowers researchers by providing high-quality reagents, instruments, custom manufacturing, and testing services. Our family of brands, including R&D Systems™, Novus Biologicals™, Tocris Bioscience®, ProteinSimple® and ACD, deliver a large array of solutions tailored to your needs. Whether you are at the cutting-edge of academic research or at a facility that requires the highest level of diagnostic testing, our innovative products and services provide the solutions you need to succeed.

BIT.BIO

The Dorothy Hodgkin Bldg
Babraham Research Campus
Cambridge, England CB22 3FH UK
http://www.bit.bio/
Booth 827
bit.bio combines the concepts of coding and biology to provide human cells for research, drug discovery and cell therapy, enabling a new generation of medicines for every patient, everywhere. This is possible with our proprietary cell coding technology opti-oxTM- a breakthrough gene engineering approach that enables unlimited batches of any human cell to be manufactured consistently at scale through direct reprogramming of stem cells.

BLUECHIIP LIMITED

1 Dalmore Drive
Melbourne, Victoria 3179 Australia
http://www.bluechiip.com
sales@bluechiip.com
Booth 729
Bluechiip Advanced Sample Management Bluechiip's unique and patented technology is designed to operate across a wide temperature range from -196°C to over +100°C, creating the perfect system for managing sensitive samples. Bluechiip Enabled Sample Storage, Readers and Software combine to provide an unparalleled ability to track and store sample level data, including temperature across the cold chain process. Bluechiip understands that every sample is critical, our objective is to manage each one with optimal quality in the most efficient way. Bluechiip's solution is the only system providing sample temperature with ID in cryogenic environments to deliver confidence in every sample.

BLUEROCK THERAPEUTICS

1 Broadway
Cambridge, MA 02142 USA
www.bluerocktx.com
BlueRock Therapeutics is a leading engineered cell therapy company with a mission to create authentic cellular medicines to reverse devastating diseases, with the vision of improving the human condition. Our cell+gene platform harnesses the power of cells to create new medicines in neurology, cardiology, immunology and ophthalmology. Founded in 2016 by Versant Ventures and Bayer AG and fully acquired by Bayer in 2019, our culture is defined by the courage to persist regardless of the challenge, the urgency to transform medicine and deliver hope, integrity guided by mission, and community-mindedness with the understanding that we are all part of something bigger than ourselves.

BMG LABTECH

13000 Weston Parkway, Suite 109
Cary, NC 27513 USA
https://www.bmglabtech.com/
Booth 538
BMG LABTECH is a German-based company that focuses exclusively on microplate readers and our technological innovations have made us a leader in the field. We offer a variety of plate readers ranging from single-mode, absorbance detection readers to multi-detection readers with up to eight detection modes and our instruments are used for a multitude of applications in life science, drug discovery and research.

BRAINXELL, INC.

455 Science Drive, Suite 210
Madison, WI 53711 USA
http://www.brainxell.com
Booth 530
BrainXell provides iPSC-derived human neurons to the pharmaceutical industry and other research organizations for CNS drug discovery and development. Utilizing proprietary technology developed over the last two decades by Professor Su-Chun Zhang at the University of Wisconsin, we generate subtype-specific neurons that rapidly mature. Additionally, custom neuron batches at small to very large scale can be produced from any iPSC or ESC line provided.

BULLDOG BIO

One New Hampshire Avenue, Suite 125
Portsmouth, NH 03801 USA
http://www.bulldog-bio.com
Booth 322
On display will be the NEPA21 Electro-kinetic Transfection System. This one-of-a-kind electroporator is the gold standard for transferring large DNA plasmids and gene editing reagents into immortalized/primary cells. This includes iPSCs and other stem cell types. We'll also be demonstrating how the new PicoPipet (also from Nepa Gene) "pipets" individual cells, intact and alive from slide to culture plate and back.

BURROUGHS WELLCOME FUND

P.O. Box 13901
21 T.W. Alexander Drive
Research Triangle Park, NC 27709 USA
www.bwfund.org
The Burroughs Wellcome Fund serves and strengthens society by nurturing a diverse group of leaders in biomedical sciences to improve human health through education and powering discovery in frontiers of greatest need. Two BWF awards to highlight are the Innovation in Regulatory Science Award and the Career Awards at the Scientific Interface, a bridging award for postdocs transitioning from the physical sciences into biological sciences.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (CIRM)

PO Box 980790
West Sacramento, CA 95798-0790 USA
http://www.cirm.ca.gov
Booth 241
The California Institute for Regenerative Medicine (CIRM) was created by the people of California to accelerate stem cell treatments to patients with unmet medical needs, and act with a sense of urgency to succeed in that mission. To meet this challenge, our team of highly trained and experienced professionals actively partners with both academia and industry in a hands-on, entrepreneurial environment to fast track the development of today's most promising stem cell technologies. With $5.5 billion in funding and more than 150 active stem cell programs in our portfolio, CIRM is the world's largest institution dedicated to helping people by bringing the future of cellular medicine closer to reality.

CANCER TOOLS.ORG

100 Summer St, Ste 1600
Boston, MA 02110 USA
http://www.cancertools.org/
marketing@cancertools.org
Booth 209
Cancer Tools.org is a non-profit, global community of cancer researchers, academic institutes and societies, with a shared mission, to accelerate cancer research discoveries. In this collaborative, researchers contribute research tools and share knowledge to deepen our understanding of cancer, and drive innovation within cancer research.

CATALENT CELL & GENE THERAPY

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14 Schoolhouse Road
Somerset, NJ 08873 USA
http://www.catalent.com
Booth 132
Catalent Cell & Gene Therapy is a full-service partner for adeno-associated virus (AAV) vectors and CAR-T immunotherapies, with deep experience in viral vector scale-up and production. Catalent recently acquired MaSTherCell, adding expertise in autologous and allogeneic cell therapy development and manufacturing to position Catalent as a premier technology, development and manufacturing partner for innovators across the entire field of advanced biotherapeutics. Catalent has a global network of clinical and commercial manufacturing facilities, and fill-finish and packaging capabilities located in both the U.S. and Europe. Catalent Cell & Gene Therapy has produced more than 100 cGMP batches across 70+ clinical and commercial programs.

CEDARS-SINAI BOARD OF GOVERNORS REGENERATIVE MEDICINE INSTITUTE

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https://www.cedars-sinai.edu/Research/Departments-and-Institutes/Regenerative-Medicine-Institute/

CELL MICROSYSTEMS

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801 Capitola Drive, Suite 10
Durham, NC 27713 USA
http://Cell Microsystems, Inc.
Booth 637
Cell Microsystems' lead products, the CellRaft AIR® System and CytoSort®Arrays, enable complex workflows to be performed on a single consumable, including clonal propagation of single cells for CRISPR gene editing, cell line development, stem cell studies, organoids and other 3D cultures, cell-based assays, and genomics research. The System uses real-time on-array image analysis under standard culture conditions that enables single cell or clones to be independently isolated for additional culturing or downstream analysis. The System enables single cell workflows with unperturbed phenotypes, high viability, and efficient yields producing results with faster turnaround times to downstream analysis and with richer datasets for discovery and translational research. Learn more at www.cellmicrosystems.com.

CELL STEM CELL

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50 Hampshire St. Suite 5
Cambridge, MA, 02139 USA
https://www.cell.com/cell-stem-cell/home
Cell Stem Cell is a broad-spectrum journal that publishes research reports describing novel results of unusual significance in all areas of stem cell research. We will consider studies from any model system that provides insights into stem cell biology, and we encourage submissions on human stem cells.

CELLBOX SOLUTIONS

https://cellbox-solutions.com/start-up pavilion

CELLINK

155 Seaport Blvd, Suite 2B
Boston, MA 02210 USA
http://www.cellink.com
Booth 732
CELLINK is creating the future of health as part of BICO, the world's leading bioconvergence company. When CELLINK released the first universal bioink in 2016, it democratized the cost of entry for researchers around the world and played a major role in turning the field of 3D bioprinting into a $1 billion industry. Today, the company's best-in-class bioinks, bioprinters, software and services have been cited in over 700 publications and are trusted by more than 1,000 academic, pharmaceutical and industrial labs. CELLINK aims to alleviate organ donor shortage with biofabricated transplantable organs and remains committed to reducing our dependence on animal testing and increasing efficiencies in drug development with more physiologically relevant bioprinted organ models.

CELLINO

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https://www.cellinobio.com

CELLISTIC

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47 Rue Adrienne Bolland
Gosseliesn 6041 Belgium
http://www.cellistic.com
Booth 222
At Cellistic, we believe human induced pluripotent stem cell (iPSC)-based technologies are the future of cell therapy. At our core, we have a foundational expertise in iPSC differentiation and human biology, earned by experts who have pursued and supported iPSC therapies since the science was in its infancy. Surrounding that expertise, we are developing bespoke platforms for scaling iPSC-based cell therapies efficiently, effectively and consistently. We help therapeutic developers take their cell therapy innovations beyond today's one-batch-for-one-patient models. Our work combines their knowledge of their cell types with our iPSC expertise to deliver the differentiation and scale-up required for allogeneic cell therapies to assume their rightful place in the advancement of human health.

CELLVOYANT

http://www.cellvoyant.com/
Start-Up Pavilion
CellVoyant is an AI-first biotechnology company with a mission to create novel stem cell-based therapies for chronic diseases. Our technology uses AI-first live cell imaging to predict and optimise stem cell differentiation, to controllably manufacture any cell and tissue in the body at scale.

CELOGICS

12123 Harbour Reach Dr., Suite 106
Mukilteo, WA 98275 USA
http://www.celogics.com
Start-Up Pavilion
Celogics strives to manufacture user-centered quality human induced pluripotent stem (iPS)-derived cells and provide a seamless user experience. Our mission is to improve the quality of human cell culture and become the go-to manufacturer of iPSC-derived cells for all applications. Our initial product offering will be research-use-only iPSC-derived cell products under our Celo.Cells brand. Celo.Cardiomyocytes have been validated on multiple platforms, including the Axion Maestro, Nanion Cardioexcute96, ACEA Cardio ECR & Curi Bio MantaRay. The quality control process is central in ensuring that users get accurate and consistent results that match the validated data and our certificate of Analysis (CoA). Celogics also offers extensive technical support so that even first-time users can be productive right from the start.

CELVIVO

Ny Vestergaardsvej 21
Vaerloese, Hovedstaden 35009 Denmark
http://celvivo.com/
Booth 843
CelVivo provides 3D cell culture technology that can mimic in vivo performance. The ClinoStar can grow 3D structures in a low shear-stress environment allowing the cells to maintain functionality resembling tissue of origin. 3D structures such as spheroids, organoids or tumoroids are highly relevant when studying cancer progression and treatment.

CONCEPTION

626 Bancroft Way, Suite A
Berkeley, CA 94114 USA
http://www.conception.bio
Start-Up Pavilion
Conception is working on turning pluripotent stem cells into viable human eggs. We do this by creating ovarian organoids that support early derived germ cells into becoming mature eggs. Our technology could allow women to have children at a much older age, potentially allow gay couples to be able to have children together, and allow for much wider genetic selection of embryos against certain known disease risks. We are a heavily scientist-driven culture with almost everyone on the team being either a stem cell scientist or reproductive biologist. If you would like to work with us, please get in touch at hello@conception.bio

CORNING LIFE SCIENCES

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836 North St Ste 300
Tewksbury, MA 01876 USA
http://www.corning.com/lifesciences
Booth 710
Corning Life Sciences is a global, leading manufacturer of lab tools for growing cells, bioprocess manufacturing, liquid handling, benchtop equipment, among other solutions for life sciences. Corning strives to improve efficiencies and develop innovations that enable researchers to harness the power of cells to create breakthrough discoveries in research areas like cancer, primary cells, stem cells, drug discovery, cell and gene therapy and lab automation. Learn more about 3D culture solutions including tools for organoid, spheroid and tissue models at www.corning.com/3D.

CURI BIO

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3000 Western Ave, Ste. 400
Seattle, WA 98121 USA
http://www.curibio.com
Booth 738
Curi Bio provides innovative human stem cell maturation platforms and services for cell and tissue engineering, disease modeling, and fundamental cell biology research. NanoSurface™, Cytostretcher™, Nautilus™, and Mantarray™ (3D tissue) technologies advance stem cell maturity using a variety of bioengineering techniques that mimic the signals cells normally receive in the body.

CURIOSIS

4F, 10, Teheran-ro 38gil
Seoul, Korea
http://www.curiosis.com
Booth 331
Curiosis Inc, is a company that develops, produces, and supplies laboratory equipment in the field of life science. We provide solution for improving the efficiency of cell-based research processes and endeavor to become a leading company in the bioindustry. Based on our core technologies in mechanical engineering, biophysics, and electrical engineering; we aim to provide high-quality products to our customers as well as contribute towards a better future for humanity.

CYTENA

Neuer Messplatz 3
Freiburg, Baden-Wurttemberg 79108 Germany
http://www.cytena.com
Booth 732
CYTENA is a leading provider of high-precision instruments for isolating, dispensing, imaging, analyzing and handling biological cells, and continues to build on the success of the single-cell dispensing technology the company patented as a spin-off from the University of Freiburg, Germany, in 2014. Today, as part of BICO, the world's leading bioconvergence company, CYTENA's award-winning devices are still manufactured in Germany and used at prestigious academic and pharmaceutical labs around the world to automate workflows in numerous application areas, including stable cell line development, single-cell omics, high-throughput screening and drug discovery. CYTENA's breakthrough innovations for the lab combine advanced automation, state-of-the-art software engineering and the latest insights in cell biology to maximize efficiencies in the life sciences.

CYTOSURGE AG

Sägereistrasse 25
8152 Opfikon, Switzerland
http://www.cytosurge.com
info@cytosurge.com
Booth 746

DANA-FARBER CANCER INSTITUTE

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450 Brookline Avenue
Boston, MA 02215 USA
http://www.dana-farber.org
Dana-Farber Cancer Institute is one of the world's leading centers of cancer research and treatment. Our mission is to reduce the burden of cancer through scientific inquiry, clinical care, education, community engagement, and advocacy. Dana-Farber is dedicated to a unique and equal balance between cancer research and care, translating the results of discovery into new treatments for patients locally and around the world.

DEFINED BIOSCIENCE INC

7770 Regents Road, Suite 113-238
San Diego, CA 92122, USA
http://www.definedbioscience.com
Start-Up Pavilion
Defined Bioscience is a San Diego-based startup focused on making robust, fully-defined, high-quality ingredients for stem cell culture, with applications in the life science, biopharmaceutical, and cultured meat sectors. Defined has received ~$1.75M in grant funding, licensed IP, and recently launched two products with early adopters, all in 2021. Our team includes protein engineering and production, stem cell growth and technologies, and business development expertise. Our current products include HiDef-B8, a highly optimized stem cell supplement for weekend-free iPS cell maintenance, and FGF2-G3, a thermostable variant of basic fibroblast growth factor that enables fewer medium changes and weekend-free cell culture. Both have been validated in over 40 stem cell lines with academic and industrial customers and collaborators.

DISPENDIX

Stuttgart, Germany
http://www.dispendix.com
Booth 732
DISPENDIX is a young, fast-growing deep-tech company with products that enable scientists and researchers around the world to make new discoveries in areas such as drug discovery, diagnostics and personalized medicine. Our passion drives us to develop high-tech premium liquid handling instruments for laboratory automation in the life science industry. In 2018, DISPENDIX joined the BICO group. BICO is the leading bio convergence company in the world, equipping hundreds of laboratories and thousands of scientists with cutting-edge life science technologies. By combining different technologies, such as robotics, artificial intelligence, computer science, and 3D bioprinting with biology, BICO enables customers to improve people's health and lives for the better. Our vision is: Create the Future of Health.

ELEVATE BIO

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200 Smith Street
Waltham, MA 02451 USA
https://www.elevate.bio/
(Bio)Technology Company Powering Transformative Cell and Gene Therapies Today and for Many Decades to Come.

EMULATE, INC.

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27 Drydock Avenue
Boston, MA 02210 USA
https://www.emulatebio.com
Booth 728
Emulate develops a breadth of Organ-on-a-Chip models with a focus on recreating the microenvironment and mechanical forces cells experience in vivo. Hardware automating media flow and stretch, Bio-Kits including chips and qualified human cells, and a range of standard and custom services are available.

eNUVIO

5524 Saint-Patrick St, Suite 460
Montreal, QC H4E 1A8, Canada
http://enuvio.com
Booth 542
eNUVIO provides cutting-edge solutions for the drug development industry using patent-pending microfabrication and microfluidic technology to produce scalable next-generation research tools. Their unique devices and microplates are specifically designed to allow scientists to harness the potential of stem cell (e.g. iPSC) and 3D cell culture (e.g. organoid) technologies in the neuroscience and neuromuscular research space. In this way, physiological relevance can be easily incorporated on the path to develop innovative in vitro disease models for the discovery of novel therapeutics.

EPPENDORF SE

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Barkhausenweg 1
Hamburg, Germany
http://www.eppendorf.com
Booth 737
Eppendorf is a leading life science company that develops and sells instruments, consumables, and services for liquid-, sample-, and cell handling in laboratories worldwide. Its product range includes pipettes and automated pipetting systems, dispensers, centrifuges, mixers, spectrometers, and DNA amplification equipment as well as ultra-low temperature freezers, fermentors, bioreactors, CO2 incubators, shakers, and cell manipulation systems. Consumables complement the range of highest-quality premium products.

ESSENT BIOLOGICS

6278 S Troy Cir
Centennial, CO 80111 USA
http://www.essentbiologics.org
Booth 201
Essent Biologics is a nonprofit biotechnology company setting a new standard in human-derived biomaterials and comprehensive data for research. Starting with the donor, Essent Biologics acts as the catalyst to advance regenerative medicine, biopharmaceutical and cell therapy research from benchtop to bedside. We provide primary cells, scaffold materials and tissue.

EUROPEAN BANK FOR INDUCED PLURIPOTENT STEM CELLS (EBISC)

Porton Manor Farm Rd
Salisbury SP4 0JG UK
https://ebisc.org/
Booth 546
The European Bank for Induced Pluripotent Stem Cells is a centralised, not-for-profit iPSC bank providing researchers across academia and industry with access to an extensive range of high-quality, research-grade, and fully consented iPSCs for use in disease modelling and other forms of pre-clinical research. The collection currently holds iPCs generated from a wide range of donors representing specific disease backgrounds and healthy normal donors.

EVIDENT

48 Woerd Avenue
Waltham, MA 02453, USA
http://www.EvidentScientific.com
Booth 629
Evident Life Science empowers scientists and researchers through collaboration and cutting-edge life science solutions. Dedicated to meeting the challenges and supporting the evolving needs of its customers, Evident Life Science advances a comprehensive range of clinical research, educational, and premium microscopes and microscope systems. Stop by the Evident booth today or visit www.EvidentScientific.com.

FATE THERAPEUTICS

3535 General Atomics Court, Suite 200
San Diego, CA 92121 USA
www.fatetherapeutics.com
Fate Therapeutics is a clinical-stage biopharmaceutical company dedicated to the development of first-in-class cellular immunotherapies for patients with cancer. The Company has established a leadership position in the clinical development and manufacture of universal, off-the-shelf cell products using its proprietary induced pluripotent stem cell (iPSC) product platform.

FRAUNHOFER PROJECT CENTER FOR STEM CELL PROCESS ENGINEERING

Neunerplatz 2
Würzburg, Bayern 97082 Germany
https://www.spt.fraunhofer.de/en.html
Booth 643
The Fraunhofer Project Center for Stem Cell Process Engineering (PZ-SPT) supports you in stem cell research and process automation to improve drug-development and cell- therapy approaches. The PZ-SPT is a joint venture between the Fraunhofer Institutes for Biomedical Engineering (IBMT) and for Silicate Research (ISC). As a non-profit organization it is supporting industry for the betterment of the society, offering non-competitive collaborations and contract developments with focus on hiPSC. Additionally IBMT coordinates the EU project 'European Bank for induced pluripotent Stem Cells' EBiSC. Here IBMT provides scale-up, biobanking of hiPSCs and their derivatives, fulfilling industry standards. Fraunhofer ISC adds its competences in 3D cell culture, material sciences, bioreactor design and automation for the development of tissue-based models and test systems.

FUJIFILM CELLULAR DYNAMICS, INC.

525 Science Dr.
Madison, WI 53711 USA
http://www.fujifilmcdi.com/
Booth 537
FUJIFILM Cellular Dynamics, Inc. (FCDI) is a leading developer and supplier of human induced pluripotent stem cells (iPSCs) utilized in drug discovery and cell therapies. Leveraging its expertise in iPSC technologies to create iPSCs and differentiated tissue-specific cells, FCDI is committed to enhance the beauty of modern cell biology, drive innovations in discovery, and advance medicine. FCDI's life science iCell® Products are highly pure, highly reproducible, and available in industrial quantities required for drug and cell therapy development. For more information, please visit: FujifilmCDI.com

GATES BIOMANUFACTURING FACILITY

12635 E. Montview Blvd, Suite 380
Aurora, CO 80045 USA
https://gatesbiomanufacturing.com/
Booth 237
The Gates Biomanufacturing Facility at the University of Colorado Anschutz Medical Campus is a 20,000 square ft. GMP compliant facility that provides cell-based therapies and protein biologics for use in preclinical investigations and Phase I and Phase II human clinical trials. The GBF was established in 2015 through partnership with the Gates Center for Regenerative Medicine, University of Colorado Health, Children's Hospital Colorado, University of Colorado-School of Medicine, and the Gates Frontiers Fund. The facility excels in the pre-clinical/process development setting to facilitate scale up for human use, reproducibility, product quality control, IND submission, meticulous materials management and state of the art GMP manufacturing.

GENETECH, INC.

1 DNA Way MS 258A
South San Francisco, CA, 94080 USA
https://www.gene.com/

GENSCRIPT USA INC

860 Centennial Avenue
Piscataway, NJ 08854 USA
http://www.GenScript.com
Booth 632
GenScript is a leading biotech company that provides variety of products such as antibodies, cytokines, reagents and instrumentation for western blotting and protein purification products as well as custom gene, peptide, protein, antibody services for life science researches. Most recently GenScript introduced new lines of products related to the gene and cell therapy industries such as magnetic beads for T-cell isolation and activation, as well as variety of CRISPR CAS enzymes for gene editing.

GETINGE

Contributing Sponsor
1 Geoffrey Way
Wayne, NJ 07470 USA
www.getinge.com
Booth 532
With a firm belief that every person and community should have access to the best possible care, Getinge provides hospitals and life science institutions with products and solutions that aim to improve clinical results and optimize workflows. The offering includes products and solutions for intensive care, cardiovascular procedures, operating rooms, sterile reprocessing, life science, and Applikon bioreactor systems. Getinge employs over 10,000 people worldwide and the products are sold in more than 135 countries. Booth 532

GLADSTONE INSTITUTES

1650 Owens Street
San Francisco, CA 94158, USA
https://gladstone.org/
Gladstone is an independent, nonprofit life science research organization located in the epicenter of biomedical and technological innovation in the San Francisco Bay Area. Gladstone has created a research model that disrupts how science is done, funds big ideas, and attracts the brightest minds. Above all at Gladstone, we champion highly interactive, creative, and innovative approaches to science as we seek prevention, treatments, and cures for major diseases.

HARVARD BIOSCIENCE

84 October Hill Road, Suite 10
Holliston, MA 01746 USA
http://www.harvaredbioscience.com
Booth 321
Harvard Biosciences. Stronger. Together For well over a century, Harvard Bioscience has served the changing needs of life scientists in over 100 countries and an expanding portfolio that includes instruments for organ and animal research, cell analysis, molecular biology, fluidics, as well as laboratory consumables. Visit our brands BTX®—Electroporation, electrofusion, CMA Microdialysis—Microdialysis, Heka Elektronik—Electrophysiology, electrochemistry, Hugo Sachs Elektronik—Isolated organ, tissue perfusion. Multi Channel Systems—Electrophysiology, extra-cellular recordings, microelectrode arrays. Visit us at booth #321 and at www.harvardbioscience.com.

HORIZON DISCOVERY

2650 Crescent Drive, Suite 100
Lafayette, CO 80026 USA
https://horizondiscovery.com/
Booth 213
Horizon Discovery, a PerkinElmer company, drives the application of gene editing and gene modulation to enable world-leading academic institutes, pharmaceutical and biotechnology companies, as well as clinical diagnostic laboratories, to identify the genetic drivers behind human disease, develop and validate diagnostic workflows, and deliver new therapies for precision medicine.
With more than a decade of experience in the engineering of cell lines, Horizon offers innovative tools and services based upon the ability to modulate, or permanently alter, the function of almost any gene in human and other mammalian cell lines
Horizon is headquartered in Cambridge, UK with offices in USA and Japan.

HYPOXYGEN

5350 Partners Court
Frederick, MD 21703 USA
https://www.hypoxygen.com/
Booth 334
HypOxygen will be exhibiting our line of HypOxystations, the only hypoxic chambers purpose built for physiological cell culture research. Specifically designed to create normoxic, hypoxic and anoxic conditions within a controlled and sustained workstation environment, these hypoxic incubators are ideal for research requiring the ability to accurately control O2, CO2, temperature and humidity. Our NEW line of GMP HypOxystations exceed the requirements of Grade A air cleanliness (EU GMP) and ISO 14644-1 Class 3 both at rest and in operation. They combine sterile laminar airflow, positive operating pressure, and physical isolation, to provide highly effective product protection. Due to being a completely closed, re-circulating, isolator system, these workstations can be housed in a Grade D cleanroom during GMP compliant use.

I PEACE

809 San Antonio Rd, Suite 7
Palo Alto, CA 94303 USA
https://ipeace.com/
Booth 421
I Peace, Inc. is a leading CDMO (contract development and manufacturing organization) of clinical-grade cell products. The founder and CEO Dr. Koji Tanabe earned his doctorate at Kyoto University under Nobel laureate Dr. Shinya Yamanaka and was the second author of the groundbreaking article on the development of human iPSCs. With our proprietary manufacturing platform that enables parallel production of discrete iPSCs from multiple donors in a single room, I Peace can provide a large volume of high-quality clinical-grade iPSCs. Our goal is to create custom iPSCs for every individual to become their stem cells for life while supporting drug and cell therapy companies to accelerate their development to make cell therapy an affordable option.

INNOVATIVE SURFACE TECHNOLOGIES

1045 Westgate Dr., Suite 100
Saint Paul, MN 55114 USA
http://www.isurtec.com
Booth 232
ISurTec invents and manufactures surface coating products for medical device, cell culture, and industrial applications. The company specializes in lubricous, hydrophilic, hydrophobic, primers and many combination coatings to solve coating challenges.

INTEGRA

22 Friars Drive
Hudson, NH 03051 USA
http://www.integra-biosciences.com
Booth 540
INTEGRA is a leading provider of high-quality laboratory tools and consumables for liquid handling and media preparation. We are committed to fulfilling the needs of laboratory professionals in research, diagnostics, and quality control within the life sciences industry. INTEGRA's globally recognized products include our EVOLVE manual pipettes, VIAFLO and VOYAGER electronic pipettes, VIAFLO 96/384, ASSIST and ASSIST PLUS, VIAFILL reagent dispensers, PIPETBOY serologic pipettors, VACUSAFE and VACUSIP aspiration systems, DOSE IT peristaltic pumps, FIREBOY safety Bunsen burners, and lastly our MEDIACLAVE and MEDIAJET media preparation equipment. Visit www.integra-biosciences.com to see our full line of innovative products.

IOS PRESS

Nieuwe Hemweg 6B 1013 BG
Amsterdam, Noord-Holland 1010 Netherlands
http://iospress.com/stemjournal
Booth 215
IOS Press, based in Amsterdam, publishes StemJournal. Guided by co-Editors-in-Chief Chad A. Cowan (Harvard Stem Cell Institute) and Niels Geijsen (Leiden University Medical Center), it is an open access journal for communicating outstanding stem cell research, covering basic biology, clinical applications, disease modeling, computational and systems biology, and data science.

IOTA SCIENCES

Centre of Innovation and Enterprise
Begbroke Science Park
Oxford, UK
www.iotasciences.com
Booth 414
iotaSciences offers compact automation for highly efficient single-cell cloning. Our cloning platform will accelerate your genome-editing projects with powerful automation, assurance of monoclonality and high cloning efficiency for diverse cell lines, including iPSCs. The platform uniquely automates all the fluid-handling steps of the single-cell cloning workflow and enables easy clone tracking which ensures consistency in every cloning experiment.

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Lucid Scientific (lucidsci.com) is a biotechnology tools company working to accelerate drug discovery and basic biological research by providing systems for real-time cellular analysis. Lucid's patented RESIPHER system, originally developed at MIT, monitors cellular metabolism via non-invasive optical sensors, streaming information to researchers in real-time via a collaborative web platform. The information provided by Lucid's systems saves time and enhances value to researchers performing millions of experiments annually.

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

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NIPPI/MATRIXOME

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http://matrixome.co.jp/en/
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Nippi, Inc. based out of Tokyo, Japan, has been doing business for well over 100 years producing collagen and gelatin products for numerous industries. With the creation of the Nippi Research Institute of Biomatrix, Nippi has begun innovating the biotech space with products such as MatriMix™ and technologies such as spERt™, while differentiating themselves with their medigrade collagen and gelatin products. Matrixome, Inc. is a venture company born out of Osaka University and over 20 years of ECM research by Professor Sekiguchi. With the creation of the laminin E8 fragment, a unique product line was created called iMatrix™ with numerous advantages over other cell culture substrates. iMatrix-511, available in clinical and research grades, has already been utilized in clinical trials.

NIPRO/CELL SCIENCE & TECHNOLOGY INSTITUTE

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www.cstimedia.com/index.html
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The Cell Science & Technology Institute, Inc. develops unique, high-performance serum-free culture media, using advanced animal sell-culturing technologies. We aim to contribute to society through supporting cell culture technology that is playing an increasingly important role in the fields of research on regenerative medicine / cell therapy and pharmaceutical production that have benn making dramatic strides in recent years, as well as basic research, and through supplying high-performance serum-free culture media.

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PeptiGrowth(Headquarters: Chiyoda-ku, Tokyo, President: Jiro Sugimoto) is a joint venture established in April 2020, between Japan's PeptiDream with its proprietary Peptide Discovery Platform System (PDPS), and Mitsubishi Corporation, known for its global network reach in healthcare product manufacture and distribution. The mission is to address various challenges faced by the regenerative medicine and cell therapy industry and to contribute to its growth. Together they've made available the first synthetic growth factor compounds for cell culture media featuring no animal components, unparalleled purity, consistency, and stability, at a cost that makes them the rational choice.

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http://www.synthego.com
Booth 639
Synthego is a genome engineering company that enables the acceleration of life science research and development in the pursuit of improved human health. The company leverages machine learning, automation, and gene editing to build platforms for science at scale. With its foundations in engineering disciplines, the company's full-stack platform vertically integrates proprietary hardware, software, bioinformatics, chemistries, and molecular biology to advance both basic research and therapeutic development programs. By providing both commercial and academic researchers and therapeutic developers with unprecedented access to cutting-edge genome engineering products and services, Synthego is at the forefront of innovation in engineered biology.

TAKEDA-CIRA JOINT RESEARCH PROGRAM FOR iPS CELL APPLICATIONS (T-CIRA)

Shonan Health Innovation Park
26-1, Muraoka-Higashi 2-Chome
Fujisawa, Kanagawa 251-8555 Japan
https://www.takeda.com/what-we-do/t-cira/
T_CiRA@takeda.co.jp
T-CiRA - Transform Medicine with the unlimited potential of iPS cells, T-CiRA is a 10-year joint research program by Center for iPS Cell Research and Application (CiRA), Kyoto University and Takeda Pharmaceutical Company Limited. In this unique partnership, academic and industry researchers work together at Takeda's laboratories to realize cutting-edge iPSC applications, such as cell therapies, drug discoveries, and platform technologies to cure neuro-psychiatric disorders, cancer, intractable muscle diseases, and gastrointestinal diseases that currently have no established effective treatments. Pursuing its mission, discovering the seeds for treatment options and nurturing them for clinical application, T-CiRA has delivered many research achievements in the past five years and may more are to come. Discover more about our science at T-CiRA website.

THE COMPANY OF BIOLOGISTS

Bidder Building, Station Road
Histon, Cambridge, England CB249LF
http://www.biologists.com
Booth 634
The Company of Biologists is a not for profit publishing organisation dedicated to supporting and inspiring the biological community. The Company publishes five specialist peer-reviewed journals: Development, Journal of Cell Science, Journal of Experimental Biology, Disease Models & Mechanisms and Biology Open. It offers further support to the biological community by facilitating scientific meetings and communities, providing travel grants for researchers and supporting research societies.

THE NEW YORK STEM CELL FOUNDATION (NYSCF) RESEARCH INSTITUTE

619 West 54th Street, 3rd Floor
New York, NY 10019 USA
http://www.nyscf.org
Booth 805
The New York Stem Cell Foundation (NYSCF) Research Institute accelerates cures for the major diseases of our time through stem cell research and technology innovation. The NYSCF Research Institute invented a high-throughput automated platform for standardized iPSC derivation, differentiation, and quality control (The NYSCF Global Stem Cell Array®), which has generated a community repository of thousands of lines used by laboratories worldwide. Independent and privately funded, NYSCF takes a "team science" approach —collaborating with and funding leaders in the stem cell community to advance the understanding and treatment of disease. NYSCF also hosts a comprehensive education and outreach program to bring the excitement of science to all audiences, and an annual conference showcasing the latest on translational stem cell research.

THERMO FISHER SCIENTIFIC

SILVER SPONSOR ISSCR 2022 ANNUAL MEETING

5791 Van Allen Way
Carlsbad, CA 92008 USA
http://www.thermofisher.com
Booth 120
Thermo Fisher Scientific supplies innovative solutions for the world's stem cell research. With applications that span basic research and commercial scale-up to disease modeling and downstream clinical research – we provide a broad range of products and services including high quality media, non-integrating reprogramming technologies, reagents and instruments for characterization and analysis, and cutting edge plastics.

THEWELL BIOSCIENCE INC.

675 US Highway 1
North Brunswick, NJ 08902 USA
http://www.thewellbio.com
Booth 541
TheWell Bioscience manufactures an advanced animal-origin-free hydrogel, VitroGel®, for 3D culture for organoids, spheroids, and 3D stem cell scale-up for precision medicine, cell therapy, bioprocessing, and more. As a pioneer of the xeno-free 3D extracellular matrix (ECM) platform, we mimic the human microenvironment to bridge in vitro to in vivo for clinical applications.

THRIVE BIOSCIENCE, INC.

SILVER SPONSOR ISSCR 2022 ANNUAL MEETING

100 Cummings Center, Suite 306-P
Beverly, MA 01915 USA
http://www.thrivebio.com
Booth 410
Thrive Bioscience's instruments and software provide automated imaging and analytics of live cells and tissues for research and drug discovery. Thrive instruments automatically build extensive databases of terabytes of time-series images at 100 focal planes of all the cells in all the wells in cell culture plates.

TREEFROG THERAPEUTICS

Contributing Sponsor
https://treefrog.fr/
TreeFrog Therapeutics is a French-based biotech company aiming to provide access to safe and affordable cell therapies for millions of patients. Using proprietary C-Stem™ technology, TreeFrog Therapeutics announced in April 2021 the production of a single batch of 15 billion human induced pluripotent stem cells (hiPSC) in a 10L bioreactor with an unprecedented expansion factor of 276-fold per week. Biomimetic C-Stem™ technology - which overcomes current bottlenecks in cell therapy manufacturing regarding scalability and costs - also introduces: - A new quality standard for hiPSC-derived cell products, with preservation of genomic integrity at scale - Ready-to-transplant hiPSC-derived 3D microtissues, for faster time to effect and improved safety.

UCSF BAKAR AGING RESEARCH INSTITUTE

BRONZE SPONSOR ISSCR 2022 ANNUAL MEETING

513 Parnassus Ave
San Francisco, CA 94143 USA
https://geroscience.ucsf.edu/
The UCSF Bakar Aging Research Institute brings together scientists and clinicians from all UCSF campuses to address the most critical and intractable questions related to the Science of Aging.Our members draw from the Memory and Aging Center, the Hillblom Center for the Biology of Aging, the Division of Geriatrics, which supports the Claude D. Pepper Center, and the Institute for Health and Aging, as well as many departments.

UCSF ELI AND EDYTHE BROAD CENTER OF REGENERATION MEDICINE AND STEM CELL RESEARCH

BRONZE SPONSOR ISSCR 2022 ANNUAL MEETING

35 Medical Center Way
San Francisco, CA 94143 USA
https://stemcell.ucsf.edu/
In more than 140 labs across UCSF, scientists are carrying out discovery, translational and clinical studies with the goal of understanding and developing treatment strategies for conditions as heart disease, diabetes, epilepsy, multiple sclerosis, spinal cord injury and cancer. Structured around eight research pipelines aimed at driving discoveries from the lab bench to bedside. Each pipeline focuses on a different organ system, including the blood, pancreas, liver, heart, reproductive organs, nervous system, musculoskeletal tissues, skin and eyes. Like all of UCSF, the Center fosters a highly collaborative culture, encouraging the cross-pollination of ideas between scientists of different disciplines and years of experience. The opportunity to work in this culture has drawn some of the country's premier scientists to the center.

UNION BIOMETRICA, INC.

84 October Hill Rd
Holliston, MA 01746 USA
http://www.unionbio.com
Booth 410
Union Biometrica Large Particle Flow Cytometers automate the analysis and sorting of objects that are too big / fragile for traditional cytometers. Examples include large cells / cell clusters, cells in/on beads and small model organisms. COPAS and BioSorter models cover the full 10-1500um range of particle sizes. The COPAS VISION cytometer adds brightfield image capture of selected sample objects.

UPM-KYMMENE CORPORATION

Alvar Aallon katu 1
Helsinki 00100, Finland
http://www.growdex.com
Booth 333
We are the forerunner in producing high quality nanofibrillar cellulose for medical and life science applications. More than 300 patents protect the existing and future products that rely on the Finnish birch pulp. We actively collaborate with universities, research centers and key industrial partners on future innovations and products in the field of high throughput drug screening, personalized medicine, advanced cell therapies, 3D bioprinting, tissue engineering and advanced wound care.

VECTORBUILDER INC.

1010 W 35th St, Ste 515
Chicago, IL 60609, USA
http://vectorbuilder.com
Booth 638
VectorBuilder is a revolutionary online platform that provides researchers with a one-stop solution for all vector design, custom cloning, and virus packaging needs. VectorBuilder also offers many molecular biology services such as stable cell line generation, library construction, BAC modification (recombineering), mutagenesis, and more. The easy to use web-based platform serves as both a design tool and ordering portal. This allows researchers from around the globe to design and order custom vectors and viruses in a matter of minutes. Furthermore, our expansive database of components allows for us to minimize gene synthesis, decreasing cost and turnaround time. Vectors are just complex reagents. Let VectorBuilder work on developing these while you focus on theory generation and the more important downstream experiments.

WICELL

504 South Rosa Road, Suite 101
Madison, WI 53719, USA
http://www.wicell.org
Booth 509
As a recognized leader in cell line characterization and cell banking, WiCell provides researchers with accurate and reliable characterization testing as well as high-quality hPSC lines for basic and translational research. Characterization service offerings include cGMP compliant karyotype and FISH testing as well as research grade karyotype, FISH, identity by STR, Spectral Karyotyping (SKY), SNP microarray, and mycoplasma testing. WiCell Stem Cell Bank offerings include human ES, iPS, disease models, and engineered cell lines as well as cell lines banked under cGMP conditions. In addition, WiCell offers long-term liquid nitrogen storage and customizable services such as quality control testing and cell banking . Contact WiCell today at info@wicell.org and let us be Your Lab Partner!

WORTHINGTON BIOCHEMICAL CORPORATION

730 Vassar Ave
Lakewood, NJ 08701, USA
http://Worthington-Biochem.com
Booth 722
Register to win an iPAD at our booth! New! Animal/Xeno Free Collagenases, DNAses, RNAses and STEMxyme® Collagenase/Neutral Protease Blends. Connect with us for our Catalog, Manuals and NEW Cell Isolation/Tissue Guide and FREE Collagenase Sampling Program. Worthington is an ISO9001 Certified primary supplier of enzymes and biochemicals for primary & stem cell isolation, bioprocessing, biopharm and related applications. Connect at Worthington-Biochem.com

ZENBIO, INC

3920 South Alston Ave
Durham, NC 27713, USA
http://www.zen-bio.com
Booth 416

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

INNOVATION SHOWCASES

THURSDAY, 16 JUNE

8:00 AM – 8:30 AM

ADDING A NEW DIMENSION TO IN VITRO RESEARCH: SINGLE CELL AND SPATIAL SOLUTIONS FOR ORGANOIDS *

PRESENTED BY 10X GENOMICS

Room 2011 Level 2

Organoids are reshaping how we research developmental biology, model disease, determine drug interactions in vitro, and more. Capturing the molecular underpinnings of these phenomena requires characterizing gene expression profiles, transcriptional profiles, and epigenomic phenomena. However, the cellular heterogeneity of organoids means bulk sequencing approaches fail to capture the whole story. Join us to discover how Chromium Single Cell and Visium Spatial technologies can help you add a new dimension to your organoid research. Explore how these tools and technologies can help you to identify novel cell subtypes, obtain new insights into development, and uncover the cellular basis of transcriptomic and epigenetic changes in health and disease.

PRESENTERS:

Samantha Shelton, *10x Genomics, USA*

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

8:00 AM – 8:30 AM

HIGH THROUGHPUT CRISPR EDITING AND GENOMIC CHARACTERIZATION

PRESENTED BY SYNTHEGO

Room 2012 Level 2

The power of CRISPR gene editing is reflected in its rapid development from a research tool to a therapeutic. A key problem for researchers is balancing throughput and speed for developing editing approaches with downstream clinical compatibility and ensuring cell safety profiles. In this presentation we highlight Synthego's synthetic guide RNA platform HALO and the linkage to our engineered cells platform ECLIPSE. We end by detailing analytical approaches to assessing genomics characterization and safety profiles.

PRESENTERS:

Rebecca Nugent, *Synthego, USA*

8:00 AM – 8:30 AM

HOW TO CHOOSE THE RIGHT NEURAL CELL CULTURE MODEL FOR YOUR RESEARCH QUESTION*

PRESENTED BY STEMCELL TECHNOLOGIES INC.

Room 2001 Level 2

Examining the nervous system at a cellular and molecular level is foundational to interpreting anatomical and psychological studies from live subjects, and choosing the optimal model for your question is key to obtaining relevant results. This Innovation Showcase will review the use of in vitro model systems and offer specific examples of the types of questions that can be answered with each model. Cultured rodent primary neurons provide mature cell types for neurotoxicity studies; we will present an example using BrainPhys™ medium to support and characterize neuron activity. For human context in flexible workflows, we will provide examples using STEMCELL's STEMdiff™ product line to generate human pluripotent stem cell-derived cell types, such as pure sensory neuron cultures for pain modeling. Applications of culture systems with increasing complexity, such as neuron-astrocyte-microglia co-cultures for injury modeling and gene-edited organoid cultures for developmental modeling, will also be discussed. Throughout this session, we will demonstrate how STEMCELL's tools can help overcome technical barriers to human stem cell culture and differentiation and enable the culture of complex, multi-cellular constructs when they are relevant.

PRESENTERS:

Erin Knock, *STEMCELL Technologies Inc, Canada*

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

8:00 AM – 8:30 AM

INNOVATION SHOWCASE – AGILENT TECHNOLOGIES INC

PRESENTED BY AGILENT TECHNOLOGIES INC

Room 2004 Level 2

8:00 AM – 8:30 AM

NEXT GENERATION GENE ENGINEERING OF HSPC: LESSONS FROM FIRST-IN-HUMAN STEM CELL GENE EDITING TRIAL

PRESENTED BY MAXCYTE

Room 2003 Level 2

Cell engineering via genome editing has revolutionized medical research and opened new avenues for therapeutic intervention, from correction of genetic diseases to target-specific immunotherapies. We conducted the first clinical trial in which autologous stem cells were gene edited and infused into patients (NCT-02500849). In this session, we will pres-

ent data of the manufacturing of gene-edited hematopoietic stem progenitor cells (HSPC) using first-generation zinc-finger nuclease technology, and relevant clinical data, as the first subjects reach 6 years post-infusion. The challenges and lessons from this trial have guided us to the development of custom, closed-system workflows for the clinical manufacture of genetically-engineered HSPC, and of more efficient gene-editing platforms. We will discuss some data using next-generation gene editing constructs and the challenges and opportunities of translating these technologies into the clinic.

PRESENTERS:

Angelo Cardoso, *Laboratory for Cellular Medicine (LCM). Beckman Research Institute at City of Hope, USA*

8:00 AM – 8:30 AM

MODELING CONTRACTILE DISEASES USING SCALABLE 3D ENGINEER MUSCLE TISSUES FOR DRUG DISCOVERY

PRESENTED BY CURI BIO

Room 2008 Level 2

Stem cell models hold great promise for improving the predictive power of preclinical in vitro assays for drug discovery, basic scientific research, and disease modeling. Complex 3D platforms, such as Engineered Muscle Tissues (EMTs) fabricated from iPSC-derived cells, can be used to directly measure tissue contractility, which is challenging in conventional 2D platforms where cells are rigidly attached to a surface. However, traditional methods to fabricate EMTs demand extensive bioengineering expertise, and measuring contractility often involves laborious, serial, and low-throughput optical measurements.

Here, we report on the design, fabrication, and validation of a novel EMT platform that uses 1) facile and scalable bioengineering approaches to generate tissues from a variety of cell sources, and 2) a label-free parallel measurement technique. Our platform can be used to generate physiologically relevant cardiac and skeletal muscle constructs from healthy and diseased cells, including isogenic cell lines. We can detect 24 contractions simultaneously with a measurement rate of 100Hz, which is suitable for measuring various aspects of contractility such as force amplitude, upstroke velocity, decay time, and fatiguability. We demonstrate how this platform can be used in a multiplexed manner across various industry-standard assay modalities.

PRESENTERS:

Shawn Luttrell, *Curi Bio, USA*

Heejoon Choi, *Curi Bio, USA*

Hamed Ghazizadeh, *Curi Bio, USA*

8:00 AM – 8:30 AM

THE EBISC ONE-STOP-SHOP FOR HIPSCS – HOW THE EBISC BIOBANK'S SUSTAINABLE INFRASTRUCTURE SUPPORTS YOUR RESEARCH**

PRESENTED BY EUROPEAN BANK FOR INDUCED PLURIPOTENT STEM CELLS (EBISC)

Virtual

The not-for-profit EBiSC Biobank has implemented pharma industries' high-quality standards for the culture, expansion, cryopreservation and biobanking of human induced pluripotent stem cells. To date, EBiSC facilitates access to ~900 healthy and disease-specific human iPSC lines for research worldwide. Leading EBiSC scientists focus on the wide range of EBiSC customer services from reprogramming of somatic cells into hiPSCs, gene editing, harmonized quality control of research-grade stem cells and production and cryopreservation scale-up of hiPSC cultures and of hiPSC-derived cells. Scientists using EBiSC cell lines and customer services share insights about impacts on their research and how the deposition of their valuable iPSC lines in EBiSC supports the safeguarding of their research without additional costs on their side.

PRESENTERS:

Julia Neubaue, *Fraunhofer Institute for Biomedical Engineering (IBMT), Germany*

Ralf Kettenhofen, *Fraunhofer Institute for Biomedical Engineering (IBMT), Germany*

Andreas Kurtz, *Fraunhofer Institute for Biomedical Engineering (IBMT), Germany*

Ina Meiser, *Fraunhofer Institute for Biomedical Engineering (IBMT), Germany*

Charlie Arber, *University College London, UK*

Christian Clausen, *Bioneer A/S, Denmark*

Eugenia Jones, *Fujifilm Cellular Dynamics, Inc., USA*

Juliana Laze, *NYU Langone Medical Center, USA*

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

8:00 AM – 8:30 AM

WHY DOES TREEFROG THERAPEUTICS LAUNCH A $100,000 RESEARCH GRANT IN THE FIELD OF STEM-CELL DERIVED CELL THERAPIES?

PRESENTED BY TREEFROG THERAPEUTICS

Room 2007 Level 2

French-based cell therapy biotech TreeFrog Therapeutics was created in 2018 by two post-doctoral scientists conducting stem cell research as the crossroad of biophysics and developmental biology. To date, TreeFrog Therapeutics raised over $82M and is developing a pipeline of cell therapies using proprietary C-Stem technology, allowing for the mass production of induced pluripotent stem cells and their differentiation into ready-to-transplant microtissues with un-

precedented scalability and cell quality. With the $100,000 Stem Cell Spaceshot Grant, TreeFrog Therapeutics aims at supporting scientists willing to explore unchartered territories in the field of stem cell-based regenerative medicine.

PRESENTERS:

Maxime Feyeux, *TreeFrog Therapeutics, France*

THURSDAY, 16 JUNE

11:30 AM – 12:30 PM

A CLOSED-SYSTEM SOLUTION DESIGNED TO GENTLY AND RAPIDLY PROCESS PSC SPHEROIDS FROM BIOREACTORS

PRESENTED BY THERMO FISHER SCIENTIFIC

Room 2011 Level 2

Large-scale growth of pluripotent stem cells (PSCs) is a bottleneck for many therapeutic and screening applications requiring substantial cell quantities. This challenge can be overcome using bioreactors to grow three-dimensional (3D) PSC spheroid suspension cultures. However, processing the yields generated in a closed-system environment is often difficult. Therefore, we sought to alleviate this issue using the Cell Therapy Systems (CTS) Rotea Counterflow Centrifugation system. Here, we describe how to transfer spheroids grown in StemScale PSC Suspension Medium from a bioreactor into the Rotea, dissociate the spheroids into single cells, and harvest the cell suspension, all while maintaining a closed system environment. With optimized centrifugation speed, the 3L bioreactor spheroid yield can gently flow through the Rotea tubing with minimal shear stress in under 40 minutes. Once loaded, spheroids can be rapidly dissociated in under 10 minutes, 3-4 times faster than water bath protocols. The resulting cell yield was seeded into new suspension cultures, enabling growth of pluripotent spheroids in subsequent passages and their use in downstream differentiation. Overall, this optimized protocol demonstrates the in-line use of bioreactors and the Rotea system to be a convenient method to efficiently process large amounts of PSC spheroids in a therapeutic-friendly, closed system environment.

PRESENTERS:

Michael Akenhead, *Thermo Fisher Scientific, USA*

11:30 AM – 12:30 PM

ENDING DISEASE: THE STEM CELL, CAR T-CELL, AND ANTIBODY REVOLUTION IN MEDICINE – AN EXCLUSIVE SCREENING OF A POWERFUL NEW DOCUMENTARY FOR ISSCR CONFERENCE ATTENDEES**

PRESENTED BY AMERICANS FOR CURES

Virtual

Ending Disease is a documentary film that takes the viewer through a powerful journey as it weaves human stories of patients, doctors, and scientists in the era of revolutionary new FDA-approved clinical trials for stem cell, CAR-T cell, and antibody therapies.

"A tremendously important film"
Lael Lowenstein KPCC FILMWEEK

Granted unprecedented access to groundbreaking trials taking place at top research facilities in the United States, we follow ten clinical trials using regenerative medicine to treat brain cancer, breast cancer, leukemia, lymphoma, HIV, spinal cord injury, retinitis pigmentosa, and severe combined immunodeficiency (SCID), and witness as the patients' illnesses are profoundly transformed by these pioneering treatments.

"These are visions of the future..."
Adrian Horton, The Guardian

Produced by Emmy winning director, Joe Gantz, Ending Disease makes it clear that we are in a historical time in medicine, as regenerative medicine is leading to powerful new therapies, and even cures.

https://vimeo.com/465162755

PRESENTERS:

Joe Gantz, *Medical Revolution, USA*
**This Innovation Showcase will be available only on the virtual meeting platform.

11:30 AM – 12:30 PM

FROM CULTURE TO VISUALIZATION: EYE-OPENING SOLUTIONS FOR PLURIPOTENT STEM CELLS*

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

Room 2001 Level 2

In the first part of this talk Sebastian Knöbel, PhD, Senior R&D Manager at Miltenyi Biotec B.V.& Co.KG will present recent product developments for pluripotent stem cell (PSC) culture, expansion, and characterization. He will highlight how manual PSC workflows can benefit from these developments and pave the way for manufacture in a closed system like the CliniMACS Prodigy® Adherent Cell Culture process. Moreover, he will introduce our growing MACS® Imaging and Microscopy portfolio and highlight how it can support stem cell researchers. In the second part of the talk Kåre Kryger Vøls, DVM, PhD, Research Scientist at Novo Nordisk A/S, will introduce the importance of innovative microscopy techniques in the stem cell field. He will give a special focus to light sheet fluorescence microscopy (LSFM), a technique that plays a central role in the development of cell therapies at Novo Nordisk. In fact, before transplantation, organoids are characterized by a combination of conventional histology and LSFM in order to describe their cell composition and spatial organization. After transplantation, cell delivery, biodistribution, graft size and graft survival are evaluated by in vivo imaging and ex vivo LSFM. These readouts are key parameters linked to the efficacy and safety of cellular products.

PRESENTERS:

Kåre Kryger Vøls, *Novo Nordisk A/S, Denmark*

Sebastian Knöbel, *Miltenyi Biotec B.V.& Co.KG., Germany*
*This Innovation Showcase will be available in-person and on the virtual meeting platform.

11:30 AM – 12:30 PM0

INNOVATION SHOWCASE – CORNING LIFE SCIENCES

PRESENTED BY CORNING LIFE SCIENCES

Room 2004 Level 2

PRESENTERS:

Austin Mogen, *Corning Life Sciences , USA*

Rob Vries, *HUB Organoid Technology (HUB), Netherlands*

11:30 AM – 12:30 PM

INNOVATIVE SOLUTIONS FOR PLURIPOTENT STEM CELL WORKFLOWS

PRESENTED BY BIO-TECHNE

Room 2008 Level 2

Pluripotent stem cells are emerging as powerful tools in basic, translational and clinical research. These cells have revolutionized the way researchers are able to investigate developmental biology, disease mechanisms, discover drugs and develop therapeutics for regenerative and personalized medicine. In this session we present Bio-techne's innovative solutions to culture, differentiate and characterize pluripotent stem cells and organoids. Our first presentation will introduce our key reagents to optimize pluripotent stem cell culture workflows, including matrices, media, proteins, small molecules, and analytical tools. In our second presentation, Dr. Miriel Ho and Dr. Mirabelle Ho will focus on the application of these solutions to develop and optimize iPSC-based in vitro human models. In particular, they will describe the use of iPSC models to study the effect of maternal use of addictive substances on early fetal development.

PRESENTERS:

Brittni Peterson, *Bio-Techne, USA*

Miriel Ho, *ReATe Fertility Centre, Toronto, Canada*

Mirabelle Ho, *CReATe Fertility Centre, Toronto, Canada*

11:30 AM – 12:30 PM

SYSTEM TO GENERATE THOUSANDS OF GMP-GRADE IPSCS PER YEAR--AND THE FUTURE IT WILL USHER

PRESENTED BY I PEACE INC.

Room 2003 Level 2

To solve the multiple bottlenecks for iPSC-derived cell therapy industry, I Peace succeeded to develop a system to manufacture thousands of GMP iPSCs per year. We have a state-of-the-art, licensed and FDA-registered GMP facility with both manual and automated cell manufacturing capabilities. We invented iPSC induction and culturing process more suitable for industrialization. Our system enables mass manufacturing of discrete clinical-grade iPSCs to open up a wide range of new, previously thought impossible, possibilities for the industry.
Donor identification is another bottleneck for the industry. To address this, we have developed a high-throughput algorithm to identify thousands of potential donors with specified HLA haplotypes to enable allogeneic cell therapy, and succeeded to identify 1,547 HLA homozygous potential donors already. Combined with our iPSC mass manufacturing capabilities, we can manufacture and provide a large variety of iPSC lines with specified genotypes, including those with genetic predispositions. Our SAB member Dr. Marius Wernig will present a case study of clinical application of GMP iPSCs.

PRESENTERS:

Koji Tanabe, *I Peace Inc., USA*

Marius Wernig, *Stanford University, USA*

11:30 AM – 12:30 PM

ROBUST WORKFLOWS FOR THE EXPANSION OF PLURIPOTENT STEM CELLS IN 3D SUSPENSION CULTURE*

PRESENTED BY STEMCELL TECHNOLOGIES INC.

Room 2007 Level 2

A challenge for scalable culture of human pluripotent stem cells (hPSC) is the lack of reproducible methods to do so without prior adaptation of cells to the higher shear levels imposed in stirred suspension. A critical balance exists between the agitation rate to maintain aggregates in suspension and the agitation-generated shear. We tested various agitation methods for their ability to maintain aggregate suspensions and cell growth rates. Experiments in which cells were serially expanded in suspension cultures up to 500 mL were conducted with 6 different cell lines (3 ESC and 3 iPSC) cultured in STEMCELL's portfolio of TeSR™ 3D-based media products, developed specifically for robust and scalable suspension culture of hPSCs in aggregates. Aggregates were non-enzymatically passaged using Gentle Cell Dissociation Reagent and filter-based trituration. We found that the PBS-MINI MagDrive Bioreactor with a low-shear Vertical-Wheel® impeller design provided the most reproducible growth across cell lines. With this workflow, hPSCs underwent greater than 1.5- to 1.9-fold expansion per day while maintaining the hallmarks of hPSC quality. Our work demonstrates that the combination of TeSR™ 3D workflows and low-shear bioreactors provides a robust, scalable system suitable for the expansion of a wide range of hPSC lines.

PRESENTERS:

Eric Jervis, *STEMCELL Technologies Inc., Canada*
*This Innovation Showcase will be available in-person and on the virtual meeting platform.

11:30 AM – 12:30 PM

SUCCESS STORIES OF RELIABLE PSC DIFFERENTIATION IN 2D AND 3D CELL CULTURES

PRESENTED BY BIOLAMINA AB

Room 2012 Level 2

The possibility to culture cells with a biorelevant matrix has already solved many challenges in stem cell culture, resulting in maintained pluripotency with the potential of clinical translation under streamlined work conditions. Providing tissue-specific support to cells in culture is equally relevant for effective and reliable cellular differentiation protocols. Here, you will hear from three top scientists about their biorelevant processes toward functional tissue engineering. Dr. Lynn Yap (the National University of Singapore, professor Tryggvason laboratory) introduces us to the clinical-grade differentiation process of pluripotent cells toward cardiomyocytes for future treatment of chronic heart disease. Dr. Dave Mann (Vascugen Inc) presents their efficient iPSC differentiation platform for vascular regeneration to treat severe conditions caused by restricted blood flow to tissues. Moreover, Dr. Alessandro Fiorenzano (Lund Stem Cell Center, Professor Parmar laboratory) describes their recent advances in reproducible 3D differentiation for functional, long-term ventral midbrain organoids in spider silk matrix. Come and get inspired!

PRESENTERS:

Lynn Yap, *Duke-NUS Medical School, Singapore*

Dave Mann, *Vascugen Inc, USA*

Alessandro Fiorenzano, *Lund University, Sweden*

FRIDAY, 17 JUNE

8:00 AM – 8:30 AM

A SERUM-FREE, CHEMICALLY-DEFINED WORKFLOW SOLUTION FOR T CELL CULTURE AND CHARACTERIZATION

PRESENTED BY BIOLEGEND

Room 2008 Level 2

Cancer immunotherapy has become one of the most promising fields in the treatment of oncologic related disorders, by harnessing the power of T-cells. Expansion and/or differentiation of cells with the right therapeutic profiles, in a consistent and safe manner, requires the use of defined cell culture, handling, and characterization reagents. One major cause of variability is serum or serum-derived component, with its undefined composition. The presence of undefined reagents can lead to the inability to reproduce results between labs, and stop the progression from discoveries to clinical applications. Here we introduce a chemically-defined serum substitute and other critical ancillary reagents such as a chemically-defined, low DMSO cryopreservation solution specially designed for T cells. Our development work was allowed to gain in depth knowledge of the impact of each component in T cell biology, allowing us at BioLegend to provide custom tailored solutions. The development of defined reagents provides a smooth transition and reproducibility between research and clinical development.

PRESENTERS:

Jessie Ni, *BioLegend, USA*

8:00 AM – 8:30 AM

BREAKFAST + IPSCS: FROM 2D CELL LINE DEVELOPMENT TO 3D ORGANOIDS, AUTOMATE AND SIMPLIFY COMPLEX IPSC WORKFLOWS USING THE CELLRAFT AIR® SYSTEM

PRESENTED BY CELL MICROSYSTEMS

Room 2003 Level 2

Join us over breakfast for a showcase of our fully automated, one-platform solution for culturing, phenotyping, and isolating iPSCs in 2D and 3D culture. We'll demonstrate how the AIR® System can simplify these complex workflows, improving cell viability and the success rate of cell line development using these sensitive cells. With the AIR System, users can grow and maintain iPSCs, serial image over time, perform on-array phenotypic and pluripotency assessment, and automatically isolate viable single-cell derived iPSC clones or organoids at multiple time points - all on one instrument. In this workshop, you'll get a look at our technology and proprietary analytical software, then follow along as we explore workflows for iPSC reprogramming, cell line development, and custom iPSC-derived organoid generation.

PRESENTERS:

Jessica Hartman, *Cell Microsystems, USA*

8:00 AM – 8:30 AM

FAST, GENTLE AND EASY SINGLE CELL SORTING: A BENCHTOP SOLUTION FOR CELL ENGINEERING

PRESENTED BY NAMOCELL, INC.

Room 2011 Level 2

Single cell isolation and sorting has traditionally been a challenging step for single cell cloning, single cell genomics, rare cell isolation, synthetic biology and many other applications. Traditional methods such as FACS often result in low cell viability and poor outgrowth, contamination, clogging, involve operational complexity and require high maintenance. Therefore, there has been an urgent need for fast and easy single cell technology that is at the same time gentle to the cells. We will discuss Namocell's innovative single cell technology for gentle cell sorting and single cell cloning. It combines the benefits of three technologies, microfluidics, flow cytometry, and liquid dispensing, in one platform to achieve sorting and single cell deposition in one step. This enables scientist to get single cells from sample to plate in minutes at their bench,

while the gentle sorting preserves cell viability and delivers good outgrowth. We will also discuss how to use the Namocell Single Cell Dispenser to isolate CRISPR-edited iPSC cells.

PRESENTERS:

Thompson Lu

8:00 AM – 8:30 AM

SURROZEN - WNT MODULATING ANTIBODIES FOR TISSUE REGENERATION

PRESENTED BY SURROZEN, INC.

Room 2004 Level 2

WNTs are essential factors for stem cell biology, critical during embryonic development and in maintaining homeostasis and tissue repair in adults. Difficulties in purifying WNTs and their lack of frizzled (FZD) receptor selectivity have hampered research and regenerative medicine development. Surrozen's breakthroughs in WNT and RSPO mimetic development have overcome many of these difficulties, We have developed WNT and R-Spondin mimetic platforms based on a stable and easily manufacturable full- length IgG frameworks. These two new WNT- activating platforms can be broadly applied to organoids, pluripotent stem cells, in vivo research, and serve as bases for future therapeutic development. We will describe pre-clinical data for several different disease programs including evidence for potent, selective regenerative activity in models of colitis, liver injury and retinopathy. We will also describe the strategy for two clinical development candidates entering clinical trials in 2022.

PRESENTERS:

Trudy Vanhove, *Surrozen Inc, USA*

8:00 AM – 8:30 AM

INTEGRATED IPSC AND GENOME ENGINEERING SOLUTIONS TO ADVANCE NEXT GENERATION REGENERATIVE THERAPIES

PRESENTED BY ELEVATE BIO

Room 2012 Level 2

The ability to generate cell therapies from pluripotent stem cells is changing the way we think about diseases and how to treat them. Regenerative medicines derived from induced pluripotent stem cells (iPSCs) have the potential to treat a large number of diseases, many of which currently lack efficacious therapies, by identifying the deficient or non-functional cell type involved in the disease and generating the corresponding healthy cell type from pluripotent stem cells. Genome editing and induced pluripotent stem cells (iPSCs) represent incredible breakthrough technologies in their own right. However, when combined, they become valuable tools for many different areas of research and could offer drug developers new tools to develop cutting edge-next generation therapies. Having access to integrated solutions could just be the key to catalyzing these two scientific disciplines to revolutionize regenerative, cell, and gene therapies for patients around the world.

PRESENTERS:

Austin Thiel, *ElevateBio, USA*

Clare Murray, *Life Edit Therapeutics, UK*

8:00 AM – 8:30 AM

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

PRESENTED BY PEPTIGROWTH

Room 2007 Level 2

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 by biological impurities, low stability, and high cost. PeptiGrowth's proprietary technology offers an unlimited range of synthetic peptide growth factors for use in cell culture media, starting with its HGF/c-Met agonist, TGFβ1 inhibitor, and BDNF/TrkB agonist. They possess the same capabilities for receptor activation, cell proliferation, and differentiation as conventional growth factors. Along with greater ease of use, longer shelf life, and non-contamination by biological components, they provide uniformity in quality that can improve effi¬ciency and data reproducibility and thus, reduce the cost of R&D, manufacturing, and quality control of cell therapy and regenerative medicine products. In this presentation, we provide more details of our first 3 products – HGF Alternative Peptide, TGFβ1 Inhibitor Peptide, and BDNF Alternative Peptide.

PRESENTERS:

Jes G. Kuruvilla, *Mitsubishi International Food Ingredients, USA*

Jiro Max Sugimoto, *PeptiGrowth Inc - Mitsubishi Corporation, Japan*

8:00 AM – 8:30 AM

THE EBISC ONE-STOP-SHOP – HOW EBISC'S OPERATIONS SUPPORT SHARING AND SAFEGUARDING OF HIPSC **

PRESENTED BY EUROPEAN BANK FOR INDUCED PLURIPOTENT STEM CELLS (EBISC)

Virtual

Are you regularly using human induced pluripotent stem cells or planning your first research project? Have you generated human iPSCs that you want to share for future R&D at industry standard? The not-for-profit EBiSC Biobank has implemented pharma industries' high-quality standards for biobanking of research-grade human iPSCs. Leading EBiSC scientists will highlight how to identify and order lines of interest by refined searching and filtering the EBiSC online catalogue.
Researchers wishing to leave a legacy and enable future R&D can learn from other scientists about the advantages of free-of-charge deposition of their hiPSC lines into the EBiSC Bank while retaining legal ownership.

EBiSC supports grant applications from early stages as well as peer-reviewed publications with an embargo before the cell line is made available to the scientific community.

PRESENTERS:

Alex Ashby-Lumsden, *European Collection of Authenticated Cell Culture (DH-ECACC), UK*

Sabine Müller, *Fraunhofer Institute for Biomedical Engineering (IBMT), Germany*

Ralf Kettenhofen, *Fraunhofer Institute for Biomedical Engineering (IBMT), Germany*

Andreas Kurtz, *Fraunhofer Institute for Biomedical Engineering (IBMT), Germany*

Zameel Cader, *University of Oxford, UK*

Charles Arber, *University College London, UK*

Eugenia Jones, *Fujifilm Cellular Dynamics, Inc., USA*

Minal Patel, *Wellcome Trust Sanger Institute, UK*

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

8:00 AM - 8:30 AM

RELIABLE IN VITRO CULTURE SOLUTIONS FOR YOUR ALVEOLAR RESEARCH*

PRESENTED BY STEMCELL TECHNOLOGIES INC.

Room 2001 Level 2

In vitro models for culturing human pulmonary epithelial cells have emerged as powerful tools for studying lung cell biology. This session will focus on the alveoli—the breathing units of the lung—located in the most distal portion of the airway. The alveoli are composed of a mixture of alveolar epithelial cells, stromal cells, endothelial cells, immune cells, and extracellular matrix molecules. Alveolar type 2 (AT2) cells are the stem cells of the alveolar region; they are capable of self-renewal and differentiation into alveolar type 1 cells that are involved in the process of gas exchange. Traditional two-dimensional culture techniques have proven insufficient for the long-term culture and study of AT2 cells. Our novel and standardized PneumaCult™ Alveolar Organoid Media and protocols can be used for the expansion and differentiation of primary human tissue-derived alveolar epithelial cells. In addition, our STEMdiff™ product line includes kits for the efficient and reproducible differentiation of hPSCs into branching lung organoids and Nkx2.1+ lung progenitors. These new tools will enable researchers to focus their efforts on addressing scientific questions regarding alveolar biology and respiratory diseases, such as COVID-19 and chronic obstructive pulmonary disease, rather than on optimizing and troubleshooting reagents to ensure consistent, high-quality cultures.

PRESENTERS:

Johanna Finn, *STEMCELL Technologies Inc., Canada*

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

FRIDAY, 17 JUNE

11:30 AM – 12:30 PM

ADDING THE EXTRA DIMENSION: DEVELOPING A 3D CULTURE MEDIUM AND SCALABLE BIOMANUFACTURING OF EMBRYOID BODIES TOWARDS ORGAN ENGINEERING

PRESENTED BY SARTORIUS

Room 2008 Level 2

A promising approach to overcoming production of hPSC in high quantities is 3D suspension culture. Aggregate suspension culture enables reproducible production of high number of pluripotent cells as well as proceeding toward desired differentiation. We will briefly describe the development of ACF medium suitable for hPSC expansion using recombinant matrices in 2D culture and aggregates in suspension dynamic culture. The Team from Stanford University will highlight how the tissue engineering field now finds itself critically limited by a lack of patient-specific cells. They demonstrate the billion cell-scale cultures of hiPSC in the form of embryoid bodies (EBs) using an automated 250 mL stirred tank bioreactor system. They characterized the impact of seeding density, initial and final impeller rotation speeds, on the daily trends of viable cell density, fold-expansion, size and circularity of the hiPSC EBs. The Team shows the capability achieving double digit fold expansion while maintain >94% expression of pluripotency markers. EBs were obtained with diameters ranging from 250-300µm for downstream organoid differentiation (cardiac, vascular, cortical and intestinal) or 300-450µm for maintenance and continuous culture, and 3D bioprinting. Printed structures were differentiated into vascular and cortical tissue. Thus we have an avenue for future billion cell-scale culture and bioprinting.

PRESENTERS:

Sharon Daniliuc, *Sartorius Stedim Biotech, Israel*

Mark Skylar-Scott, *Stanford University, USA*

Debbie Ho, *Stanford University, USA*

11:30 AM – 12:30 PM

IF MICE LIE AND MONKEY'S EXAGGERATE WHAT ABOUT IPSCS?: A PANEL DISCUSSION ON ADDRESSING THE CELL PROBLEM WITHIN RESEARCH AND DRUG DISCOVERY

PRESENTED BY BIT.BIO

Room 2003 Level 2

Considerations and insights from academics and industry leaders into the consistency and scalability of iPSC-derived cell models, with discussions around disruptive technologies and novel techniques to overcome the challenges of modelling disease in vitro.

11:30 AM – 12:30 PM

INNOVATION SHOWCASE – EMULATE

PRESENTED BY EMULATE

Room 2011 Level 2

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

11:30 AM – 12:30 PM

NEXT-GENERATION IN-VITRO ASSAYS: CHARACTERIZING THE ACTIVITY OF HUMAN IPSC-DERIVED NEURONS IN 2D AND 3D CULTURES AT HIGH RESOLUTION*

PRESENTED BY MAXWELL BIOSYSTEMS

Room 2001 Level 2

Both 2D and 3D brain models derived from human induced pluripotent stems cells (hiPSCs) are emerging as promising tools for investigating brain development and disease progression, as well as to test drug toxicity and efficacy in-vitro. In order to adopt hiPSC-derived 2D and 3D neuronal networks for rapid and cost-effective phenotype characterization and drug screening, it is necessary to assess their cell type composition, gene expression patterns, and physiological function. In this innovation showcase, our invited speakers will showcase studies where MaxWell Biosystems' advanced high-density microelectrode arrays (HD-MEAs) as the core of easy-to-use platforms, MaxOne (single-well) and MaxTwo (multi-well), allowed to capture neuronal activity across multiple scales, from sub-cellular to single cells, up to full networks and facilitated the characterization of the neuronal activity of hiPSC-derived neurons. During this session speakers will introduce how brain development disorders are modeled in 2D and 3D in-vitro. Overall, the presentations will provide an overview on how HD-MEA technology can efficiently advance research in 2D and 3D hiPSC-derived brain models and accelerate drug discovery for neurodegenerative diseases.

PRESENTERS (In-Person):

Urs Frey, *MaxWell Biosystems , Switzerland*

Marie Obien, *MaxWell Biosystems , Switzerland*

Bruna Paulsen, *Harvard University, USA*

PRESENTERS (Virtual):

David Jackel, *MaxWell Biosystems , Switzerland*

David Pamies , *University of Lausanne, Switzerland*

Kenta Shimba, *University of Tokyo, Japana*

11:30 AM – 12:30 PM

NEW ADVANCES IN INTESTINAL ORGANOID APPLICATIONS: DRUG DISCOVERY AND IMMUNOTHERAPY*

PRESENTED BY STEMCELL TECHNOLOGIES INC.

Room 2007 Level 2

Intestinal organoid cultures offer greater physiological relevance than traditional cell culture platforms. As a tool for drug discovery, we have optimized the use of intestinal organoids—grown with IntestiCult™ Organoid Growth Media—as a model for studying the response to treatment with common drugs known for intestinal toxicity. Drug responses in organoids were compare against those in Caco2 cell cultures. While some responses were similar in both models, organoids provided new insights on the responses to colchicine and gefitinib, which were not captured by Caco2 cell cultures. Furthermore, we used organoid monolayer cultures established with IntestiCult™ Organoid Differentiation Media for barrier permeability assays, measuring both TEER and FITC-dextran permeability as readouts for barrier integrity. Organoid monolayer cultures, but not Caco2 cells, were effective at demonstrating the responses to the drugs colchicine and AZD8931. Finally, we employed a colorectal cancer (CRC) organoid model and optimized a media formulation for the maintenance of an organoid-T cell co-culture. This allowed us to treat CRC organoids with patient-matched tumor-infiltrating lymphocytes as a killing assay, providing an in vitro model for immunotherapy. Together, our data demonstrates the utility of organoids as new models for drug discovery in academic, clinical, and industrial settings.

PRESENTERS:

Ryan Conder, *STEMCELL Technologies Inc., Canada*

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

11:30 AM – 12:30 PM

PRECLINICAL STUDY OF ORGANOID BASED REGENERATIVE MEDICINE(ATORM) AND CONSIDERATION FOR FIRST-IN-HUMAN TRIALS

PRESENTED BY ORGANOIDSCIENCES

Room 2004 Level 2

ORGANOISCIENCES one of the leading biotech companies developing an innovative organoid technology with the aim of contributing to human health by developing medical technologies, which can solve problems of organ damage and shortage based on advanced science. Organoids are promising strategies in the field of regenerative medicine and transplantation with high levels of regenerative capacities. We have successfully developed a platform called "ATORM (Adult Tissue derived Organoid based Regenerative Medicine)" with oncoming phase 1 clinical trial pipelines and its GMP process for organoid therapeutics. ATORM-C (colon) is applicable to various indications such as refractory ulcers by IBD, radiation

proctitis, and other diseases. Salivary glands are destroyed by various factors such as radiation therapy, autoimmunity, and aging and cause permanent salivary function decline of Xerostomia. ATORM-C and ATORM-S includes a high population of stem cells to regenerate and repopulate the damaged tissue. Organoids is an ideal in vitro tool in the field of drug discovery with reflecting the patient heterogeneity. Accumulating evidence suggests that patient-derived organoids have great value for drug development and personalized medicine. In particular, we are specialized to evaluate the efficacy of patient-specific immune checkpoint inhibitors by using our own ADIO (Autologous organoids-based Discovery for Immuno-Oncology drug) platform.

PRESENTERS:

Kyung Jin Lee, *ORGANOIDSCIENCES, Korea*

11:30 AM – 12:30 PM

SONY CGX10 CELL ISOLATION SYSTEM: AN INTRODUCTION AND EXAMPLES OF USE IN PROTOCOLS FOR GENERATING CELL THERAPY PRODUCTS USING MULTIPARAMETRIC SELECTION*

PRESENTED BY SONY BIOTECHNOLOGY INC.

Room 2012 Level 2

Here we describe the use of the Sony CGX10 Cell Isolation System, a fully closed system suitable for GMP-compliant cell sorting. The CGX10 Cell Isolation System utilizes a novel microfluidics technology to achieve high purity cell isolation within a closed and sterile microfluidics chip.

PRESENTERS:

Aditi Singh, *Sony Biotechnology Inc., USA*

Manoja Eswara, *CCRM, Canada*

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

11:30 AM – 12:30 PM

THE HUMAN TRIAL: BEHIND EVERY BREAKTHROUGH ARE THOSE WHO RISK EVERYTHING FOR EVERYBODY ELSE**

PRESENTED BY AMERICANS FOR CURES

Virtual

Join us for a special ISSCR screening of the feature documentary THE HUMAN TRIAL, before it is released in theaters and on campuses this summer.

ABOUT THE FILM:
One Research Team. One Stem Cell Line. And a history-making trial that could change the course of medicine.

A century after the discovery of insulin, there is hope for a cure for diabetes. In 2011, Lisa Hepner and her husband Guy Mossman heard about a radical stem cell treatment for diabetes. Driven by a desire to cure Lisa of her own type 1 diabetes (T1D), the filmmakers were given unprecedented, real-time access to a clinical trial -- only the sixth-ever embryonic stem cell trial in the world. The Human Trial peels back the headlines to show the sweat, passion and sacrifice poured into every medical breakthrough. It interweaves the stories of the patients -- who have borne the physical and financial burdens of type 1 diabetes (T1D) — with the researchers who epitomize the struggle of innovating cures. Combining these two points of view, the filmmakers reveal the emotional and physical rollercoaster that scientists and patients go through as they travel along the road to a cure for disease.

Learn more at www.thehumantrial.com or by emailing thehumantrial@rocofilms.com

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

MICRO THEATER

Micro-Theater Located Behind ISSCR Central in the Exhibit & Poster Hall

WEDNESDAY, 15 JUNE

6:15 PM – 6:30 PM

SONY CGX10 CELL ISOLATION SYSTEM: ENABLING GMP READY CELL THERAPY PRODUCT MANUFACTURING USING MULTIPARAMETRIC SELECTION

PRESENTED BY SONY BIOTECHNOLOGY INC.

Strategies for harnessing the immune cells or stem cells to combat cancer and autoimmune disorders using cell therapy represent a promising approach in the field of personalized medicine. In this context, many efforts are emerging for developing and engineering more potent T cell, Stem cell and NK cell–based cell and gene therapies.
Commonly employed cell purification platforms for large-scale enrichment and isolation of immune cells or stem cells for cell therapy applications, separate cells based on a single surface antigen. Enrichment based on multiple cell surface markers or different expression levels of these markers often requires the use of a traditional cell sorter.
Here we describe the use of the Sony CGX10 Cell Isolation System, a fully closed system suitable for GMP-compliant cell sorting. The CGX10 Cell Isolation System utilizes a novel microfluidics technology to achieve high purity cell isolation within a closed and sterile microfluidics chip.

PRESENTERS:

Aditi Singh, *Sony Biotechnology Inc., USA*

6:45 PM – 7:00 PM

IMPROVING CELL EXPANSION IN BIOREACTORS: AUTOMATED MEDIA EXCHANGE AND CELL SEPARATION STRATEGIES

PRESENTED BY GETINGE

Optimal culture conditions increase cell expansion, so bioreactors are a logical step in upstream cell and gene therapy production. Media exchange and cell separation are two critical operations performed routinely on a repeated and regular schedule to maintain favorable culture conditions in small scale cultures. Through use of automation tools and purpose-built reactor components these two operations can be successfully automated in bioreactors. These tools will directly improve product yields and quality and will also free personnel to perform other critical tasks. In this presentation we will introduce the concepts, techniques, and the components of highly automated and efficient systems to perform media exchange and cell separation in stirred tank bioreactors used for cell and gene therapy applications.

PRESENTERS:

George Barringer, *Getinge Applikon Bioreactors, USA*

7:15 PM – 7:30 PM

LARGE-SCALE GENERATION OF CELL MODELS USING CRISPR FOR THE IPSC NEURODEGENERATIVE DISEASE INITIATIVE (INDI)

PRESENTED BY SYNTHEGO

The iPSC Neurodegenerative Disease Initiative (iNDI), led by the National Institutes of Health (NIH) and started in mid-2020, is the largest-ever iPSC genome engineering project attempted. The goal of the iNDI project is to generate a standardized set of disease models for over 100 single nucleotide variant (SNV) mutations associated with Alzheimer's disease and related dementias (ADRD) in isogenic iPSC lines. The iNDI cell lines and related phenotypic data sets will be broadly shared by the NIH. Synthego, a genome engineering company, was selected as a partner to generate a significant number of the required iPSC lines. Utilizing state of the art CRISPR knock-in methods (editing design, optimization, zygosity control, analysis) and automation (cell transfection and clonal isolation), we generated clonal lines for 23 of the target mutations in the KOLF2.1 iPSC line. In less than 6 months spanning late 2020 to early 2021, at least 3 clonal homozygous and 6 clonal heterozygous mutation lines were generated for a total of 264 clonal lines (>8,000 vials of cells produced). Here we describe the use of our automated, high throughput CRISPR editing platform, ECLIPSE, for rapidly generating these isogenic iPSC lines as part of a valuable contribution to the iNDI project.

PRESENTERS:

Kevin Holden, *Synthego, USA*

7:45 PM – 8:00 PM

THE CELLRAFT AIR SYSTEM: AN AUTOMATED ALL-IN-ONE SOLUTION FOR IMAGING, IDENTIFYING, AND ISOLATING STEM CELLS

PRESENTED BY CELL MICROSYSTEMS

The CellRaft technology developed by Cell Microsystems allows for streamlined and efficient cell line development by leveraging the combined power of our CytoSort Array tissue culture consumable with our automated isolation and imaging instrument, the CellRaft AIR® System. The AIR System offers an automated solution to an otherwise labor-intensive workflow and supports cell health, time-course imaging for clonal verification, and automated isolation for downstream propagation, altogether providing an alternative that is more time, labor, and cost efficient for cell line development. We have extensively demonstrated that the CellRaft AIR System can accelerate workflows for both 2D and 3D cell culture using a variety of cell types, including sensitive cells such as embryonic and induced pluripotent stem cells.

PRESENTERS:

Jessica Hartman, *Cell Microsystems, USA*

8:15 PM – 8:30 PM

GMP-COMPLIANT IPSC LINES AND DIFFERENTIATION WORKFLOWS FOR CELL THERAPY

PRESENTED BY CATALENT CELL AND GENE THERAPY

Induced pluripotent stem cells (iPSCs) are emerging as a powerful starting material in regenerative medicine and cancer therapy, offering a promising allogeneic approach for a broad patient population. Our presentation will highlight key initiatives in iPSC banking and differentiation to make these therapies both process efficient and regulatory compatible.

Key Learnings:

1. How Catalent is developing an HLA-homozygous (HLA-h) universal cell bank from cord blood units accounting for key regulatory aspects such as donor eligibility and consent, GMP manufacturing and commercial use consent.

2. Our characterization criteria of the banks to ensure high genomic integrity, effectiveness of reprogramming and unlimited self-renewal.

3. Our initiatives to develop advanced GMP-compliant protocols are suitable for differentiating iPSCs into various cell types of medical interest including retinal pigment epithelium, mesenchymal stromal cells, natural killer cells and more.

PRESENTERS:

Boris Greber, *Catalent Cell & Gene Therpay, USA*

THURSDAY, 16 JUNE

3:15 PM – 3:30 PM

MICRO-THEATER: EMULATE

PRESENTED BY EMULATE

3:45 PM – 4:00 PM

BIOPRINTED TISSUE THERAPEUTICS: DEVELOPMENT THROUGH PARTNERSHIP

PRESENTED BY ASPECT BIOSYSTEMS

Bioprinting technology shows tremendous translational promise in regenerative medicine, but a true impact on patients' health has yet to be realized. By enabling the controlled combination of cells and biomaterials, bioprinting may be integral to implementing and scaling-up new cell-based therapies. At Aspect Biosystems, we are working to make this a reality using microfluidic 3D bioprinting to develop implantable tissue therapeutics. Our preclinical R&D team, in collaboration with leaders in the field, is developing tissue therapeutics to treat type 1 diabetes and liver failure. We also provide the bioprinting platform to experts in academia who see its promise in addressing other unmet medical needs and work with them to expand its potential applications. This talk will describe how the technology is being used to develop tissue therapeutics, how our partnership program is expanding its application, and who we are looking to partner with moving forward.

PRESENTERS:

Erin Bedford, *Aspect Biosystems, Canada*

4:15 PM – 4:30 PM

ACHIEVING MATURE, BIOLOGICALLY RELEVANT, SOMATIC CELL PHENOTYPES FROM IPSCS WITH CELLVO MATRICES

PRESENTED BY STEMBIOSYS

Human primary cells secrete extracellular matrices in vitro that retain properties of the tissue of origin. These tissue-specific ECMs promote maturation of iPSC-derived somatic cells in 2D culture. At StemBioSys we have developed processes for reproducibly manufacturing matrices capable of promoting rapid and spontaneous maturation of iPSC-derived cardiomyocytes, neurons, hepatocytes, and beta cells in high-throughput. Moreover, iPSCs from patients with inherited diseases exhibit the disease phenotype in 2D culture. Thus, this technology has the potential to dramatically improve the utility of iPSCs in preclinical drug testing applications for efficacy or toxicity screening.

PRESENTERS:

Travis Block, *StemBioSys, Inc., USA*

4:45 PM – 5:00 PM

STEM CELL & OTHER BIOMARKER IDENTIFICATION IN PATIENT-DERIVED 3D CELL MODELS USING AN AUTOMATED MICROFLUIDIC SYSTEM

PRESENTED BY PROTEIN FLUIDICS, INC.

Physiologically relevant 3D cell models are essential for pre-clinical research and drug discovery. 3D cell cultures enable better representation of the in vivo conditions such as tumor microenvironment. 3D cell models offer the possibility to understand cancer progression better functionally as compared to 2D cultures. In this session, we present an advancement in biomarker staining and detection – the automated immunofluorescence staining of patient-derived 3D cell models using our proprietary microfluidic Pu·MA System combined with high resolution confocal imaging. The Pu·MA System can perform tedious protocols such as supernatant sampling, dose responses and IF staining with minimum perturbation to the samples. The Pu·MA System with proprietary microfluidic flowchips, performs "hands-off" automated fluid transfers at the touch of a screen. Using this system, we studied the expression of epithelial-to-mesenchymal transition and stem cell markers in patient derived breast cancer models. Here we used cells from primary TNBC tumors, that were grown into 3D tumoroids. Two patient-derived models with different metastatic potential were evaluated for the expression of different biomarkers, in response to different drug treat-

ments, along with viability response. These methods using the Pu·MA System demonstrate applications such as tumor drug-sensitivities to an in-depth analysis of organoids and 3D cell models.

PRESENTERS:

Evan F. Cromwell, *Protein Fluidics, Inc., USA*

Katya Nikolov, *Protein Fluidics, Inc., USA*

FRIDAY, 17 JUNE

3:15 PM – 3:30 PM

DEVELOPING PATIENT SPECIFIC TISSUE MODELS USING A HIGH THROUGHPUT LIGHT-BASED BIOPRINTER

PRESENTED BY CELLINK

Using a novel DLP based bioprinting method, we developed a patient specific biomimetic model for spinal cord injury repair. The model effectively captured the spinal cord anatomy and mechanical property leading to effective neural stem cell delivery and maturation in vivo at the spinal cord lesion site. Given the microscale printing resolution of our bioprinter, linear microchannels were readily fabricated in the biomimetic implant to align and guide regenerating axons for functional recovery. The bioinks used for printing the model were highly biocompatible with tunable degradation rate which significantly reduced foreign body reaction to the implant and further improved functional outcomes. The bioprinting platform and methodology developed here can be readily extended to other stem cell delivery and therapeutic applications as well as disease modeling purposes.

PRESENTERS:

Wei Zhu, *Allegro 3D, USA*

3:15 PM – 3:30 PM

FUELING AUTOMATED HIPSC PRODUCTION IN STIRRED-TANK BIOREACTORS BY EXPLOITING MULTI PROCESS PARAMETER MONITORING AND FEEDBACK-BASED PROCESS REGULATION

PRESENTED BY EPPENDORF SE

Routine cell therapies for solid organs such as the heart, pancreas, liver or brain will require large cell quantities estimated at 10^8 to 10^9 cells per patient. Robust, efficient, and economically viable systems are required to produce such amounts of cells in a reproducible manner. Stirred-tank bioreactors have emerged as promising cultivation systems, which facilitate close control of critical process parameters and have proven their value for efficient process scaling. In three-dimensional (3D) aggregate-based hPSC suspension cultivation, cells, nutrients, and gases are distributed homogenously. Controlling the aggregate size is a key factor specific to hPSC bioprocessing, because large aggregates might reach physical and physiological limits. Innovations in impeller designs, such as the 8-blade impeller, improve the cultivation of stem cells as aggregates or on microcarriers in the DASbox® Mini Bioreactor System. The use of this impeller supported the formation and growth of stem cell aggregates in stirred-tank bioreactors. The presentation demonstrates the advantages of process monitoring and control with the DASbox Mini Bioreactor System. By using the 8-blade impeller and precisely monitoring and controlling critical process parameters, the process strategy yielded a 70-fold expansion of the cells in seven days, achieving an unmatched cell density of 35 X 10^6 cells/mL.

PRESENTERS:

Philipp Nold, *Eppendorf SE, Germany*

4:15 PM – 5:00 PM

PROMOTING DIVERSITY IN STEM CELL MODELS

PRESENTED BY THE INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Join us to learn about the importance of using genetically diverse stem cell models to promote the development of inclusive regenerative medicine technologies. Together, we will discuss how the stem cell community can increase the genetic diversity of cell lines and disease models so that the resulting scientific discoveries can be used to develop targeted cures and improve health among genetically diverse groups.

MODERATOR

Raeka Aiyar, *New York Stem Cell Foundation, USA*

PANELISTS

Joseph Wu, *Stanford University School of Medicine, USA*

Marisa Medina, *UCSF School of Medicine, USA*

PLENARY I: PRESIDENTIAL SYMPOSIUM
12:30 PM – 2:45 PM
LEVEL 3

1:10 PM – 1:30 PM

STEM CELL CLONALITY AND THE NICHE, AND 20 YEARS OF A NICHE FOR STEM CELL RESEARCH - THE ISSCR

Zon, Leonard I.

Boston Children's Hospital, Boston, MA, USA

Blood stem cells are supported by a niche in the bone marrow that includes stromal cells, endothelial cells and other blood cell types. We have examined cells of the niche using the zebrafish. Using imaging technologies, we found endothelial cells "cuddle" stem cells, stromal cells support stem cell divisions and melanocytes protect stem cells from damage. Using cellular barcoding technologies, we have found that mutations associated with clonal hematopoiesis in humans leads to clonal dominance. The mature myeloid lineage cells express inflammatory cytokines, whereas the mutant stem cells produce anti-inflammatory genes. This anti-inflammation mechanism allows the stem cells to selectively grow in the marrow. We have found that macrophages interact with stem cells and provides a quality assurance mechanism for blood stem cells as they develop. Using a combination of genetics and chemical biology, we have probed the stem cell niche to define the mechanism of this quality assurance mechanism. In a short introduction, I will also discuss the early days of ISSCR and how it grew over 20 years to become the niche for stem cell research.

Keywords: zebrafish, hematopoiesis, niche

1:30 PM – 1:45 PM

UNDERSTANDING HUMAN REPROGRAMMING: A JOURNEY FROM EPIBLAST TO TROPHOBLAST AND INTO IBLASTOIDS

Polo, Jose

The University of Adelaide, Australia

In 2007 Shinya Yamanaka demonstrated that human fibroblasts can be reverted back to a pluripotent state by the forced expression of four transcription factors; OCT4, SOX2, KLF4 and cMYC (OSKM). These so called induced pluripotent stem cells (iPSCs), like embryonic stem cells (ESCs) derived from the epiblast of blastocysts, can give rise to any cell types of the body. Furthermore, iPSCs carry the promise of personalized regenerative medicine and hold tremendous potential for applications such as cell replacements therapeutics, disease modelling and in vitro drug screening. However, the molecular mechanisms of these cellular transitions into primed or naive human-induced pluripotency remained poorly understood. To address this, we reconstructed the molecular reprogramming trajectories using single cell transcriptomics. This revealed that reprogramming into primed and naive human pluripotency follows diverging and distinct trajectories into the pluripotent states. The integration of regulatory element usage with transcriptomics unveiled an unexpected role of trophectoderm (TE) lineage-associated transcription factors as well as a subpopulation of cells that transiently upregulated a TE-like signature during reprogramming. We demonstrated that this TE state could be stabilised by changing the culture condition, allowing the derivation of induced Trophoblast Stem Cells (iTSCs). Further inspection of this cell cultures revealed also the upregulation of a primitive endoderm like signature in some of the cells. Unexpectedly, when all these cells are allowed to contact each other in a 3D culture, they self-organised giving rise to blastocyst-like structures which we have called iBlastoids. iBlastoids are capable of modelling in vitro, many molecular, morphological and functional aspects of embryonic development during the early stage of implantation. During my talk, we will explore how these results provided a high-resolution roadmap for human reprogramming and novel insights into early human lineage specification, revealing an unanticipated role of the TE-lineage specific regulatory program during this process, facilitating the direct reprogramming of somatic cells into iTSCs and iBlastoids.

Keywords: Reprogramming, iPSCs, iBlastoids, Blastoids, Pluripotency, Trophoblast, Blastocyst

1:45 PM – 2:00 PM

MODELING GASTRULATION WITH HUMAN PLURIPOTENT STEM CELLS

Warmflash, Aryeh

Rice University, TX, USA

During embryonic development, an entire organism is generated from a single cell. Genetics and biochemistry have identified developmental signaling pathways, however, how embryonic patterns emerge in space and time remains more obscure. I will discuss our work studying the early developmental patterning events associated with gastrulation in vitro starting from human embryonic stem cells. A combination of geometric confinement and treatment with growth factors harnesses the intrinsic ability of stem cells to create patterns similar to those in the embryo. We use these systems together with live cell imaging to dissect how self-organized signaling underlies cell fate patterning. I will also discuss our work using these systems to model interactions between embryonic and extra-embryonic tissues. This work demonstrates that a combination of quantitative analysis and controlled stem cell culture can be used to address fundamental questions in developmental biology.

Keywords: pluripotent stem cells, spatial patterning, gastrulation, signaling, morphogens, self-organization, live-cell imaging

2:00 PM – 2:15 PM

DECODING THE DESIGN PRINCIPLE OF TISSUE ORGANISATION

Liberali, Prisca

Friedrich Miescher Institute for Biomedical Research, Switzerland

Multicellular organisms are composed of cells and tissues with identical genomes but different properties and functions. They all develop from one cell to form multicellular structures of astounding complexity. During development, in a series of spatio-temporal coordinated steps, cells differentiate into different cell types and establish tissue-scale architectures and functions. Throughout life, continuous tissue renewal and regeneration is required for tissue homeostasis, which also requires fine-tuned spatio-temporal coordination of cells. How cellular interactions generate the specific contexts and spatio-temporal coordination underlying development and regeneration is a key question in biology and we specifically investigate what are the molecular and physical mechanisms that allow a cell, in a tissue, to sense its complex environment, to take individual coordinated decisions. And what are the design principles governing coordinated cellular behavior during tissue organization? Specifically, I will present different multiscale imaging frameworks: (1) High-content imaging of hundred thousand individual organoids and the inference of devel-

opmental trajectories from imaging data in order to study initial symmetry breaking events. (2) A framework capable of turning long term light-sheet imaging of organoids into digital organoids. In this context I will discuss the molecular mechanisms of intestinal organoid self-organization and the role of cell-to-cell variability in populations of differentiating cells.

Keywords: Organoids, intestinal stem cells, regeneration, Imaging, cell-to-cell variability

2:15 PM – 2:35 PM

CARDIOVASCULAR DISEASE MODELS BASED ON HUMAN PLURIPOTENT STEM CELLS

Mummery, Christine L., Bellin, Milena, Orlova, Valeria and Davis, Richard P.

Anatomy and Embryology, Leiden University Medical Center, Leiden, Netherlands

Our lab creates models for cardiovascular disease based on pluripotent stem cells (hPSCs). We use these for understanding disease mechanisms and cardiotoxic effects of drugs. We can predict the toxic effects of test drugs with almost 80% accuracy in (immature) cardiomyocyte monolayer cultures When we require mature cells, we combine hPSC-cardiomyocytes with cardiac fibroblasts and endothelial cells in “microtissues”. The cardiomyocytes develop electrical, metabolic and functional features allowing us to model postnatal onset diseases or dissect which cell types in the heart are actually responsible for the disease phenotype. We showed for example fibroblasts in the heart can contribute to abnormal heart contraction in patients with arrhythmogenic cardiomyopathy. These complex cell systems are paving the way towards better understanding of disease mechanisms and drug discovery.

Keywords: Heart, disease model, pluripotent stem cells

TRACK: CLINICAL APPLICATIONS (CA) PLENARY II: PUSHING THE BOUNDARIES IN STEM CELL THERAPY AND REGENERATION 3:30 PM – 5:40 PM LEVEL 3

3:35 PM – 4:05 PM

ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE: HIGHER-ORDER CHROMATIN ARCHITECTURE MECHANISMS ENCODING GENOME INSTABILITY IN REPEAT EXPANSION DISORDERS

Phillips-Cremins, Jennifer E.

University of Pennsylvania, Philadelphia, PA, USA

The Cremins Lab focuses on higher-order genome folding and how chromatin works through long-range, spatial mechanisms to govern neural specification and synaptic plasticity in healthy and diseased neural circuits. We have developed molecular and computational technologies to create kilobase-resolution maps of chromatin folding and have built synthetic architectural proteins to engineer loops with light, together catalyzing new understanding of the genome’s structure-function relationship. We applied our technologies to discover that topologically associating domains (TADs), nested subTADs, and loops undergo marked reconfiguration during neural lineage commitment, somatic cell reprogramming, neuronal activity stimulation, and in models of repeat expansion disorders. We have demonstrated that loops induced by neural circuit activation, engineered through synthetic architectural proteins, and miswired in fragile X syndrome (FXS) are tightly connected to transcription, thus providing early insight into the genome’s structure-function relationship. Moreover, we have also demonstrated that cohesin-mediated loop extrusion can position the location of human replication origins which fire in early S phase, revealing a role for genome structure beyond gene expression in DNA replication. Recently, we have discovered that nearly all unstable short tandem repeat tracts in trinucleotide expansion disorders are localized to the boundaries between TADs, suggesting they are hotspots for pathological instability. We have identified that Mb-scale H3K9me3 domains decorating autosomes and the X chromosome in FXS are exquisitely sensitive to the length of the CGG STR tract. H3K9me3 domains spatially connect via inter-chromosomal interactions to silence synaptic genes and stabilize STRs prone to instability on autosomes. Together, our work uncovers a link between subMegabase-scale genome folding and genome function in the mammalian brain, thus providing the foundation upon which we will dissect the functional role for chromatin mechanisms in governing defects in synaptic plasticity and long-term memory in currently intractable and poorly understood neurological disorders.

Keywords: heterochromatin, epigenetics, 3D genome folding, repeat expansion disorders, short tandem repeat tracts, human iPSCs

4:05 PM – 4:25 PM

ENGINEERING PLURIPOTENT STEM CELLS TO EVADE AND PROMOTE IMMUNITY

Bhattacharya, Deepta

University of Arizona College of Medicine, Tucson, AZ, USA

Many of the most problematic infectious diseases have proven recalcitrant to vaccination despite decades of research on the microorganisms that cause these illnesses. Efforts to develop vaccines against HIV serve as useful examples. A small proportion of the HIV-seropositive population develops exceptionally potent antibodies capable of neutralizing >90% of clinical HIV isolates. Yet these antibodies are rare and structurally unusual with an exceptionally high number of somatic mutations. Thus, it may not be possible to generate this type of immunity in the general population through vaccination. Given the inability of natural immune responses to confer immunity to many pathogens, how can protection be achieved? One possible solution is to devise ways to provide ‘unnatural’ immunity. By taking the lessons learned from very rare people who mount protective responses, it may be possible to engineer immunity by manipulating plasma cells, which are the normal source of antibody protection. For plasma cell-based therapies, pluripotent stem cells hold much promise as a starting point because they grow indefinitely in culture and can be genetically manipulated easily. In this talk, I will discuss our ongoing work on 1) genome engineering to create minimally immunogenic pluripotent stem cells as a potential starting point for transplantable plasma cells; 2) engineering these stem cells to encode broadly neutralizing HIV antibodies at their endogenous loci; 3) defining developmental pathways from pluripotent stem cells that promote B cell development; and 4) cell-intrinsic programs that promote plasma cell lifespan and promote durable humoral immunity.

Keywords: Pluripotent stem cells, plasma cells, infectious disease

4:25 PM – 4:45 PM

ENGINEERING NEXT-GENERATION CAR-T CELL THERAPY FOR CANCER

Chen, Yvonne Y.

University of California, Los Angeles, CA, USA

The adoptive transfer of T cells expressing chimeric antigen receptors (CARs) has demonstrated clinical efficacy in the treatment of advanced cancers, with anti-CD19 CAR-T cells achieving up to 90% complete remission among patients with relapsed B-cell malignancies. However, challenges such as antigen escape and immunosuppression limit the long-term efficacy of adoptive T-cell therapy. Here, I will discuss the development of and clinical data on next-generation T cells that can target multiple cancer antigens and resist antigen escape. I will also present recent work on tuning CAR signaling activities via rational protein design to achieve greater in vivo anti-tumor efficacy. This presentation will highlight the potential of synthetic biology in generating novel mammalian cell systems with multifunctional outputs for therapeutic applications.

Keywords: Cancer immunotherapy, CAR-T cell therapy

4:45 PM – 5:05 PM

CAN SINGLE CELL OMICS GUIDE DEVELOPMENT OF SECOND GENERATION STEM CELL DERIVED DA NEURONS FOR CELL THERAPY IN PD?

Parmar, Malin, Fiorenzano, Alessandro and Storm, Petter

Experimental Medical Science, Lund University, Sweden

Cell based transplantation aimed at the replacement of lost dopamine (DA) neurons holds great potential for the treatment of Parkinson's disease (PD) and clinical trials have been initiated at several centers around the world. We have used single cell RNA sequencing (scRNAseq) to trace the developmental trajectory from pluripotency to different therapeutic cell types in vitro and also to map the cellular graft composition in vivo after transplantation into xenograft models of PD. Additionally, in more recent studies we have integrated barcode linage tracing and axonal retrograde transport to experimentally address lineage diversification as well as to link molecular DA subtype identity with function and integration. These data will serve as the foundation to develop second generation stem cell derived DA neurons for cell therapy in PD.

Keywords: dopamine neurons, parkinson's disease, bar code, singel cell transcriptomics, molecular lineage tracing, xenograft

5:05 PM – 5:30 PM

ERNEST MCCULLOCH MEMORIAL LECTURE: CELLULAR REPROGRAMMING FOR REJUVENATION AND REPAIR

Srivastava, Deepak

Gladstone Institutes and University of California, San Francisco, CA, USA

Cellular reprogramming offers an opportunity to not only control cell fate, but also to reprogram diseased cells into a more healthy state. However, this requires deep knowledge of normal and perturbed gene networks. We have described complex signaling, transcriptional and translational networks that guide early differentiation of cardiac progenitors, later morphogenetic events during cardiogenesis, and maintenance of homeostasis in the adult. By leveraging these networks, we have reprogrammed disease-specific human cells in order to model genetically defined human heart disease in patients carrying mutations in cardiac genes. These studies revealed mechanisms of disease and have led to new therapeutic approaches for monogenic and oligogenic heart disease. In particular, we showed that common human valve disease is caused by a cellular reprogramming event involving a valve to osteoblast state transition. This can be pharmacologically reversed in the adult, thereby rejuvenating the tissue. We also utilized a combination of major cardiac developmental regulatory factors to induce direct epigenetic reprogramming of resident cardiac fibroblasts into cardiomyocyte-like cells resulting in cardiac repair and regeneration after damage. Knowledge regarding the early steps of cardiac differentiation in vivo has led to effective strategies to generate necessary cardiac cell types for disease-modeling and regenerative approaches,and may lead to new strategies for human heart disease.

Keywords: cellular reprogramming, cardiac repair, heart disease

THURSDAY, 16 JUNE

TRACK: CELLULAR IDENTITY (CI) PLENARY III: PROGRAMMING AND REPROGRAMMING 9:00 AM – 10:55 AM LEVEL 3

9:20 AM – 9:40 AM

MAKING DESIGNER PANCREATIC ISLETS FROM STEM CELLS

Melton, Douglas A.

Harvard University, Cambridge, MA, USA

We developed a protocol for directed differentiation of human stem cells that produces a mixture of functional islet endocrine cells, including alpha (glucagon) and beta (insulin) cells. These cells provide physiological function and control glucose metabolism in diabetic animals and humans. The next phase of our work focuses on using genetic modification to gain better control of the cell composition, including the problem of providing immune protection and eliminating unwanted cells.

Keywords: diabetes, differentiation, transplantation

9:40 AM – 10:00 AM

EXPLORING DIFFERENTIATION AND DEDIFFERENTIATION IN MAMMALIAN EPIDERMIS

Watt, Fiona M.

King's College London/ EMBO, London, UK

The epidermis is the multilayered epithelium that forms the outer covering of the skin. It is maintained by stem cells that are attached to a basement membrane. Cells differentiate as they detach from the basement membrane and move towards the tissue surface. Under steady state conditions this process is irreversible. However, during wound healing some differentiated cells are able to return to the stem cell compartment. In this presentation I will describe how new experimental approaches allow us to explore the interplay between intrinsic and extrinsic factors that regulate differentiation and dedifferentiation, and how new insights from the Human Cell Atlas provide validation or challenge to existing experimental models.

Keywords: dedifferentiation, epidermis, scRNAseq

10:00 AM – 10:20 AM

THE PLURIPOTENCY TRANSITION

Smith, Austin

University of Exeter, UK

Pluripotency is the foundation of mammalian embryogenesis. Pluripotent cells emerge within the inner cell mass of the blastocyst. These early epiblast cells are described as naïve because they lack any lineage specification. They can be stably expanded ex

vivo as relatively homogeneous cell cultures. In the mouse and human embryo, epiblast cells undergo gene regulatory network rewiring and chromatin reconfiguration after implantation. These events occur prior to lineage specification and appear necessary to confer germline and somatic lineage competence. We are investigating this formative transition and how it relates to the loss of extraembryonic potency in human naïve stem cells.

Keywords: Pluripotency, embryo, stem cells

10:20 AM – 10:45 AM

ANNE MCCLAREN MEMORIAL LECTURE: GUIDING GERM CELLS TOWARD IMMORTALITY

Lehmann, Ruth, Barton, Lacy J., Lin, Benjamin and Luo, Jonathan

Department of Biology, Massachusetts Institute of Technology, Whitehead Institute, Cambridge, MA, USA

Development, morphogenesis, immune system function, and cancer metastasis rely on the ability of cells to move through diverse tissues. During embryogenesis, germ cells in many species move from their site of specification along and through a variety of tissues to the somatic part of the gonad where they complete their differentiation into egg and sperm. To dissect migratory cell behavior in vivo, we have combined genetic approaches with cell type-specific imaging and perturbation techniques using Drosophila primordial germ cells (PGCs). I will be reporting on our recent findings that show that at the start of their migration, PGCs employ global, retrograde cortical actin flow. Orientation and propulsion require AMPkinase phospho-regulated RhoGEF availability leading to local RhoA activation. As PGCs are guided towards the embryonic gonad they are attracted to the gonad by a gradient of Juvenile hormone that signals to PGC independent of canonical nuclear receptor-mediated transcription. Extending our studies to mouse PGCs we observe role of retinoic acid in germ cell attraction, suggesting that the impact of bioactive isoprenoids on embryonic germ cell migration may be broadly conserved.

Keywords: directed migration, primordial germ cells, retinoic acid

TRACK: CELLULAR IDENTITY (CI) CELLULAR IDENTITY TOWARDS TRANSLATIONAL MEDICINE 1:00 PM – 2:45 PM ROOM 2008 LEVEL 2

1:05 PM – 1:25 PM

STEM CELLS AND GENOMICS FOR PRECISION MEDICINE

Wu, Joseph C.

Stanford University School of Medicine, Stanford, CA, USA

Heart disease is the most significant cause of morbidity and mortality in the industrialized world. Human induced pluripotent stem cells (iPSCs) has enabled the generation of patient-specific and disease-specific cell types in vitro, including cardiomyocytes These iPSC-derived cardiomyocytes carry all the genetic information from the individuals from whom they are derived. Here I will discuss recent advances in this technology and how it may be used for elucidating mechanisms of rare inherited cardiovascular diseases, for drug discovery, and for clinical trial in a dish.

Keywords: iPSC, cardiovascular disease, clinical trial in a dish, precision medicine

1:25 PM – 1:35 PM

PHASE I/II OPEN-LABEL STUDY OF IMPLANTATION INTO ONE EYE OF HESC-DERIVED RPE IN PATIENTS WITH RETINITIS PIGMENTOSA DUE TO MONOGENIC MUTATION: FIRST SAFETY RESULTS

Monville, Christell[1], Bertin, Stéphane[2], Devisme, Céline[2], Brazhnikova, Elena[3], Jaillard, Céline[3], Habeler, Walter[4], Plancheron, Alexandra[4], Jarraya, Mohamed[5], Labetoule, Céline[6], Bejanariu, Ana[4], Abbas, Sarah[4], Audo, Isabelle[3], Pâques, Michel[2], Sahel, José[7], Peschanski, Marc[4], Goureau, Olivier[3] and Ben M'Barek, Karim[4]

[1]Retinopathies, INSERM U861-ISTEM, Corbeil-Essonnes, France, [2]CIC XV-XX, CHNO des Quinze-Vingts, DHU Sight Restore, INSERM-DGOS CIC 1423, Paris, France, [3]IDV, Institut de la Vision, Sorbonne Universités, INSERM, CNRS, Paris, France, [4]Istem, Centre d'Etude des Cellules Souches, Corbeil Essonnes, France, [5]Banques de Tissus Humains, Hôpital Saint Louis, AP-HP, Paris, France, [6]Institut des Biothérapies, Genethon, Evry, France, [7]Department of Ophtalmology, Institut de la Vision, Sorbonne Universités, INSERM, CNRS; CHNO XV-XX; University of Pittsburgh, PA, USA

In developed countries, retinal degenerative diseases affecting Retinal Pigmented Epithelium (RPE), including Age-related Macular Dystrophy and inherited retinal diseases such as Retinitis Pigmentosa (RP), are the predominant causes of human blindness. Despite the scientific advances achieved in the last years, there is no cure for such diseases. In this context, we have developed a cell therapy medicinal product based on our expertise in tissue engineering and in the manipulation of pluripotent stem cells. This novel tissue engineered product (TEP) consists in RPE cells derived from clinical grade human embryonic stem cells disposed on a biocompatible substrate allowing the formation of a 3D functional sheet, suitable for transplantation. After functional validation in a rodent model of RP, we have tested the safety of the surgery and local tolerance in non-human primates. A specific device was developed in order to (i) embed the TEP in gelatin, (ii) allow its transport in a specific medium and (iii) cut the transplant at the right format. We showed that ERG responses were not modified by the surgery and that it did not cause any long lasting inflammation. Moreover, transplanted cells were integrated in the retina. Our surgical method of implantation was safe and did not provoke any local inflammation or retinal deterioration. These results lay the foundations for the start of a phase I/II clinical trials in 2019 that is now on going (NCT03963154). 6 patients have been transplanted so far and first results are showing no major adverse events and preliminary efficacy data will be provided.

Keywords: retinitis pigmentosa, pluripotent stem cells, cell therapy

1:35 PM – 1:45 PM

A NEW PHYSIOLOGICAL MODEL OF INSULIN RESISTANCE IN HUMAN STEM CELL-DERIVED ADIPOCYTES REVEALS METABOLIC DEFECTS

Friesen, Max[1], Khalil, Andrew[2], Barrasa, Inma[3], Jeppesen, Jacob[4], Mooney, David[2] and Jaenisch, Rudolf[3]

[1]Biology, Whitehead Institute for Biomedical Research, Cambridge, MA, USA, [2]School of Engineering and Applied Sciences, Harvard University, Cambridge, MA, USA, [3]Biology, Whitehead Institute, Cambridge, MA, USA, [4]Global Drug Discovery, Novo Nordisk A/S, Bagsværd, Denmark

Adipocytes are key regulatory cells of human metabolism, and their dysfunction in insulin signaling is central to metabolic dis-

eases such as type II diabetes mellitus (T2D). However, the progression of insulin resistance that leads to T2D is still poorly understood. This limited understanding is due, in part, to the dearth of suitable models of insulin signaling in human adipocytes. Traditionally, in vitro adipocyte models fail to recapitulate in vivo insulin signaling, possibly due to exposure to supraphysiological nutrient and hormone conditions. Here, we have developed a sensitization protocol for human pluripotent stem cell-derived adipocytes that uses physiologically relevant nutrient conditions to produce a potent insulin signaling response comparable to in vivo adipocytes. After systematically optimizing conditions through a design-of-experiments approach, this protocol allows for robust insulin response at physiologically relevant concentrations (0.5-10nM). We demonstrate this through phosphorylation of key players in the signaling pathway, as well as insulin-stimulated translocation of GLUT4 and glucose uptake. We also determined the gene expression changes in response to insulin in these adipocytes. Next, we developed a disease model of insulin resistance by exposing these adipocytes to diabetic levels (3nM) of insulin. This pre-treatment dramatically dampens AKT2 phosphorylation in response to acute insulin stimulation, and ablates insulin-stimulated glucose uptake. We observe aberrant gene expression changes in insulin-resistant adipocytes in response to insulin stimulation, particularly in metabolic processes including glycolysis and oxidative phosphorylation. Follow-up experiments imply that the insulin-resistant adipocytes are misregulating their mitochondrial metabolism and redox state. Overall, this sensitization methodology provides a novel platform for the study of insulin signaling and resistance using human pluripotent stem cell-derived adipocytes. In the future we can use this model to mechanistically understand insulin resistance, but also other nutrient and hormone-related metabolic insults including inflammation.

Keywords: Insulin signaling, Type 2 diabetes, Adipocyte

1:45 PM – 1:55 PM

EFFICIENT IN VIVO DELIVERY OF CRISPR/CAS9 RIBONUCLEOPROTEIN COMPLEX IN SKELETAL MUSCLE

Geijsen, Niels[1], Shang, Peng[1], Sage, Fanny[1], Gayraud-Morel, Barbara[2], Martinez-Mir, Clara[1], Zhao, Zhihan[1], Vinke, Dorien[1], Hicks, Michael[3], Brito Armas, José Miguel[4], De Poorter, Isabel[1], Kranenburg, Melissa[1], Kammeron, Darnell[1], Wasala, Nalinda[5], Robin, Catherine[6], Smit, Veronique[4], Freire, Raimundo[4], Duan, Dongsheng[5], Pyle, April[3], Acevedo-Arozena, Abraham[4] and Shahragim, Tajbakhsh[2]

[1]Anatomy and Embryology, Leiden University Medical Center, Leiden, Netherlands, [2]Developmental and Stem Cell Biology, Institut Pasteur, Paris, France, [3]Microbiology, University of California, Los Angeles, Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research, Los Angeles, CA, USA, [4]Unidad de Investigacion, Hospital Universitario de Canarias, La Laguna, Spain, [5]Neurology, University of Missouri, Columbia, MO, USA, [6]Hubrecht Institute, Utrecht, Netherlands

Most in vivo studies to date use viral vector-based expression system to deliver CRISPR/Cas9 genome editing system into tissues and organs. This leads to a prolonged expression of the CRISPR/Cas9 system in vivo, which may cause increased risk of off-target edits. CRISPR/Cas9 ribonucleoprotein complex (RNP)-based deliveries, allow a shorter presence of the editing effector and might represent a safer approach. We report how we have developed and optimized iTOP1, an efficient, non-viral delivery of CRISPR/Cas9 RNP into skeletal muscle in vivo. iTOP delivery of CRISPR/Cas RNP allows efficient and consistent gene editing in over 80% of the muscle fibers without prior tissue conditioning. We have characterized and quantified the editing at single-fiber resolution and demonstrate that each fiber contains multiple, independent editing events. We demonstrate that the pre-existing immunity against Cas9 protein does not affect CRISPR/Cas delivery or editing efficiency. As a result, the iTOP-delivered CRISPR/Cas9 RNP can be serially applied in different skeletal muscle types and allows robust and consistent restoration of Dystrophin expression in a humanized murine model of Duchenne Muscular Dystrophy2. We believe that the present study establishes iTOP delivery of CRISPR/Cas9 RNP as a simple, safe, and efficient genome editing approach targeting inherited skeletal muscle disorders.

Funding Source: This project was supported, in part, by grants from the Novo Nordisk Foundation (NNF21CC0073729) and The Princes Beatrix Muscle Foundation
Keywords: CRISPR/Cas9, RNP-delivered genome editing, Duchenne Muscular Dystrophy

1:55 PM – 2:05 PM

HIPSC-DERIVED AECS CONSTITUTE A NOVEL PLATFORM TO STUDY IONOCYTES IN A CONTEXT OF MUCOCILIARY CLEARANCE

Vilà-González, Marta[1], Pinte, Laëtitia[1], Fradique, Ricardo[2], Causa, Erika[2], Floto, Andres[3], Cicuta, Pietro[2] and Vallier, Ludovic[1]

[1]Cambridge Stem Cell Institute, University of Cambridge, UK, [2]Department of Physics, University of Cambridge, UK, [3]Department of Medicine, MRC Laboratory of Molecular Biology, University of Cambridge, UK

Cystic Fibrosis (CF) is caused by biallelic mutations in the CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) gene. These lead to increased mucus viscosity which reduces clearance in the airway and predisposes to bacterial infection and biofilm formation. Ciliated cells are directly involved in this process as they orchestrate mucus movement in the airways to keep them free of pathogens and external particles. More recently, ionocytes have been identified as the cell type which expresses the highest level of CFTR, and they have been hypothesised to have a key role in CF. However, their exact function in the airway epithelium and their interactions with ciliated cells remain to be elucidated. The study of human airway ionocytes and their role in disease remains challenging because of their rarity and the low availability of fresh tissue/brushings, among others. To bypass this limitation, our group uses human induced pluripotent stem cell (hiPSC) technology to study airway epithelial cells (AECs), especially in the context of CF. We have developed a differentiation protocol to produce AECs, including ionocytes, from hiPSCs. After a sorting step to enrich for NKX2.1+ progenitors, the cells can be expanded as 3D spheroids before being further differentiated into functional airway cells. Maturation of the resulting cells in air-liquid interface using an in-house chemically defined medium leads to the formation of a polarised pseudostratified epithelium that includes basal cells, secretory cells, ciliated cells with motile cilia and ionocytes, as shown by qPCR and immunocytochemistry analyses. To further study the role of ionocytes, we generated a FOXI1 (a transcription factor essential for their differentiation) knockout in hiPSC lines. FOXI1KO hiPSCs were differentiated into AECs and, when compared to their isogenic wildtype control, we observed a decrease in ciliated cells at mRNA and protein level. In terms of functionality, the cells showed no significant difference in epithelial barrier properties (TEER) while ciliary function is currently being characterised. Our approach constitutes a unique platform to investigate the importance of human ionocytes in cilia motility in health and disease. Furthermore, it provides new opportunity to model lung diseases and to develop new regenerative therapies.

Funding Source: UK Cystic Fibrosis Trust, Wellcome Trust
Keywords: iPSCs, Ionocytes, Cystic Fibrosis

2:05 PM – 2:15 PM

UNDERSTANDING CELL TYPES IN THE DEVELOPING HUMAN CORTEX

Bhaduri, Aparna and Nano, Patricia

Biological Chemistry, University of California, Los Angeles, CA, USA

The human brain is comprised of myriad cell types organized into distinct regions, including the cerebral cortex, the outermost layer of the human brain which enables aspects of cognition and other higher order processes. Compared to other mammals and even primates, the human cortex is substantially expanded. These size differences emerge during developmental timepoints and the cell types and gene expression programs enriched in humans at these developmental timepoints also make humans uniquely susceptible to neurodevelopmental and neuropsychiatric disorders. In order to study the emergence of these functional cortical regions, cell types, and gene expression networks, we have leveraged single-cell RNA-sequencing to identify cell types across developmental time. These data have highlighted the early specification of frontal and occipital poles of the cortex, and suggest that in between regions become further specified at later timepoints. We have also identified extremely dynamic gene expression programs, with the specific gene signatures that define cortical areas varying immensely both across developmental time and between cell types across the differentiation spectrum. In an effort to inventory and compare these gene signatures, we have compiled a meta-atlas of datasets from peak neurogenesis. This compendium of single-cell data enables us to identify biological pathways that driv these cell fate specification events. In turn, these data sets can be compared across species, in vivo and in vitro model systems, and across developmental epochs. Paired with experiments in primary tissue and cortical organoids, we can begin to decipher the logic of neural specification in the developing human cortex.

Keywords: Human cortical areas, Single-cell RNA-sequencing, Cortical organoids

2:15 PM – 2:35 PM

RETINAL PIGMENT EPITHELIAL STEM CELLS - FROM DISCOVERY TO TRANSLATION

Temple, Sally and Stern, Jeffrey

Neural Stem Cell Institute, Rensselaer, NY, USA

The retinal pigment epithelium (RPE) is a central nervous system tissue specialized to support the neural retina and is essential for vision. Dysfunction of the RPE can lead to blinding conditions such as age-related macular degeneration (AMD), a highly prevalent, neurodegenerative disease. Several RPE cell-replacement strategies are being pursued, including using embryonic or induced pluripotent stem cells and, in our work, adult RPE stem cells. We previously showed that the adult human retina contains a rare population of cells capable of being activated to a stem cell state after exposure to mitogens in culture. Starting with adult cadaver eyes donated to eye banks, the RPE layer is extracted and retinal pigment epithelial stem cells (RPESCs) are activated, efficiently expanding in culture to produce over a billion cells per single donor. Preclinical testing demonstrated promising safety and efficacy following subretinal transplantation of a progenitor stage cell derived from the adult RPESC in animal models. These findings supported an investigational new drug application to the FDA for a cell replacement therapy for patients suffering from age-related macular degeneration (AMD), and launch of a Phase I/IIa clinical trial. Translating basic stem cell research towards the clinic presents challenges, including how to manufacture and define these complex cell products more efficiently and reliably. Characterization of the adult RPESC product demonstrates significant differences from pluripotent stem cell-derived RPE cells, which are already showing promise in clinical trial. This comparison between cell products opens future opportunities to study the impact of cell characteristics on transplant outcome for patients suffering from AMD, helping to define critical quality attributes that reliably define effective cell replacement.

Keywords: retina, transplant, human

TRACK: CLINICAL APPLICATIONS (CA)
STEM CELL BIOENGINEERING - ENHANCING CELL FUNCTION
1:00 PM – 2:45 PM
ROOM 2004
LEVEL 2

1:05 PM – 1:25 PM

ENGINEERING BLOOD PRODUCTS FROM PLURIPOTENT STEM CELLS

Daley, George

Harvard University Medical School, MA, USA

Through their differentiation in vitro, pluripotent stem cells can be employed for the study of embryonic hematopoietic development, and hold promise for modeling genetic diseases of the blood like immune deficiency, bone marrow failure, and hemoglobinopathy. Current protocols for directing hematopoietic differentiation faithfully recapitulate myeloid, red cell, platelet, NK, B and T cell development, recapitulating the various stages of hematopoietic ontogeny. However, producing bona fide hematopoietic stem cells (HSC) without genetic manipulation has proven challenging. Novel strategies to achieve the production of specific hematopoietic lineages for medical applications, and to achieve the ultimate goal of HSC derivation will be discussed.

Keywords: hematopoiesis, iPSCs, immunotherapy

1:25 PM – 1:35 PM

CELLULAR SENESCENCE AND INFLAMMATION: UNINTENDED SIDE EFFECTS OF CRISPR-CAS9 GENE EDITING IN HEMATOPOIETIC STEM AND PROGENITOR CELLS

Conti, Anastasia[1], Tavella, Teresa[2], Beretta, Stefano[2], Della Volpe, Lucrezia[2], Ferrari, Samuele[2], Brombin, Chiara[3], Merelli, Ivan[4], Naldini, Luigi[5] and Di Micco, Raffaella[2]

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Gene editing (GE) by artificial nucleases hold promise for gene therapy in Hematopoietic Stem and Progenitor Cells (HSPC). Despite rapid advances in GE-based therapies, a few challenges remain to be faced to improve GE efficiency and HSPC repopulating potential. We showed that the combination of nuclease-induced Double Strand Break with DNA repair template for Homology Directed Repair (HDR) delivered by AAV6 caused cumulative activation of the p53-mediated DNA Damage Response (DDR) pathway constraining HSPC proliferation and yield. Protracted DDR signaling leads to the establishment of cellular senescence,

a condition of permanent cell cycle arrest. By integrating transcriptional analysis (up to the single cell level) with innovative imaging-based cellular assays we reported induction of cellular senescence markers (p16 and Senescence-Associated β-Galactosidase) and pro-inflammatory programs across edited HSPC subtypes and in vivo upon transplantation. Consistently, we found open chromatin at promoters of several senescence-gene categories and inflammatory genes of the IL1 axis (an upstream mediator of DDR-dependent inflammation) and NF-kB pathway (a key regulator of inflammatory genes upon several stressors) especially in HDR-edited cells. Mechanistically, we reported an ATM-p53 dependent activation of inflammatory cytokines in edited HSPC. In this context, temporary inhibition of IL1 and NF-kB pathways at the time of GE increased edited HSPC clonogenicity in vitro and ameliorated long-term hematopoietic reconstitution in xenotransplanted mice with a concomitant decrease in senescence markers in both cord blood and mobilized peripheral blood-derived HSPC upon GE. By a barcoding-based strategy, we performed in vivo clonal tracking of HDR-edited HSPC revealing that IL1 inhibition improved polyclonal reconstitution and better preserved self-renewal and multi-potency of individual edited HSPC. Our findings define senescence and inflammatory programs as long-term consequences of CRISPR-Cas9 engineered human HSPC and pave the way for the development of novel strategies based on senescence modulation and anti-inflammatory molecules to overcome cellular barriers for efficient HSPC-based clinical applications.

Keywords: Senescence upon CRISPR-Cas9 gene editing, New strategies for senescence modulation, Cord blood/Mobilized PB-derived HSPC

1:35 PM – 1:45 PM

CHEMOTHERAPY-FREE ENGRAFTMENT OF GENE EDITED HUMAN HEMATOPOIETIC STEM CELLS LEVERAGED ON MOBILIZATION AND MRNA-BASED ENGINEERING

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Hematopoietic stem/progenitor cell gene therapy (HSPC-GT) is proving successful to treat several genetic diseases. HSPCs are mobilized and harvested from the patient, genetically corrected ex-vivo and infused back to the patient, after administration of toxic myeloablative conditioning to deplete the bone marrow for the modified cells. However, these regimens are associated with severe short- and long-term toxicity. Here we address a major hurdle posed by the requirement for toxic conditioning and ex-vivo manipulation that limits safe and broad use of HSPC-GT. We leverage on recent advances in mobilizing agents to show that they create a window of opportunity for seamless engraftment of exogenous cells as they may substantially, albeit transiently, empty bone marrow niches. We show that donor HSPCs effectively outcompete mobilized recipient HSPCs for engraftment in the depleted bone marrow niches. We present proof-of-principle of the therapeutic efficacy of mobilization based - hematopoietic stem cell transplantation (M-HSCT) in a primary immunodeficiency mouse model of Hyper IgM Syndrome I (HIGM-1). We further developed our strategy using human hematochimeric mouse models of haematopoiesis, showing its applicability to human HSPCs and its versatility when coupled to genetic engineering strategies. By exploiting recently optimized RNA-based delivery, we show that ex-vivo manipulated HSPCs can be transiently engineered for robust but transient overexpression of key biological effectors improving their homing and engraftment features, thus providing further competitive advantage, and establishing stable long-term chimerism in hematochimeric models, following our M-HSCT strategy. Importantly, this transient enhancement of engraftment ability could also overcome detrimental impacts of ex-vivo gene correction strategies, such as gene editing. The M-HSCT strategy is highly versatile and can be adapted to other emerging biological reagents to achieve more complete niche depletion and exchange with exogenous cells, potentially from allogenic sources. Overall, our findings encourage the eventual disposal of conventional genotoxic conditioning in HSCT and should provide a transformative strategy paving the way to a broader and safer use HSPC-GT in a relevant number of inherited diseases.

Funding Source: Telethon Foundation, the Italian Ministry of Health, the Italian Ministry of University and Research, the EU Horizon 2020 Program, Louis-Jeantet Foundation, the Marie Skłodowska-Curie Individual Fellowship
Keywords: Hematopoietic Stem Cells, Non-genotoxic conditioning, CRISPR/Cas9

1:45 PM – 1:55 PM

MECHANISMS FOR ATTAINING HYPO-IMMUNOGENICITY OF STEM CELL DERIVED PANCREATIC ISLETS BY GENE EDITING, PURSUED BY SINGLE CELL RNA SEQUENCING AND WHOLE GENOME CRISPR SCREENING

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Type 1 diabetes (T1D) is an autoimmune disorder leading to the selective destruction of insulin-producing β-cells in the pancreas. Human embryonic stem cells (hESCs) provide new opportunities for cell replacement therapy of T1D. Therapeutic quantities of human stem cell-derived islets (SC-islets) that contain glucose sensitive β-cells (SC-β), can be generated in vitro following a stepwise differentiation protocol. Yet, preventing immune rejection and recurring autoimmunity of grafted cells, without the use of life-long immunosuppressants, remains a major challenge, and the optimal goal is to transplant 'naked' cells that are genetically modified to evade the immune system and induce tolerance. To characterize immunogenicity of SC-islets in inflammatory environments, we performed a droplet based single-cell RNA sequencing (scRNA-seq) of SC-islet cells, under immune attack by allogeneic perihelial blood mononuclear cells (PBMCs) in humanized mouse transplants or in in vitro models. scRNA-seq data analysis identified upregulated genes that contribute to the inflammatory stimulation of T-cells and NK cells. An in vivo whole genome CRISPR screen further detected targets with beneficial effects on SC-islet cell survival under immune attack. Subsequent experiments have shown that genetic perturbation of such genes in SC-islets, can reduce activation of immune cells and increase β-cell survival both in vitro and upon transplantation in humanized animals. These results unfold some insights into the nature of immune destruction of β-cells during allogeneic attack and provide means to prevent both autoimmune and allogeneic rejections of SC-islets, transplanted into patients.

Funding Source: JDRF, JPB Foundation
Keywords: Diabetes, Allogeneic response, Islets

1:55 PM – 2:05 PM

THE 3 DIMENSIONS OF IMMUNE EVASION: IMMUNE EDITING MAKES CELL THERAPEUTICS ESCAPE ALL ALLOGENEIC ADOPTIVE IMMUNE CELLS, INNATE IMMUNE CELLS, AND CYTOTOXIC ANTIBODIES

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Allogeneic off-the-shelf cell therapeutics for cancer therapy or regenerative medicine are appealing as affordable, universal, ready-to-use living medicines. However, allogeneic cells are susceptible to alloimmune rejection involving adaptive immune cells, innate immune cells, and cytotoxic antibodies. For autoimmune diseases like type-1 diabetes mellitus (T1DM) or Hashimoto's thyroiditis (HT), additional autoimmunity responsible for destroying the target organ needs to additionally be overcome. We herein report a comprehensive immune editing strategy that makes engineered cells completely resistant against alloimmunity and autoimmunity including cytotoxic IgG antibodies. Hypoimmune cells lacking HLA class I and II through the inactivation of the B2M and CIITA genes and overexpressing CD47 are resistant against allogeneic adaptive and innate immune cells. However, they are susceptible to cytotoxic non-HLA IgG antibodies against cell surface proteins and rhesus blood type antigen D (RhD). Such IgG can mediate antibody-dependent cellular cytotoxicity (ADCC) by NK cells and complement-dependent cytotoxicity (CDC). Thyroid epithelial cells are expeditiously killed by IgG against thyroid peroxidase (TPO) whether recombinant or in the serum of HT patients. Pancreatic beta cells and CAR T cells are susceptible to HLA-antibodies and various non-HLA antibodies. We now report that human and mouse iPSC-derived endothelial cells (iECs) overexpressing the IgG receptor CD64 or its intracellularly-truncated analog CD64t increase their resistance against IgG antibodies approximately 100,000-fold. CD64 receptors effectively snatch monomeric IgG, occupy their Fc domains, and prevent ADCC and CDC. When combined with hypoimmune edits, B2M-/-CIITA-/- CD47/CD64 transgenic iECs became resistant against all cellular and IgG antibody-mediated immune killing in vitro and in humanized mice in vivo. Human CD64t-engineered thyroid epithelial cells, pancreatic beta cells, and CAR T cells were able to withstand clinically relevant levels of graft-directed antibodies and fully evade antibody-mediated killing. Comprehensive immune editing will be crucial for the clinical success of allogeneic cell therapeutics.

Keywords: Immune evasion, Gene editing, Cell therapeutics

2:05 PM – 2:15 PM

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

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Induced pluripotent stem cells (iPSCs) can provide autologous and allogeneic replacement tissues, potentially for all degenerative diseases. Autologous tissues have the advantage of not requiring immune-suppressive drugs that have deleterious side-effects. The safety and feasibility of autologous iPSC-based therapies hasn't been established. Here, we developed an autologous iPSC-based therapy for age-related macular degeneration (AMD), a blinding eye disease that affects over 30 million people world-wide. AMD is caused by the progressive degeneration of retinal pigment epithelium (RPE), a monolayer tissue that maintains photoreceptor function and survival. We tissue engineered a clinical-grade iPSC-RPE-patch on a biodegradable scaffold using autologous cells from AMD patients. Preclinical investigational new drug (IND)-enabling studies performed on iRPE-patch derived from multiple AMD patients demonstrated reproducible manufacturing, validating our manufacturing process - a key requirement for an autologous phase I trial. Functional validation of clinical-grade iRPE-patches allowed determination of tissue barrier resistance, purity of RPE cells, and RPE cell shape metrics as key critical quality attributes now used as clinical product release criteria. Preclinical animal studies performed in immune-compromised rats confirmed safety of the auto-iRPE-patch and efficacy studies performed in a porcine laser-induced RPE injury model that mimics AMD-like eye conditions demonstrated integration and functionality of RPE patches. A phase I/IIa IND-application for an auto-iRPE-patch to treat AMD was recently cleared by the FDA. This Phase I/IIa clinical trial will test safety, feasibility, and integration of an auto-iRPE-patch in twelve advanced AMD patients. The trial is currently being run as a single site study at the NIH and targets patient enrollment in two cohorts - with visual acuity between 20/100 to 20/500 and between 20/80 to 20/500.

Funding Source: NIH IRP; NIH Common Fund

Keywords: iPSC-based therapies, autologous cell therapies, macular degeneration

2:15 PM – 2:35 PM

TISSUE SPECIFIC BIOMATERIAL INKS FOR 4D+ BIOPRINTING

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In many end stage diseases, transplantation is the only potential therapy but it is hampered by a chronic lack of suitable organ and donor tissues. Generating tissue ex vivo using bioengineering approaches is one potential strategy to meet this unmet clinical need but manufacturing approaches and biomaterials which can be used are not yet identified for most organs. One emerging approach is through the use of 3D printing. While the immense potential of 3D printing for bioengineering tissue is easily recognizable, there are a number of major hurdles which need to be overcome to make this a potential reality. Several promising bioinks have been developed to date, but the majority of those used thus far lack tissue specificity. Furthermore, generating tissues with viable vasculature, needed for the bioengineered grafts survival upon transplantation, have been lacking. Here we describe the development of extracellular matrix reinforced bioinks for 3D bioprinting human tissue. These pepsin-extracted decellularized extracellular matrix solutions (dECM) can be used to reinforce alginate biomaterial inks (rECM) to generate 3D printed constructs of physiologically relevant shapes, such as airways, vessels and branching structures, These structures can be constructed with regionally specified primary human cells through the use of multi-extrusion 3D printers to generate human tissue such as small airways, with multiple concentric cell layers. The inclusion of dECM confers additional biological properties such as enhanced differentiation of primary human airway epithelial cells as well as suppression of a pro-inflammatory M1 phenotype upon transplantation into murine models of transplantation. We demonstrate that 3D printed constructs containing ECM are pro-angiogenic and that bioengineered grafts subcutaneously implanted into immunodeficient and immunocompetent mice support the development of vasculature derived from the host through the entire thickness of the 3D printed construct (as assessed by label-free,

whole graft light sheet microscopy). Thus, the inclusion of specific dECM in these bioinks helps direct tissue-specific differentiation of printed cells as well as provides multiple beneficial properties for the regulation of key events in transplantation: host immune response and angiogenesis.

Funding Source: Swedish Research Council (VR) (2018-02352), Knut and Alice Wallenberg Foundation, European Research Council (805361) and the Swedish National Infrastructure for Computing at LUNARC partially funded by the VR (2018-46205973)

Keywords: 3D printing, bioinks, airway basal epithelial cells, tissue engineering

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)
MODELING EARLY DEVELOPMENT AND DYNAMIC PROCESSES
1:00 PM – 2:45 PM
ROOM 2011
LEVEL 2

1:05 PM – 1:25 PM

X CHROMOSOME INACTIVATION IN PRIMATES

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X chromosome inactivation (XCI) in mammals is an essential epigenetic process which compensates for X chromosome imbalance between sexes. XCI is established early during female development, at peri-implantation stages, and is triggered by the accumulation of the long noncoding RNA XIST. This process has been mainly studied in the mouse where embryonic stem cells (ESCs) have been instrumental to characterize the actors of the process, and to unravel the kinetics of the molecular events leading to the transcriptional silencing of one of the two X chromosomes. However, it is now known that X-inactivation initiates through remarkable diverse strategies in different species. We are using primate ESCs as a model system for early primate development, to characterize the early stages of X chromosome inactivation and to identify regulators of the process in primates. We are in particular exploring the extent to which long noncoding RNA contribute to the variation in XCI strategies between species.

Keywords: X chromosome inactivation, Noncoding RNAs

1:25 PM – 1:35 PM

DIFFERENTIATION OF UNIPARENTAL HUMAN EMBRYONIC STEM CELLS INTO GRANULOSA CELLS REVEALS A PATERNAL CONTRIBUTION TO GONADAL DEVELOPMENT

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Genomic imprinting is presented in mammals as a parent-of-origin dependent monoallelic expression of a subset of genes, and is required for normal growth and development. Imprinting is considered to stand behind the mammalian requirement for sexual reproduction. Nonetheless, the relative contribution of the maternal versus the paternal genomes to the formation of the various tissues during human embryonic development is not fully understood. In this regard, a fascinating question is whether the formation of the gonad, i.e., the ability to reproduce is by itself dependent on the contribution from both parental genomes. Androgenetic and parthenogenetic human pluripotent stem cells (hPSCs) are uniparental hPSCs which contain only paternal or maternal genomes, respectively, and thus serve as powerful tools to study the involvement of imprinted genes during early embryogenesis. Here we differentiate uniparental hPSCs into granulosa-like cells, which constitute part of the somatic female gonad. We show that while both bi-parental and androgenetic hPSCs show a high differentiation potential, parthenogenetic hPSCs present a reduced capacity to differentiate into granulosa-like cells. We further identify the paternally expressed gene IGF2 as the most upregulated imprinted gene during the differentiation. Remarkably, while androgenetic cells that harbor an IGF2 knock-out mutation fail to properly differentiate into granulosa-like cells, the differentiation efficiency of parthenogenetic cells, grown in the presence of exogenous IGF2, is partly rescued. Our findings unravel a surprising essentiality of genes which are expressed from the paternal genome to the development of the female reproductive system. Importantly, these findings could pave the road for the development of improved differentiation protocols which could be used for basic research as well as for reproductive medicine.

Keywords: Human pluripotent stem cells, Parental imprinting, Reproductive system

1:35 PM – 1:45 PM

EFFICIENT GENERATION OF HUMAN PRIMORDIAL GERM CELL-LIKE CELLS IN A BIOENGINEERED AMNIOGENIC NICHE.

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Primordial germ cells (PGCs) are the embryonic precursors of sperm and eggs. Germline defects play a key role in genetic diseases and infertility. Therefore, understanding the mechanisms of germ cell development has important implications for reproductive medicine. Yet, human germline specification and development remain an elusive process. The mammalian germ cell development mechanisms have been studied using the mouse as a model organism. However, there exists a substantial cross-species mechanistic divergence between mice and humans. Due to the scarcity of human embryo samples for research purposes, in vitro generation of human primordial germ cell-like cells (hPGCLCs) from human pluripotent stem cells (hPSCs) is crucial in studying human germ cell specification. Current methods of hPGCLC derivation require the induction of hPSCs into either a putative naïve-like state or an incipient mesoderm-like cell state before hPGCLC specification. However, recent studies of post-implantation primate monkey embryos show that monkey PGCs are specified during the development of the embryonic sac, with the earliest emergence of monkey PGCs in the nascent amnion. Here, we demonstrate an efficient method for hPGCLC derivation in a synthetic bioengineered environment mimicking the posterior end of the primate embryonic sac. Within a simple, homogeneous 3D Geltrex overlay condition, hPSCs cluster and undergo lumenogenesis and amniogenesis to form an embryonic-like sac, with hPGCLCs emerging spontaneously during this process. Eight days of cell culture in this bioengineered amniogenic niche led to an hPGCLC derivation efficiency greater than 20%. Moreover, our co-culture experiments suggest that amniotic ectoderm-like cells induce hPGCLC specification from hPSCs. Importantly, using this synthetic system, we, for the first time, reveal a critical role of ISL1 in hPGCLC specification using ISL1-knockout hPSC lines. Giv-

en its simplicity, high efficiency, and in vivo-like environment, our biomimetic method provides a convenient and efficient strategy to derive hPGCLCs and advance human embryology and reproduction biology.

Keywords: Amniogenic niche, Human primordial germ cell-like cells, Bioengineering platform

1:45 PM – 1:55 PM

A NOVEL HUMAN IMPLANTATION MODEL TO DECIPHER EMBRYO-ENDOMETRIUM INTERACTION

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The endometrium represents the first contact and interaction site of the blastocyst. To welcome and nest the nascent embryo, the endometrium must reach a receptive state ('window of implantation' (WOI)), driven by the coordinated action of ovarian estrogen and progesterone. Despite being quintessential for human reproduction, insights into the prime first steps toward successful pregnancy, in particular the interaction between embryo and endometrium, remain limited since occurring hidden in the womb. Recently, we developed organoids from human endometrium, faithfully recapitulating the tissue's physiology including its menstrual cycle phases. Moreover, we developed epithelial organoid models from diseased (infertile) endometrium as obtained from endometriosis patients. Endometriosis affects 10% of reproductive-age women of which 30-50% are burdened with infertility. Underlying causes remain poorly understood. In a recent study, we developed an 'open-faced endometrial layer' (OFEL) from the closed 3D epithelial organoids, thereby making the apical surface accessible like in the uterine cavity. When depositing human blastoids, a newly achieved stem cell-derived blastocyst model, onto the OFEL, the blastoids attached to the endometrial layer in a proper directional manner (i.e. through the polar trophectoderm). Importantly, attachment only occurred when the OFEL was hormonally primed toward the receptive WOI state, whereas the contraceptive levonorgestrel impaired blastoid attachment. Now, we are applying this novel implantation model to explore the endometrial factor in infertility of endometriosis patients. The patients' endometrium was found to display several aberrant pathways which may underlie the deficient interaction with the embryo. Moreover, we are tuning the OFEL into a still more advanced endometrium mimic by adding the endometrial stromal compartment, as well important in WOI development and embryo implantation. Taken together, in vitro modeling of human implantation using cutting-edge organoid and blastoid models will enable to shed light into the embryo-endometrium interplay at implantation, both in fertile and infertile conditions.

Keywords: Implantation, Endometrium, Embryo

1:55 PM – 2:05 PM

MICROGEL CULTURE AND SPATIAL IDENTITY MAPPING ELUCIDATE THE SIGALING REQUIREMENTS FOR PRIMATE EPIBLAST AND AMNION FORMATION

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Amnion formation prior to gastrulation and widespread extraembryonic lineage diversification are hallmarks of primate embryogenesis. These complex tasks are resolved through an intricate combination of signals controlling the induction of extraembryonic lineages and, at the same time, safeguarding the pluripotent epiblast. Here, we delineate the signals orchestrating primate epiblast and amnion identity. We encapsulated marmoset pluripotent stem cells into agarose microgels and identified culture conditions for the development of epiblast and amnion spheroids. Spatial identity mapping authenticated spheroids generated in vitro by comparison to marmoset embryos in vivo. We leveraged the microgel system to functionally interrogate the signalling environment of the postimplantation primate embryo. Single-cell profiling of the resulting spheroids demonstrated that ACTIVIN/NODAL signalling is required for embryonic lineage identity. BMP promoted amnion formation, which was counteracted by FGF-signalling. Our combination of microgel culture, single-cell profiling and spatial identity mapping provides a powerful approach to decipher the essential cues for embryonic and extraembryonic lineage formation in primate embryogenesis.

Funding Source: Wellcome Trust, Centre for Trophoblast Research, and European Research Council. C.M is the recipient of a Gates Cambridge Scholarship. T.E.B is a WT-Royal Society Sir Henry Dale Fellow.
Keywords: Embryogenesis, Development, Amnion

2:05 PM – 2:15 PM

MULTIMODAL CELL LINEAGE TRACING REVEALS THE EXISTENCE OF MULTI GERM-LAYERS PROGENITORS DURING VERTEBRATE DEVELOPMENT.

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During vertebrate embryogenesis, cells become specified into three distinct germ layers by the end of gastrulation. These three germ layers – ectoderm, endoderm and mesoderm – differentiate into tissue-specific lineages during body formation. However, several retrospective lineage clonal analysis indirectly identified potential bi-fated progenitors and therefore challenged the classical definitions of mono-fated progenitors after gastrulation. Here, we identified a population of cells in the posterior growth zone of the zebrafish embryos generating derivatives in the paraxial mesoderm (somites), axial mesoderm (notochord) and tail neural ectoderm (spinal cord). Using photoconversion fate mapping in a light-sheet microscope we described the differentiation dynamics of the multi germ-layers progenitors. We show that the progenitors acquire a pluri-fated behavior early during the axis elongation

and then differentiate into monopotent mesodermal progenitors. Using temporally resolved single-cell RNA sequencing (scRNA-seq) we have identified a conserved population of progenitors previously identified as potential NeuroMesodermal Progenitors (NMPs). Based on our scRNAseq data we characterized their dynamics and developmental trajectories using two computational methods, RNA velocity and Pseudotime analysis. We observed the reinduction of pluripotency factors that transiently reactivate multi germ-layers progenitors. Finally, by in-toto single-cell tracking of the tail elongation using a light-sheet microscope we established a precise dynamic fate map of the progenitors during axis elongation. All together we proposed for the first time at the single-cell level a comprehensive multimodal description, from the transcriptome to the cell tracking, of the tail progenitors lineage and identified transient populations of multi germ-layers progenitors after the end of gastrulation. Our study provides a general framework for multimodal cell lineage reconstruction during embryogenesis.

Keywords: Cell-Lineage, Embryogenesis, Neuro Mesodermal Progenitors

2:15 PM – 2:35 PM

TOWARDS RECONSTITUTING HUMAN SOMITOGENESIS IN VITRO

Alev, Cantas, Yamanaka, Yoshihiro, Yoshioka-Kobayashi, Kumiko, Hamidi, Sofiane, Munira, Sirajam, Zhang, Yi, Kurokawa, Yuzuru, Sunadome, Kazunori, Moris, Naomi, Martinez-Arias, Alfonso, Yamamoto, Takuya and Tsujimura, Taro

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Somitogenesis, a core developmental event during which the metameric body plan of vertebrates is laid out, has been extensively studied using model organisms such as mouse, chick or zebrafish, but remains largely elusive and poorly understood when it comes to human. Using embryonic development-inspired induction of presomitic mesoderm (PSM) from mouse and human pluripotent stem cells, we previously succeeded to quantify oscillatory activity of the so-called segmentation clock, a molecular oscillator believed to control somite formation. Interestingly, these in vitro models of the segmentation clock did not show any sign of segmentation or somitogenesis despite the clear presence of oscillatory activity of clock genes such as HES7. Extending on these earlier findings we then asked whether we could recapitulate not only the clock but also the actual process of segmentation and epithelial somite formation in vitro. Utilizing again pluripotent stem cells as starting material and following the guiding principles of the embryo we were able to establish a 3D model of human axial development, which resembles and reconstitutes diverse aspects of the tail and axis of the developing embryo, including the presence of traveling wave like oscillatory activity of HES7 coupled with the sequential formation and patterning of epithelial somite-like structures. Our newly established bottom-up model system of somitogenesis thus provides a promising new platform to study various aspects of axial development and disease in human and other species.

Keywords: human development, somitogenesis, mesoderm

TRACK: NEW TECHNOLOGIES (NT)
NEW AVATARS OF ORGANOGENESIS
1:00 PM – 2:45 PM
ROOM 2012
LEVEL 2

1:05 PM – 1:25 PM

SYNTHETIC MULTISTABILITY IN MAMMALIAN CELLS

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In multicellular organisms, gene regulatory circuits generate thousands of molecularly distinct,mitotically heritable states through the property of multistability. Designing synthetic multistable circuits would provide insight into natural cell fate control circuit architectures and would allow engineering of multicellular programs that require interactions among distinct cell types. We created MultiFate, a naturally inspired, synthetic circuit that supports long-term, controllable, and expandable multistability in mammalian cells. MultiFate uses engineered zinc finger transcription factors that transcriptionally self-activate as homodimers and mutually inhibit one another through heterodimerization. Using a model-based design, we engineered MultiFate circuits that generate as many as seven states, each stable for at least 18 days. MultiFate permits controlled state switching and modulation of state stability through external inputs and can be expanded with additional transcription factors. These results provide a foundation for engineering multicellular behaviors in mammalian cells.

Keywords: multifate

1:25 PM – 1:35 PM

GENOMIC LOCI FOR GENETIC ENGINEERING OF PLURIPOTENT STEM CELLS AND THEIR PROGENY

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The identification of genomic loci within the human genome that can permit safe and reliable expression of novel transgenes is of critical importance when considering the efficient and stable modification of human pluripotent stem cells (hPSCs) and their progeny. The AAVS1 site has been cited as a potential safe harbour locus for insertion of exogenous transgene cassettes in cultured cells, including hPSCs. However AAVS1 is commonly associated with transgene expression that is highly variable, particularly in hPSCs which are extremely adept at silencing transgenes driven by viral, minimal or non-specific promoters. As such, a strong need exists for the identification of additional loci. Using RNAseq datasets from differentiating iPSCs, we identified numerous candidate loci that exhibit ubiquitous gene expression. CRISPR/Cas9-based gene editing was used to insert a T2A-linked fluorescent reporter just upstream of the candidate gene's stop codon whereby reporter expression could be used as read-out of both targeting efficiency and gene expression levels. Using this approach, we have identified several genomic loci that can be targeted efficiently in the absence of drug selection and can permit low, medium or high transgene expression that is stable in hPSCs and their differentiated progeny. These candidate loci can be exploited to incorporate multiple transgenes in a single step, facilitating many downstream modifications including but not limited to the incorporation of; Cas proteins for genetic screens, synthetic arrays/barcodes for lineage tracing applications, transgene cassettes that monitor cell

cycle and other cellular processes, or suicide switches for generation of safe cell products for transplantation.

Funding Source: This work is supported by the Novo Nordisk Foundation Center for Stem Cell Medicine (reNEW,) Novo Nordisk Foundation grant number NNF21CC0073729
Keywords: Gene editing, Pluripotent stem cell, Transgene

1:35 PM – 1:45 PM

OPTOGENETIC REPORTERS DELIVERED AS MRNA FACILITATE REPEATABLE ACTION POTENTIAL AND CALCIUM HANDLING ASSESSMENT IN HUMAN IPSC-DERIVED CARDIOMYOCYTES

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Human PSC-derived cardiomyocytes (hPSC-CMs) provide a platform to investigate the mechanisms underlying cardiac disease, as well as to perform compound screens to identify not only potential new therapeutic strategies but also for toxicity studies. In this regard it is important to evaluate various aspects of cardiac physiology, including the cardiomyocyte's electrical activity and intracellular calcium transients. These can be measured optically using, for example, organic fluorescent dyes. However, many of these dyes cause cytotoxicity and cannot be used for long term measurements due to bleaching effects. As an alternative to organic dyes, we have investigated whether genetically-encoded voltage and Ca2+ indicators (GEVIs and GECIs) delivered as modified mRNA (modRNA) into human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) would be accurate alternatives allowing measurements over a prolonged time period. We find transfection of in vitro transcribed mRNA into hPSC-CMs to be efficient with low toxicity, and a rapid way to evaluate the sensitivity of different reporters. The signal from these genetically-encoded indicators is maintained at detectable levels in the hPSC-CMs for several days, and is less prone to photobleaching. While expression of these indicators results in some effect on the baseline functional characteristics of the hPSC-CMs, it does not affect the response of the cells to known pro-arrhythmogenic compounds. Furthermore, using the GEVI ASAP2f we observed action potential prolongation in Long QT syndrome models, while the GECI jRCaMP1b facilitated the repeated evaluation of Ca2+ handling responses for various tyrosine kinase inhibitors. This study demonstrates modRNAs encoding optogenetic constructs report cardiac physiology in hiPSC-CMs with low toxicity and circumvents the need to generate genetically modified cell lines, thereby illustrating their value as alternatives to organic dyes or other gene delivery methods for expressing transgenes.

Funding Source: NovoNordisk Foundation - ReNEW #NNF21CC0073729 ERC-StG - STEMCARDIORISK #638030 A Netherlands Organization for Scientific Research (NWO)-funded VIDI fellowship - ILLUMINATE #91715303 Gravitation project - NOCI #024.003.001
Keywords: hiPSC-derived cardiomyocytes, Genetically encoded reporters, Cardiac voltage and calcium dynamics

1:45 PM – 1:55 PM

A NOVEL MICROPATTERNED DIFFERENTIATION SYSTEM SHOWS THAT GEOMETRIC CONSTRAINT FUNDAMENTALLY CHANGES THE OUTCOME OF WNT AND FGF MEDIATED DIFFERENTIATION.

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Gastrulation is a key developmental event in which the pluripotent epiblast differentiates into the three germ layers: ectoderm, endoderm and mesoderm. This event occurs in the primitive streak where cells are exposed to morphogens including FGF and WNT. However, how these signals orchestrate cell differentiation into specific cell fates remains incompletely understood. Using human embryonic stem cells (hESCs), we studied how FGF and WNT affect the differentiation of the epiblast, and discovered that in standard culture, these signals do not fully differentiate hESCs to either mesoderm or endoderm, but when they are applied to cells spatially constrained via micropatterning technology, two organized populations arise in distinct layers: an epiblast-like disk-shaped cell population (SOX2+/OCT4+/ECAD+) on top of a definitive endoderm cell population (SOX17+/FOXA2+/NCAD+). Surprisingly, increasing WNT levels do not change the identities of these two fates, only the proportion of cells adopting each one. By directly observing and manipulating signaling activities, we uncovered an essential role for endogenous Nodal in these events, as well as different trajectories of canonical Wnt signaling that correlate with maintaining the epiblast state or differentiating into endoderm. These findings show the importance of spatial control in shaping how cells interpret intercellular signaling and make cell fate decisions.

Funding Source: -NIH (R01GM126122) -CONACYT
Keywords: human embryonic stem cells, micropattern, endoderm differentiation

1:55 PM – 2:05 PM

SELF-ORGANIZATION OF PLURIPOTENT MOUSE EMBRYONIC STEM CELLS TO GENERATE FUNCTIONAL MAMMARY ORGANOID

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The self-organization of embryonic stem cells (ESCs) to form organoids has opened new avenues to our understanding of stem cell and regenerative biology, organogenesis, and disease mechanisms. Although organoid culture conditions have been developed to generate "mini-organs" from tissue adult stem cells and pluripotent stem cells, the generation of mammary organoids from ESCs is a challenge. Taking cues on how the mammary gland develops in vivo, here we report an optimized in vitro condition for the generation of the mammary organoids, that mimic the tissue organization of a functional mammary gland. We have customized an organoid culture system by self-organizing mouse ESCs that differentiate to form complex skin and associated skin appendages. We use stepwise modulation of BMP, TGFβ, and FGF signaling pathways to co-induce surface ectoderm and mammary mesenchymal cells within an embryoid body. We show that an antagonistic interaction between BMP and Hedgehog signaling in the spherical cell aggregate can block the formation of hair follicles in the dermal mesenchyme and promotes mammary lineages, concomitant with embryonic mammary commitment. We recapitulate the dermal-epidermal interaction in these organoids and the development of mammary lineages characterized by hormone sensing luminal and myoepithelial cells. The lactogenic hormonal stimulation led to the secretion of milk proteins into

the organoid lumen further confirming the functional capacity of mammary organoids. We anticipate that the mammary organoids derived from mESCs will be a powerful model to study the evolution of skin appendages, understand mammary organogenesis, and could be used as a complementary system to remodel breast cancer tumorigenesis.

Keywords: Embryonic Stem cells, Mammary organoid, Organogenesis

2:05 PM – 2:15 PM

PROGRAMMED BENDING OF A 3D BIOPRINTED HEART TUBE INSPIRED BY CARDIAC MORPHOGENESIS

Bliley, Jacqueline[1], Joshua, Tashman[1], Maria, Stang[2], Coffin, Brian[2], Behre, Annie[1], Shiwarski, Dan[1], Lee, Andrew[1] and Hinton, TJ[1]

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A long-term goal of the cardiac tissue engineering field has been organ-scale biofabrication in order to repair or regenerate the adult heart. However, to date recreating the complex 4-chambered architecture and differentiating stem cells into the diverse cell types has proved challenging, with even the most advanced examples displaying limited contractility. As an alternative, we looked at embryonic heart development from a linear tube that bends, loops and septates to form its 3D structure, and how these shape changes impart mechanical stresses that are critical to later heart structure and function. Here, we sought to develop an experimental tissue engineered model system that uses embryonic cardiogenesis as design inspiration for building a functional human heart. To do this, we engineered a linear human heart tube using Freeform Reversible Embedding of Suspended Hydrogels (FRESH) 3D bioprinting with bioinks composed of (i) collagen and (ii) embryonic stem cell derived cardiomyocytes and primary fibroblasts. Heart tubes demonstrated synchronized contraction, linear action potential propagation, and unidirectional pumping of fluorescent beads through the lumen at 400 µm/s. To mimic the heart tube bending observed during cardiac morphogenesis, structural and mechanical asymmetries were designed into 3D printed tissue to drive bending via cell-mediated compaction forces. Over 7 days of culture, tube bending resulted in region-specific changes in structure and function with the outer curvature of the bent tube displaying increased cardiomyocyte alignment and conduction velocity compared to the inner curvature, similar to findings observed in utero. Differences in conduction paths were also observed, with bent tubes initiating action potentials at the outer curvature, comparable to the mature apex-to-base conduction switch that occurs during embryonic heart development. These results show that it is possible to mimic changes in tissue structure and function that are similar to early heart morphogenesis, including stress-induced cell alignment, tissue 3D structure, and conduction pathways.

Funding Source: Additional Ventures
Keywords: 3D Bioprinting, Heart Tube, Cardiac

2:15 PM – 2:35 PM

MECHANICS REGULATE HUMAN EMBRYONIC STEM CELL SELF-ORGANIZATION TO SPECIFY MESODERM

Weaver, Valerie[1], Ayad, Nadia M. E.[2], Muncie, Jon[1], Lakins, Jon and Fu, Jianping[3]

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Morphogens direct embryogenesis and tissue-specific differentiation in the context of a defined tissue structure. Tissue structure is mediated by cell-cell and cell-extracellular matrix (ECM) adhesions and stromal ECM stiffness that modulate cellular tension and tissue-level force. We have been studying how cell adhesion-dependent tension and tissue-level forces regulate morphogen signaling to direct tissue-specific development. We used human embryonic stem cells (hESCs), which exhibit an intrinsic capacity for self-organization, in combination with ECMs of defined geometries and stiffness, as a tractable model of early human embryogenesis. Studies revealed that a compliant ECM permits the development of localized regions of tissue tension and increases cell-cell force that direct the "gastrulation-like differentiation of hESCs in response to BMPs. Engineered patterned substrates with defined geometries and ECM stiffness induced localized nodes of high cell-adhesion tension that drove BMP-dependent gastrulation by enhancing phosphorylation and nuclear translocation of β-catenin to promote Wnt signaling and mesoderm specification. Causality between cell tension and tissue-level force-dependent mesoderm specification was established through gain of function loss of function studies that involved localized tissue stretching and exploitation of engineered tissue geometries with decreased local tension. Links between tension-induced beta catenin phosphorylation mediated through exposure of cryptic regions and Wnt signaling was demonstrated using a dephosphomimetic mutant beta catenin (Y654F) which ablated force-dependent gastrulation induction. The findings underscore links between tissue organization, cell tension, and morphogen-dependent differentiation.

Keywords: hESCs, mechanics, gastrulation

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)
EVOLUTION OF STEM CELL FUNCTION AND TISSUE ARCHITECTURE
1:00 PM – 2:45 PM
ROOM 2007
LEVEL 2

1:05 PM – 1:25 PM

A MECHANISM BASED ON MECHANICAL FORCES STEMMING FROM INCOMPLETE DELAMINATION GUIDES THE ALLOCATION OF PROGENITOR CELLS IN ZEBRAFISH

Concha, Miguel L., Pulgar, Eduardo, Schwayer, Cornelia, López, Loreto, Guerrero, Néstor, Márquez, Susana, Härtel, Steffen, Soto, Rodrigo and Heisenberg, Carl-Philipp

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A critical step in embryonic development is the allocation of progenitors at the site of differentiation. This early phase can be challenging, as progenitors often travel long distances and face conflicting signals and in mass morphogenetic movements that

can derail their normal development. The different developmental strategies used by progenitors to withstand these challenges and move on to other phases of differentiation are still poorly understood. Here we combine in vivo imaging and biomechanical manipulation in zebrafish embryos to uncover a mechanism of progenitor cell allocation mediated by mechanical forces that stems from an incomplete process of epithelial delamination. Progenitors of the zebrafish laterality organ originate from the superficial epithelial enveloping layer through an apical constriction process of cell delamination. During this process, a subset of progenitors retains long-lasting apical contacts that allow the epithelial layer to pull them on their way to the vegetal pole. The remaining delaminated cells follow the movement of apically attached progenitors by a co-attraction mechanism dependent on cell-cell contact and cell protrusions, preventing sequestration by the adjacent endoderm, ensuring their collective fate and allocation at the site of differentiation. Thus, we reveal that incomplete delamination serves as a cellular platform for coordinated tissue movements during development, allowing progenitors to coordinate their movement with adjacent extraembryonic tissues. This tissue-tissue mechanical coupling provides leader cell properties to a subset of progenitors that guide the directed movement of the progenitor pool and its allocation at the site of organ differentiation while protecting them from unwanted loss.

Keywords: progenitors, cell delamination, apical constriction, mechanical forces, collective locomotion, dorsal forerunner cells, zebrafish

1:25 PM – 2:45 PM

MICRORNAS AND INCREASED CHROMATIN ACCESSIBILITY EXPAND DEVELOPMENTAL POTENTIAL OF CRANIAL NEURAL CREST

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The potency of a cell is defined by networks which incorporate chromatin structure, transcription factors, regulatory elements, and post transcriptional regulators. Developmental potential is progressively restricted after germ layer specification and cells typically can only give rise to derivates within their lineage. However, cranial neural crest cells are an exception and arise from anterior ectoderm yet give rise to both mesodermal derivatives that contribute to the craniofacial skeleton and ectodermal derivatives that contribute to the peripheral nervous system. How cranial neural crest undergo reprogramming and expand their ability to give rise to multiple lineages of derivatives is poorly understood. During somatic cell reprogramming, microRNAs induce a permissive chromatin structure and chromatin hyperaccessibility poises pluripotency loci for subsequent activation. Whether microRNAs and chromatin accessibility regulate the acquisition of expanded developmental potential of cranial neural crest has not been studied. Here we demonstrate that a transient state of increased chromatin accessibility promotes expression of both transcription factors and microRNAs from pluripotency. We find that at the time of specification, cranial neural crest cells are biased towards a neuronal or ectomesenchymal fate and each lineage reactivates different components of pluripotency. Further, we uncover a miRNA-dependent mechanism for increased chromatin accessibility and expanded developmental potential. We demonstrate that pluripotency microRNA miR-302 is required for increased chromatin accessibility during cranial neural crest specification and represses genes involved in condensing chromatin. Upon miR-302 deletion we find a reduction in chromatin accessibility specifically around pluripotency loci in early premigratory neural crest. Further, we find that miR-302 is required for terminal differentiation of peripheral neurons and chromatin accessibility around neuronal genes. Thus, miR-302 is required to endow developmental potential to the ectodermal lineage of neural crest. Our findings identify miRNAs as regulators of chromatin accessibility and reactivation of pluripotency factors within cranial neural crest to expand developmental potential.

Funding Source: National Institutes of Health T32 ES027801-04 (RAK), R01-HD099252, R01-HD09813 (RJP.); CPRIT Scholar in Cancer Research RR150106 (RJP.); Andrew McDonough B+ Foundation (RJP.); V Scholar in Cancer Research #V2017-017 (RJP)
Keywords: Multipotency, MicroRNAs, Cranial Neural Crest

1:35 PM – 1:45 PM

REPROGRAMMED BLASTOIDS CONTAIN AMNION-LIKE CELLS BUT NOT TROPHECTODERM

Zhao, Cheng[1], Reyes, Alvaro[2], Schell, John[2], Weltner, Jere[2], Ortega, Nicolás[2], Zheng, Yi[3], Björklund, Åsa[4], Rossant, Janet[5], Fu, Jianping[3], Petropoulos, Sophie[2] and Lanner, Fredrik[2]

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With the advancement of human stem cell cultures and interest in understanding human embryogenesis, human blastocyst-like structures, or human blastoids, are being developed. Thus far, two different strategies have been taken, generating blastoids from naïve human pluripotent stem cells (hPSC) or through reprogramming of adult human somatic cells. All these studies utilize comparative transcriptome analyses to authenticate blastoid cells and identify their counterparts in the human blastocyst. However, the validity of comparative transcriptome analysis is critically hinged on including relevant reference data, not only those from targeted cell types but also from potential alternative cell lineages. Thus, we sought to reevaluate the single-cell transcriptome data from the blastoids based on a more comprehensive cellular reference, which includes data from in vitro cultured human, non-human primate (NHP, Cynomolgus macaque) blastocysts, a human stem cell-based post-implantation amniotic sac embryoid (PASE) model, and an in vivo gastrulation-stage human embryo specimen, using four different analysis strategies. Our analyses unequivocally support that blastoids developed by reprogramming adult human somatic cells largely fail to generate cells with a transcriptome profile consistent with the human blastocyst trophectoderm. Instead, cells identified as trophectoderm-like have a transcriptional profile more similar to the amniotic ectoderm in the gastrulating human and NHP embryos. To facilitate cell lineage identifications in human embryo models, we further identified a set of human amniotic ectoderm and trophectoderm markers that could be utilized to distinguish these two lineages. Finally, we further built a neural-network based online prediction tool, which accurately discerns the full cellular composition of blastoids.

Funding Source: Swedish Research Council Ragnar Söderberg Foundation Natural Sciences and Engineering Research Council of Canada Discovery Grant, The Canadian Institutes of Health Research Päivikki and Sakari Sohlberg Foundation
Keywords: blastoids, amnion, trophectoderm

1:45 PM – 1:55 PM

LYMPHATIC CAPILLARIES RESIDE IN THE INTESTINAL STEM CELL NICHE AND REGULATE STEM CELL ACTIVITY

Niec, Rachel[1], Chu, Tinyi[2], Gur-Cohen, Shiri[1], Schernthanner, Marina[1], Hidalgo, Lynette[1], Pasolli, Hilda Amalia[3], Kataru, Raghu[4], Mehrara, Babak[4], Pe'er, Dana[2] and Fuchs, Elaine[1]

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Barrier epithelia depend on resident stem cells for tissue maintenance, defense and repair. Intestinal stem cells (ISCs) of the small and large intestines respond to their local microenvironments (niches) to fulfill a continuous demand for tissue turnover to maintain the absorptive and barrier functions of the intestinal epithelium. The complexity of the intestinal niches is still unfolding. Here, we report an extensive lymphatic network that intimately associates with ISCs within the small and large intestinal crypts. Devising a lymphatic:organoid coculture system, we show that lymphatic-secreted factors maintain ISCs while inhibiting precocious differentiation. Employing a new deconvolution algorithm, BayesPrism, to pair single-cell and spatial transcriptomics, we cartograph the spatially restricted lymphatic:ISC interactome at high resolution. We unearth crypt lymphatics as a major source of known ISC niche factors, including WNT-signaling factors (WNT2, R-SPONDIN-3), and REELIN, a hitherto unappreciated ISC regulator secreted by lymphatics at the crypt base. Together, our studies expose lymphatics as a central hub for secreted niche factors that govern the regenerative potential of ISCs.

Funding Source: UL1 TR001866 and KL2TR001865 NIAMS R01-AR050452 STARR Foundation
Keywords: Intestinal Stem Cell Niche, Lymphatic, Spatial Transcriptomics

1:55 PM – 2:05 PM

BONE-LINING OSTEOPROGENITORS AMPLIFY CHOLINERGIC SIGNALING IN BONE AND BONE MARROW

Gadomski, Stephen[1], Fielding, Claire[2], Garcia-Garcia, Andres[2], Korn, Claudia[2], McCaskie, Andrew[3] and Mendez-Ferrer, Simon[2]

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The sympathetic nervous system regulates body homeostasis primarily through norepinephrine; however, sympathetic cholinergic fibers have been shown to innervate periosteum and cortical bone with smaller branches reaching the trabecular bone. In recent studies, cholinergic innervation has been shown to promote bone formation, and regulate hematopoietic stem cell quiescence and mobilization, yet little is known about the propagation of the cholinergic signal to the bone marrow (BM). Therefore, we characterized the cholinergic system in bone and BM using Airyscan2 supra-resolution imaging. Choline acetyltransferase (ChAT)-IRES-cre mice were crossed with Ai35D or Ai14D reporter mice, which resulted in genetic labelling of cholinergic neurons in long bones and skulls, as expected. However, ChAT-traced cells were also found to be lining bone surfaces, and co-localized with osteogenic markers CD51, osterix (SP7), alkaline phosphatase (ALPL), and Runt-related transcription factor 2 (RUNX2). ChAT-labelling, ChAT gene expression, and acetylcholine (ACh) intracellular content was higher in downstream PDGFRα- osteoprogenitors compared to more primitive PDGFRα+ and Nes-Gfp+ cells. Since CD51+ cholinergic bone-lining cells express nicotinic receptors and are proximal to periosteal and cortical cholinergic nerve fibers, we supposed that these osteogenic cells transmit the cholinergic signal to the BM parenchyma. Therefore, we treated CD51+ cells with cholinergic agonists and antagonists daily for 4 days in vitro. Cholinergic agonist treatment (i.e., nicotine, ACh) increased ChAT and VAChT mRNA expression, as well as ACh content in cultured CD51+ cells, while these effects were attenuated upon co-treatment with the nicotinic antagonist, hexamethonium. To confirm this data in vivo, we used two models of neural cholinergic expansion: moderate treadmill exercise and BM transplantation in ChAT-IRES-cre;Ai14D mice. Cholinergic nerve fiber density was increased ~2-fold after exercise and ~5-fold after BM transplantation; importantly, matching the cholinergic neural response in both models, the frequency of ChAT-labelling in osteogenic cells increased, supporting the notion that osteolineage cells transmit and amplify cholinergic neural signals in bone and BM.

Funding Source: This work was supported by core grants from MRC to the Cambridge Stem Cell Institute; National Health Service Blood and Transplant (UK), EU's Horizon 2020 research, MRC-AMED grant, & a Programme Foundation Award from Cancer Research UK.
Keywords: Cholinergic, Osteogenic, Bone marrow

2:05 PM – 2:15 PM

BLOOD STEM CELLS GENERATE THEIR OWN MICROENVIRONMENT

Sacma, Mehmet[1], Mulaw, Medhanie A.[2], Hageb, Ali[1], Bogeska, Ruzhica[3], Sakk, Vadim[1], Vollmer, Angelika[1], Marka, Gina[1], Soller, Karin[1], Milsom, Michael D.[3], Florian, Maria Carolina[4] and Geiger, Hartmut[1]

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Quantitative 3D imaging of organ-wide cellular and subcellular components is central for revealing and understanding complex interactions between stem cells and their microenvironment. In situ or in vivo 3D quantitative imaging remains technically challenging, which restricts its more widespread use in stem cell research. The quantitative nature of the interrelationship of hematopoietic stem cells (HSCs) with their progeny, which count for the vast majority of bone marrow (BM) cells, and with other niche components remains only partially characterized. We recently designed a fast but gentle methodology termed iFAST3D that enables reproducible and quantitative high-fidelity 3D imaging of HSCs and their progeny within BM or various niche components, all simultaneously. iFAST3D is a very versatile and easy to apply resource. Using this approach, we demonstrate that HSCs are frequently localized proximal to a subset of early lymphoid progenitor cells (ELPs). HSCs located in the central-sinusoidal BM build a microenvironment by their own megakaryocytes, whereas HSCs in the endosteal-arteriolar BM are frequently localized proximal to a subset of ELPs, produced by themselves, which generate their microenvironment. In addition, the microenvironment in which quiescent HSCs reside are themselves proliferation quiescent BM regions, which imply a coupling of the activation status of HSCs

and the niche. In summary, we show that individual HSCs are contributing to their own microenvironment.

Keywords: hematopoietic stem cell, microenvironment, niche

2:15 PM – 2:35 PM

CONSERVED AND DIVERGENT FUNCTIONS OF SOX10 IN NEURAL CREST DEVELOPMENT ACROSS SPECIES

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Neural crest cells are pluripotent embryonic stem-like cells that give rise to more than 30 different adult cell and tissue types including the craniofacial bone and cartilage and the peripheral and enteric nervous systems. Much of what we know about the mechanisms that regulate neural crest development has been identified independently in a handful of model organisms, and the findings have been incorporated into a neural crest gene regulatory network (GRN) model to resolve protein-gene interactions. However, we lack confirmation of the functional conservation of proteins across species including their targets, partners, and roles in development, thereby making comprehensive understanding of neural crest evolution and development challenging. Although the factors that regulate neural crest development are conserved across species, we do not know if they function at the same developmental time, regulate the same targets, or if changes in these factors drive phenotypic variation across species. We have identified both conserved and divergent developmental mechanisms and timing by comparing spatiotemporal expression of genes and proteins that control neural crest cell development in quail (Coturnix japonica), chick (Gallus gallus), and peafowl (Pavo cristatus) embryos. Functional perturbation of the commonly used neural crest marker, SOX10, has additionally identified its differential roles in the progression of neural crest differentiation and migration in chick and quail embryos. Although SOX10 is necessary for neural crest cell formation and normal migration in both species, it is sufficient to drive differentiation in chick embryos and migration in quail embryos. Our results demonstrate potentially different roles for SOX10 at different stages of development in two closely related organisms. Future work will focus on understanding the embryonic environments that drive these different phenotypes. Collectively, this work will shed light on the molecular, cellular, and organismal-level mechanisms that drive neural crest cell formation and will significantly increase our understanding of how organisms use the same factors to drive differential morphogenesis.

Keywords: embryogenesis, neural crest, Sox10, chick, quail, neural tube

TRACK: CELLULAR IDENTITY (CI)
EPIGENETIC REGULATION OF STEM CELLS
5:15 PM – 7:00 PM
ROOM 2008
LEVEL 2

5:20 PM – 5:40 PM

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Abstract not available at time of printing

5:40 PM – 5:50 PM

B1 SINE-BINDING ZFP266 IMPEDES REPROGRAMMING THROUGH SUPPRESSION OF CHROMATIN OPENING MEDIATED BY PIONEERING FACTORS

Kaji, Keisuke[1], Kaemena, Daniel[1], Yoshihara, Masahito[2], Ashmore, James[1], Beniazza, Meryam[1], Zhao, Suling[1], Bertenstam, Marten[3], Olariu, Victor[3], Katayama, Shintaro[2], Okita, Keisuke[4], Tomlinson, Simon[1] and Yusa, Kosuke[5]

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Induced pluripotent stem cell reprogramming is inherently inefficient and understanding the molecular mechanisms underlying this inefficiency holds the key to successfully control cellular identity. In the previous ISSCR, we report 16 novel reprogramming roadblock genes identified by CRISPR/Cas9-mediated genome-wide knockout (KO) screening. Of these, we report that depletion of the predicted KRAB zinc finger protein (KRAB-ZFP) Zfp266 strongly and consistently enhanced iPSC generation in several iPSC reprogramming settings, emerging as the most robust roadblock. Further analyses revealed that ZFP266 binds Short Interspersed Nuclear Elements (SINEs) adjacent to binding sites of pioneering factors, OCT4 (POU5F1), SOX2 and KLF4, and impedes chromatin opening. Replacing the KRAB co-suppressor with a co-activator domain converted ZFP266 from a reprogramming inhibitor to a potent reprogramming facilitator. This work proposes SINE-KRAB-ZFP interaction to be a critical regulator of chromatin accessibility at enhancers for efficient cellular identity changes and also serves as a resource to further illuminate molecular mechanisms hindering reprogramming.

Funding Source: This project is supported by SNIC, ERC, MRC, Baillie Gifford, AMED, BBSRC, JSPS, SSF and Swedish Research Council.
Keywords: Reprogramming, iPS cells, SINE

5:50 PM – 6:00 PM

M6A EPITRANSCRIPTOME MEDIATED RNA STRESS GRANULE ASSEMBLY GOVERNS BLOOD DEVELOPMENT AND REGENERATION

Gunage, Rajesh D.[1], Bauer, Daniel[2], C, Stephen[2], Calo, Eliezer[3], Choudhary, Avik[4], Gregory, Richard[2], Han, Tianxio[5], L., Shuibin[2], Shah, Arish[3], Yang, Song[2], Zhou, Yi[2] and Zon, Leonard[1]

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Hematopoietic stem cell (HSC) form diverse cell types and requires transcription and translation regulation. Using CD34+ human hematopoietic stem and progenitor cells combined with N6-methyladenosine (m6A) seq we identified a novel, stress granule regulation during erythropoiesis. Transcriptome-wide single-nucleotide resolution m6A analysis identified ~4800 transcripts to be m6A modified and showed demethylation (>2-14 fold) during erythropoiesis. Genome-wide CHIP-seq of CD34+ cell erythropoiesis with anti-Gata1 showed an enhancer enrichment at the Alkbh5 RNA demethylase gene. CD34+ cell Alk5 CRISPR Cas9 KO led to erythropoiesis failure validating Alk5 role in erythropoiesis. CD34+ Alk5 KO cells showed a failure of RNA

m6A demethylation and we discovered stress granule (SGs) transcripts m6A levels to be upregulated (>2-4 fold, p=0.01). SGs are membrane-less organelles composed of various RNA-binding proteins. SGs form a hub in the cytoplasm, govern RNA metabolism and global proteome by translational regulation. We show ATXN2, G3BP1/2, Tia-1, and PABPC1 SGs transcripts are m6a modified at 3'UTR. K562 cell Alk5 KO erythropoiesis model led to massive m6A upregulation on ATXN2 3'UTR (>14 fold, p=0.001) and other SGs transcripts. Mass spectrometry of CD 34+ Alk5 KO cell proteome showed ATXN2 downregulation (>2 fold, -log P value2), confirming 3' UTR m6A mediated regulation. Alk5 KO led to the aggregation of SGs protein in the cytoplasm due to altered SG protein stoichiometry(>4-10 fold, p=0.001). Our Zebrafish Alk5 KO has defective blood development characterized by anemia, increased myeloid and lymphoid lineages indicating early lineage bias. CD34+ ATXN2 KO cells with colony formation assay showed defects in erythroid and myeloid lineages. Super-resolution microscopy of CD34+ ATXN2 KO cells phenocopied the presence of disease-associated ALS (amyotrophic lateral sclerosis) stress granules with TDP-43, G3BP1/2, PABPC1, and Tia-1 enriched for m6A mRNAs. Next, the K562 Alk5 KO erythropoiesis model and ATXN2 lentiviral overexpression effectively resolved stress granules and rescued erythropoiesis. In summary, ATXN2 mRNA m6A regulates SG biology to affect HSC function, impacting blood development. SG-mediated regulation of HSC fate may highlight new therapeutic strategies for blood disorders.

Keywords: Hematopoietic stem cell, stress granule, N6-methyladenosine (m6A) seq

6:00 PM – 6:10 PM

UNDERSTANDING THE BINDING DYNAMICS OF ASCL1 AND HES1 TRANSCRIPTION FACTORS DURING DIRECT REPROGRAMMING OF MOUSE EMBRYONIC FIBROBLASTS TO INDUCED NEURONAL (IN) CELLS

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The ability to directly convert differentiated somatic cell types into neuronal cells provides critical information about what defines a neuron. Elucidation of the mechanisms underlying this direct conversion has the potential to generate more comprehensive models of neurological disorders with which to study disease biology, perform drug screening, and produce more efficient regenerative medicine methods. Ascl1, a proneural basic helix loop helix (bHLH) transcription factor (TF), directly converts mouse embryonic fibroblasts into functional induced neuronal (iN) cells. In neural progenitor cells (NPCs), Ascl1 is repressed by Hes1, another bHLH TF which is expressed in fibroblasts and inhibits the reprogramming process. These TFs oscillate with a 2-3 hour period in NPCs, and this oscillation is necessary for maintaining the progenitor state, suggesting the dynamic action of these factors is critical for their cellular function. However, it is unclear how precisely these TFs locate and interact with their chromatin targets in real time. This project utilizes live-cell imaging to understand how Ascl1 and Hes1 act at their binding sites to control downstream gene expression during iN reprogramming. Using fluorescence recovery after photobleaching (FRAP) to estimate residence times, it was shown that, like other known TFs, Ascl1 displays a fast recovery, while Hes1 displays much slower recovery kinetics, suggesting a longer residence time. This was supported by single molecule imaging, using highly inclined and laminated optical sheet (HILO) microscopy to directly measure residence time. Structure-function studies show that the DNA binding domain of Hes1 is necessary but not sufficient to confer slow recovery. Similarly, the domain responsible for interactions with its co-repressor TLE is necessary, but not sufficient on its own, to confer slow recovery onto the fast-recovering Ascl1. Instead, replacing the entire C-terminal of Ascl1 with that of Hes1 converts Ascl1 into a slow-recovering factor, suggesting additional regulatory sites. Slow recovery was not unique to Hes1, but was seen in a subset of repressive transcription factors, suggesting this could be important for the mechanism of action of certain repressors. Future work will explore how longer DNA binding influences target gene expression.

Funding Source: This worked was funded by an NINDS F32 NRSA Postdoctoral Fellowship.
Keywords: iN reprogramming, transcription factors, live-cell imaging

6:10 PM – 6:20 PM

MODELLING HUMAN ZYGOTIC GENOME ACTIVATION IN 8C-LIKE CELLS IN VITRO

Taubenschmid-Stowers, Jasmin[1], Rostovskaya, Maria[1], Santos, Fátima[1], Ljung, Sebastian[1], Argelaguet, Ricard[1], Krueger, Felix[1], Nichols, Jennifer[2] and Reik, Wolf[1]

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The activation of the embryonic genome marks the first major wave of transcription in the developing organism. Zygotic genome activation (ZGA) in mouse 2-cell embryos, and 8-cell embryos in humans is crucial for development. Here we report the discovery of human 8-cell like cells (8CLCs) among naïve embryonic stem cells, that transcriptionally resemble the 8-cell human embryo. They express ZGA markers including ZSCAN4 and LEUTX and transposable elements such as HERVL and MLT2A1. 8CLCs show reduced SOX2 levels, and can be identified using TPRX1 and H3.Y marker proteins in vitro. Overexpression of the transcription factor DUX4 and spliceosome inhibition increase human ZGA-like transcription. Excitingly, the 8CLC markers TPRX1 and H3.Y are also expressed in ZGA stage 8-cell human embryos and may thus be relevant in vivo. 8CLCs provide a unique opportunity to model human ZGA-like transcription in vitro, and might provide critical insights into early events in embryogenesis in humans.

Keywords: 8-cell like cells, zygotic genome activation, in vitro model system

6:20 PM – 6:30 PM

THE LOSS OF HETEROCHROMATIN DURING STEM CELL AGING IS DRIVEN BY A DEPLETION OF S-ADENOSYLMETHIONINE SECONDARY TO INCREASED POLYAMINE SYNTHESIS

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The global loss of heterochromatin during aging has been observed in all eukaryotes from yeast to humans, and this has been shown to be a cause of aging. The heterochromatin loss induces transcriptional deregulation and leads to changes in global nuclear architecture. A more relaxed chromatin structure is predictive of genomic instability, including higher levels of DNA breaks, damaged foci formation, and inter-and intrachromosomal translocations. However, we are currently limited in our knowledge of the cause of heterochromatin loss during aging. Here we show that heterochromatin markers including histone H3K9 di-/tri-methylation and HP1, decrease with age in murine muscle stem cells

(MuSCs). Since S-adenosylmethionine (SAMe) is a major methyl donor for histone methylation, depletion of SAMe could lead to the loss of heterochromatin. Indeed, our metabolomic analysis in young and old MuSCs reveals decreased levels of intracellular SAMe with age. We find that restoration of the intracellular SAMe content in aged MuSCs increases heterochromatin to a youthful state and rejuvenates aging-associated features including increased DNA damage, delayed activation, and defective muscle regeneration. SAMe is not only a methyl group donor for transmethylation but it is also an amine group donor for polyamine synthesis. Excessive consumption of SAMe in polyamine synthesis may reduce its availability for transmethylation. Consistent with this premise, we observe that SAMe utilization in transmethylation is decreased, whereas polyamine synthesis is concomitantly increased in aged MuSCs. Furthermore, perturbation of polyamine synthesis restores the intracellular SAMe content of aged MuSCs as well as heterochromatin formation, and this improves aged MuSC function and regenerative capacity. Together, our studies demonstrate a direct link between polyamine metabolism and epigenetics during aging of MuSCs. The decreased availability of SAMe in global histone methylation due to overactivated polyamine synthesis could be one of the main mechanisms of loss of heterochromatin during aging.

Keywords: Aging, Epigenetics, Metabolism

6:30 PM – 6:50 PM

CAPRIN1 LINKS EARLY EMBRYONIC STEM CELL DIFFERENTIATION WITH RNA METABOLISM

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Embryonic stem cells (ESCs) are self-renewing and pluripotent. In recent years, an increasing number of factors controlling pluripotency, mostly nuclear, have been identified. To reveal non-nuclear regulators of ESCs, we screened an endogenously-labelled fluorescent fusion-protein library, which we previously generated in mouse ESCs. One of the more compelling hits was the cell cycle-associated protein, CAPRIN1. CAPRIN1, a Stress Granule (SG) component, exhibited a strikingly cyclical localization pattern in sync with mitosis, and localized to SGs, in response to stress. CAPRIN1 knockout had little effect in ESCs, but dramatically skewed differentiation and gene expression programs. RIP-seq and SLAM-seq revealed that CAPRIN1 associates with, and promotes the degradation of, thousands of RNA transcripts. CAPRIN1 interactome identified XRN2 as the likely ribonuclease. Upon early differentiation or stress, XRN2 colocalizes with CAPRIN1 inside SGs in a CAPRIN1-dependent manner. We propose that CAPRIN1 regulates an RNA degradation pathway operating during early ESC differentiation, eliminating undesired spuriously transcribed transcripts in ESCs.

Keywords: Embryonic stem cells; Pluripotency; RNA; Differentiation; CAPRIN1; XRN2

TRACK: CLINICAL APPLICATIONS (CA) BIOTECH, PHARMA AND ACADEMIA - BRINGING STEM CELLS TO PATIENTS
5:15 PM – 7:00 PM
ROOM 2004
LEVEL 2

5:20 PM – 5:40 PM

DEVELOPING PLURIPOTENT STEM CELL-DERIVED THERAPIES

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Abstract not available at time of printing.

Keywords: Pluripotent Stem Cell, Translation, Manufacturing

5:40 PM – 5:50 PM

IPSC-DERIVED IMMUNE CELLS IMPROVE COGNITION AND NEURAL HEALTH IN AGING MICE

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The ability of young blood or plasma to improve cognitive function in aged animals has been demonstrated by several studies, and our lab has shown beneficial effects of young mouse-derived bone marrow transplants into aged mice. However, the potential of graft vs. host disease and immune system rejection presents significant practical drawbacks that limit the therapeutic potential of these strategies. Induced pluripotent stem cells (iPSCs) offer the ability to generate an autologous therapy. Therefore, the aim of the current study is to identify the cell type responsible for the regenerative effects previously observed using plasma and bone marrow, and to test the potential of using these cells as a therapeutic. We generated macrophages from human iPSCs (iMACs) and administered them to aged, genetically immunocompromised NOD-scid-gamma (NSG) mice via tail vein injection. Aged mice receiving iMAC treatment showed significant improvements in behavioral tasks relying on spatial working memory and on hippocampal-dependent short-term memory. Additionally, treatment with iMACs had significant effects on several key neuronal health markers. That is, while expression of the synaptic transporter, VGLUT1, was decreased in aged mice, it was restored in aged mice treated with iMACs. Aged mice also had increased numbers of astrocytes and microglia, as well as decreased microglial branching; changes that were reversed by treatment with iMACs. Profiling of the plasma proteome revealed several proteins that were significantly different between young and aged mice, but restored with iMAC treatment, pointing to potential pathways that may be underlying the regenerative effects observed in iMAC-treated aged mice. Additionally, we find beneficial effects of these cells in initial studies using rodent models of neurodegenerative diseases. Thus, iMACs present a promising novel therapeutic strategy in aging as well as in neurodegeneration.

Funding Source: Cedars-Sinai Center for Women's Health and Sex Differences; Cedars-Sinai Board of Governors Regenerative Medicine Institute
Keywords: Macrophage, Aging, Neural health

5:50 PM – 6:00 PM

A UNIVERSAL APPROACH TO TREAT CNS MANIFESTATIONS IN LYSOSOMAL STORAGE DISEASES USING IPSC-DERIVED MICROGLIA

Irion, Stefan[1], Douvaras, Panos[1], Lepack, Ashley[1], Buenaventura Caldas, Diego[1], Stitt, Nick[1], Sun, Bruce[1], Sira, Elizabeth[1], Ibourk, Mariam[1], Kosmyna, Brian[1], Pereira, Elizabeth[1], Ebel, Mark[1], Srinivas, Maya[1], Simpson, Libby[1], LoSchiavo, Deven[1], Dilworth, David[2], Wilkinson, Dan[1], Keightley, Angela[2], Domian, Ibrahim[3], Soh, Chew-Li[1], Wang, Jing[1], Fisher, Stephanie[4], Tomishima, Mark[1], Paladini, Carlos[1] and Patsch, Christoph[1]

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BlueRock's mission is to create authentic cellular therapies in areas of unmet medical need. Inherited, lysosomal storage diseases (LSDs) are characterized by the pathologic build-up of toxic material in the body's cells because of a genetic defect resulting in enzyme deficiencies. There are over 70 LSDs and most have a progressive, neurodegenerative phenotype. While enzyme replacement therapies using recombinant proteins, bone marrow, and gene therapies are promising options, they often fall short in delivering therapeutically relevant levels of the enzyme to the CNS. Since microglia, the resident myeloid cells of the brain, are dispersed throughout the brain and microglia progenitors can readily be derived from human induced pluripotent stem cells (hiPSCs) we identified them as a potentially ideal cell therapy for LSDs. Here we demonstrate that wildtype donor microglia progenitors can cross-correct the enzymatic deficiency in several LSDs in vitro and in vivo by transferring the missing enzyme to diseased cells. This novel approach allows us to develop an off-the-shelf therapy, available even prior to disease onset. We developed a method to generate CX3CR1 positive microglia progenitors from healthy donor hiPSCs. Initially, we focused on Hurler Syndrome, with its underlying alpha-L-iduronidase (IDUA) deficiency. In transwell cultures, we showed that healthy microglia progenitors release IDUA enzyme into the culture media leading to a reduction of the toxic accumulation of glycosaminoglycans (GAG) in the recipient IDUA knockout microglia. Importantly, this general mechanism of cross-correction was true for several other LSDs as we could show in additional in vitro models of disease. To establish animal proof of concept, we treated Hurler mice with a single infusion of microglia progenitor cell product (MG01). After 1 and 5-months in vivo, we confirmed the presence of the grafted TMEM119, IBA1, CX3CR1, and CD163 positive cells, the presence of IDUA enzyme, and the reduction of GAGs in the brain, spinal cord, and CSF. In summary, hiPSC-derived microglia offer a potentially exciting new therapeutic approach to the treatment of LSDs, where our MG01 therapy can potentially treat several LSDs. This contrasts with enzyme replacement and gene therapies where each therapy is tailored to the specific genetic defect.

Keywords: microglia, lysosomal storage disease, cell therapy

6:00 PM – 6:10 PM

SAFETY AND EFFICACY OF FIRST-IN-HUMAN INTRATHECAL TRANSPLANTATION OF HUMAN ASTROCYTES (ASTRORX) DERIVED FROM EMBRYONIC STEM CELLS IN ALS PATIENTS: FROM BENCH TO BEDSIDE.

Izrael, Michal[1], Gotkine, Marc[2], Ben-Hur, Tamir[2], Caraco, Yoseph[3], Chebath, Judith[1], Estrin, Elena[1], Hasson, Arik[1], Kuperstein, Graciela[1], Lerner, Yossef[2], Revel, Ariel[1], Slutsky, Shalom Guy[1], Sonnenfeld, Tehila[1] and Revel, Michel[1]

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AstroRx® is a cell-based therapy, composed of healthy and functional human astrocytes derived from embryonic stem cells. We showed in preclinical studies that AstroRx® protect neurons in ALS by several mechanisms of action, including reduction of toxic compounds (e.g. reuptake of glutamate), reducing oxidative stress, and secretion of various neuroprotective factors. The clinical study hypothesis is that transplantation of AstroRx® can compensate for the malfunction of ALS patients' own astrocytes. We conducted a phase I/IIa, open label, dose-escalating clinical trial to evaluate the safety, tolerability and therapeutic effects of AstroRx® transplantation in patients with ALS. Five patients were injected intrathecally by lumbar puncture (LP) with a single dose of 100*106 AstroRx® cells and 5 patients with 250*106 cells (low and high dose, respectively). Safety and motor function assessments were recorded during a period of 3-month pre-treatment and 12-month post-treatment follow-up. A single dosing of AstroRx® at either low or high dose was safe and tolerable. No adverse events (AE) related to AstroRx® cells were reported. Transient AEs related to the LP procedure were observed in 70% of patients and were all resolved. A comparison between the ALSFRS-R change before and after treatment demonstrated a significant decline of at least 50% in disease progression rate, which was maintained for the first 3 months after treatment. The beneficial effect was consistent in both AstroRx® doses and was even more profound in Rapid Progressors. No significant change was found between pre- and post-treatment periods in HHD, JAMAR, ALSAQ-40, and serum biomarkers. The study results indicate that a single dose of AstroRx® cells is safe and tolerable, and provides a clinical signal of therapeutic benefit. These results support the path for the assessment of AstroRx® in a randomized, placebo controlled, multi-dose clinical trial in ALS.

Keywords: Amyotrophic Lateral Sclerosis, human embryonic stem cells, Astrocytes

6:10 PM – 6:20 PM

RESCUE OF A METABOLIC LIVER DISEASE MODEL BY GENETICALLY ENGINEERED HYPOIMMUNOGENIC HUMAN HEPATOCYTES

Yi, Fei[1], Vo, Karen[2], Kim, Junmo[2], Juang, Charity[2], Mikesell, Glen[2], Geng, Tao[3], Stewart, Leslie[3], Lopez, Sandy[3], Orrego, Esequiel[3], Hulse, Jason[3], Shabbir, Ayesha[3], Stumpf, Kaitlin[3], Witek, Rafal[2], Peixoto, Gabriel[2], Mendoza, Alan[2], Wilson, Elizabeth[3], Herrera, Tanya[3], Mao, Tin[4], Hollenbach, Stanley[3], Grompe, Markus[5], Holmes, Michael[5] and Hickey, Raymond[2]

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Primary human hepatocyte (PHH) transplantation has been pursued to address the huge unmet needs of liver disease, demonstrating clinical efficacy in multiple liver indications. However, two major factors have limited the widespread use of hepatocyte-based cell therapy: 1) a shortage of high-quality hepatocytes; and 2) the longitudinal loss of transplanted cells due to immune rejection. We hypothesized that PHH could be engineered ex vivo to be hypoimmunogenic and that such engineered hepatocytes could be expanded in an in vivo bioreactor to generate high quality "universal" hepatocytes suitable for therapeutic applications in many liver disease indications. Utilizing clinically validated genetic delivery modalities, a platform was optimized to efficiently engineer PHH ex vivo. >80% double-editing efficiency in PHH ex vivo was consistently achieved for both knock-out and knock-in engineering events . To engineer hypoimmunogenicity in PHH, HLA class I expression was blocked, to prevent CTL recognition, by CRISPR/Cas9 nuclease-mediated B2M gene knockout. In addition, lentiviral vector (LV) overexpression of decoy genes, inc. HLA-E and CD47, was used to inhibit NK cell clearance. Engineered PHH demonstrated protection from mismatched donor CTL and NK cells in killing assays, while maintaining normal human hepatocyte function, in vitro. Finally, the in vivo functionality and expandability of these engineered hypoimmunogenic hepatocytes were tested by transplantation into an immune-deficient mouse model of hereditary tyrosinemia type 1 (FRG mice). Engineered human hepatocytes proliferated and readily repopulated FRG mice, demonstrating the ability to expand the quantity of engineered cells in vivo >100-fold. Importantly, engineered hepatocytes expanded in vivo at comparable kinetics to non-edited cells, and thus rescued hereditary tyrosinemia mice at levels comparable to normal functioning, non-edited hepatocytes. This is the first report of fully functional universal human hepatocytes. We expect that combining this engineering approach with our ongoing development of the FRG rat bioreactor for large-scale expansion of primary human hepatocytes will provide large quantities of high-quality hypoimmunogenic hepatocytes for transplantation.

Keywords: Cell therapy, Hepatocyte, Liver disease

6:20 PM – 6:30 PM

A NEW TRIAL TRANSPLANTING NEURAL PROGENITORS MODIFIED TO RELEASE GDNF INTO THE MOTOR CORTEX OF PATIENTS WITH ALS

Svendsen, Clive N.[1], Avalos, Pablo[1], Lewis, Richard[2] and Mamelak, Adam[2]

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ALS is an incurable disease with no effective treatments that is caused by the death of both spinal cord and cortical motor neurons. Over the past 10 years we have developed a novel combined ex vivo gene and stem cell therapy treatment approach. Fetal derived cortical neural progenitor cells have been expanded under cGMP conditions and modified to release the powerful growth factor GDNF to create a product termed CNS10-NPC-GDNF. Once transplanted these cells slow down motor neuron death in animal models of ALS through a combination of providing new healthy astrocytes and the release of biologically active GDNF (which cannot cross the blood brain barrier). These have been unilaterally transplanted into the lumbar spinal cord of 18 ALS patients in a Phase 1/2A safety study (NCT02943850) and we have shown safety, cell survival and GDNF release for up to three years. Through new animal studies we have now shown that CNS10-NPC-GDNF can also protect upper motor neurons and improve function in rodent models of ALS. Recent pre-clinical primate and rodent tumorigenicity and toxicology studies have allowed us to move forward with a new Phase 1/2A safety trial in ALS patients where we will be transplanting these cells unilaterally into the hand knob region of the motor homunculus (NCT05306457). Secondary outcome measures will include a comparison of hand function on the treated vs untreated side over time. We will present summary data from the first spinal cord trial and a synopsis of the ongoing cortical trial and the potential impact this may have on this devastating disease.

Funding Source: This work was funded by CIRM, the DoD and the Cedars-Sinai Board of Governors Regenerative Medicine Institute
Keywords: Neural progenitor cell, Growth factor, ALS

6:30 PM – 6:50 PM

DEVELOPMENT OF A CANCER IMMUNOTHERAPY BASED ON DENDRITIC CELL REPROGRAMMING

Pereira, Filipe, Zimmermannova, Olga, Ferreira, Alexandra G., Ascic, Ervin, Kurochkin, Ilia, Caiado, Inês, Rosa, Fábio, Pires, Cristiana, Benonisson, Hreinn, Cabrera, Diego Soto, Tenreiro, Ariane, Gomez-Jimenez, David, Bernardo, Carina, Bauden, Monika, Anderson, Roland, Höglund, Mattias, Miharada, Kenichi, Nakamura, Yukio and Lindstedt, Malin

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Cell fate can be experimentally reversed or modified by enforced expression of lineage specific transcription factors leading to pluripotency or the identity of another somatic cell type for regenerative medicine. The possibility to reprogram fibroblasts into induced dendritic cells (DC) competent for antigen presentation creates a paradigm shift for modulating the immune system with direct cell reprogramming. We identified PU.1, IRF8 and BATF3 (PIB) as sufficient and necessary to impose conventional DC type 1 (cDC1) fate in mouse and human fibroblasts as well as mesenchymal stromal cells. cDC1 are rare cells specialized in cross-presentation of antigens to cytotoxic CD8+ T cells. The identification of the cDC1 minimal gene regulatory network provides an opportunity to merge cell fate engineering and cancer immunotherapy. We hypothesized PIB could reprogram tumor cells into antigen presenting cells (APCs) to counteract tumor evasion mechanisms including immunosuppression and downregulation of antigen presentation. We show that enforced expression of PIB is sufficient to induce hematopoietic and cDC1 markers in mouse and human tumor cell lines. We further show that reprogramming restores the expression of antigen presentation complexes along with co-stimulatory molecules at cell surface. PIB gradually overwrites the cancer transcriptional program imposing global antigen presentation and cDC1 gene signatures. Importantly, tumor antigen presenting cells (tumor-APCs) present endogenous antigens

on MHC-I and become prone to CD8+ T cell mediated killing. Furthermore, reprogrammed tumor-APCs secrete inflammatory cytokines, uptake and process exogenous proteins and dead cells. Importantly, tumor-APCs cross-present antigens to naïve CD8+ T cells and control tumor growth in vivo. We also provide evidence that reprogramming is efficient in primary tumor cells. We have now founded the start-up company Asgard Therapeutics for the development of in situ reprogramming of cancer cells into cDC1. Our approach combines cDC1's antigen processing and presenting abilities with the endogenous generation of tumor antigens and serves as a platform for the development of an entirely new approach to cancer immunotherapy.

Keywords: Reprogramming, Immunotherapy, Dendritic Cell

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)
MODELING ORGANOGENESIS AND DEVELOPMENTAL DISORDERS
5:15 PM – 7:00 PM
ROOM 2011
LEVEL 2

5:20 PM – 5:40 PM

EXAMINATION OF THE ROLE OF TBX3 AND TBX2 IN PANCREATIC BETA CELL DEVELOPMENT

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TBX3 has long been known as a marker of liver development and mouse models carrying mutations in this gene display defects in liver development. Using human pluripotent stem cells (PSCs), we generated TBX3 null lines via CRISPR/Cas9 based genome engineering. As expected, loss of TBX3 led to defects in liver development. Surprisingly, markers of pancreas development that are normally not expressed when using a liver differentiation protocol were also induced such as PDX1, MNX1 and ISL1. Other more mature pancreatic markers such as NEUROG3 and NKX2.2, while not expressed during the liver differentiation protocol, did display more accessible chromatin in the mutant as determined by ATAC-seq. When using a pancreatic differentiation protocol, the TBX3 null line displayed enhanced efficiency in generating PDX1+NKX6.1+ pancreatic progenitors. Loss of TBX3 was found to induce upregulation of a closely related family member, TBX2, suggesting potential compensation. To investigate this possibility, we generated TBX3/TBX2 compound null stem cell lines. When generating pancreatic beta-like cells, we found that loss of TBX3 decreased the proportion of polyhormonal cells and the compound null decreased the unwanted polyhormonal population further. Interrogation of published datasets revealed that human beta cells from diabetic individuals (both T2D and T1D) display an upregulation of TBX2 or both TBX2 and TBX3, suggesting a possible link to diabetes pathogenesis. Overall, these data highlight a role of TBX3 in regulating hepatic and pancreatic domains during foregut patterning, as well as the development of beta-like cells, with implications for enhancing the generation of mature pancreatic populations from PSCs.

Keywords: diabetes, pancreas, beta cells

5:40 PM – 5:50 PM

HELICASE VARIANTS ALTER THE TRAJECTORY OF NK CELL DEVELOPMENT FROM THE EARLIEST PRECURSORS

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Natural killer (NK) cells are innate lymphocytes that play a critical role in controlling viral infection and tumor immunity. Individuals with primary immunodeficiencies with a specific loss of NK cells have severe, recurrent viral infections and increased malignancy. Such NK cell deficiencies (NKDs) can be caused by mutations in DNA replicative helicase components, including MCM and GINS proteins. We hypothesized that the effects of these variants, namely impaired cell cycle progression and replication stress, accumulate throughout hematopoietic development and maturation to ultimately manifest in NK cell-specific vulnerability. To test this hypothesis, we generated induced pluripotent stem cells (iPSCs) from individuals with NKD due to compound heterozygous GINS4 variants (NKD lines), clinically unaffected family members, and unrelated healthy controls. As predicted by the de-stabilizing effect of these variants, NKD lines had significantly decreased GINS4 expression at pluripotency and throughout NK cell differentiation. While the most significant difference in GINS4 expression was observed when CD34+ precursors were being generated, distinct cell cycle phenotypes arose on day 28 of differentiation specifically in CD45+ lymphocytes. By the end of 42-day long differentiation, the NKD cell lines showed significantly lower frequency and number of terminally differentiated PERF+/GZMB+ NK cells, recapitulating the clinical phenotype previously described in the affected individuals. Cell cycle and impaired NK cell development of the NKD line were rescued with CRISPR correction, confirming the causal relationship between the NKD and GINS4 variation. Furthermore, primitive hematopoietic differentiation was unaffected in NKD lines, underscoring the specific vulnerability of lymphocytes to these variants. By measuring DNA accessibility, transcription, protein expression, and cell cycle throughout differentiation, we describe the developmental trajectory of human NK cells and demonstrate how decreased GINS4 expression changes this landscape to impair NK cell development from the earliest time point.

Funding Source: This work is supported by R01AI137275
Keywords: NK cell development, Helicase, NK cell deficiency

5:50 PM – 6:00 PM

FUNCTIONAL CONNECTIVITY OF SYMPATHETIC NEURONS WITH CARDIOMYOCYTES IN A HUMAN IPSC-DERIVED INNERVATED CARDIAC MUSCLE MODEL

Schneider, Lennart V.[1], Bao, Guobin[1], Liaw, Norman[1], Jensen, Ole[2], Schmoll, Kea[1], Brockmoeller, Juergen[2], Zimmermann, Wolfram-Hubertus[1] and Zafeiriou, Maria-Patapia[1]

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The dysregulation of the sympathetic nervous system greatly contributes to arrhythmia development and heart failure. Despite

increasing evidence underlining the importance of neuro-cardiomyocyte crosstalk in disease progression, no human models are currently available. To emulate the complex heart-brain interplay in the physiologic as well as diseased state, we developed a human sympathetic neuron organoid (SNO) and fused it with engineered human myocardium (EHM). SNO were generated from iPSC embedded in a defined collagen hydrogel and differentiated by stepwise modulation of BMP4, TGFβ and Wnt signalling. At day (d)15 SNO contained 55±1% PHOX2B-positive autonomic neuron progenitors (n=9, N=3) and presented robust transcript as well as protein expression of SN-marker dopamine-beta-hydroxylase and tyrosine hydroxylase (DBH 7123±981-fold and TH 3.86±0.52-fold to iPSC) at d41. Defined sympathetic fate was characterised by the low expression of other neuronal subtype marker (MNX1, GAD1, PAX6) as well as glia marker (GLAST, OLIG2). Further SN-properties such as high norepinephrine (60.4±6.2 pmol/mg tissue) and low cholinergic neurotransmitter acetylcholine (18.4±4.9 pmol/mg tissue) abundance were verified by liquid chromatography-mass spectrometry. Wholemount immunofluorescence analysis of innervated EHM (iEHM) revealed dense innervation of the myocardium by sympathetic neurons. For optogenetic control of iEHM, SNO were engineered from genetically modified iPSC with a red-light activatable channelrhodopsin (Chrimson). Light stimulation of optogenetic iEHM evoked a clear positive chronotropic response (increase in beating rate: 24±4% in iEHM, n=40, N=3 vs 1±3% in EHM, n=16, N=3). Acute treatment with autonomic neuron stimulant nicotinic acid (30 µM) induced a similar increase in beating rate in 19 out of 27 iEHM (38±13% to baseline, n=19, N=5). This response was inhibited by beta-receptor blockade (10 µM propranolol) and was entirely absent in EHM controls. In conclusion, our data designate iEHM as a pertinent human pre-clinical model for studying neurocardiac interactions in a spaciotemporal fashion as well as investigating diseases of the heart-brain-axis.

Funding Source: DFG (Deutsche Forschungsgemeinschaft) DZHK (German Center for Cardiovascular Research) MBExC (Multi-Scale Bioimaging Excellence Cluster), Goettingen
Keywords: neurocardiac interaction, autonomous nervous system, innervated cardiac muscle bioengineering

6:00 PM – 6:10 PM

CHARACTERIZATION OF DARK KINASES IMPLICATED IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

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Although kinases are highly desirable targets with unparalleled success in cancer therapeutics research their potential has not yet been realized in neuroscience. The intrinsic complexity linked to central neural system (CNS) drug development and a lack of validated targets has hindered progress in developing kinase inhibitors for CNS disorders. Rather than focusing on the widely studied kinases (around which most of the data, reagents and small molecules have been generated), we concentrated on elucidating the biology, and enabling the characterization, of lesser studied kinases also called dark kinases from the Illuminating the Druggable Genome (IDG) program. Through data mining, we have identified genetic links between kinases on the IDG list and Amyotrophic Lateral Sclerosis (ALS). Following expression analysis in human spinal cord motor neurons derived from stem cells, prioritized kinases were selected for CRISPR-mediated genetic knockout in pluripotent stem cells to better understand their role in propagating ALS biology. IDG kinases, including NEK1, DYRK2, CSNK1G3, PXK, SCYL3, STK36, and TTBK2, were knockout in iPS cells using the two-exon targeting method with the CRISPR system, and later differentiated into neural progenitor cells (NPC) and motor neurons (MN) using the dual SMAD inhibitor protocol. Then, we looked at phenotypes including primary cilia and DNA damage response. We found that the loss of a single understudied kinase such as DYRK2 or TTBK2 had a profound effect on primary cilia formation and elongation, and demonstrated that chemical inhibition of those kinases in WT iPSCs and NPCs mimics the KO phenotype. Similar results were observed with the DNA damage response in iPSCs and NPCs, distinct mechanistic pathways lead to similar outcomes. These observations support a small molecule campaign targeting the understudied kinases of interest. We demonstrate that the identification and characterization of new kinases as potential drug targets for ALS create opportunities for the development of CNS drugs.

Keywords: Dark kinases, CRISPR, ALS

6:10 PM – 6:20 PM

AUTISM GENES CONVERGE ON ASYNCHRONOUS DEVELOPMENT OF SHARED NEURON CLASSES

Paulsen, Bruna[1], Velasco, Silvia[1], Kedaigle, Amanda[1], Pigoni, Martina[1], Quadrato, Giorgia[1], Deo, Anthony[1], Adiconis, Xian[2], Uzquiano, Ana[1], Sartore, Rafaela[2], Yang, Sung Min[1], Simmons, Sean[2], Symvoulidis, Panagiotis[3], Kim, Kwanho[1], Podury, Archana[3], Boyden, Edward[3], Regev, Aviv[4], Levin, Joshua[2] and Arlotta, Paola[1]

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Genetic risk for autism spectrum disorder (ASD) is associated with hundreds of genes spanning a wide range of biological functions. The alterations in the human brain resulting from mutations in these genes remain unclear. Furthermore, their phenotypic manifestation varies across individuals. Here we used organoid models of the human cerebral cortex to identify cell-type-specific developmental abnormalities that result from haploinsufficiency in three ASD risk genes—SUV420H1 (also known as KMT5B), ARID1B and CHD8—in multiple cell lines from different donors, using single-cell RNA-sequencing (scRNA-seq) analysis of more than 745,000 cells and proteomic analysis of individual organoids, to identify phenotypic convergence. Each of the three mutations confers asynchronous development of two main cortical neuronal lineages—γ-aminobutyric-acid-releasing (GABAergic) neurons and deep-layer excitatory projection neurons—but acts through largely distinct molecular pathways. Although these phenotypes are consistent across cell lines, their expressivity is influenced by the individual genomic context, in a manner that is dependent on both the risk gene and the developmental defect. Calcium imaging in intact organoids shows that these early-stage developmental changes are followed by abnormal circuit activity. This research uncovers cell-type-specific neurodevelopmental abnormalities that are shared across ASD risk genes and are finely modulated by human genomic context, finding convergence in

the neurobiological basis of how different risk genes contribute to ASD pathology.

Keywords: Human brain organoids, Modeling disease, Neurodevelopmental disorders

6:20 PM – 6:30 PM

CAPTURING THE PATHOMECHANISMS OF DIFFERENT DISEASE SEVERITIES IN A HUMAN CEREBRAL ORGANOID MODEL OF LIS1-LISSENCEPHALY

Rossetti, Andrea Carlo[1], Krefft, Olivia[1], Maillard, Camille[2], Hoffrichter, Anne[1], Zillich, Lea[3], Poisel, Eric[3], Jabali, Ammar[1], Wilkens, Ruven[1], Marsoner, Fabio[1], Bahi-Buisson, Nadia[2], Koch, Philipp[1] and Ladewig, Julia[1]

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Lissencephaly is a malformation of cortical development which is characterized by a smooth brain (agyria) and a disorganized cortex. Heterozygous mutations in the LIS1 gene, encoding a microtubule-associated protein, were identified to cause lissencephaly with different clinical severities. While the clinical severity generally correlates with the degree of agyria, location and type of mutation in the LIS1 gene does not. Here, we present that cerebral brain organoids derived from patients diagnosed with mild, moderate or severe LIS1-lissencephaly exhibit disease-related phenotypes reflecting the clinical severity of the donors. This association is evident in the degree of alterations of the cytoarchitecture of the ventricular zones, progenitor cell division and neurogenesis. These observations are supported by scRNAseq data that point toward a dysregulation of the progenitor cells homeostasis. Furthermore, we identified increased alterations in the ventricular zone niche dependent WNT-signaling with increased severity grade of the patient. Pharmacological attenuation of the phenotypic changes could be achieved by either EpothiloneD treatment (a microtubule stabilizing drug) or by using a GSK3ß inhibitor (acting as WNT activator). Thus, our data identify a clear association between the genetic background and the clinical severity grade in LIS1-lissencephaly patients and demonstrate that organoid-based disease modeling is a sensitive system capable to recapitulate different disease severities in vitro.

Funding Source: Ministry of Innovation Science and Research of North Rhine-Westphalia; ERA-NET NEURON, JTC 2015 Neurodevelopmental Disorders, STEM-MCD; Hector Stiftung II.
Keywords: Lis1-lissencephaly, Neurodevelopment, Cerebral organoids

6:30 PM – 6:50 PM

DEVELOPMENTAL STRATEGIZING TOWARDS KIDNEY DISEASE MODELING

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Organoid-directed disease modeling promises new insights into human disease and enables the development of novel therapeutic strategies. To these ends, we have employed single cell technologies to better understand pathways of mammalian kidney development, comparing mouse and human, uncovering species differences, and a genetic link to human disease. Using micro-fabricated plates, we developed a mini-kidney organoid model in which each structure develops on average 1-2 nephrons, with thousands of reproducible mini-organoids per plate. Mini-organoids lacking either of the two genes associated with autosomal dominant polycystic kidney disease (ADPKD), PKD1 or PKD2, develop cysts, enabling screens to identify cyst suppressing small molecules, one of which has potent (IC50 – 5-10 nM) activity in both cyst initiation and cyst expansion assays. These findings support further optimization of the mini-organoid system to develop new insight into human kidney development and to extend human kidney disease modeling.

Keywords: Kidney, organoid, disease modeling

TRACK: NEW TECHNOLOGIES (NT)
PREDICTIVE MODELS OF STEM CELL BEHAVIOR
5:15 PM – 7:00 PM
ROOM 2012
LEVEL 2

5:20 PM – 5:40 PM

MOLECULAR NOISE AND THE ROBUSTNESS OF CELL FATE DECISION DYNAMICS

Stumpf, Michael, Coomer, Megan and Ham, Lucy

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During the development of multi-cellular organisms, such as humans, the right cell types arrive in their right numbers, at the right time, in the right place. The mechanisms that govern this process are nowhere near fully understood. What makes this even more puzzling is that the fundamental processes that drive and control cellular behaviour are random and to a large extent unpredictable. Despite this randomness, biological behaviour can be highly predictable with cells dividing and differentiating in a reproducible manner. Here, we show that noise affects the geometry of cell fate decisions; it can shape the epigenetic landscape profoundly and is even capable of changing qualitative features of the cell differentiation dynamics. This limits our ability to learn regulatory processes from single-cell data and I will discuss to what extent we can overcome this.

Keywords: gene regulation dynamics, cell fate decision dynamics, transition states

5:40 PM – 5:50 PM

VIRTUAL CELLS IN VIRTUAL MICROENVIRONMENT REVEAL HOW GRN INTERACTIONS MEDIATE TISSUE PATTERNS DURING HUMAN PLURIPOTENT STEM CELL DIFFERENTIATION

Kaul, Himanshu[1], Werschler, Nicolas[2], Jones, Ross[2], Siu, Mona[2], Tewary, Mukul[3], Hagner, Andrew[4], Ostblom, Joel[5], Aguilar-Hidalgo, Daniel[2] and Zandstra, Peter[2]

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Gastrulation results in the three germ layers required for all tissues and organs. The mechanisms underpinning human gastrulation are poorly understood. Stimulating micropatterned human pluripotent stem cells (hPSCs) with BMP4 results in radially structured peri-gastrulation patterns. This technique has shed key insights into the underlying signals, but the multiscale regulation of these patterns remains elusive. To understand this, we created a gene regulatory network (GRN) of human germ layer patterning and embedded it into agents (virtual cells) coupled

with a dynamic virtual microenvironment (simulated via reaction-diffusion equations). Thus, the GRN activity within individual agents shaped the microenvironment via ligand release (BMP4, WNT3), ie. individual shaping the continuum; and the altered microenvironment impacted GRN activity via agents, ie. continuum shaping the individual. For validation, we engineered hPSC lines with Doxycycline-inducible silencing of OCT4 expression. Control colonies had normal OCT4 expression. Our simulations revealed that OCT4 dynamics control the peri-gastrulation pattern order and are central to the emergence of three distinct germ-layers (ie. significant spatial separation between all markers). To validate these findings in vitro, we silenced OCT4 expression pre-differentiation, with no impact on SOX2 and NANOG. Upon differentiation, TBXT+ cells did not emerge in these colonies and SOX17+ cells were localized closer to the colony edge vs control ($p=0.01$), consistent with simulations. As predicted by the model, dynamic inhibition of OCT4 expression during differentiation in vitro halted mesendoderm divergence: TBXT vs SOX17 spatial loci were not significantly apart ($p=0.98$) vs control ($p< 0.0001$); NANOG expression was not impacted ($p=0.8$ vs control). Further, OCT4 spatial locus lay anterior to the TBXT locus ($p< 0.0001$), consistent with the mouse gastrula. We conclude that OCT4 patterning dynamics are critical to the spatiotemporal emergence of three spatially distinct germ layers. Our work offers a computational platform to understand how single cell-based regulatory interactions scale to tissue domains in space and time. This foundation provides new opportunities to simulate the impact of network motifs on normal and aberrant tissue development.

Funding Source: Canadian Institutes of Health Research Foundation Grant (FDN-154283) Michael Smith Foundation for Health Research Trainee Award (18427) Royal Academy of Engineering Grant (RP12G0511)
Keywords: Gene regulatory network, Gastrulation, Multiscale modeling

5:50 PM – 6:00 PM

CONTROLLED SPATIAL COUPLING OF ORGANOIDS UNCOVERS MECHANISMS OF HUMAN AXIAL ELONGATION

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During human development, the embryo forms an anterior-posterior (A-P) axis and elongates axially, positioning the progenitors that give rise to the various organ systems of the body. The infeasibility of conducting studies of human axial elongation in vivo necessitates the use of in vitro human pluripotent stem cell derived organoids. However, large organoid to organoid variability in A-P symmetry breaking imposes challenges in extracting mechanistic insight from these systems. We develop a bioengineering and statistical learning framework to optimize symmetry breaking by controlling the spatial coupling between organoids. We use this framework to reproducibly direct hundreds of organoids to form an A-P axis, elongate, and generate neural tube-like structures with a single lumen and tailbud. Single-cell RNA sequencing and multiplexed spatial transcriptomic profiling of elongating organoids reveal spatially polarized activity of FGF/ERK and noncanonical WNT pathways. Through biochemical perturbations in conjunction with live imaging, we show that noncanonical WNT induces cellular rearrangements to drive elongation downstream of FGF/ERK and canonical WNT signaling. Although canonical WNT signaling is continuously required for elongation, we can sustain elongation in the absence of external stimuli by inducing a SOX2+ TBXT+ neuromesodermal progenitor-like WNT signaling center at the tailbud, suggesting that elongating organoids behave as an excitable system. As predicted by theories of excitability, we show that secreted inhibitors of WNT in the form of SFRPs are required for stable axial elongation with a single tailbud. We hereby present a novel in vitro system to dissect the mechanisms of human axial elongation.

Keywords: axis elongation, pluripotent stem cells, statistical learning

6:00 PM – 6:10 PM

GROWTH CONTROL AND SCALING OF MESENDODERM IN MICRO-PATTERNED MOUSE PLURIPOTENT STEM-CELL COLONIES

Aguilar Hidalgo, Daniel[1], Gui, Jonathan[1], Siu, Mona[1], Fang, Nancy[1], Ostblom, Joel[2] and Zandstra, Peter[1]

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Two-dimensional gastruloids constitute a simple framework to study early embryogenic events in vitro, such as the emergence of the 3-germ layers and the dorso-ventral body axis. Understanding the dynamics of such events can lead to applications in tissue and organoid engineering. Whether such a simple system can be used to study growth dynamics of cellular patterns remains unknown. To explore this, we computationally simulated the emergence of patterns in micro-patterned stem-cell colonies based on a simple Turing-like activator-repressor (AR) model with activator-intensity-dependent flux at the colony edge, combined with an intensity threshold to activate intracellular markers. We found that this model recapitulated previous results of centro-symmetric patterns in large colonies, and also that in simulated small colony sizes, patterns developed spontaneous asymmetries. We next computed the growth dynamics of these patterns and found that it transitions from a power law to an exponential decay, with the latter allowing for pattern growth arrest. Interestingly, this complex dynamics was preserved between colonies sizes, with a linear colony-size-dependent scaling factor. These results suggest that a simple AR system can provide predictive information on the collective behavior of cellular patterns. To test these predictions, we performed experiments on micro-patterned mouse pluripotent stem cell (mPSC) colonies of different sizes stimulated with BMP4, and used BRA+ cells as pattern readout. We found that while large colony sizes showed centro-symmetric BRA patterns, colonies of around 200um of diameter expressed polarized patterns. Additionally, these patterns showed complex growth dynamics transitioning from a power-law to an exponential decay independently on the pattern shape. We further showed that the patterned area scales linearly with the colony size. These results indicate that a simple AR system can provide cells with collective features capable of initiating a body-axes plan, organizing cellular patterns with scaling of size regulation, and providing mechanisms of growth arrest. These findings constitute a theoretical foundation for the engineering of developmental systems, and a strategy to guide the self-organization of size and shape of functional cellular patterns.

Keywords: Growth control and scaling, pluripotent stem cells, mathematical model and experiments

6:10 PM – 6:20 PM

A NEW SPATIAL SINGLE CELL TRANSCRIPTOMICS METHOD FOR DETECTING SIGNALING RELATIONSHIPS IN STEM CELL NICHES

Wang, Yuting[1], Ding, Ke[2], Sokol, Jan[1], Zhao, Liming[1], Ambrosi, Thomas[1], Takematsu, Eri[1], Hoover, Malachia[1] and Chan, Charles[1]

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A thorough understanding of the regulatory mechanism within stem cell niches is essential to develop efficient and specific strategies to stimulate stem cell mediated regeneration in response to injury or disease. Although there has been significant progress in identifying specific signaling pathways involved in stem cell niches, the major challenge now is learning how to determine the key arrangements of signals that translate to specific commands from niche cells to stem cells. With current approaches, spatial information related to essential co-localized cells are either unavoidably disturbed in the dissociation process before sc-RNA-seq analysis in 10X or smart-seq, or down-graded to 2D while a-priori knowledge of differentially expressed genes, which has limited genetic coverage, is required for in situ hybridization technique such as MerFish, or RNA scope. In the present study, we introduced a new 3D, single cell spatial transcriptomic method (TESSERACT) to map crosstalk within stem cell niches and can be widely applied for different type of tissues and organoids. The spatial information of intact clusters size around 50-100 cells from rainbow mice were recorded by confocal before enzymatically dissociated and index sorted for single cell sequencing by high coverage Smart-seq2 scRNA-seq, and further analyzed for their precise cellular identity and signaling state. Fish-seq, along with in situ methods such as RNA Scope and CODEX have also been used to validate and expand on unbiased discovery results as detected by TESSERACT. Gene regulatory networks of interacting cells was analyzed by Boolean analysis. We proved that our approach could implement efficient mapping between confocal and FACs profiles and provided both in-depth and reliable spatial transcriptomic information in both soft tissue as bone marrow and hard tissue as growth plate. With TESSERACT, we achieved to reveal real 3D spatial regulatory relationship within stem cell niches and determine the essential arrangements of signals between niche cells and stem cells. In conclusion, we have developed a new spatial single cell transcriptomics method for detecting regulatory relationships in clusters of interacting cells, which provides a vital new tool for on-the-spot elucidation of cellular mechanisms and key niche signals in various tissue.

Keywords: spatial transcriptomics, stem cells, skeletal stem cell

6:20 PM – 6:30 PM

IN VITRO NEURONS EXHIBIT GOAL-DIRECTED LEARNING WHEN EMBODIED IN A SIMULATED GAME-WORLD: A SYSTEM FOR TESTING THE COMPUTATIONAL PROPERTIES OF SYNTHETIC NEURONS

Kagan, Brett J[1], Kitchen, Andy[2], Saatlou, Forough[3], Watmuff, Brad[1], Duc, Daniela[1], Tran, Nhi[4], Parker, Bradyn[5], French, Chris[6], Burkitt, Anthony[3], Razi, Adeel[7] and Friston, Karl[8]

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Impressive advancements have been made in differentiating stem cell populations to a plethora of neural cell fates. While significant work has been performed to characterize the resulting morphological and molecular phenotypes, an enduring limitation is identifying how these populations functionally process information. We have developed the DishBrain system, a real-time method of providing electrophysiological stimulation and recording to embody biological neural networks (BNNs) in a closed-loop virtual environment. This system provides a simulation of the classic arcade game 'Pong', where cultures received spatial information of a ball through stimulation and were able to modulate network wide activity to move a paddle. Proof of concept was established through leveraging neurocomputational concepts derived from active inference via the Free Energy Principle. Cortical neuronal cells were differentiated from human induced pluripotent stem cells (hiPSCs), and primary cultures from embryonic day 15.5 C57BL/6 mice used as a non-synthetic comparison. Cultures demonstrated robust evidence of learning to hit the ball within five minutes of real-time gameplay – learning was not observed across multiple control conditions. Follow up experiments identified that it was the closed-loop aspect of this system which yielded these learning effects. Further evidence found network wide reorganization of activity, including changes in complexity and markers of criticality only seen when cultures are embodied within the simulated game. As such, BNNs displayed goal-directed self-organization when provided feedback about the consequences of the system activity. These findings support the utility of the DishBrain system in assessing the capacity of neural cells to process sensory information. We anticipate that this system will be of widespread interest to those seeking a novel mode of investigation to test the functional capacity (e.g. learning) of neural cells differentiated from pluripotent stem cells as it has the potential to unlock a new mode of investigations with unprecedented depth.

Keywords: Functional assessment, Neural cells, Electrophysiology

6:30 PM – 6:50 PM

MAPPING TISSUES IN VIVO AND IN VITRO

Vento-Tormo, Roser

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The study of human tissues requires a systems biology approach. Their development starts in utero and during adulthood, they change their organization and cell composition. Our team has integrated comprehensive maps of human developing and adult tissues generated by us and others using a combination of sin-

gle-cell and spatial transcriptomics, chromatin accessibility assays and fluorescent microscopy. We utilise these maps to guide the development and interpretability of in vitro models. To do so, we develop and apply bioinformatic tools that allow us to quantitatively compare both systems and predict changes.

Keywords: MAPPING, TISSUES

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)
AGING AND REGENERATION
5:15 PM – 7:00 PM
ROOM 2007
LEVEL 2

5:20 PM – 5:40 PM

STEM CELL COMPETITION AND SENOLYTIC CELL ELIMINATION PROMISE AGELESS REGENERATION OF THE EPIDERMIS

Nishimura, Emi K.

The University of Tokyo, Japan

Genomic integrity and stability are crucial in stem cells yet they gradually deteriorate with aging. Cells suffer continuous endogenous and exogenous genomic insults from development until death. Our previous studies with fate tracing of aged stem cells in vivo have revealed that elimination of aged stem cells immediately causes tissue atrophy and functional decline in hair follicle but tolerates skin aging through Collagen XVII-mediated epidermal stem cell competition in the epidermis. To further study the cellular fate and dynamics of DNA-damaged stem cells in the skin, we devised an in vivo fate tracing system for epidermal stem cells (EpiSCs) that acquired DNA double-strand breaks (DSBs) and found that EpiSCs with DSBs are highly selectively eliminated from the skin through their differentiation and desquamation through the DNA damage response (DDR)-p53-Notch axis with the downregulation of ITGB1. Moreover, concomitant enhancement of symmetric cell divisions of surrounding stem cells indicates that the selective elimination of cells with DSBs is coupled with the augmented clonal expansion of intact stem cells. These data collectively demonstrate that the dynamic coupling of cell-autonomous and non-cell-autonomous elimination mechanisms coordinately maintains the genomic quality of the epidermis yet deteriorates by aging.

Keywords: stem cell competition, epidermis, DNA damage, senolysis, p53

5:40 PM – 5:50 PM

EXERCISE REPROGRAMS THE INFLAMMATORY LANDSCAPE OF MULTIPLE STEM CELL COMPARTMENTS DURING MAMMALIAN AGING

LIU, LING[1], Buckley, Matthew[2], Jeong, Mira[3], Kim, Soochi[4], Reyes, Jaime[5], Rodriguez-Mateo, Cristina[6], Wang, Mingqiang[7], Wu, Joseph[8], Goodell, Margaret[5], Brunet, Anne[2] and Rando, Thomas[1]

1Neurology, University of California, Los Angeles, CA, USA, 2Genetics, Stanford University, Stanford, CA, USA, 3Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA, 4Neurology, Stanford University, Palo Alto, CA, USA, 5Molecular and Cellular Biology, Baylor College of Medicine, Houston, TX, USA, 6Neurology, Stanford University, Stanford, CA, USA, 7Cardiovascular Institute, Stanford University, Stanford, CA, USA, 8Medicine, Stanford University, Stanford, CA, USAExercise has the ability to rejuvenate stem cells and improve tissue homeostasis and regeneration in aging animals. However, the cellular and molecular changes elicited by exercise have not been systematically studied across a broad range of cell types in stem cell compartments. To gain better insight into the mechanisms by which exercise affects niche and stem cell function, we subjected young and old mice to aerobic exercise and generated a single cell transcriptomic atlas of muscle, neural and hematopoietic stem cells with their niche cells and progeny. Complementarily, we also performed whole transcriptome analysis of single myofibers from these animals. We identified common and unique pathways that are compromised across these tissues and cell types in aged animals. We found that exercise has a rejuvenating effect on subsets of stem cells, and a profound impact in the composition and transcriptomic landscape of both circulating and tissue resident immune cells. Exercise ameliorated the upregulation of a number of inflammatory pathways as well as restored aspects of cell-cell communication within these stem cell compartments. Our study provides a comprehensive view of the coordinated responses of multiple aged stem cells and niche cells to exercise at the transcriptomic level.

Keywords: exercise, inflammation, stem cells

5:50 PM – 6:00 PM

A MOLECULAR SWITCH OF SEC-PTEFB ACTIVITY CONTROLS PROGENITOR SELF-RENEWAL VERSUS DIFFERENTIATION INITIATION

Lloyd, Sarah, Bao, Xiaomin and Leon, Daniel

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Self-renewing somatic tissues, such as skin epidermis, rely on the actions of progenitors to continuously undergo self-renewal and differentiation to safeguard tissue integrity. The earliest events initiating progenitor differentiation, a process that suppresses self-renewal and induces genes driving tissue-specific functions, remain incompletely understood. Using human epidermal tissue as a research platform, here we show that the Super Elongation Complex (SEC), which controls gene expression at the step of transcription elongation, plays essential roles in regulating progenitor self-renewal and differentiation. SEC inhibitors lead to rapid induction of differentiation-activating transcription factors within 3 hours, which precedes the downregulation of key proliferation genes such as MYC and DNMT1. Both SEC scaffolding proteins, AFF1 and AFF4, are necessary for sustaining progenitor self-renewal; AFF1, however, plays a distinct essential role in suppressing differentiation. Mechanistically, this occurs through AFF1 interacting with HEXIM1 to hold CDK9 in an inactive state, directly suppressing the induction of differentiation-initiating genes such as ATF3 in the progenitor state. In response to SEC inhibitors or PKC signaling, AFF1 and HEXIM1 mediate the rapid induction of ATF3, and we found that ATF3 overexpression is sufficient to promote differentiation and suppress self-renewal. Altogether, our data suggest a model that SEC directly controls the rapid activation of early-response transcription regulators such as ATF3 in a signaling dependent manner to initiate progenitor fate switch from self-renewal to differentiation.

Keywords: Skin, Transcription, Super Elongation Complex

6:00 PM – 6:10 PM

AGE ASSOCIATED INDUCTION OF SENESCENT TRANSCRIPTIONAL PROGRAMS IN HUMAN GLIAL PROGENITOR CELLS

Mariani, John N[1], Madsen, Pernille[1], Mansky, Benjamin[1], Huynh, Nguyen[2], Kuypers, Nicholas[1], Kesel, Erin[1], Chandler-Militello, Devin[1], Benraiss, Abdellatif[1] and Goldman, Steven[1]

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Glial progenitor cells, a primary source of oligodendrocytes and astrocytes in the human CNS, emerge during the 2nd trimester to colonize the brain, in which a parenchymal pool remains throughout adulthood. While fetal human GPCs (hGPCs) are highly migratory and proliferative, their expansion competence and phenotypic potential may diminish with aging, as well as following demyelination-associated turnover. To determine the basis for this age-related decline in the mobilization capacity of hGPCs, we used both bulk and single cell RNA-Sequencing to compare the transcriptional programs of fetal and adult hGPCs. We identified age-associated changes in gene expression suggesting a loss of proliferative competence with aging, concurrent with the onset of both differentiation and senescence-associated transcriptional programs. Whereas the maintenance of the fetal glial progenitor state was associated with enrichment of the transcriptional activators MYC, NFIB, HMGA2 and TEAD2, and the repressors BCL11A, EZH2 and HDAC2, the maturation of adult hGPCs was associated with the concurrent appearance of the transcriptional activator STAT3, and the repressors ZNF274, MAX, E2F6, and IKZF3. Individual over-expression of each of these adult transcriptional repressors in human iPSC-derived GPCs, which otherwise express a fetal-like transcriptional signature, led to a loss of proliferative gene expression and an induction of markers of senescence, which replicated the transcriptional changes incurred during glial aging. We then coupled these transcriptional data with miRNA profiling of fetal and adult hGPCs, which identified an adult-selective miRNA expression signature whose targets may further constrain the expansion competence of aged GPCs. These observations indicate that the aging of hGPCs proceeds through the acquisition of a MYC-repressive environment, and suggest that the suppression of age-associated repressors of glial expansion may permit the rejuvenation of aged hGPCs.

Keywords: Glial progenitor cell, Oligodendrocyte, Aging

6:10 PM – 6:20 PM

MICRORNA-205 PROMOTES HAIR REGENERATION BY MODULATING CELL CONTRACTILITY AND MECHANOSENSITIVITY

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Actomyosin contractility is an intrinsic mechanical property of animal cells required for the shaping of mammalian tissues and organs. However, whether tissue stem cells located within distinct stem cell niche compartments have different contractile behaviors that govern their activity in mammals is unknown. Here we directly visualize the behaviors of hair follicle stem cells (HF-SCs) and hair germ (HG) progenitors in live animals, showing that HG cells but not HF-SCs periodically enlarge and contract during the quiescent phase of the hair cycle in mice. Upon transition to activation, the contraction of HG cells is significantly reduced, a process that is associated with weakening of the actomyosin network and nuclear YAP accumulation. To modulate mechanical property of HG cells, we identify microRNA-205 as a potent regulator of actomyosin contractility and mechanosensitivity through the direct regulation of many targets, including Actb, Ctnna1, Rock2 and Piezo1. Induction of microRNA-205 reduces actin contractile forces, promotes nuclear YAP accumulation in the HG, and activates hair regeneration in young and old mice. Furthermore, deletion of Piezo1, a mechanosensitive calcium channel and a target of microRNA-205, recapitulates rapid hair regeneration by driving changes in the actin cytoskeleton and nuclear YAP localization. This study reveals the control of tissue stem cell activities by spatiotemporally compartmentalized mechanical forces and demonstrates the possibility to stimulate tissue regeneration by fine-tuning cell mechanics.

Funding Source: National Institute of Health Grant AR066703, AR071435, AR075087, AR043380, AR041836 National Science Foundation CBET 2029559 Singapore Ministry of Education and the National University of Singapore (Research Scholarship Block)

Keywords: Stem cell contractility, Tissue regeneration, hair follicle stem cells

6:20 PM – 6:30 PM

THE TICKING CLOCK, AN AGING STUDY OF A COLONIAL CHORDATE LINKS STEM CELL AGING TO MOLECULAR DECLINE OF CIRCADIAN REGULATION

Voskoboynik, Ayelet[1], Voskoboynik, Yotam[2], Glina, Aidan[2], Kowarsky, Mark[3], Anselmi, Chiara[1], Neff, Norma[4], Ishizuka, Katherine[1], Palmeri, Karla[1], Levy, Tom[1], Quake, Stephen[5], Weissman, Irving[6], Ben-Shlomo, Rachel[7] and Sahoo, Debashis[8]

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Expression levels of circadian clock genes, which regulate 24-hour biological cycles, have been shown to change with age. However, due to limitations of tissue sampling, a comprehensive study comparing circadian gene expression across multiple time points and age groups is missing. Using the colonial chordate Botryllus schlosseri, a long-lived organism that exhibits weekly stem cell-mediated asexual tissue regeneration and replacement of all body organs, we studied the link between stem cell aging and circadian gene expression. Colonial tunicates, like B. schlosseri are unique amongst chordates in possessing a stem cell mediated asexual development pathway, termed blastogenesis. Unlike most species, where the body is long lived and maintained by cellular replacement, B. schlosseri regenerates new colonial units (zooids) on a weekly basis replacing the previous generation's zooids, which then die through massive apoptosis. While the colony can live for upwards of 20 years, the zooids live for only a week. The colony is thus aged according to its stem cells, which migrate from one generation to the next and are maintained throughout life through self renewal, allowing for the study of stem cell aging's effects at the organismal level. Here we characterize global gene expression changes across time and age and link them to morphological, physiological and cellular aging phenotypes. Using a computational pipeline we developed to comprehensively quantify gene expression patterns across time points and age groups, we identified unique and shared molecular characteris-

tics at each timepoint and age. These analyses revealed that B. schlosseri clock and clock-controlled genes oscillate daily with age-specific amplitudes and frequencies. These age-related patterns persist at the tissue level, where dramatic variations in the cyclic gene expression link to morphological and physiological aging phenotypes. Similar cyclical expression differences were found in hundreds of pathways associated with known hallmarks of aging, as well as pathways that were not previously linked to aging. The molecular clock atlas we developed suggests alterations in circadian gene expression as a key regulator of aging, linking stem cell aging and loss of regenerative potential with molecular decline of circadian regulation.

Funding Source: National Institutes of Health grant R01AG037968, RO1GM100315, R21AG062948 Chan Zuckerberg investigator program Larry L Hillblom foundation Stanford School of Medicine Dean's Postdoctoral Fellowship
Keywords: Aging, circadian rhythm, stem cells

6:30 PM – 6:50 PM

MECHANISMS OF DEVELOPMENT AND REGENERATION IN HYDRA

Juliano, Celina, Cazet, Jack, Primack, Abby and Morris Little, Hannah

University of California, Davis, CA, USA

Hydra vulgaris is a small and simple aquatic animal capable of whole-body regeneration. The entire animal, including the nervous system, is composed of about 25 cell types, and can regenerate from a fragment of tissue as small as ~300 cells. In addition, all cell types are continually renewed in the uninjured adult as part of normal homeostasis; every differentiated cell type is replaced approximately every 20 days. These remarkable features are enabled by three distinct populations of stem cells that support the three lineages that make up the adult Hydra – the ectodermal epithelial lineage, the endodermal epithelial lineage, and the interstitial lineage (includes the neurons). A major goal of our laboratory is to understand the gene regulatory networks that control the specification of all Hydra cell types in the uninjured (homeostatic) state and then understand how injury triggers these differentiation pathways at unexpected locations during regeneration. Using high throughput genomics approaches such as scRNA-seq, ATAC-seq, and Cut and Tag, we have transcriptionally defined every cell type in Hydra and identified putative transcriptional regulators for each cell type. This includes the 11 neuronal subtypes that comprise the nerve net that spans the entire length of the Hydra body. We are currently leveraging these data to conduct functional testing of key putative regulators and to identify injury inputs into cell specification events during regeneration.

Keywords: Hydra, regeneration, gene regulatory networks

FRIDAY, 17 JUNE

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)
PLENARY IV: DEFINING STEM CELLS ACROSS SPACE AND TIME
9:00 AM – 10:35 AM
LEVEL 3

9:05 AM – 9:25 AM

AN UNDERSTANDING OF BLOOD PROGENITOR DEVELOPMENT THROUGH THE LENSES OF SENSORY PERCEPTION

Mukherjee, Tina

Institute for Stem Cell Science and Regenerative Medicine (inStem), India

Our laboratory focuses on exploring long-range, systemic cues governing hematopoietic development and progenitor homeostasis. In this regard, our ongoing findings have elucidated the influence of sensory odor perception in the development of a competent repertoire of blood-progenitor cells. The findings not only put forth neuro/immune cross-talk in hematopoiesis, but the revelation of environmental triggers and their sensing modules as key determinants of hematopoietic progenitor competency and ultimately immune-priming are unexpected observations. My talk will share our recent findings and how the use of Drosophila as the model system has lent us an additional edge to uncover such newer principles underlying blood development and function.

9:25 AM – 9:45 AM

CARDIOIDS UNRAVEL MECHANISMS OF COMPARTMENT-SPECIFIC HEART DEFECTS

Mendjan, Sasha, Schmidt, Clara, Deyett, Alison, Ilmer, Tobias and Torres, Aranxa

Institute of Molecular Biotechnology (IMBA), Vienna, Austria

The number one cause of fetal death are defects in heart development. Determining the underlying causes faces many challenges, including the complexity and inaccessibility of the embryonic heart, the unclear impact of drugs and environmental factors during pregnancy, and the lack of in vitro models representing all the compartments of the human heart. Here, we established a cardioid organoid platform recapitulating the development of the major compartments of the human embryonic heart, including the right and left ventricles, the atria, the outflow tract, and the atrioventricular canal. These cardioids have the compartment-specific in vivo-like gene expression profile, morphology, and functionality. We use this platform to unravel the developmental electrophysiology of interacting heart chambers and dissect how genetic and environmental factors cause specific defects in different regions of the developing human heart.

Keywords: cardiac organoids, congenital heart defects, heart development, cardiac differentiation

9:45 AM – 10:05 AM

USING FUNCTIONAL GENOMICS TO DECODE GENE REGULATORY CIRCUITRY IN DEVELOPMENT

Sauka-Spengler, Tatjana

University of Oxford, UK

Abstract not available.

10:05 AM – 10:25 AM

UNDERSTANDING THE SOURCES OF REGENERATIVE CAPACITY IN ANIMALS

Sanchez Alvarado, Alejandro

Stowers Institute for Medical Research, IA, USA

Under normal physiological conditions, the functions of many organs depend on the continuous destruction and renewal of their cells. Equally remarkable is the fact that the adult tissues and organs of many organisms can be fully restored after amputation. In fact, metazoans have evolved a series of renewal and repair mechanisms to respond to both trauma and normal wear and tear. Such mechanisms are under tight regulatory control such that the form and function of tissues, organs, and systems can be maintained throughout life. As important as repair and restoration are to the survival of multicellular organisms, we know little about how these processes are effected and regulated at the cellular and molecular levels. Here, I will discuss how the study of two research organisms, the planarian Schmidtea mediterranea and the African killifish Nothobranchius furzeri is beginning to shed light on the way adult animals regulate tissue homeostasis and the replacement of body parts lost to injury.

TRACK: CELLULAR IDENTITY (CI) SPHEROIDS AND ORGANOIDS 1:00 PM – 2:45 PM ROOM 2008 LEVEL 2

1:05 PM – 1:25 PM

CREATION OF TISSUE ASSEMBLOIDS THAT RECAPITULATE IN VIVO TISSUE DYNAMICS AND CANCER

Shin, Kunyoo

School of Biological Sciences, Seoul National University, Korea

Current organoid models are limited by their inability to mimic mature organ architecture and associated tissue microenvironment. Here, we create multi-layered bladder assembloids by reconstituting tissue stem cells with various stromal components to represent an organized architecture with an epithelium surrounding stroma and an outer muscle layer. These assembloids exhibit the characteristics of mature adult bladders in the context of cell compositions at the single-cell transcriptome level, and recapitulate the in vivo tissue dynamics of the regenerative response to injury. As a malignant counterpart, tumor assembloids are also developed to recapitulate the in vivo pathophysiological features of patient-derived urothelial carcinomas. Using the genetically manipulated tumor assembloid platform, we identify tumoral FOXA1, induced by stromal BMP, as a master pioneering factor driving enhancer reprogramming for the determination of tumor phenotype, suggesting the importance of the FOXA1–BMP–HH signaling feedback axis between tumor and stroma in the control of tumor plasticity.

Keywords: Organoid, Assembloid, tumor plasticity, tumor stroma, bladder

1:25 PM – 1:35 PM

IMPROVED PROXIMAL TUBULE MATURATION AND CONTROL OF NEPHRON ALIGNMENT IN KIDNEY ORGANOIDS

Vanslambrouck, Jessica M., Wilson, Sean, Tan, Ker Sin, Groenewegen, Ella, Kynan, Lawlor, Howden, Sara, Mah, Sophia, Scurr, Michelle and Little, Melissa

Kidney Regeneration, Cell Biology Theme, Murdoch Children's Research Institute, Melbourne, Victoria, Australia

The human kidney is composed of millions of functional filtration units, or nephrons, that are segmented with respect to both structure and function. While the highly specialised proximal tubule (PT) segment of the nephron performs the bulk of kidney functions, its high metabolic activity also renders it acutely vulnerable to disease. As a result, the PT is a key objective for regenerative therapies, toxicity screening, and disease research. Although induced pluripotent stem cell (iPSC)-derived kidney organoids represent a promising approach, the PT segment remains immature, lacking the full complement of membrane transporters required for PT functionality. Here, using standard and fluorescent reporter iPSC lines, we report that prolonged iPSC differentiation, precisely-timed morphogen exposure, and tight control of organoid biophysical properties can generate PT-enhanced kidney organoids with elongated and aligned nephrons. Improved upregulation of PT-specific markers compared to standard organoids was strengthened by evidence of transporter functionality, including uptake of albumin, organic cations, and appropriate upregulation of Kidney Injury Marker 1 (KIM1) upon exposure to the nephrotoxic chemotherapeutic agent, cisplatin. The enhanced conditions also provided more stringent control over nephron spatial arrangement, with striking radial proximo-distal nephron orientation resulting from a central WNT antagonism sink. Removing this sink by altering organoid shape and size eliminates this radial patterning, identifying spatial control of WNT signalling as critical for control of nephron orientation. This model represents an opportunity to better understand human PT maturation, inherited and acquired PT disease, and study drug toxicity.

Keywords: Kidney organoid, Pluripotent stem cell, Proximal tubule

1:35 PM – 1:45 PM

GENERATION OF THE ORGANOTYPIC KIDNEY STRUCTURE SOLELY FROM PLURIPOTENT STEM CELLS

Tanigawa, Shunsuke, Tanaka, Etsuko and Nishinakamura, Ryuichi

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Organs consist of the parenchyma and stroma, the latter of which coordinates the generation of organotypic structures. Despite recent advances in organoid technology, induction of organ-specific stroma and recapitulation of complex organ configurations from pluripotent stem cells (PSCs) have remained challenging. By elucidating the in vivo molecular features of the renal stromal lineage at a single-cell resolution level, we herein establish an in vitro induction protocol for stromal progenitors (SPs) from mouse PSCs. When the induced SPs are assembled with two differentially induced parenchymal progenitors (nephron progenitors and ureteric buds), the completely PSC-derived organoids reproduce the complex kidney structure, with multiple types of stromal cells distributed along differentiating nephrons and branching ureteric buds. Thus, integration of PSC-derived lineage-specific stroma

into parenchymal organoids will pave the way toward recapitulation of the organotypic architecture and functions.

Keywords: Kidney, Pluripotent stem cell, Renal stroma, Kidney organoid, Nephron progenitor, Nephron, Ureteric bud, Branching morphogenesis

1:45 PM – 1:55 PM

EFFECTS OF MICROGRAVITY ON HUMAN IPSC-DERIVED 3D BRAIN MODELS OF PARKINSON'S DISEASE AND MULTIPLE SCLEROSIS

Marotta, Davide[1], Barbar, Lilianne[1], Bratt-Leal, Andres[2], Clements, Twyman[3], Fossati, Valentina[1], Grisanti, Paula[4], Ijaz, Laraib[1], Joshi, Harshad[5], Loring, Jeanne[2], Noggle, Scott[5], Stein, Jason[2] and Stoudemire, Jana[6]

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Microgravity in low-Earth orbit (LEO) is known to impact cardiac, musculoskeletal, and immune system; however, there is still scant information on its effects on the central nervous systems (CNS). Our team has been investigating the role of microglia – the resident immune cells of the CNS – in multiple sclerosis (PPMS) and Parkinson's disease (PD) by developing in vitro iPSC-derived 3D models of human brain cells. In addition, we have adapted these model systems to investigate the effects of microgravity on microglia and neurons to improve our understanding of pathogenic mechanisms of neuroinflammation underlying neurodegeneration. Leveraging differentiation protocols previously developed, we integrated human iPSC-derived microglia into 3D cultures of dopaminergic and cortical neurons and established the first long-term cultures of patient-specific neural cells in LEO onboard the International Space Station (ISS). Our experiment involved four human iPSC lines, derived from one person with primary progressive multiple sclerosis (PPMS) and one with idiopathic Parkinson's disease (PD) and their age/sex-matched healthy controls. At the ISS U.S. National Laboratory, the brain organoids were transferred to CubeLab flight hardware – designed by Space Tango – and launched onboard a SpaceX Falcon 9 rocket as part of the 18th, 19th, and 24th SpaceX Commercial Resupply Services mission for NASA (SpX CRS-18, SpX CRS-19, and SpX CRS-24). Upon returning to Earth, cortical and dopaminergic organoids show significant differences in gene expression and protein secretion when cultured for 30 days in microgravity. In addition, gene set enrichment analysis (GSEA) of spaceflight samples suggests dysregulation of cell division, DNA repair and packaging, and post-translational modifications of proteins. This unique study is the first long-term 3D cell culture using patient-derived dopaminergic and cortical organoids with microglia to study Parkinson's disease and multiple sclerosis in microgravity. Overall, the results of these experiments are laying the groundwork for further studies to dissect the fundamental neurodegenerative mechanisms and understand the impact of microgravity on these disease-relevant processes to develop potential treatments for patients on Earth and countermeasures for astronauts.

Funding Source: National Stem Cell Foundation
Keywords: Neurodegeneration, Brain Organoids, Microgravity

1:55 PM – 2:05 PM

GENERATION OF PULMONARY TYPE II ALVEOLAR EPITHELIAL CELLS FROM HUMAN PLURIPOTENT STEM CELLS WITHOUT INTERMEDIATE ENRICHMENT STEPS

Matkovic Leko, Ivana[1], Liu, Hsiao-Yun[2], Schneider, Remy[2], Thimraj, Tania[2], Beitler, Daniel[2] and Snoeck, Hans Willem[2]

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The development of organoid models for different types of tissues has been one of the most exciting advancements in stem cell research of the past decade. Among others, major progress has been made in the generation of lung organoids. The lung contains multiple cell types, including basal, ciliated, secretory, goblet and neuroendocrine (NE) cells in the airways, and alveolar type I (ATI) and surfactant-producing, cuboidal alveolar type II (ATII) cells in the alveoli, where gas exchange takes place. In particular ATII cells have garnered major interest, as they can function as alveolar progenitors after injury, play an important role in viral infection of the distal lung, and as ATII cell dysfunction is a driver of interstitial lung diseases, including familial and sporadic idiopathic pulmonary fibrosis and genetic surfactant deficiencies. Generating these cells from human pluripotent stem cells would therefore have important applications for disease modeling and potentially for cellular therapies for some distal lung diseases. Currently available protocols however require repeated cell sorting for surface markers that lack absolute specificity or for fluorescent reporters, making these difficult to implement universally. We have previously developed a strategy where lung progenitors generated from hPSC were embedded in Matrigel where a process akin to branching morphogenesis ensued. No isolation or sorting steps are required to generate these organoids, which, as judged by expression analysis and structural features, reached the second trimester of human gestation and allowed modeling of fibrotic lung disease. The dilated tips of the organoids contained ATII cells that could take-up and secrete surfactant proteins after more than 100 days of culture. Here, we show how these organoids can be dissociated at much earlier stages of development and can be induced to generate spheres containing only ATII cells that can be passaged and expanded. We also show how these can efficiently be infected with both SARS-CoV2 and influenza A viruses without the need to dissociate or culture in air-liquid interphase cultures. This model therefore allows the generation of large numbers of bona fide ATII cells without any isolation steps, and will be useful for future studies in disease modeling and cellular therapies.

Keywords: Pulmonary type II cells, Disease modeling, Organoids

2:05 PM – 2:15 PM

RECONSTRUCTION OF HUMAN SOMITOGENESIS WITH PLURIPOTENT STEM CELLS

Miao, Yuchuan[1], Djeffal, Yannis[1] and Pourquié, Olivier[2]

[1]Pathology, Brigham and Women's Hospital, Boston, MA, USA, [2]Genetics, Harvard Medical School, Boston, MA, USA

The metameric organization of vertebrates is first implemented when somites, which contain the precursors of skeletal muscles and vertebrae, are rhythmically generated from the presomitic mesoderm (PSM). This process of somitogenesis is vital for body plan development, yet very little is known about human somitogenesis given limited access to early embryos and ethical concerns. Stem-cell based embryo models provide a promising alternative to in vivo studies. Mouse pluripotent stem cells (PSCs) have been used to achieve a striking recapitulation of all somitogenesis stages in 3D, yet no such protocols have so far been

reported for human PSCs. Here we introduce two novel 3D culture systems of human PSCs, called Somitoids and Segmentoids, which can recapitulate the formation of epithelial somite-like structures with antero-posterior (AP) identity revealed by live cell imaging and single-cell RNA sequencing. In contrast to gastruloids or Trunk-Like Structures which harbor cell lineages derived from the three germ layers, our two models contain almost exclusively paraxial mesoderm. Somitoids recapitulate the temporal sequence of somitogenesis, with all cells undergoing differentiation and morphogenesis in a synchronous manner. This system can provide unlimited amounts of cells precisely synchronized in their differentiation and will allow exploring these patterning processes at an unprecedented level of detail. On the other hand, Segmentoids reconstruct the spatio-temporal features of somitogenesis, including gene expression dynamics, tissue elongation, sequential somite morphogenesis, and AP polarity patterning. They therefore provide an excellent proxy to study human somitogenesis. Together, these two complimentary models provide a valuable platform to decode general principles of somitogenesis and advance knowledge of human development.

Keywords: Somitogenesis, Organoid, Human development

2:15 PM – 2:35 PM

MODELING EARLY HUMAN DEVELOPMENT BY INTEGRATED STEM CELL BASED EMBRYO MODELS

Wu, Jun

Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX, USA

Our cellular, molecular and genetic understanding of human pre-/peri-implantation development is limited. This gap in knowledge is a key obstacle to understanding the basis of developmental defects. However, studying early human development is challenging due to the restricted access to human embryos available for research. Rodent models play an important role in understanding early human development, where a powerful array of modern genetic tools has been successfully applied. However, rodent models are not ideal because many aspects of human development are molecularly and temporally distinct from the rodents. To relieve the dependency of human embryos for studying human embryogenesis, last year we first reported a method for the generation of 3D human blastocyst-like structures (termed human blastoids) from naive human pluripotent stem cells (hPSCs), which recapitulate all three embryonic tissue types. We have further improved the method, which now supports highly efficient (as high as >90%) and large-scale production (~24,000 per plate) of human blastoids. We also developed a strategy to enable efficient attachment and development of human blastoids into early post-implantation stages. Human blastoids represent a well-controlled cellular substrate to test biological hypotheses, and will facilitate an improved fundamental understanding of the key signaling events and cellular interactions of pre-/peri-implantation human development, which will help us understand the molecular and cellular contributors of developmental failures in humans.

Keywords: Human blastoids, integrated stem cell embryo models, Naive human pluripotent stem cells, implantation, trophoblast, epiblast, hypoblast

TRACK: CLINICAL APPLICATIONS (CA) STEM CELLS - FROM DEVELOPMENT TO THERAPY
1:00 PM – 2:45 PM
ROOM 2004
LEVEL 2

1:05 PM – 1:25 PM

MODELING HUMAN DEVELOPMENT FOR NEW CELL THERAPIES

Keller, Gordon

McEwen Stem Cell Institute, University Health Network, Canada

Human pluripotent stem cells (hPSCs) represent a novel and potentially unlimited source of functional cell types for developing new cell therapies to treat disease. For these hPSC-based therapies to be effective, it is essential to generate the appropriate target cell population for the disease to be treated. To address this challenge, our lab has used developmental biology guided strategies to produce specific cardiovascular, hematopoietic and vascular lineage cells from hPSCs. With this approach, we were able to show that fates are specified early and that different cardiovascular and blood cell lineages derive from distinct mesoderm subpopulations. Within the cardiovascular system, we found that CD235a/b is expressed on ventricular mesoderm but not on the mesoderm that gives rise to atrial cardiomyocytes. Similarily, we showed that expression of CD235a/b distinguishes mesoderm that generates the primitive hematopoietic lineages from the mesoderm that contributes to definitive hematopoiesis. By optimizing induction of these mesoderm subtypes, one can generate populations highly enriched for specific cardiac or hematopoietic cells without the use of cell enrichment strategies. Our most recent studies have shown that it is possible to further segregate these mesoderm populations and in doing so to specify an even broader spectrum of hPSC-derived cardiovascular and hematopoietic lineages. Access to these different cell types provides the foundation necessary for developing cell replacement therapies to treat a range of different cardiovascular, hematopoietic and immune related diseases.

Keywords: mesoderm, hematopoietic, cardiovascular

1:25 PM – 1:35 PM

ENGRAFTMENT OF HPSC-DERIVED LUNG PROGENITORS IN A XENO-TRANSPLANT MODEL CONDITIONED BY DE-EPITHELIALIZATION

Liu, Hsiao-Yun[1], Predella, Camilla[2], Liang, Songjingyi[2], Chen, Ya-Wen[3], Vunjak-Novakovic, Gordana[4], Snoeck, Hans-Willem[1] and Dorrello, N. Valerio[2]

[1]Medicine, Columbia University Medical Center, New York, NY, USA, [2]Pediatrics, Columbia University Irving Medical Center, New York, NY, USA, [3]Otolaryngology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [4]Biomedical Engineering, Columbia University, New York, NY, USA

A major challenge in lung regeneration has been to remove only injured epithelium while preserving the surrounding lung architecture to allow engraftment of exogenous lung cells and identify the progenitor or stem cells that engraft. We have established an in vivo model of regional de-epithelialization (removal of epithelium) in Sprague-Dawley rats, by de-epithelializing up to 20% of the total alveolar surface of a single lobe via airway cannulation. The technique is based on an ex vivo rodent model. Putative distal tip progenitors were generated and expanded from lung organoids. These cells express SOX2, SOX9, NKX2.1 but not markers of mature airway cells. 48h after de-epithelialization, progenitor cells were administered intratracheally to the lower left lung. Multidrug

immunosuppression was applied during the entire experiment. Lungs were harvested 24-48hrs after injury to validate the regional de-epithelization in vivo (n=26) and at 10 days post-cell-engraftment to assess endogenous recovery and engraftment with human cells (n=21). All the treated animals were not only clinically stable during both procedures, but also did not show any alteration in hematological, renal, or hepatic profiles. After 24-48 hours, we showed loss of alveolar epithelial type I and type II cells and preservation of endothelial cells in the de-epithelialized region. Endogenous recovery was complete after 10 days. 10 days after administration of human progenitor cells, patches of human lung cells were detected in the rodent host lung by immunofluorescence staining for human EpCAM, HT1-56 (human type I alveolar epithelial cells), and HT2-280 (human type II cells) (IF), and further quantified flow cytometry with human EpCAM, and species-specific gDNA qPCR as well as RT-qPCR. We have established an in vivo xenogeneic lung model combining regional de-epithelialization and re-cellularization with hPSC-derived lung progenitors. We envision that this strategy can be applied to lung epithelial diseases where exogenous cells can replace injured epithelium to promote repair.

Keywords: Strategy can be applied to lung diseases, In vivo xenogeneic lung model, Remove and re-cellularization in lung

1:35 PM – 1:45 PM

THERAPEUTIC CORRECTION OF HEMOPHILIA A BY TRANSPLANTATION OF HPSC-DERIVED LSEC PROGENITORS

Gage, Blair K.[1], Merlin, Simone[2], Olgasi, Cristina[2], Follenzi, Antonia[2] and Keller, Gordon[3]

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Liver sinusoidal endothelial cells (LSECs) form the predominant microvasculature in the liver where they carry-out many functions including the secretion of coagulation factor VIII (FVIII). To investigate the early origins of human LSECs we developed an efficient and scalable protocol to produce human pluripotent stem cell (hPSC)-derived venous endothelium from different mesoderm subpopulations. This new protocol generates approximately 1 venous endothelial cell (VEC) for each input hPSC such that in 13 days, one cryovial of hPSCs yields 90 million purified CD34+ venous cells (60 cell therapy doses in mice). Using a sensitive and quantitative vascular competitive transplantation assay, we demonstrate that VEC populations generated from BMP4 and Activin A induced mesoderm characterized by KDR+CD235a/b+ expression was 50 fold more efficient at engrafting the LSEC compartment in the liver of NSG mice than venous populations generated from KDR+CD235a/b- mesoderm induced by BMP4 and WNT agonism. When transplanted into immunocompromised Hemophilia A mice (NSG-HA), these VECs engrafted the liver, proliferated, and generated functional LSECs that secreted bioactive FVIII capable of correcting the severe Hemophilia A bleeding phenotype. Together, these findings highlight the importance of appropriate mesoderm induction for the generation of specific cell types from hPSCs and demonstrate that with this approach, it is possible to generate LSECs capable of functioning in a pre-clinical model of Hemophilia A.

Funding Source: This work was funded in part by the University of Toronto's Medicine by Design Initiative (G.M.K), which receives funding from Canada First Research Excellence Fund (CFREF), and the Canadian Institutes of Health Research (G.M.K.).
Keywords: Hemophilia A - FVIII, Liver Sinusoidal Endothelial Cells, hPSC - Cell Therapy

1:45 PM – 1:55 PM

FIRST-IN-HUMAN CLINICAL TRIAL OF TRANSPLANTATION OF IPSC-DERIVED NS/PCS IN SUBACUTE COMPLETE SPINAL CORD INJURY: THE FIRST CASE

Okano, Hideyuki[1], Sugai, Keiko[2], Tsuji, Osahiko[2], Nagoshi, Narihito[2], Yamaguchi, Ryo[3], Kohyama, Jun[1], Kawashima, Shihoko[1], Fujiyoshi, Kanehiro[4], Kanemura, Yonehiro[5] and Nakamura, Masaya[2]

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We performed cell transplantation of human iPSC-derived neural progenitor cells for the first participant in the clinical research of "Regenerative Medicine using iPSC-derived Neural Progenitor Cells for Subacute Spinal Cord Injury" on December 8, 2021, according to the protocol approved by the Ministry of Health, Labor and Welfare Japan (Clinical Trial Numbers: UMIN000035074, jRCTa031190228). In this study, the transplanted neural progenitor cells were prepared at a Good Manufacturing Practice-grade cell processing facility using a clinical-grade integration-free hiPSC line established by the iPSC Stock Project organized by the Kyoto University Center for iPS Cell Research and Application. After performing all quality checks, the long-term safety and efficacy of cells were confirmed using immunodeficient mouse models. In the present case, after the consent was obtained, the cryopreserved cells were thawed and prepared through a multi-step process, including treatment with γ-secretase inhibitors to promote cell differentiation. Approximately 2 million iPSC-neural progenitor cells (20μl as cell suspension volume) were then transplanted into the epicenter of the injury. The surgery was successfully completed, and the patients are in good condition. The present clinical trial uses an open-label, single-arm design. The initial follow-up period is 1 year. The primary objective is to evaluate the safety of hiPSC-NS/PC transplantation in patients with subacute SCI. The secondary objective is to obtain preliminary evidence of its impact on neurological function and quality of life. 4 patients with C3/4-Th10 levels and complete subacute SCI (within 24 days of injury) will be enrolled in total. This surgery is the world's first transplantation of human iPSC-neural progenitor cells for spinal cord injury. To prioritize the safety of the research participant, the number of cells to be transplanted was determined based on the number of cells for which the research team was able to confirm safety in their non-clinical study conducted with small animals. So, although there is a possibility that therapeutic efficacy may be observed, the primary objective of this clinical study was to first and foremost confirm the safety of the transplanted cells and method of transplantation. The follow-up data will be presented.

Funding Source: Research grants from AMED (JP21bm0204001 and JP21bk0104120).
Keywords: iPSCs, neural progenitor cells, spinal cord injury

1:55 PM – 2:05 PM

HUMAN INHIBITORY NEURON CELL THERAPY ENTERS PHASE I/II CLINICAL INVESTIGATION FOR CHRONIC FOCAL EPILEPSY

Nicholas, Cory R., Priest, Catherine, Banik, Gautam, Blum, David, Bulfone, Alessandro, Adler, Andrew, Lee, Seonok, Parekh, Mansi, Hampel, Philip, Kim, Hannah, Watson, Michael, Zhou, Robin, Havlicek, Steven, Kriks, Sonja, Bershteyn, Marina, Maury, Yves and Fuentealba, Luis

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Drug-resistant seizures represent a significant unmet medical need for more than one-third of people diagnosed with epilepsy. Surgical resection or ablation of the seizure focus can be an option for chronic focal-onset epilepsy, however, these surgeries are destructive to surrounding tissue, can cause serious adverse cognitive effects, and many patients are not eligible. Alternative non-destructive therapeutic options are needed, and we have developed a human inhibitory neuron candidate, NRTX-1001, to potentially provide a regenerative cell therapy option. NRTX-1001 is derived from human pluripotent stem cells and comprises GABAergic inhibitory neurons of a specific pallial interneuron lineage, and specific post-mitotic, migratory stage. An investigational new drug (IND) application was recently cleared by the FDA to allow a phase I/II clinical trial (NCT05135091) of NRTX-1001 for drug-resistant temporal lobe epilepsy (TLE). Here, we present the IND-enabling data, including the molecular and functional criteria used to release three lots of cGMP clinical product. Transcriptomic profiling by single cell RNA sequencing confirmed an enriched composition of medial ganglionic eminence (MGE) pallial-type interneurons. In a rodent model of TLE, NRTX-1001 significantly suppressed temporal lobe seizures, reduced hippocampal granule cell dispersion and sclerosis, and improved survival of epileptic animals. No behavioral abnormalities, untoward migration, tumors, or other pathologies were detected in a GLP toxicology study. Using an MRI-guided delivery system, on-target NRTX-1001 distribution was demonstrated in a large animal model. The clinical trial design includes open-label dose escalation followed by randomized controlled evaluation of NRTX-1001 safety and efficacy in people with drug-resistant TLE.

Funding Source: Funded in part by the California Institute for Regenerative Medicine (TRAN1-11611; DISC2-10525; DISC2P-11700).
Keywords: GABA interneuron, MGE neuron, Epilepsy TLE seizure

2:05 PM – 2:15 PM

ENCOURAGING RESPONSIBLE STEM CELL RESEARCH AND INNOVATION WITH ANTICIPATORY GOVERNANCE AND FORESIGHT

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This paper builds on proposals for anticipatory governance to encourage responsible stem cell research and innovation. The field of stem cell research spans multiple domains of basic science and clinical translation that are regulated under myriad of national laws and legislative frameworks. While these frameworks are broadly aimed at balancing the social and moral goods of scientific knowledge and biomedical research with concerns for the moral status of early human life and protection of groups vulnerable to exploitation, amongst others, they vary widely across international jurisdictions from highly permissive to strictly prohibitive. Their fitness for purpose in responding to ongoing uncertainties in translating stem cell research into clinical applications and the emergence of biotechnologies, such as induced pluripotency and genome editing, has come into question. That has also prompted proposals for more responsive governance mechanisms that offer greater flexibility and adaptiveness to the rapidly changing technoscientific field. The paper will outline and defend the need for those mechanisms before articulating the concept of foresight as ethical principle for guiding research towards achieving socially and morally-desirable outcomes. This principle accounts for anticipated benefits as well as risks of harm in contrast with precautionary approaches that often guide law and policymakers in regulating for scientific uncertainty.

Keywords: Bioethics, Science policy, Research regulation

2:15 PM – 2:35 PM

DEVELOPING A DOPAMINERGIC CELL THERAPY FOR PARKINSON'S DISEASE

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Parkinson's Disease involves the loss of dopamine neurons in the midbrain, giving rise to the main motoric symptoms of the disease. Previous work has shown that replacement of the lost dopamine neurons through transplantation of new neurons from human fetal ventral midbrain can, when successful, restore dopamine levels in the brain and lead to marked clinical improvement. We have developed a novel ATMP cell product (STEM-PD), consisting of human dopaminergic neuron progenitor cells derived from human embryonic stem cells. STEM-PD has been manufactured under GMP and undergone extensive in vitro quality control as well as full preclinical safety and efficacy testing following regulatory guidelines. These studies have provided evidence that the cell product is efficacious in restoring motoric function in animal models of Parkinson's Disease, while showing long-term persistence of grafts with no toxicological concern or biodistribution to other tissues. Here will be presented data on the regulatory-guided testing of the dopaminergic cell product as well as exploratory studies on in vivo circuit integration and preliminary efforts on a generating cholinergic cell therapy for targeting Parkinson's Disease with dementia.

Keywords: ATMP, cell therapy, dopaminergic neurons, Parkinson's Disease, clinical trial, human embryonic stem cells

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)
MODELING DEGENERATIVE DISEASES AND CANCER
1:00 PM – 2:45 PM
ROOM 2011
LEVEL 2

1:05 PM – 1:25 PM

NEUROMUSCULAR ORGANOIDS TO STUDY HUMAN DEVELOPMENT AND DISEASE

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The control of body movement is achieved by a complex neuromuscular network that includes the generation of rhythmic patterns of neuronal activity essential for locomotion. Defects in this network are the cause of incurable neuromuscular diseases that result in paralysis and death. Studying the diseases that affect this system has been difficult due to the limited availability of reliable human in vitro models. We have established a complex 3D organ-

oid model that allows the simultaneous generation of spinal cord neurons, skeletal muscle cells and Schwann cells from human pluripotent stem cells through a bipotent neuromesodermal progenitor (NMP). NMPs, located in the posterior part of the embryo, are important for axial elongation and coordinated growth of the trunk neuromuscular system. We have coaxed human NMPs to develop into neuromuscular organoids (NMOs) that form functional neuromuscular junctions supported by the presence of terminal Schwann cells. Strikingly, the NMOs contract in response to central pattern generator-like circuits and can be maintained in culture from several months to years. We have successfully used NMOs to accurately model the neuromuscular junction dysfunction observed in myasthenia gravis. We are currently harnessing NMOs to model genetic diseases that affect the neuromuscular junction using patient derived induced pluripotent stem cells (iPSCs). The diverse genetic origins and onset of debilitating neuromuscular diseases have hampered the development of patient specific therapeutics. The unique advantage of the system is that for first time we have access to a completely patient-derived neuromuscular junction 3D model. This approach promises to provide greater insight into the mechanisms that lead to specific neuromuscular diseases by tackling previously inaccessible features due to the lack of human-based models that recapitulate neuromuscular junction biology.

Keywords: Neuromuscular Organoids; Neuromuscular junction; Disease modelling

1:25 PM – 1:35 PM

GENIPIN RESCUES SENSORY NEURON DEFECTS IN FAMILIAL DYSAUTONOMIA VIA CROSSLINKING OF EXTRACELLULAR MATRIX PROTEINS

Zeltner, Nadja[1], Saito-Diaz, Kenyi[2], Dietrich, Paula[3], Patel, Archie[2], Wzientek, Camryn[5], Prudden, Anthony[4], Boons, Geert-Jan[4], Chen, Shuibing[5], Studer, Lorenz[6] and Dragatsis, Ioannis[3]

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Familial Dysautonomia (FD) is a devastating, early-childhood, genetic disorder that affects the peripheral nervous system (PNS), specifically the sensory and sympathetic neurons. To date, FD has no available cure or disease-specific treatment. A mutation in the ELP1 gene causes developmental and degenerative defects in the sensory and autonomic lineages, which are associated with loss of pain perception, heart-rate instability and dysautonomic crisis. Current FD treatments are supportive in nature, but do not address the disease mechanism. There is a need for a model system that allows discovery and testing opportunities of novel therapeutics for FD. We previously employed the human pluripotent stem cell (hPSC) technology to show that peripheral sensory neurons (SNs) are not generated efficiently and that they degenerate over time in FD. Here, we conducted a chemical high-throughput screen to identify compounds that were able to rescue this SN differentiation defect. Upon validation of the top three hits, we discovered genipin, a compound with neurogenic and neuroprotective properties that is prescribed as a Traditional Chinese Medicine for neurodegenerative disorders, mainly in the brain. Genipin has not been assessed in the PNS yet. Genipin is also used to crosslink extracellular matrix (ECM) proteins in bioengineering approaches. We found that genipin restores neural crest and SN development in FD. It further protects against neurodegeneration and leads to longer neurites. Geinipin also rescues sympathetic neuron defects in FD. We found that Genipins action is exerted specifically via ECM crosslinking, since alternative ECM crosslinkers have similar effects and crosslinking defective genipin can no longer rescue FD phenotypes. Lastly, when genipin was given to FD mice in utero, it was able to cross the placenta and successfully restored SN and autonomic neuron phenotypes. Our results indicate that genipin is a promising future drug candidate for FD. Genipin might further be a candidate for treatment of other, more common peripheral neuropathies, where there is currently a dramatic lack of treatment options.

Funding Source: NIH/NINDS 1R01NS114567-01A1
Keywords: disease modeling and drug discovery, Familial Dysautonomia and neuropathy, sensory neurons

1:35 PM – 1:45 PM

ARTIFICIAL EXTRACELLULAR MATRIX SCAFFOLDS ENHANCE THE MATURATION AND AGING OF HUMAN STEM CELL DERIVED NEURONS AND ENABLE THE MODELING OF NEURODEGENERATIVE DISEASE PATHOLOGY

Kiskinis, Evangelos[1], Alvarez, Zaida[2], Ortega, Alberto[3] and Stupp, Samuel[2]

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Human induced pluripotent stem cell (iPSC) technologies offer a unique resource for modeling neurological diseases. However, iPSC models are fraught with technical limitations including abnormal aggregation and inefficient maturation and ageing of differentiated neurons. These issues are in part due to the absence of synergistic cues derived from the architecture, chemical composition and molecular dynamics of the native extracellular matrix (ECM). To solve these problems we purified the ECM from the spinal cord of early postnatal and adult mice and profiled its protein composition by mass spectrometry (MS)-based proteomics. We identified several candidate proteins that were significally more abundant in aged ECM, including laminin alpha 1 chain. We hypothesized that laminin alpha 1, which engages with neuronal surface receptors through the bioactive pentapeptide sequence IKVAV, might enhance the maturation of neurons. We functionalized IKVAV on three artificial ECMs based on supramolecular nanofibers containing peptide amphiphile (PA) molecules. All nanofibers displayed on their surface the same IKVAV signal but differed in the nature of their non-bioactive domains. We found that nanofibers with greater intensity of internal supramolecular motion had enhanced bioactivity toward iPSC-derived motor and cortical neurons. Proteomic, biochemical and functional assays revealed that scaffolds with highly mobile molecules lead to enhanced b1-integrin pathway activation, reduced aggregation, increased arborization, and mature electrophysiological activity of neurons. Neurons cultured on the ECM mimetic PA for an extended time exhibited an increase in markers of ageing including DNA damage and oxidative stress. Critically, neurons derived from ALS patients harboring a disease-causing mutation in the SOD1 gene exhibited pronounced neuropathology including aggregation of ubiqutinated SOD1 protein. Our work resolves long-standing limitations of culturing iPSC-derived neurons, and highlights the importance of designing bioactive ECMs to study the development, function and dysfunction of human neurons in vitro.

Funding Source: NYSCF, NIH/NINDS
Keywords: Neuronal aging, ALS, extracellular matrix

1:45 PM – 1:55 PM

DECODING NEURONAL VULNERABILITY AND RESILIENCE IN AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Souza, Cleide S.[1], Souza, Cleide[1], Kok, Jannigje[1], Shaw, Allan[1], El-Khamisy, Sherif[2] and Ferraiuolo, Laura[1]

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Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by progressive loss of motor neurons (MNs). Although ALS is primarily an MN disease other neurons and glial cells have an important role in its pathogenesis. A number of studies have shown that beyond motor impairments patients with ALS often display behavioral and cognitive deficits. Neuropathological and anatomical studies and impaired physiology suggest that the striatum might be involved. The mechanism behind the role of the striatum in ALS however, remains unclear. The aim of this study is to characterise the ALS hallmarks in MNs and striatal GABAergic neurons (SGNs) and identify the mechanisms of vulnerability through which MNs respond to stress. In this study, we used iPSC-derived MNs and SGNs from controls (n=3), familial ALS patients (n=3), and isogenic controls (n=2). Our data shows that MNs derived from ALS patients carrying a repeat expansion in the C9ORF72 gene display the main ALS hallmarks, in terms of neuronal death, TDP-43 proteinopathy, p62 accumulation and RNA foci. In comparison to MNs, SGN derived from ALS appear to be less affected by the mutation and do not display TDP-43 proteinopathy. On the other hand, SGNs display an increase in cell death, p62 accumulation and RNA foci. Several studies have shown increased DNA damage as a consistent feature of sporadic and familial ALS. In addition, we found that, although both MNs and SGNs carry the C9orf72 mutation, MNs accumulate higher amounts of DNA damage. It was hypothesised that MNs from ALS patients are more vulnerable to cell death due to impairment in the DNA damage response. To test this, we induced DNA damage in MNs and SGNs with camptothecin and subjected the cells to immunostaining to assess expression of various DNA damage markers and potential downstream effectors over time. Importantly we showed through DNA damage repair (DDR) kinetic studies that, unlike controls that activate the DDR cascade, ALS MNs do not seem to activate the downstream pathways and as a result accumulate DNA damage. On the contrary, similar to controls cells, SGN derived from ALS patients activated the DDR downstream pathway. In conclusion, our work identifies DNA damage as a possible mechanism by which ALS MNs are more susceptible to stressors that can induce DNA damage, such as oxidative stress.

Funding Source: This work has been supported by AstraZeneca Postdoctoral programme.
Keywords: ALS, Striatum, DNA Damage

1:55 PM – 2:05 PM

SINGLE CELL PROTEOMIC ATLAS OF CARTILAGE REVEALS MULTIPLE REGENERATIVE AND PATHOLOGICAL POPULATIONS

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The recent advent and accessibility of single cell technologies-both transcriptional and proteomic-has made it possible to have a high-resolution understanding of the composition, architecture and functioning of tissues in health and disease. Using a single cell mass cytometry approach, we have built a 'cellular atlas for human Cartilage' in healthy and OA patients. These analyses identified distinct subpopulations in healthy and OA cartilage, including regenerative populations, senescent cells and inflammation-associated populations. Three distinct cartilage-progenitor cells (CPC) were identified-CPC I that are depleted in OA, CPC II and CPC III that are enriched in OA. Intriguingly, CPC III clusters were high in inflammatory markers such as pNFK-B, pSTAT3, BCAT and HIF2A although other CPCs were non-inflamed. An inflammation amplifying (Inf-A) population was identified, characterized by the co-expression of two cytokine receptors, IL1R1 (CD121A) and TNFRII (CD120B). Inf-A clusters showed exclusive signaling through pJNK and pSMAD1/5 compared to the rest of the chondrocyte clusters. Inhibition of Inf-A using a JNK1/2 inhibitor or an inhibitor of Smad signaling, led to a significant reduction of the CCL2 and CCL7 cytokines secreted by OA cartilage thereby demonstrating that this chondrocyte subpopulation is Inflammation-amplifying. In addition, an inflammation dampening (Inf-D) subpopulation was characterized by the expression of CD24, a molecule we had previously identified as a negative regulator of NFkB mediated inflammation. Using additional markers, we have now identified p16 INK4a expressing 'senescent' cell populations in OA cartilage. Interestingly, Inf-A is distinct from the p16 INK4a expressing 'senescent' cell populations in OA cartilage, revealing that there are multiple cell populations that contribute to cartilage homeostasis and disease by altering the balance of the inflammatory milieu. These high resolution analyses also revealed the heterogeneity between patient populations especially in the distribution of the regenerative and pathological population, paving the way to identify ways for patient stratification and precision medicine approaches for disease-modifying OA therapeutics.

Funding Source: These studies were supported by NIAMS/NIH grants AR070864 and AR077530
Keywords: Cartilage, single cell omics, Osteoarthritis

2:05 PM – 2:15 PM

CIRCUMVENTING INTESTINAL STEM CELL DIFFERENTIATION UPON NOTCH INHIBITION IN THE TREATMENT OF T CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Gamma Secretase Inhibitors (GSIs), which can effectively block the activation of oncogenic protein Notch homolog-1 (Notch1), are potential candidates for the treatment of T-cell Acute Lymphoblastic Leukemia (T-ALL). However, severe gastrointestinal toxicity due to the inhibition of Notch signaling, also a key regulator of intestinal stem cell maintenance and progenitor differentiation, has mainly limited the clinical applications of GSI. Here we demonstrate that combination therapy of GSI and MLN4924, a small molecule that inhibits the neddylation pathway, circumvents the GSI-induced gut toxicity in vivo. We leveraged LS174T colorectal adenocarcinoma line as a model to study goblet cell differentiation as it recapitulates the transcriptional network of differentiating intestinal stem cells upon Notch inhibition. Genome-wide CRISPR loss-of-function screen in LS174T cells treated with GSI revealed the neddylation pathway as the main regulators of massive goblet cell differentiation upon Notch inhibition. Genetic deletion or pharmacologic inhibition of the neddlylation pathway in LS174T cells rescued GSI-induced differentiation and cell death. Mechanistically, neddylation inhibition by MLN4924 increases the protein stability of Hairy and enhancer of split-1 (Hes1), a known regulator of absorptive and secretory cell fate decisions. Combined treatment of GSI and MLN4924 in Notch1-induced T-ALL mice showed leukemia regression and improved overall survival without any associated gut toxicity. Overall, these results substantiate the potential of targeting Notch and neddylation pathway in the treatment of Notch1-induced T-ALL.

Keywords: intestinal stem cells, gut toxicity, therapeutics

2:15 PM – 2:35 PM

REGENERATIVE POTENTIAL AND STABILITY OF HPSC-DERIVED ARTICULAR CARTILAGE

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We established a directed differentiation model whereby both joint-lining articular cartilage tissues and transient growth plate cartilage tissues (ultimately remodeled into bone) can be generated from human pluripotent stem cells (hPSCs). hESC-derived articular cartilage effectively repaired osteochondral defects in the knee joints of rats, maintaining its proteoglycan and collagen-rich extracellular matrix (ECM) and facilitating integration with native tissue. Where the human cartilage implant interfaced with bone marrow cavities within the subchondral bone region, however, the implant began to remodel and new bone formation was initiated, similar to the fate of growth plate cartilage, or events associated with osteoarthritis/degenerative joint disease. While the articular surface remained intact in these implants, the site-specific remodeling result suggests the signaling niche plays a role in ultimate fate of the articular chondrocytes and cartilage tissues in vivo. To address this question of stability, we performed a series of experiments that provide evidence that hPSC-derived articular chondrocytes possess regenerative capacity, and we define a point at which the cells no longer remain bi-potent (i.e., able to undergo chondrocyte hypertrophy, a process associated with growth plate cartilage development and OA). We determined that the ECM generated by the hPSC-derived articular chondrocytes contributes to the stability of the tissues, which we are currently exploring greater depth in a newly established iPSC model of a rare monogenic progressive degenerative OA-like disease in children, Progressive Pseudorheumatoid Arthropathy of Childhood. These new insights into the molecular and matrix-related mechanisms of cartilage cell fate and tissue stability will contribute to our ongoing regenerative medicine-based efforts to repair damaged cartilage and our evolving understanding of degenerative diseases affecting the joint.

Keywords: cartilage, iPSCs, disease modeling

TRACK: NEW TECHNOLOGIES (NT)
MODELING STEM CELLS THROUGH SPACE AND TIME
1:00 PM – 2:45 PM
ROOM 2012
LEVEL 2

1:05 PM – 1:25 PM

TOWARDS DEVELOPMENT OF A HD VIDEO RECORDER OF THE CELL

Yachie, Nozomu

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The dynamic behaviors of cells during development, tumorigenesis, and other disorders remain largely unclear. Our lab is developing "DNA event recording" systems by which high-resolution information of cells is progressively stored in cell-embedded "DNA tapes." Using high-throughput single-cell sequencing, such a system enables access to molecular and cellular history information of cells at the time of observation and provides a way of observing the dynamics of complex biological systems in high resolution. We envision mapping the whole-body cell lineage and differentiation trajectories of mouse development and have been actively progressing towards this goal. I will share our grant vision and recent progress in developing new genome editing tools and high-performance computing technologies.

Keywords: DNA barcode, cell lineage tracing, genome editing

1:25 PM – 1:35 PM

ELUCIDATING THE MOLECULAR BASIS OF DEVELOPMENTAL COMPETENCE DURING HESC LINEAGE-SPECIFICATION

Pulecio, Julian[1], Tayyebi, Zakieh[2], Liu, Dingyu[1], Rickert, Robert[1], Kaplan, Samuel[2], Wong, Wilfred[3], Shukla, Abhijit[1], Luo, Renhe[1], Murphy, Dylan[2], Apostolou, Effie[4], Leslie, Christina[3] and Huangfu, Danwei[1]

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Current models suggest that chromatin regulatory regions (CRRs) become transcriptionally competent upon binding of pioneer transcription factors (TFs), which reshape the 3D organization of the chromatin around them and initiate the cascade of events required for gene activation. However, the molecular determinants that confer transcriptional competence only to a defined set of CRRs at specific developmental stages remains elusive. Likewise, it is not clear if the chromatin conformation at early embryonic stages determines the future competence of a regulatory region or if the contact points between regulatory elements and promoters are gradually established after pioneer TF binding. Here we study the CRRs of PDX1 (a pancreatic progenitor TF) as a model to study how transcriptional competence is established during development. To identify the CRRs able to promote PDX1 expression at the earliest developmental stage we performed CRISPR-a screens, using the SAM activation system as a targetable pioneer TF, and discovered four CRRs able to cause PDX1 expression in hESC. These early competent CRRs did not have any noticeable enrichment in chromatin accessibility or H3K27ac signal. To determine if there were additional PDX1 CRRs that will be utilized later in the cell-lineage specification program, we performed CRISPR-i screens during the differentiation from hESC to the pancreatic lineage and discovered four additional PDX1 enhancers. This suggests that the binding of a pioneer TF to a CRR does not necessarily cause its activation, and that additional factors must influence its ability to promote gene expression. To dissect this, we performed chromatin conformation assays at the ES stage and found that a higher number of contact points between an enhancer and the PDX1 gene body does not correlate with its transcriptional competence. In parallel, we devised an epigenetic compound screen at the ES stage and found that HDAC inhibitors significantly increase the ability of the competent CRRs to activate PDX1 expression at early stages, but do not induce competence de novo to the other set of enhancers. This effect has been validated on multiple enhancers of several developmental genes. We are currently investigating how HDAC chromatin binding at the ES stage influences the competence of candidate CRRs of multiple genes.

Keywords: Developmental Competence, CRISPR screens, Chromatin Conformation

1:35 PM – 1:45 PM

SINGLE CELL TRACKING SHOWS INTEGRATED BMP SIGNALING PREDICTS FATE IN HUMAN PLURIPOTENT STEM CELLS

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Despite uniform application of exogenous signaling factors, directed stem cell differentiation typically results in uncontrolled and poorly understood cell fate heterogeneity. This is a practical problem for applications of stem cell technology and exposes a gap in our understanding of how cell signaling controls differentiation. Recent work has shown that endogenous modulation of signaling downstream of initially uniform exogenous cues leads to highly dynamic and heterogeneous signaling activity. Here we show that this heterogeneity in signaling dynamics quantitatively explains cell fate heterogeneity at the single cell level. Specifically, we used live cell microscopy and single cell tracking to measure SMAD1 and SMAD4 signaling activity linked to cell fate in BMP4-dependent differentiation of human pluripotent stem cells (hPSCs). Surprisingly, we found that cells do not show a graded initial response to stimulation with different ligand concentrations, but rather differ in how long the response is sustained. We inferred the joint probability distributions of cell fate markers and features of the single cell signaling history and found that integrated BMP signaling activity predicts cell fate with high accuracy. Furthermore, we show that prediction based on the integral achieves close to maximal accuracy based on the information content of the signaling data determined by machine learning. Our work quantifies for the first time the signaling response to exogenous differentiation cues linked to fate in hPSCs at the single cell level and establishes a generally applicable methodology to dissect heterogeneous stem cell differentiation. This led us to a simple model for how cells decide their fate in a changing signaling environment that challenges the idea of static concentration thresholds in BMP response.

Keywords: pluripotent stem cells, single cell tracking, signaling dynamics

1:45 PM – 1:55 PM

ENGINEERED BARCODE IPSCS COUPLED WITH UNSUPERVISED DATA ANALYSIS PIPELINES FOR SCALABLE ANALYSIS OF MULTI-LINEAGE CELL DIFFERENTIATION

Shen, Sophie[1], Sun, Yuliangzi[2], Shim, Woo Jun[2], Werner, Tessa[2], Andersen, Stacey[2], Lukowski, Samuel[3], Chiu, Han Sheng[2], Chen, Xiaoli[2], Xia, Di[2], Powell, Joseph[4], Nguyen, Quan[2] and Palpant, Nathan[2]

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This study develops a cost-effective and versatile cell multiplexing platform with an unsupervised computational data analysis pipeline to upscale data generation and knowledge gain into mechanisms controlling cell differentiation. Using CRISPR gene editing, we engineered transcribed barcodes into the AAVS1 locus in WTC induced pluripotent stem cells (iPSCs), enabling parallel analysis of up to 20 isogenic cell lines without additional processing prior to capture for single-cell RNA-seq. Pairing barcoded iPSCs and Cell Hashing for multiplexing, we performed 62 experimental permutations multiplexed into 4 single-cell reactions to capture 62,208 single cells differentiating from pluripotency in vitro over 8 timepoints and 9 different small molecule-mediated signalling perturbations with biological duplicates. These data reveal temporal and signalling-dependent mechanisms guiding differentiation of iPSCs into diverse mesendodermal cell types. Next, we designed a novel unsupervised data analysis pipeline to classify, cluster, and evaluate molecular control of cell differentiation. First, we use consortium-level epigenetic data to cluster cells based on expression of cell type-specific regulatory genes, identifying the most well-defined cell states to anchor biological diversity in the data. Second, we use label transferring to classify cell populations against benchmark in vivo multi-lineage single-cell developmental time course data. These two independent biological reference points provide a basis for classification, identifying 48 cell types spanning cell lineages from all three germ layers. We then use NIH Epigenome Roadmap data to infer epigenetic co-modulation of genes, providing an unsupervised computational method to reveal structural and regulatory basis of individual cell types. Collectively, this study links new cellular barcoding with unbiased computational methods to deconstruct molecular control of cell types, with applications in drug discovery, cell-cell interactions, organoid biology, disease modelling, and cell differentiation to accelerate knowledge into genetic control of cell decisions.

Funding Source: ARC Special Research Initiative in Stem Cell Science. SR1101002
Keywords: iPSC, Single-cell RNA-seq, Multiplexing

1:55 PM – 2:05 PM

HIGH RESOLUTION MAPPING OF CELL LINEAGES DURING MOUSE GASTRULATION

Bowling, Sarah[1], Van Egeren, Debra[1], Kuhl, Bianca[1], Ton, Mai-Linh[2], Sritharan, Duluxan[3], Gottgens, Berthold[2] and Camargo, Fernando[1]

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Understanding the routes through which a single cell populates the adult organism is one of the most fundamental yet elusive areas of biology. In recent years, immense progress has been made in cataloguing cell identity during mouse development through single-cell RNA sequencing, though these data alone do not shed light on the ancestry and fate choices taken by cells. While the elucidation of whole embryo lineage trees has been achieved in C. elegans, there has been limited progress towards this goal in more complex animal models. To address this, we have recently developed and published a new mouse model, named CARLIN, that uses CRISPR-mediated cellular barcoding to trace thousands of cells in vivo with unique, transcribed tags in an inducible manner. Here, we describe our generation of an improved "CARLIN 2.0" system, which contains additional expressed barcodes that enable increased barcode capture efficiency at the single-cell level and increased barcode diversity. Using this new system, we have generated single-cell RNA sequencing libraries of whole early mouse embryos (E9.5) barcoded at different time points during gastrulation, allowing us to decipher the earliest lineage decisions taken by cells. Our data reveal the major clonal groupings that form during early development, including those that separate pools of mesoderm, endoderm and ectoderm cells. Our data point toward an early separation of endoderm lineages away from mesoderm lineages, and also indicate that a major clonal group links spinal cord, hindbrain, and somitic mesoderm lineages, thus providing further evidence for the existence of neuromesodermal progenitors in vivo. We have also used our data to elucidate di-

verse lineage origins of cardiac and endothelial cells. Our work sheds light on long-standing questions in developmental biology and can be used to understand the cell-of-origin of many pediatric diseases, and to bring insight into very basic biological questions about cell fate commitment.

Funding Source: European Molecular Biology Organization (EMBO), Wellcome Trust
Keywords: Embryogenesis, Barcoding, Ontogenesis

2:05 PM – 2:15 PM

INVESTIGATING PHENOTYPIC DIVERSITY OF THE HUMAN POSTERIOR CNS USING STEM CELLS AND SINGLE-CELL RNA-SEQUENCING

Iyer, Nisha, Shin, Junha, Roy, Sushmita and Ashton, Randolph

Wisconsin Institute for Discovery, University of Wisconsin, Madison, WI, USA

Our inability to derive the vast neuronal diversity of the posterior central nervous system (pCNS) using human pluripotent stem cells (hPSCs) poses a major impediment to understanding human neurodevelopment and disease in the hindbrain and spinal cord. Here we establish a modular differentiation paradigm that recapitulates patterning along both the rostrocaudal (R/C) and dorsoventral (D/V) axes of the pCNS, enabling derivation of any neuronal phenotype with discrete regional specificity in monolayer culture. First, neuromesodermal progenitors (NMPs) with discrete Hox profiles are efficiently converted to pCNS progenitors (pCNSPs). Then by tuning D/V signaling, pCNSPs are directed to ventral Shh-dependent MNs (MNs) and locomotor interneurons (INs) or dorsal TGF-β-dependent proprioceptive INs and TGF-β-independent sensory INs. Cultures with over 95% neuronal yield can be generated in as little as 16 days. We applied D/V protocols to pCNSPs spanning the R/C axis for expansive single-cell RNA-sequencing (scRNAseq) analysis, which confirmed discrete sample-specific Hox gene profiles, representation of all major motor and somatosensory spinal cell types, and the presence of human-specific cell populations. Finally, by implementing a novel computational pipeline comprising sparse non-negative matrix factorization, consensus clustering, and combinatorial gene expression pattern identification, we detect hundreds of transcriptional markers within region-specific neuronal phenotypes, enabling discovery of gene expression patterns along the developmental axes. We anticipate these findings will advance a mechanistic understanding of spinal development, expand the potential and accuracy of in vitro models, provide insight into novel therapeutic targets, and represent clinically relevant populations for cell transplantation.

Keywords: spinal cord and hindbrain, interneurons, HOX genes

2:15 PM – 2:35 PM

WHOLE EMBRYO-BARCODING FOR GENETIC INTERROGATION OF VERTEBRATE DEVELOPMENT

Wagner, Daniel E.

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From the moment of conception until death, multicellular organisms face constant assault on their genomes, cells, and tissues. The ability of functioning biological structures to withstand these dynamic challenges is essential for adult life but is tested first – and perhaps most critically – during embryonic development. Early failures of embryonic patterning can lead to rapid and premature lethality, birth defects, and/or life-long developmental disorders. Over the years, developmental biologists have made great progress in understanding many of the links connecting environmental and genetic perturbations to their consequences in embryos, generally by applying reductionist approaches (e.g. single-gene mutant phenotypes). However, a significant proportion of human pregnancies still result in developmental defects or miscarriages of unknown cause. At present, we also often fail to understand why certain perturbations result in failed embryogenesis in some individuals, but not in others. We are leveraging recent technological advances in single-cell genomics and lineage barcoding (e.g. TracerSeq) to implement and optimize methods for rapid in vivo genetic interrogations in whole embryos. We will present recent progress in the development of "TracerScreen", a barcoding technique that couples CRISPR-based genetic perturbations to transcribed clonal barcode reporters in mosaic zebrafish embryos. This approach enables the phenotyping of cell-autonomous functions for many genes in parallel across all embryonic tissues and at single-cell resolution. At present, we are deploying TracerScreen in zebrafish assess the post-gastrulation roles of BMP signaling in the specification of posterior embryonic fates. Recent results and potential implications for feedback-level control of posterior tissue patterns will be discussed.

Keywords: zebrafish, single-cell, lineage, embryo

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)
MOLECULAR CONTROL OF CELL FATE TRANSITIONS
1:00 PM – 2:45 PM
ROOM 2007
LEVEL 2

1:05 PM – 1:25 PM

MITOCHONDRIAL STATES ARE CRITICAL TO DEFINE STEM CELL HETEROGENEITY IN PLANARIA

Palakodeti, Dasaradhi, Haroon, Mohammed, Arora, Ankit, Sarkar, Souradeep, Lakshmanan, Vairavan, Lei, Kai and Vemula, Praveen

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Dissecting the mechanisms of stem cell function is key to understand the principles of regeneration in planaria. A major limitation of studying stem cell biology has been in characterizing stem cell populations in finer detail. Multifaceted role of mitochondria in maintenance of cellular energetics, redox and ion balance, metabolism-driven epigenetic regulation have been implicated in stem cell state transitions. However, the molecular details of how regulation of mitochondrial state affects stem cell homeostasis and differentiation have not yet been fully understood. Recent findings from our work show that planarian stem cell states can be defined using mitochondrial states and the perturbation of the mitochondrial activity resulted in the inhibition of stem cell differentiation. This principle also enabled us to identify and characterize 2N pluripotent stem cells in these animals. Next, single-cell transcriptomic analysis of various mitochondrial states identified heterogeneous populations of stem cells with various potencies in planaria with distinct metabolic states. Further, our work also highlights the translation regulation as a key mechanism to control mitochondrial states in the stem cell population of planarians.

Keywords: Planaria, neoblast, pluripotent, Mitochondria

1:25 PM – 1:35 PM

A HUMAN FETAL LUNG CELL ATLAS UNCOVERS HIDDEN STATES AND KEY REGULATORS OF EPITHELIAL FATES

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We present a multiomic cell atlas of human lung development, surveying multiple lineage compartments from 5 to 22 post conception weeks. Coupling single cell methods with spatial analysis, we identifed new cell states in all compartments. These include developmental-specific secretory progenitors that resemble cells in adult fibrotic lungs and a new subtype of neuroendocrine cell related to human small cell lung cancer. Finally, guided by our multiomic atlas, we were able to predict key transcription factors and demonstrate using organoid models the sufficiency of NEUROD1 and ASCL1 in neuroendocrine subtype specification. Our study provides a comprehensive reference of human fetal lung with the highest resolution to date and strengthens the connections between development and disease/regeneration.

Keywords: single-cell, development, lung

1:35 PM – 1:45 PM

HIF-1A REGULATES CARDIAC FIBROBLAST (CF)-STATE TRANSITIONS

Janbandhu, Vaibhao and Harvey, Richard

Developmental and Stem Cell Biology, Victor Chang Cardiac Research Institute, Darlinghurst, Australia

Cardiac fibroblasts (CFs) are cells of mesenchymal origin and represent a heterogeneous population in the mammalian heart. Our previous work has revealed an unprecedented degree of CF heterogeneity and dynamics in healthy and infarcted hearts using single-cell RNA sequencing (scRNA-seq), however, regulatory mechanisms governing CF-state transition remain unclear. Here, we now show that a sub-compartment of CFs enriched in mesenchymal stem cell properties maintain intracellular hypoxia and stabilize hypoxia-inducible factor 1a (HIF-1a). HIF-1a functions as master regulator of oxygen homeostasis and induces the transcription of genes involved in the metabolism and behaviour of stem/progenitor cells. CF-specific deletion of HIF-1a resulted in increased mesenchymal progenitors in uninjured hearts and increased CF activation without proliferation following sham injury suggesting that they have entered a primed (alert) but uncommitted state, as demonstrated using scRNA-seq. After myocardial infarction (MI), however, there was ~50% increase in CF proliferation and excessive scarring and contractile dysfunction in HIF-1a-deficient mice, a scenario replicated in 3D engineered cardiac microtissues. Notably, there was a marked increase in reactive oxygen species (ROS) in HIF-1a-null CFs compared with wild-type CFs that correlated with changes in expression of genes that regulate ROS. Importantly, wild-type mice treated with the mitochondrial ROS generator MitoParaquat (MitoPQ) phenocopied HIF-1a-null mice, whereas treatment with the mitochondrial-targeted antioxidant MitoTEMPO resulted in reversion of the HIF-1a-deficient CF phenotype. Thus, HIF-1a provides a critical braking mechanism against excessive post-ischemic fibrotic response, a function that is required for optimal cardiac repair. Our results provide novel insights into how HIF-1a regulates the CF-state transition and recognize CFs as potential cellular targets for designer antioxidant therapies in cardiovascular disease.

Funding Source: National Health and Medical Research Council (NHMRC, Australia), Leducq Foundation (France), Australian Research Council (ARC, Australia), Australia-India Strategic Research Fund, National Institutes of Health (NIH, USA)
Keywords: Cardiovascular disease/ Cardiac fibroblasts, Cardiac mesenchymal progenitors, Hif-1a and hypoxia

1:45 PM – 1:55 PM

GATA2 AT MITOSIS-TO-G1 TRANSITION IS CRITICAL FOR DEFINITIVE HEMATOPOIESIS

Alves, Rita S.[1], Kurochkin, Ilia[2], Rydström, Anna[2], Haider, Jakob[2], Lindgren, Aida[2], Thelaus, Louise[2], Ferreira, Alexandra[2], Larsson, Jonas[2], Gonzalez, Javier[3] and Pereira, Carlos-Filipe[2]

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In mitosis, many transcription factors (TFs) disperse across the cytoplasm, still some are retained on condensed chromatin and mark genomic sites, a mechanism termed mitotic bookmarking. This mechanism is important for pluripotency, lineage inheritance and cell reprogramming. However, the role of bookmarking in vivo is yet to be addressed. Hematopoietic stem cells (HSCs) undergo drastic changes in cell cycle during development, whilst balancing self-renewal and differentiation, suggesting a possible role for bookmarking. Here, we first addressed the mitotic retention of the hemogenic TFs GATA2, GFI1B and FOS. We show that GATA2 remains bound to chromatin at all phases of cell cycle, in contrast to GFI1B and FOS. Moreover, the C-terminal zinc finger (C-ZF) and the nuclear localization signal domains are required for GATA2 mitotic binding. Point mutations in the C-ZF associated with leukemia also impact GATA2 retention. Next, we preformed ChIP-sequencing analysis of mitotic K562 cells to define bookmarked genes and found that GATA2 binds to a subset of its interphase targets. Mitotic peaks are enriched for GATA, RUNX1 and PU.1 motifs, critical regulators of HSC fate specification. To assess the impact of GATA2-mediated mitotic bookmarking in definitive hematopoiesis we have fused GATA2 to the Cyclin-B1 mitosis degradation (MD) domain, which promotes protein destruction at mitosis-to-G1 transition (M-G1) and evaluated its impact on the reprogramming of fibroblasts to hemogenic cells. Degradation of GATA2 at M-G1 results in mis-regulation of important genes for definitive hematopoiesis. Finally, to uncover the role of GATA2 during M-G1 in vivo, we have generated a mouse model with the MD domain inserted upstream the Gata2 gene. Remarkably, homozygous mice are lethal, phenocopying Gata2 null mice which die at the onset of definitive hematopoiesis. Interestingly, deleting GATA2 at M-G1 has a specific impact on both aorta-gonad-mesonephros and placental hematopoiesis, but not on yolk sac hematopoiesis, as assessed by colony-forming unit and transplantation assays. All together, these findings implicate GATA2 as a mitotic bookmarker critical for definitive hematopoiesis. Overall, our study highlights a dependency on mitotic bookmarkers for in vivo lineage commitment.

Funding Source: PD/BD/135725/2018
Keywords: Mitotic bookmarking, GATA2, Definitive hematopoiesis

1:55 PM – 2:05 PM

REGENERATIVE CHECKPOINTS REGULATE EPITHELIAL CELL FATE PLASTICITY IN A MODEL OF ESOPHAGEAL-TO-SKIN LINEAGE CONVERSION

Bejar, Maria T.[1], Jimenez-Gomez, Paula[1], Moutsopoulos, Ilias[1], Colom, Bartomeu[2], McGinn, Jamie[1], Han, Seungmin[3], Skrupskelyte, Greta[1], Calero-Nieto, Fernando[1], Gottgens, Berthold[1], Mohorianu, Irina[2,1], Simons, Benjamin[3] and Alcolea, Maria[1]

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Epithelial stem cells have been shown to present a high degree of fate plasticity in response to tissue perturbation. In order to restore the epithelial barrier, epithelial cells are able to reacquire stem cell-like behavior and widely contribute to regenerate different compartments of the damaged tissue. However, inadequate regulation of epithelial cell fate programs can lead to disease and cancer. Despite the clinical relevance of understanding how epithelial cell fate plasticity is controlled in response to injury, the lack of robust and efficient models has limited our knowledge about the specific molecular mechanisms controlling the dynamic changes in epithelial cell fate. Here we developed a novel 3D regenerative culture system that allows co-culturing epithelium and stroma of different origins, and demonstrated that when exposed to the foreign stroma of adult skin, esophageal cells are able to re-establish the epithelial skin architecture. However, only a subset of them transition towards and acquire skin stem cell identity, suggesting the existence of barriers to changes in cell identity during regeneration. Combining our esophageal-skin heterotypic system with lineage tracing and single-cell transcriptomics, we investigated the little-known regulatory processes that restricted fate permissibility. Single-cell RNA-seq trajectory analysis and histological examination throughout the re-specification process, reveal that esophageal cells switching towards skin identity remain in an unresolved transient regenerative state and a particularly strong hypoxic signature. Furthermore, chemical and genetic gain and loss of function experiments demonstrate the central role of HIF1a-Sox9 axis regulating epithelial cell plasticity, limiting changes in cell identity during active tissue re-epithelialization. Taken together, our results unveil the existence of control checkpoints for lineage conversion during tissue regeneration that restrict the ability of cells to respond to signals instructing alternative fate choices.

Funding Source: M.T.B received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement No 794664 (OESOPHAGEAL FATE).
Keywords: Epithelial plasticity, Esophageal 3D organ culture, Cell fate transitions

2:05 PM – 2:15 PM

BASIS OF CHROMATIN SCANNING BY PIONEER TRANSCRIPTION FACTORS

Lerner, Jonathan, Zaret, Kenneth and Zhang, Jingchao

Cell and Developmental Biology, University of Pennsylvania, Philadelphia, PA, USA

Over the past years, advances in live-cell single-molecule microscopy elicited unprecedented insights on how transcription factors scan chromatin to find specific genomic sites. Cell fate changes, such as development or reprogramming, are triggered by the accession of regulatory sites in closed chromatin by a subset of transcription factor labeled as pioneers. Previously, using Single-Molecule Tracking (SMT) we showed that the strong affinity for nucleosomal DNA of pioneer factors measured in vitro correlates with the ability to scan constrained chromatin regions in living cells, like heterochromatin regulators. Nevertheless, how the different types of chromatin interactions established by pioneer factors (specific and nonspecific DNA binding, histone interactions) contribute to chromatin scanning during cell fate induction have yet to be fully understood. In addition, the way chromatin scanning is affected by the cell lineage context over the days or weeks necessary to establish new gene regulatory networks remains unclear. Here, using SMT and ChIPseq, we show that (1) the ability of pioneer transcription factor FOXA1 to scan closed chromatin domains is impaired by loss of direct histone contacts but not by decreased DNA binding (2) over the course of iPS reprogramming, Sox2 pioneering activity is reflected by a progressive invasion of compact chromatin, as well as by an enhanced interaction with chromatin reflected by increasing residence times.

Funding Source: Fondation pour la Recherche Medicale, NIH
Keywords: pioneer transcription factors, chromatin, single-molecule microscopy

2:15 PM – 2:35 PM

IN TOTO IMAGING OF EARLY ENTERIC NERVOUS SYSTEM DEVELOPMENT REVEALS THAT RET REGULATES THE TRANSITION FROM PROLIFERATION TO DIFFERENTIATION OF ENTERIC NEURAL CREST

Uribe, Rosa A., Baker, Phillip, Venkatesh, Akshaya and Singleton, Eileen

CPRIT Scholar in Cancer Research, Rice University, Houston, TX, USA

The enteric nervous system (ENS) is a vast intrinsic network of neurons and glia within the gut and is largely derived from enteric neural crest cells (ENCCs), which are multipotent progenitor cells that emigrate into and along the gut during vertebrate embryonic development. Study of ENCC migration dynamics, and their genetic and molecular regulators, provides great insights into fundamentals of collective cell migration and nervous system formation, and are a pertinent subject for study due to their relevance to the human congenital disease, Hirschsprung disease (HSCR), where enteric neurons fail to differentiate along variable regions of the gut. Mutations in Ret are the leading known cause of HSCR in humans. For the first time, we performed in toto gut imaging and single-cell lineage tracing of ENCC migration in WT and a novel ret heterozygous background zebrafish (ret^wmr1/+) to gain insight into ENCC dynamics and differentiation in vivo. We observed that ret^wmr1/+ zebrafish produced fewer ENCCs while migrating along the gut, which failed to reach the hindgut, resulting in HSCR-like phenotypes. Specifically, we observed a proliferation dependent migration mechanism, where cell divisions were associated with inter-cell distances and migration speed. Single-cell lineage tracing revealed that ret^wmr1/+ ENCCs gave rise to significantly fewer generations, and stalled along the midgut, compared with WT. Molecularly, we detected a premature neuronal differentiation gene expression signature in the stalled ret^wmr1/+ ENCCs. Overall, these results suggest that Ret signaling functions to regulate the coupling of proliferation and migration, and thereby the transition from ENCC proliferation to neuron differentiation, ultimately controlling the precise timing of ENS ontogenesis in vivo.

Keywords: enteric, migration, zebrafish

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)
PLENARY V: DISENTANGLING SINGLE CELL CONTRIBUTIONS TO ORGANOGENESIS AND PATHOLOGY
5:15 PM – 7:20 PM
LEVEL 3

5:20 PM – 5:40 PM

DECODING THE DEVELOPING HUMAN IMMUNE SYSTEM

Haniffa, Muzlifah

Newcastle University, Newcastle Upon Tyne, UK

Muzlifah has used functional genomics, comparative biology and single cell RNA sequencing to study human mononuclear phagocytes. In this seminar, she will demonstrate the applications of single cell genomics to decode the developing human immune system.

Keywords: Genomics, Sequencing, Immune System

5:40 PM – 6:00 PM

HUMAN MYOGENESIS IN DEVELOPMENT AND DISEASE

Pyle, April

University of California, Los Angeles, CA, USA

Skeletal muscle wasting disorders including neuromuscular diseases, dystrophies and sarcopenia result in inferior quality of life, loss of mobility or even early patient death. Skeletal muscle progenitor cells (SMPCs) derived from human pluripotent stem cells (hPSCs) are a promising sources for disease modeling and for cell-based therapies for muscle wasting diseases. However, currently available hPSC directed myogenic differentiation protocols result in highly heterogeneous cell populations with immature SMPCs that are unsuitable for clinical implementation. To better understand human skeletal muscle development and guide hPSC-SMPC generation and maturation, we employed multi-omics approaches to profile skeletal muscle from embryonic, fetal and postnatal stages of human limb tissues. In silico, we unbiasedly isolated the SMPCs away from other cell types present in the tissues at each individual stage and constructed a "roadmap" of human skeletal myogenesis across development in the human limb. In a similar fashion, we also profiled multiple hPSC myogenic differentiation protocols and observed variation among directed differentiation timepoints with regard to the portions of progenitor, stem, and supportive cell types. We have mapped hPSC SMPCs using our in vivo myogenic "roadmap" to a developmental period corresponding to the embryonic to fetal transition. In concert we identified co-regulated genes, transcription factors, as well as upon integration with the epigenome and proteome identified key regulatory sites present in distinct stages of human myogenesis and from hPSC-SMPCs. In parallel to molecular analysis, we have also performed in vivo functional engraftment analysis in normal and in muscle disease animal models to determine when in development the most regenerative stem cell potential arises as well as identified when emerging muscle stem cell niche formation is initiated in humans. In summary, we have identified essential molecular and functional cues advancing our knowledge of human myogenesis and providing a guide to the generation of the most regenerative cells for translational applications in muscle diseases.

Keywords: Pluripotent stem cells, human myogenesis, skeletal muscle, muscle stem cells, skeletal muscle progenitor cells, multi-omics, single cell sequencing

6:00 PM – 6:20 PM

GENETIC CRISPR/CAS9 SCREENING IN CEREBRAL ORGANOIDS BY SINGLE CELL TRANSCRIPTOMICS

Knoblich, Jürgen, Li, Chong, Fleck, Jonas Simon, Martins-Costa, Catarina, Burkhard, Thomas, Stuempfelen, Marelene, Vertesy, Ábel, Peer, Angela Maria, Esk, Christopher, Elling, Ulrich[1], Kasprian, Gregor, Corsini, Nina and Treutlein, Barbara

Institute of Molecular Biotechnology of the Austrian Academy of Science, Vienna, Austria

Development of the human brain involves processes that are not seen in many animals but can contribute to neurodevelopmental disorders. We have established cerebral organoids, a 3D culture system that allows us to recapitulate aspects of disease pathology in vitro. Cerebral organoids can be used to investigate neurodevelopmental disorders in a human context but are limited by variability and low throughput. To overcome these limitations, we have developed the CRISPR-human organoids-scRNA-seq (CHOOSE) system for parallel loss-of function screening of disease susceptibility gene panels in organoid cultures. Using verified uniquely barcoded pairs of gRNAs, inducible CRISPR/Cas9-based genetic disruption and single-cell transcriptomics in cerebral organoids we assign loss-of-function phenotypes to 36 high risk autism spectrum disorder (ASD) genes related to transcriptional regulation. We identify cell-type specific effects of their genetic perturbation on fate determination in excitatory and inhibitory neuronal, as well as glial lineages. Using pseudo time analysis of single-cell transcriptome data, we identify stage-specific vulnerabilities to ASD genetic perturbations. With single-cell profiling of chromatin accessibility, we construct gene regulatory networks in cerebral organoids and discover critical gene regulatory hubs connected with mis-regulated ASD genes. Our studies pave the way for comprehensive characterization of disease susceptibility genes in human organoid models at the level of cell types, developmental trajectories, and gene regulatory networks

Keywords: cerebral organoids, neurodegenerative disorders, genetic screen

6:20 PM – 6:40 PM

VASCULARIZED HUMAN CORTICAL ORGANOIDS (VORGANOID) MODEL CORTICAL DEVELOPMENT IN VIVO

Wang, Xiaoqun

Institute of Biophysics, Chinese Academy of Science, China

Modeling the neuronal progenitor proliferation and organization processes that produce mature cortical neuron subtypes is essential for the study of human brain development and the search for potential cell therapies. To provide a vascularized and functional model of brain organoids, we demonstrated a new paradigm to generate vascularized organoids that consist of typical human cortical cell types and recapitulate the lamination of the neocortex with a vascular structure formation for over 200 days. In addition, the observation of the sEPSCs (spontaneous excitatory postsynaptic currents) and sIPSCs (spontaneous inhibitory postsynaptic currents) and the bidirectional electrical transmission indicated the presence of chemical and electrical synapses in the vOrganoids. More importantly, the single-cell RNA-sequencing analysis illustrated that the vOrganoids exhibited robust neurogenesis and neuronal maturation that resembled in vivo

processes. The transplantation of the vOrganoids to the mouse S1 cortex showed human-mouse co-constructed functional blood vessels in the grafts that could promote the survival and integration of the transplanted cells to the host. This vOrganoid culture method could not only serve as a model to study human cortical development and explore brain disease pathology but could also provide potential prospects for new cell therapies for neural system disorders and injury.

6:40 PM – 7:15 PM

ISSCR ACHIEVEMENT AWARD LECTURE:

BEYOND FATE – MANIPULATING MATURATION AND AGE IN HPSC-DERIVED LINEAGES

Studer, Lorenz

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Abstract not available at time of printing

SATURDAY, 18 JUNE

TRACK: CELLULAR IDENTITY (CI)
PLURIPOTENT STEM CELLS
9:00 AM – 10:45 AM
ROOM 2008
LEVEL 2

9:05 AM – 9:25 AM

THE ESSENTIALOME OF HUMAN PLURIPOTENCY

Benvenisty, Nissim

The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University, Israel

Human pluripotent stem cells (hPSCs) can differentiate into all embryonic lineages while having the capacity for self-renewal. We have recently generated haploid hPSCs carrying only one set of chromosomes. Interestingly, we found that a haploid human genome is compatible not only with the undifferentiated pluripotent state, but also with differentiated somatic fates representing all three embryonic germ layers Furthermore, we demonstrated the superior utility of haploid hPSCs for loss-of-function genetic screening. To define the essentialome of hPSCs we generated a genome-wide loss-of-function library in the haploid cells utilizing CRISPR/Cas9 technology using about 180,000 guide RNAs, targeting virtually all coding genes. This library enabled us to define the genes essential for the normal growth and survival of undifferentiated hPSCs. We could also allude to an intrinsic bias of essentiality across cellular compartments, uncover two opposing roles for tumor suppressor genes and link autosomal-recessive disorders with growth retardation phenotypes to early embryogenesis. More recently, we set out to map the essential genes for the differentiation of hPSCs into the three embryonic germ layers by using our loss-of-function library. Through the analysis of essential genes for the differentiation of hPSCs into ectoderm, mesoderm and endoderm, we defined the essentialome of each germ layer separately and also identified commonly essential genes for the transition from pluripotency stage into differentiated cells. Interestingly, the latter group was enriched by genes localized within the endoplasmic reticulum-Golgi network and regulate membrane and secreted molecules, highlighting the key role of signaling events during these dynamic cell state transitions. Our data enabled analysis of all hereditary neurological disorders, uncovering essentiality of a significant fraction of microcephaly-causing genes during neuroectoderm development. We are currently defining the essentialome of somatic cells derived from hPSCs such as neuron cells. Overall, our work sheds light on the gene networks regulating pluripotency, early gastrulation, and human embryonic disorders by defining essential drivers of specific embryonic germ layer fates and essential genes for the exit from pluripotency.

Keywords: Pluripotency, human embryonic stem cells, genetic screening

9:25 AM – 9:35 AM

CHOLESTEROL BIOSYNTHETIC SIGNALING IN REGULATING PLURIPOTENCY AND EXTENDED PLURIPOTENCY

Chen, Wei-Ju[1], Huang, Wei-Kai[2], Pather, Sarshan[3], Chang, Wei-Fang[4], Sung, Li-Ying[4], Wu, Han-Chung[5], Liao, Mei-Ying[5], Lee, Chi-Chiu[5], Wu, Hsuan-Hui[6], Wu, Chung-Yi[1], Liao, Kuo-Shiang[1], Lin, Chun-Yu[1], Yang, Shang-Chih[1], Lin, Hsuan[7], Schuyler, Scott[8], Axel, Schambach[9], Lu, Frank[10] and Lu, Jean[1]

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Cholesterol metabolism has been linked to diverse biological processes, but the mechanisms by which cholesterol biosynthetic signaling orchestrates stem cell self- renewal remain unclear. Here, we characterized enriched membrane proteins in hESCs by hybridoma antibody screening. Podocalyxin-like protein 1 (PODXL) was identified and regulated actin network through integrated RAC1/CDC42 activations with the maturations of cholesterol master transcription factors, SREBP1 and SREBP2. PODXL and/or cholesterol also upregulated iPSC reprogramming efficiency and self-renewal in hESCs and human extended pluripotent stem cells (hEPSCs). In vivo study, single-cell RNA sequencing revealed PODXL overexpression enhanced chimerism in mouse host embryos. We conclude that cholesterol regulation via PODXL signaling is critical for ESC/iPSC/EPSC pluripotency.

Keywords: Metabolism, Pluripotency, Chimera

9:35 AM – 9:45 AM

NANOG PRION-LIKE ASSEMBLY MEDIATES DNA BRIDGING

Ferreon, Josephine

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NANOG controls entry to stem cell pluripotency. In particular, human NANOG expression is necessary to reset human stem cells to pluripotent ground state with unlimited self-renewal potential similar to mouse embryonic stem cells (ESC). In this study, we characterized human NANOG and identified unique features that relate to its dose-sensitive function as a master and pioneering transcription factor. NANOG is largely disordered with an N-terminal unstructured region and a C-terminal prion-like domain (PrD).

NANOG PrD easily aggregates and phase transitions to gel-like condensates. Using high-sensitivity fluorescence techniques, we show that full-length NANOG readily forms higher order oligomers at low nM concentrations, orders of magnitude lower than typical for amyloid or supramolecular assemblies. Using single molecule FRET and cross-correlation techniques, we demonstrate that NANOG oligomerization is essential for bridging DNA elements together. Using ChIP-Seq and Hi-C 3.0 in cells, we validate that NANOG PrD assembly is essential for specific DNA recognition and distant chromatin interactions. Our results provide a physical basis for NANOG's indispensable role in shaping the pluripotent genome. We propose that NANOG's unique ability to form prion-like assemblies provides a cooperative and concerted DNA bridging mechanism essential for chromatin reorganization and dose-sensitive activation of ground state pluripotency.

Funding Source: This work was supported by NIH grants R01 GM122763 to J.C.F. and R21 NS107792 to A.C.F.M. Additional funding was provided by R01 NS105874 and R21 NS109678 to A.C.M.F.
Keywords: NANOG, LLPS, reprogramming

9:45 AM – 9:55 AM

SPATIAL PROFILING OF EARLY PRIMATE GASTRULATION IN UTERO

Boroviak, Thorsten E., Bergmann, Sophie, Penfold, Christopher and Slatery, Erin

Department of Physiology, Development and Neuroscience, University of Cambridge, UK

Gastrulation controls the emergence of cellular diversity and axis patterning in the early embryo. In mammals, this transformation is orchestrated by dynamic signalling centres at the interface of embryonic and extraembryonic tissues1–3. Elucidating the molecular framework of axis formation in vivo is fundamental for our understanding of human development4–6 and to advance stem-cell-based regenerative approaches7. Here, we illuminate early gastrulation of marmoset embryos in utero by spatial transcriptomics and stem cell-based embryo models. Gaussian process regression-based 3D-transcriptomes delineate the emergence of the anterior visceral endoderm, which is hallmarked by conserved (HHEX, LEFTY2, LHX1) and primate-specific (POSTN, SDC4, FZD5) factors. WNT signalling spatially coordinates primitive streak formation in the embryonic disc and is counteracted by SFRP1/2 to sustain pluripotency in the anterior domain. Amnion specification occurs at the boundaries of the embryonic disc through ID1/2/3 in response to BMP-signalling, providing a developmental rationale for amnion differentiation of primate pluripotent stem cells (PSCs). Spatial identity mapping demonstrates that primed marmoset PSCs exhibit highest similarity to the anterior embryonic disc, while naïve PSCs resemble the preimplantation epiblast. Our 3D-transcriptome models reveal the molecular code of lineage specification in the primate embryo and provide an in vivo reference to decipher human development.

Funding Source: Wellcome Trust
Keywords: primate embryo in vivo, primate gastrulation, spatial identity of PSCs in the embryo

9:55 AM – 10:05 AM

AMNIOGENESIS OCCURS IN TWO INDEPENDENT WAVES IN PRIMATE EMBRYOS

Rostovskaya, Maria[1], Andrews, Simon[2], Reik, Wolf[1] and Rugg-Gunn, Peter[1]

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Human peri-implantation development remains a black box of developmental biology, as embryos at this stage are practically inaccessible for studies due to the ethical considerations. Moreover, we learn only little using conventional model organisms such as mouse, because human development differs in terms of timing, morphology and signalling. One notable difference between species is the formation of an extra-embryonic tissue amnion. In mice and many other mammals, the amnion is formed by folding of the ectoderm during or after gastrulation, whereas in higher primates the amnion emerges through cavitation of the epiblast earlier during implantation. How the mechanisms of amniogenesis diversified during evolution remains unknown. We performed single cell transcriptome analysis of human and monkey embryos and unexpectedly revealed two transcriptionally and temporally distinct trajectories of amnion differentiation from the epiblast. Next, we employed the naïve-to-primed transition of human pluripotent stem cells (hPSC) that closely recapitulates the progression of peri-implantation epiblast, to model these developmental events. We discovered that during this transition hPSC transiently gain the ability to differentiate into cavitating epithelium that transcriptionally and morphologically matches the early amnion of embryos. In contrast, fully primed hPSC produce cells resembling the late amnion, confirming an independent differentiation route. Thus, our hPSC-based differentiation system recapitulated and validated the two independent waves of amniogenesis in primate embryos. The early wave occurs shortly after implantation and shows similarity to trophectoderm (TE) development, including transcriptional and morphogenetic features, such as cavitation. This is followed by the late wave that ensues from early gastrulation and relies on a non-neural ectoderm-like programme, similar to mice and other mammals. The discovery of two independent waves explains how amniogenesis by cavitation emerged during the evolution via duplication of the pre-existing TE programme that resulted in the early differentiation wave preceding the conservative late pathway. Therefore, we established a powerful in vitro system that enables answering fundamental questions of human developmental biology.

Funding Source: BBSRC (BBS/E/B/000C0421, BBS/E/B/000C0422, Core Capability Grant to W.R. and P.R-G.), Wellcome Trust (215116/Z/18/Z to W.R. and P.R-G.), MRC UK (MR/R015724/1 to W.R.; MR/T011769/1 to P.R-G.; MR/V02969X/1 to W.R. and P.R-G.)
Keywords: Human embryonic development, human pluripotent stem cells, amnion

10:05 AM – 10:15 AM

GATA3 IS AN EARLY COMMITMENT GENE IN HUMAN EMBRYONIC STEM CELL DIFFERENTIATION

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Cultured embryonic stem cells (hESCs) are an important model of human post-implantation gastrulation which provides an insight into how the tissues of the embryo are formed with spatial and temporal accuracy. Strikingly, when treated with the growth factor BMP4, hESC colonies can differentiate and self-pattern to create multiple embryonic cell lineages in a clear spatial arrangement.

The transcription factor GATA3 is one of the earliest targets of the BMP4 pathway which is upregulated within hours of treatment - days before canonical lineage markers are expressed – and although well-known as a marker of extraembryonic tissues, its functions during this early stage of differentiation are unknown. In this study we have generated multiple knock-out and fluorescent-tag knock-in hESC lines and utilised ChIP-Seq, ATAC-Seq, transcriptomics, live-cell tracking, and quantitative image analysis to characterise the changing role of GATA3 in early and late hESC differentiation. We show that GATA3 acts to remodel the cellular epigenomic and transcriptomic profile of hESCs, as well as driving patterning of the cell colony by regulating expression of key morphogens such as WNT3. By tracking GATA3-expressing cells over time, we also demonstrate that hESCs which have experienced BMP4 pathway activity contribute to more than one lineage. These data characterise early molecular functions that drive hESC exit from pluripotency, as well as provide insight into mechanisms that determine eventual cell identity.

Keywords: Cell fate decision, hESC, Chromatin remodelling

10:15 AM – 10:35 AM

UNDERSTANDING HUMAN PLURIPOTENT STEM CELL STATES AND THEIR APPLICATIONS

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The past decade has seen significant interest in the isolation of pluripotent stem cells corresponding to various stages of mammalian embryonic development. Two distinct and well-defined pluripotent states can be derived from mouse embryos: “naïve” pluripotent cells that resemble the pre-implantation epiblast and display an unrestricted developmental potential, and “primed” pluripotent cells that resemble the post-implantation epiblast and exhibit a more restricted lineage potential. We and others have developed approaches to convert human pluripotent stem cells (hPSCs) into a naïve state that shares defining properties with the human pre-implantation embryo. Our recent studies have examined three interrelated aspects underpinning these discrete but interconvertible stem cell states: (i) the extrinsic signaling requirements for inducing and maintaining naïve human pluripotency based on high-throughput chemical screening; (ii) the composition and function of chromatin remodeling complexes regulating naïve and primed pluripotent states based on comparative interactome analysis of the core pluripotency factor OCT4; (iii) the potential of naïve hPSCs to differentiate into self-renewing and bipotent human trophoblast stem cells. I will discuss our recent efforts to leverage the extraembryonic potential of naïve hPSCs to establish self-renewing 3D organoids that closely correspond to the first-trimester placenta, which model human trophoblast development, X chromosome inactivation dynamics, and early placental susceptibility to emerging viral pathogens (SARS-CoV-2 and Zika virus). The ability to generate 3D trophoblast organoids from naïve hPSCs provides an accessible and patient-specific model system of the developing placenta and its selective vulnerability to emerging pathogens.

Funding Source: The work in my laboratory is supported by the NIH Director’s New Innovator Award (DP2 GM137418) and grants from the Children’s Discovery Institute (CDI-LI-2019-819), the Shipley Foundation Program for Innovation in Stem Cell Science, and the Edward Mallinckrodt, Jr. Foundation. Federal NIH/NIGMS funds were not used to develop integrated 3D models of human embryonic development.
Keywords: pluripotent stem cells; trophoblast; X chromosome inactivation

TRACK: CLINICAL APPLICATIONS (CA) PROGRAMMING AND REPROGRAMMING FOR REGENERATIVE MEDICINE
9:00 AM – 10:45 AM
ROOM 2004
LEVEL 2

9:05 AM – 9:25 AM

EFFICIENT HUMAN SENSORY NEURON GENERATION FROM PLURIPOTENT STEM CELLS

Woolf, Clifford J.[1], Bean, Bruce[3] and Singec, Ilyas[2]

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Human pluripotent stem cells (hPSCs) can be converted into neural crest spheres, which after dissociation are matured into sensory neurons with high efficiency and in large quantities. The neurons have the molecular and cellular features of high threshold pain-triggering nociceptor neurons. Automation of the cell differentiation protocol with a robotic cell culture system enables many millions of sphere-derived cells to be generated in 14 days, which can then be cryopreserved or differentiated for a further 14 -28 days to functional neurons. The in vitro-generated nociceptors, have no dendrites, are pseudo-unipolar, fire robust action potentials, and contain large dense-core vesicles. Transcriptional analysis reveals expression of nociceptor-specific genes including RUNX1, BRN3A, ISL1, TRPV1, TRPA1, NTRK1, NaV1.7, NaV1.8, and Nav1.9, and genes indicating the presence of both peptidergic (TAC1, CALCA) and non-peptidergic (P2RX3) subpopulations, but not tyrosine hydroxylase - which is only present in low threshold C-fiber mechanoreceptors, or RUNX3, a driver of the development of proprioceptive neurons. Because hPSC-derived human nociceptors express functional targets (the cells respond to α,β-methylene-ATP, capsaicin, and mustard oil) and are electrically active, they can be used in phenotypic screens for analgesic compounds that are nociceptor-selective, reduce inflammatory mediator (e.g. PGE2) generated peripheral sensitization, and prevent chemotherapy-induced neuropathy. These human nociceptors derived from an inexhaustible source, also have the potential for replacing sensory neurons lost in peripheral neuropathies.

Keywords: Nociceptors, Analgesia, Pain

9:25 AM – 9:35 AM

FIGHTING MACULAR DEGENERATION: PRECLINICAL STUDIES USING IPSC DERIVED RETINAL TISSUE IN LARGE ANIMALS

Barabino, Andrea[1], Mellal, Katia[2], Hanna, Roy[3], Hamam, Rimi[4], Kalevar, Ananda[5], Polosa, Anna[6], Nakamura, Takashi[7], Saito, Shunsuke[7], Bouchard, Jean-François[8], Griffith, May[6], Kagimoto, Tadahisa[9] and Bernier, Gilbert[1]

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Retinal degenerative diseases affect millions of people worldwide. In most cases, legal blindness is associated with loss of

cone photoreceptors located in the retina's central (macular) region. Currently, there is no treatment to delay, stop or reverse these diseases, making Macular Degenerations (MDs) incurable. We have developed a method to produce large amounts of human cones from human pluripotent stem cells based on COCO/DAND5, a member of the Cerberus-like family of soluble BMP, TGFb, and WNT antagonists, allowing the formation of a ~150um thick and polarized human retinal sheet containing a high proportion of cone precursors. We performed transplantation of 2-5 mm diameter human iPSC-derived round retinal sheets in a chemically-induced porcine model of MD, which presents the complete destruction of the ONL in an area of 8mm of diameter around the macula without affecting the INL. No residual pluripotent stem cells were detected in the graft. Grafted retinal sheets integrate the host retinal tissue and survive for several months. ERG, OCT, and histological studies suggest the formation of a new polarized ''hiPSC-derived ONL'' into the host retinal tissue, the generation of synaptic connections between grafted cells and the host INL, and restoration of bright-light responsiveness at the grafted site. This work opens new insights towards the treatments of MDs.

Funding Source: Stem Cell Network (Canada), Healios
Keywords: photoreceptors, cones, preclinical trial, tissue engineering, macular degeneration, scRNAseq, universal donor iPSC

9:35 AM – 9:45 AM

GENERATION OF MATURE IPSC-DERIVED CAR T CELLS WITH ENHANCED ANTITUMOR ACTIVITY VIA EPIGENETIC REPROGRAMMING

Jing, Ran[1], Scarfo, Irene[2], Najia, Mohamad[3], Lummertz da Rocha, Edroaldo[4], Han, Areum[3], Sanborn, Michael[3], Bingham, Trevor[5], Kubaczka, Caroline[3], Jha, Deepak[3], Falchetti, Marcelo[5], Schlaeger, Thorsten[3], North, Trista[3], Maus, Marcela[2] and Daley, George[1]

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Adoptive T cell therapy holds great promise for the treatment of immune deficiency, viral infection, autoimmunity, and cancer. However, broader application has been impeded by the cumbersome, labor-intensive protocols for engineering autologous patient-specific cells. Human induced pluripotent stem cells (iPSCs) represent an appealing source for scalable manufacture for cell therapy, which when coupled to strategies for immune matching or cloaking, could represent "off-the-shelf" products. Prior studies in murine models have engineered iPSC-derived T cells with chimeric antigen receptors (CAR) and shown proof-of-principle for cancer immunotherapy. However, iPSC-CAR T cells display features of innate-like gamma-delta T cells and are not as robustly functional as peripheral blood-derived alpha-beta T cells. Previous work from our lab demonstrated that the histone methyltransferase EZH1 plays a central role in repressing multipotency and lymphoid potential in embryonic blood progenitors, providing a key insight toward deriving mature T cells in vitro. Here, we first developed a stroma-free iPSC-T cell differentiation protocol that supports efficient in vitro T cell differentiation as well as normal TCR rearrangement. Using this differentiation system, we further show that epigenetic reprogramming via repression of EZH1 produces developmentally mature T cells (hereinafter termed EZ-T cells). Unlike previously described iPSC-T cells that exhibit innate-like T cell features characteristic of embryonic lineages, EZ-T cells are most similar to mature peripheral blood alpha-beta T cells. Moreover, scRNA-seq analysis shows that iPSC-derived EZ-T cells can give rise to both effector and memory-like T cell subpopulations upon TCR stimulation. Finally, when loaded with anti-CD19 CARs, EZ-T cells display robust antitumor activity—efficacy comparable to donor-derived CAR T cells—against B cell lymphoma in vitro and in xenograft mouse models. In conclusion, by coupling a stroma-free differentiation protocol with EZH1 repression, we have developed a new platform for the production of robust, developmentally mature iPSC-T cells. Such an approach will be compatible with commercial-scale production and broad distribution to further enable CAR T cell-based immunotherapy.

Keywords: induced pluripotent stem cells (iPSCs), chimeric antigen receptor (CAR) T-cell, Epigenetic reprogramming

9:45 AM – 9:55 AM

FAR BEYOND JUST A WNT INHIBITOR: XAV939 GLOBALLY REPROGRAMS THE PROTEOME OF HUMAN NAÏVE STEM CELLS

Zambidis, Elias T.[1], Angarita, Ariana[1], Zimmerlin, Ludovic[1], Uribe, Isabel[2], Kochendoerfer, Clara[1], Leung, Anthony[2] and Zambidis, Elias[1]

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The small molecule XAV939 is a promiscuous poly-ADP polymerase (PARP) inhibitor of multiple PARP proteins (e.g., Tankyrase (TNKS) 1 and 2, PARP1, PARP2, and PARP3). XAV939 is often utilized as a WNT pathway inhibitor via stabilizing the levels of the TNKS1/2 substrate axin, which mediates β-catenin degradation. However, TNKS and PARP1 both regulate a wider range of cellular processes that include development, cell metabolism, chromosome segregation, stress response, inflammation and cell cycle regulation. Notably, TNKS1/2 and PARP1 catalyze the PARylation of hundreds of substrates to regulate their stability and interactivity. Thus, broad PARP inhibition by XAV939 can have direct and indirect effects on the global proteome that are context dependent and reach beyond WNT modulation. For example, TNKS-mediated PARylation determines proteosomal degradation of hundreds of proteins by controlling RNF146-mediated ubiquitination. We have reported that continuous supplementation of the classical LIF-2i cocktail with XAV939 (i.e., LIF-3i) generated a new class of tankyrase/PARP inhibitor-regulated naïve (TIRN) human stem cells with greater functional pluripotency than conventional, primed hiPSCs. The mechanism by which XAV939-regulated PARP inhibition expands functional pluripotency in TIRN human stem cells remains unclear. To elucidate the potential role of XAV939 in regulating both TNKS1/2 and PARP1 (which can also regulate pluripotency-associated gene expresion through its DNA binding domain), we performed whole proteome by Tandem Mass Tag mass spectrometry and PARylome analysis, transcriptomic, whole genome bisulfite CpG methylation sequencing, and PARP1 ChIP-seq studies on Tankyrase/PARP inhibitor-regulated naïve (TIRN) human stem cells. Select TNKS targets were validated by western blotting using PAR-affinity resins. We show that continuous TNKS/PARP inhibition by XAV939 in the context of LIF-2i globally reprogrammed the proteo-genome of human naïve-epiblast-like stem cells in broad cellular processes. Inhibition of PARylation by TNKS and PARP1 rewired the pluripotency circuits of TIRN stem cells and prevented epigenomic instability. Understanding the

role of PARylome regulation may further assist the generation of improved human stem cells for regenerative medicine.

Funding Source: This work was supported by grants from the NIH/NEI (R01EY032113; R01EY023962), NIH/NICHD (R01HD082098), Research to Prevent Blindness (Stein Innovation Award), and The Maryland Stem Cell Research Fund (2020-MSCRFD-5374).
Keywords: PARP, naïve pluripotency, proteomics

9:55 AM – 10:05 AM

ENGINEERED SAFE AND IMMUNE-TOLERANT RPE CELLS TOWARDS THE TREATMENT OF AGE-RELATED MACULAR DEGENERATION

Hacibekiroglu, Sabiha[1], Jong, Eric[2], Tang, Jean[3], Oussenko, Tatiana[4], Ho, Margaret[5], Shoichet, Molly[6], Wallace, Valerie[7], Peter, Kertes[8], Yan, Peng[9] and Nagy, Andras[4]

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Despite the success of routine repeated intravitreal anti-VEGF treatment in the management of various retinal diseases including neovascular Age-Related Macular Degeneration (nAMD), the heavy treatment burden associated with frequent injection on patients, their families and the health care system are significant challenges that warrant novel treatment strategies. Gene and stem cell therapy may be the next frontier in the treatment of nAMD, but both, tumorigenicity of grafted cells and rejection of non-autologous cells, remain a concern. We hypothesize that anti-VEGF biologics could be delivered using allogeneic cells that were modified to be invisible to the immune system and that contain a cell autonomous kill switch to prevent tumors. To test this hypothesis, we have genetically engineered a novel pluripotent stem cell line (ARUNA-PSC), that combines a) a drug-inducible, local acting anti-VEGF biologic, VEGF Sticky-trap and b) control over cell growth by introducing a suicide switch to the cell's genome [FailSafe(TM) system]. Cells were then further modified to make them "invisible" [iACT Stealth(TM)] to the immune system. After differentiation to retinal pigment epithelium (RPE) cells (ARUNA-hRPE) they are grafted into the subretinal space of mice, rabbits, and pigs to assess the efficacy, safety, and toxicology of this therapeutic cell product. In published pilot studies, we have demonstrated the function of all three genome altering systems [FailSafe(TM), iACT Stealth(TM) and VEGF Sticky-trap] separately. We are now moving forward to a pre-clinical phase with small (mouse) and large animal models (rabbit, pig) to test in cell therapy settings. Thus far, we have demonstrated, in vitro and in vivo (in mice), that cells survive up to 12 months in the subretinal space and that each genetic modification continues to function in tandem. Immuno-cloaking is essential to avoid graft rejection and/or the need for immunosuppression. Simultaneously, tight regulation of cell proliferation [FailSafe(TM) system] and drug-induced VEGF Sticky-trap expression was demonstrated. No adverse events were reported in mice receiving genetically modified cells. We expect our genome-edited therapeutic cells will advance novel and improved therapies for AMD and beyond.

Funding Source: The Cedric Ritchie Fund to Cure Blindness from Fighting Blindness Canada, Canadian Research Chair and Medicine by Design (University of Toronto)
Keywords: Age-related Macular Degeneration, Neovascularization, cell and gene therapy

10:05 AM – 10:15 AM

EFFICIENT GENERATION OF LOWER INDUCED MOTOR NEURONS BY COUPLING NGN2 EXPRESSION WITH DEVELOPMENTAL CUES

Limone, Francesco[1], Mitchell, Jana, Guerra San Juan, Irune[1], Raghunathan, Kavya1, Smith, Janell[1], Couto, Alexander[1], Ghosh, Sulagna Dia[2], Meyer, Daniel[2], Mello, Curtis[3], Nemesh, James[2], Smith, Brittany[1], McCarroll, Steven[3], Pietiläinen, Olli[4], Nehme, Ralda[2], and Eggan, Kevin[1]

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Human pluripotent stem cells (hPSCs) are a powerful tool for disease modelling and drug discovery, especially when access to primary tissue is limited, such as in the brain. Current neuronal differentiation approaches use either small molecules for directed differentiation or transcription-factor-mediated programming. In this study we coupled the overexpression of the neuralising transcription factor Neurogenin2 (Ngn2) with small molecule patterning to differentiate hPSCs into lower induced Motor Neurons (liMoNes). We showed that this approach induced activation of the motor neuron (MN) specific transcription factor Hb9/MNX1, using an Hb9::GFP-reporter line, with up to 95% of cells becoming Hb9::GFP+. These cells acquired and maintained expression of canonical early and mature MN markers. Molecular and functional profiling revealed that liMoNes resembled bona fide hPSC-derived MN differentiated by conventional small molecule patterning. liMoNes exhibited spontaneous electrical activity, expressed synaptic markers and formed contacts with muscle cells in vitro. Pooled, multiplex single-cell RNA sequencing on 50 cell lines revealed multiple anatomically distinct MN subtypes of cervical and brachial, limb-innervating MNs in reproducible quantities. We conclude that combining small molecule patterning with Ngn2 can facilitate the high-yield, robust and reproducible production of multiple disease-relevant MN subtypes, which is fundamental in the path to propel forward our knowledge of motoneuron biology and its disruption in disease.

Keywords: human Motor Neuron, neuronal differentiation, single cell profiling

10:15 AM – 10:35 AM

REPETITIVE ELEMENTS AS SIGNALS FOR DEVELOPMENTAL AND REGENERATIVE HEMATOPOIESIS

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Institute for Research on Cancer and Aging, Nice, France

Repetitive elements like transposable elements (TEs) and other simpler repeats are dispersed throughout the genome and consist more than one third of it in multiple species. For many years this part of the genome was considered as "junk", but it has lately become clear that many functions can be attributed to repetitive elements. Developmental processes and cellular states exhibiting high plasticity are often accompanied by expression of repetitive

elements. Here we show that repetitive elements are transcribed during hematopoietic stem cell development and chemotherapy-induced regeneration. Repetitive element RNAs act as signals for innate immune receptors of the RIG-I-like receptor family. Activation of these receptors titrates the induction of sterile inflammatory signals that enhance hematopoietic stem cell development and chemotherapy-induced regeneration. Thus, RNA sensing of repetitive elements actively shapes cellular transitions.

Keywords: hematopoiesis, repetitive elements, regeneration

TRACK: MODELING DEVELOPMENT AND DISEASE (MDD)
IMMUNOLOGICAL RESPONSES TO FIGHT INFECTION AND DISEASE
9:00 AM – 10:45 AM
ROOM 2011
LEVEL 2

9:05 AM – 9:25 AM

IDENTIFICATION OF NOVEL REGULATORS OF NK CELL-MEDIATED ANTI-TUMOR RESPONSES

Kaufman, Dan

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Studies in our lab have defined methods to efficiently produce natural killer (NK) cells from human induced pluripotent stem cells (iPSCs). Natural killer (NK) cells are a key effector in antitumor immunity. However, tumors develop resistance mechanisms to escape NK cell-mediated immunosurveillance. Recent studies from our group used a whole genome CRISPR-Cas9 screen combined with an NK cell selection strategy to identify novel regulators used by tumor cells to inhibit NK cell-mediated activity. These studies identified CHMP2A as a key gene that mediates tumor-intrinsic resistance. CHMP2A is a member of the ESCRTIII complex and regulates secretion of tumor-derived chemokines and extracellular vehicles (EVs) that express NK cell-activating ligands MICA/B and TRAIL, which induce NK apoptosis. Deletion of CHMP2A in glioblastoma and head and neck squamous cell carcinoma (HNSCC) increases allogeneic NK cell-mediated killing both in vitro and in vivo. We have now extended these studies to use a syngeneic murine HNSCC model. Again, these studies demonstrate that CHMP2A regulates NK cell and other immune-mediated anti-tumor activity. This approach not only demonstrates that CHMP2A provides a new approach to improve immune functions, these studies also identify multiple other targets to improve cell-mediated immune responses.

Keywords: NK cells, cancer, CRISPR-Cas9 screen

9:25 AM – 9:35 AM

HUMAN PLURIPOTENT STEM CELLS PROVIDE A NEW TOOLKIT TO STUDY BIOSAFETY LEVEL 4 (BSL4) VIRUSES

Loh, Kyle M.

Developmental Biology, Stanford University, Stanford, CA, USA

Biosafety level 4 (BSL4) viruses—including Ebola and Nipah viruses (44% and 59% fatality rates, respectively)—are among the deadliest viruses on Earth, and have few to no approved treatments. Such BSL4 viruses are extraordinarily understudied, since they can only be handled by "space suit"-protected personnel in specialized facilities, few of which exist worldwide. To study viral infection of the vasculature, we generated >90% pure human artery and vein endothelial cells from pluripotent stem cells within 3-4 days. We delineated stepwise changes in extracellular signaling, gene expression, and chromatin during human arterial vs. venous differentiation. Unexpectedly, arteries were preferentially infected by Nipah virus; arteries expressed higher levels of their viral-entry receptor relative to veins. Live-imaging revealed these viruses induced more arterial, rather than venous, syncytia. Despite infecting arteries and occupying 17% of their transcriptome, Nipah virus largely eluded innate-immune detection, minimally eliciting interferon signaling. We thus introduce stem cell-based toolkits for BSL4 virology, revealing the arterial tropism and cellular effects of Nipah virus and accelerating therapeutic screens for currently-incurable BSL4 viruses.

Keywords: Human pluripotent stem cells, Endothelial cells, Biosafety level 4 viruses

9:35 AM – 9:45 AM

BENCHMARKING AND DEVELOPING HUMAN PLURIPOTENT STEM CELL MODELS OF MACROPHAGE BIOLOGY

Rajab, Nadia, Angel, Paul, Butcher, Suzanne, Choi, Jarny and Wells, Christine

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Human pluripotent stem cell (hPSC)-derived macrophages offer new opportunities to understand the role of development or tissue context in innate immune cell function. Immune responsiveness to pathogenic challenge is known to be impacted by a macrophage's history of prior exposure, as well as ontogeny and tissue context. Therefore, we explore the factors of in vitro derivation likely to influence macrophage phenotype and function, and highlight the gaps in, not only our understanding of macrophage development and function, but also in hPSC models that aim to mimic their in vivo counterparts. We developed a transcriptomic atlas to assess impact of ontogeny, experimental treatment and tissue residency on molecular phenotype. We revealed gaps in hPSC-macrophages, revealing several differences between hPSC-macrophages, monocyte-derived macrophages and primary cells. These differences include poor maturation in hPSC-macrophages in the absence of priming signals such as IFN, or repeated exposure to LPS. We demonstrate the requirement for priming in hPSC-macrophages and discover the importance of re-stimulation events in shaping macrophage activation. We further assess phenotypic heterogeneity in both monocyte- and hPSC-macrophages using single-cell sequencing. We demonstrate synchronised population responses to LPS activation and further provide evidence for priming in shaping macrophage responsiveness. These findings highlight that macrophages are shaped by prior activating, or priming, signals which can be recapitulated in the laboratory. Outcomes of this work are expected to improve routine macrophage derivation from hPSC sources, as exploitation of priming provides future opportunities to shape the quality of acute or long-term macrophage responsiveness for diverse applications.

Funding Source: The University of Melbourne Research Scholarship Centre for Stem Cell Systems CSIRO Synthetic Biology Future Science Platform Millenium Science - 10x Genomics Start Single Cell Fellowship NHMRC Synergy (Grant ID: APP1186371)
Keywords: macrophage, models, training

9:45 AM – 9:55 AM

RECAPITULATING PATIENT-SPECIFIC AUTOIMMUNE MEDIATED HEART DISEASE WITH IPSC-DERIVED ENGINEERED CARDIAC TISSUE MODELS

Fleischer, Sharon[1], Nash, Trevor[1], Tamargo, Manuel[1], Geraldino-Pardilla, Laura[2], Winchester, Robert[2] and Vunjak-Novakovic, Gordana[1]

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In Systemic Lupus Erythematosus (SLE), heart failure rates are 2-3-fold higher compared to the general population, suggesting that the adaptive autoimmune response intrinsic to SLE drives this increased risk. Interestingly, while in certain SLE patients no cardiac pathology is observed, others are diagnosed with myocarditis of varying severities. The fundamental question is what are the immunological mechanisms that lead to different myocardial phenotypes in SLE patients. Current experimental tools such as 2D cell culture and animal models have limited ability to recapitulate the biological complexity of SLE, and lack the patient-specific context. Recent advances in 3D tissue models of the adult human heart muscle engineered from iPSCs)-derived cardiomyocytes and fibroblasts, developed by our group, provide a novel alternative to investigate patient-specific autoimmune mechanisms of heart failure in vitro. Here, we investigated a cohort of SLE patients with well characterized presence and severity of different types of myocardial dysfunction. In addition to clinical data, blood sera were collected from the patients. We have generated iPSC-derived engineered cardiac tissue models and matured them by electromechanical stimulation to establish adult-like contractile behavior. These engineered tissues were cultured with supplementation of autoantibodies isolated from patient-specific sera. The alterations in tissue functionality over time were quantified by real-time bright-field and calcium imaging. We demonstrated that iPSC-derived engineered cardiac tissues recapitulate autoimmune mediated clinical cardiac dysfunction in a patient-specific context and can be used to classify patients by myocarditis severity. By utilizing the iPSC tissue model together with advanced proteomic methodologies, we were able to discover a unique population of autoantibodies that bind to adult-like cardiac tissues. We demonstrated that the binding of autoantibodies was enhanced under stress conditions, leading to impaired engineered cardiac functionality. To conclude, this study provides a comprehensive basis for a personalized approach to what is likely a mechanistically heterogeneous process and provides a better mechanistic understanding of autoimmune mediated myocarditis.

Keywords: Cardiac Tissue Engineering, Autoimmune disease, Myocarditis

9:55 AM – 10:05 AM

UTILIZING HUMAN STEM CELL-DERIVED ISLETS AS A MODEL TO STUDY THE ROLE OF IFIH1 IN ISLET RESPONSE TO COXSACKIEVIRUS B INFECTION

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Type I diabetes (T1D) is an autoimmune disease where loss of insulin-producing beta (β) cells results from interactions of genetic variation and environmental susceptibility. Coxsackievirus B (CVB) infection has long been considered an environmental factor that precipitates T1D. Interferon Induced with Helicase Domain 1 (IFIH1) encodes Melanoma Differentiation-Association Gene 5 (MDA5)—a double-stranded RNA sensor that is activated by RNA viruses and invokes an immune response. At least four single nucleotide polymorphisms (SNPs) within IFIH1 have been linked to T1D risk. However, human pancreatic islet studies focusing on the relationship between these SNPs, CVB infection, and T1D are limited due to a scarcity of primary islets from affected patients. Here, we generated human stem cell-derived islets (SC-islets) and infected them with CVB. Notably, we observed an increase in anti-viral response genes, such as ISG15 and IRF1, along with a decrease in islet identity genes, including INS, SST, and PDX1. Moreover, IFIH1 knock-down or overexpression in SC-islets resulted in blunted or enhanced, respectively, antiviral responses upon CVB infection. We then performed single-cell RNA sequencing (scRNA-seq) on infected primary human islets and identified a β cell subpopulation with increased expression of inflammatory and stress markers and decreased expression of β cell identity genes. To investigate the effects of IFIH1 SNPs associated with increased risk of T1D, we utilized CRISPR/Cas9 on human induced pluripotent stem cells (hiPSCs) to introduce the A946T SNP—a gain of function variant—at rs1990760. Edited hiPSCs were differentiated into SC-islets and treated with either a cytokine mixture or the MDA5 agonist, Poly(I:C). SC-islets expressing the risk allotype, MDA5946T, produced a stronger immune response compared to SC-islets with the common allotype, MDA5946A. Overall, our gene expression data support a connection between IFIH1 SNPs, CVB infection, and β cell health. These findings validate SC-islets as a robust in vitro model to study clinically relevant IFIH1 SNPs in regulating potentially diabetogenic CVB infections. Consequently, we can use hiPSCs from T1D patients with relevant genotypes and phenotypes to generate islets and advance our understanding of IFIH1 in a human context.

Funding Source: NSF-GRFP (DGE-2139839) NSF-GRFP (DGE-1745038)
Keywords: Stem cell-derived pancreatic islets, Coxsackievirus B infection, IFIH1

10:05 AM – 10:15 AM

A FULLY DEFINED HUMAN PLURIPOTENT STEM CELL-DERIVED VASCULAR MODEL ELUCIDATES MECHANISMS OF VASCULAR DYSFUNCTION CAUSED BY COVID-19

Khalil, Andrew[1], Friesen, Max[2], Jaenisch, Rudolf[2], Mooney, David[3] and Richards, Alexsia[2]

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The ongoing COVID-19 pandemic is caused by the novel SARS-CoV-2 respiratory virus, which can most notably cause severe and lethal lower respiratory infections. However, it also features numerous unique coronavirus properties such as anosmia and vascular dysfunction, including potentially deadly thrombosis. Disease models derived from human pluripotent cells (hPSCs) can provide research tools to study viral infections and elucidate mechanistic insights such as differences in viral tropism and cellular responses to infection by providing distinct human cell populations in defined conditions. Here, we have developed an optimized differentiation protocol for endothelial and mural cells from hPSCs using a common, defined, and uniform media for both differentiation and expansion of both cell types. This common serum-free media for both vascular and mural cells afforded direct cross-comparison of cellular responses to SARS-CoV-2 infection. After exposure of these cells to the live virus, we observed SARS-

CoV-2 selectively produces active infections in mural cells such as smooth muscle cells (SMC) and pericytes, but not endothelial cells (EC). Specifically, infection of SMC increased viral titer production over the initial inoculum by 10E5.5 plaque-forming units (PFU) after 48 hours, while exposure of SARS-CoV-2 to EC resulted in decreased PFU by 10E2.9. We additionally performed bulk RNA sequencing on EC and SMC exposed to live SARS-CoV-2, heat-inactivated virus, and supernatant from infected SMC transferred to EC. The transfer condition allowed us to observe the potential effect of infection in mural cells neighboring the endothelium. Gene set enrichment analysis revealed changes in gene expression associated with coagulation in endothelial cells. These changes were distinct in the cells exposed to live and heat-inactivated virus as well as the transfer condition. We also directly observed tissue factor and matrix metalloproteinase activity changes in infected smooth muscle cells. Taken together, the findings from this hPSC-derived model help to elucidate the cellular tropism of SARS-CoV-2 in vascular cells due to exposure of the endothelium to viral particles, infection in neighboring mural cells, and the overall ontology of vascular thrombotic dysfunction in COVID19 infection.

Keywords: COVID-19, Vascular models, Infection responses

10:15 AM – 10:35 AM

INFECTION, INNATE IMMUNE SIGNALING AND CANCER IN THE GUT

Bartfeld, Sina

Technische Universität Berlin, Germany

Infections are still a major health threat worldwide. We need new models for infectious diseases to reach a better understanding and develop new therapies. In the gastrointestinal tract, the epithelial lining acts as physical and immunological barrier between the microorganisms of the gut and the body. The epithelial cells can sense microorganisms, which activates innate immune signaling pathways and leads to an inflammatory response. Chronic inflammations, for example caused by infection with the gastric pathogen Helicobacter pylori, can cause serious disease, including cancer. We analyse the molecular basis of innate immune signaling in the epithelium of the gastrointestinal tract and the host cell response to infections such as with H. pylori or Epstein Barr Virus. To these ends, we use adult stem cell-derived organoids. We generated a biobank of human and murine organoids covering 6 sites from stomach to colon. RNA-sequencing showed that the tissue identity is conserved in the adult stem cells. Moreover, components of the epithelial innate immune sensing, such as toll like receptors, are part of the tissue identity and highly organized along the gastrointestinal tract. This organization is for a large part determined by developmental processes rather than by environmental factors. Infection of the organoids with pathogens demonstrates that normal gastric organoids can be well infected with H. pylori and single cell RNA sequencing of infected cells reveals a preferential target cell of H. pylori. EBV on the other hand does not infect healthy gastric organoids, but only gastric cancer organoids, indicating that in the case of EBV, cellular changes have to occur to enable infection.

Keywords: Organoids, Infection, Epithelium, Innate Immunity

TRACK: NEW TECHNOLOGIES (NT) MANUFACTURING AND ADVANCED THERAPEUTIC PRODUCTS 9:00 AM – 10:45 AM ROOM 2012 LEVEL 2

9:05 AM – 9:25 AM

REDEFINING MANUFACTURING; BRINGING PERSONALIZED GENE THERAPY TO THE WORLD

Golipour, Azadeh

Avrobio, MA, USA

To operationalize the vision of bringing personalized gene therapy to the world, we have developed plato; an industry leading manufacturing platform optimized for safety, performance, and scalability. plato platform is a complete approach to manufacturing and analytics which is different from traditional approaches as it addresses the known bottlenecks in the cell and gene therapy field by applying technology and innovation. plato enables production in a consistent, controlled, closed system, automated manufacturing unit using reduced manufacturing footprint. The platform covers lentiviral vector design and production, drug product manufacturing as well as analytics. The advance analytic tools enable us to trace stem cells from their initial source (apheresis), through drug product manufacturing, to multiple years after drug product infusion in patients, to understand product quality attributes. Advanced manufacturing and analytic platforms are key to achieving scalability which is required for success of personalized gene therapy.

Keywords: CELL AND GENE THERAPY, MANUFACTURING, ANALYTICS, LENTIVIRAL VECTOR, AUTOMATION, SCALABILITY

9:25 AM – 9:35 AM

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

Ullmann, Kevin, Annika, Franke, Kriedemann, Nils, Manstein, Felix, Teske, Jana, Triebert, Wiebke and Zweigerdt, Robert

LEBAO, HTTG, Hannover Medical School, Hannover, Germany

Human pluripotent stem cell (hPSCs) derivatives have great potential for advanced drug screening, in vitro disease modelling and regenerative therapies. The envisioned routine application of these cells will require robust and economically viable production processes, compatible with industry and regulatory standards. Instrumented stirred tank bioreactors (STBR) are routinely applied for mammalian cell lines cultivation in the biopharmaceutical industry. This platform has now also been adapted to the matrix-free suspension culture of hPSCs and recently enabled advanced high density bioprocessing of hPSC by metabolic control and in silico modelling by our group. To further close the gap between the research state and industry-compliance, we here demonstrate a seed train approach to ensure straightforward process upscaling. Chemical dissociation of the matrix-free cell-only hPSC aggregates from suspension culture crucially supported efficient single cell recovery, applied at each upscaling step. This strategy enabled uninterrupted maintenance of exponential cell growth over 5 passages for up to 20 days in suspension culture. Comparative analysis of differential passaging intervals revealed high process robustness and flexibility, opening the possibility for weekend-free cell production at highly controlled conditions. The strategy also enables minimal user interaction and fosters process automation.

Furthermore, we demonstrated intermediate high-density cryopreservation of suspension-derived hPSCs followed by the direct re-inoculation of 3D suspension culture in STBRs. This novel strategy makes the conventional 2D matrix-dependant cultivation of hPSC completely dispensable and facilitates the development of GMP-compliant closed system manufacturing paving the way towards the automated end-to-end production of hPS cells and their derivatives at clinically relevant conditions and quantities.

Keywords: hPSC bioprocessing, Seed Train, High-Density Cryopreservation

9:35 AM – 9:45 AM

CHROMATIN MODULATION FOR EFFICIENT CRISPR-CAS9 GENE EDITING OF HUMAN PLURIPOTENT STEM CELLS

Molugu, Kaivalya[1], Khajanchi, Namita[2], Lazzarotto, Cicera[3], Das, Amritava[4], Tsai, Shengdar[3] and Saha, Krishanu[2]

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Genome-edited human induced pluripotent stem cells (iPSCs) have broad applications in disease modeling, drug discovery, and regenerative medicine. Despite the significant development of clustered regularly interspaced short palindromic repeats (CRISPR)-Cas9 system, the gene editing process can be inefficient and can take several weeks to months to generate edited iPSC clones. One of the major challenges is that chromatin compaction limits the Cas9 protein access to the target DNA. To overcome these challenges, we developed a strategy to improve the speed and efficiency of the iPSC gene editing process via the application of a histone modifier, Trichostatin A (TSA; Class I and II histone deacetylase inhibitor or HDAC inhibitor). We observed that TSA-treated iPSCs had increased chromatin accessibility (via single nuclei ATAC-seq) and gene-editing efficiency in these cells increased ~3.5 fold at several closed and open chromatin loci without any increases in off-target modifications. The edited iPSCs retained full pluripotency and genomic integrity. We further developed an in situ nuclear imaging-based pipeline to quantify the TSA-induced global chromatin changes to enable rapid visual identification of iPSCs that are more amenable to gene editing. These methods to generate edited iPSCs rapidly and efficiently could advance the biomanufacturing of therapeutically-relevant, gene-edited iPSCs.

Keywords: CRISPR-Cas9, iPSC, Chromatin

9:45 AM – 9:55 AM

HUMAN EMBRYOID BODY BIOINKS FOR FRESH 3D BIOPRINTING OF CONTRACTILE CARDIAC TISSUE

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End-stage heart failure affects more than 64 million persons worldwide, with the vast majority ineligible for transplant due to lack of donor supply, comorbidities, or other risk factors. While whole organ biofabrication has the potential to bridge this gap, current tissue engineering approaches cannot build 3D cardiac muscle with sufficient cell density and precise anatomical structure to repair or replace the heart. As a step towards addressing this challenge, we have developed a human embryoid body (EB) based bioink that supports cell proliferation, EB fusion, and subsequent differentiation into cardiomyocytes and other cell types to form contractile 3D cardiac tissues. To create the EB bioink, human embryonic stem cell derived EBs of controlled dimensions were combined with a high concentration fibrinogen solution. We then the used Freeform Reversible Embedding of Suspended Hydrogels (FRESH) 3D bioprinting to fabricate ring, tube, and ventricle shaped cardiac constructs. Thrombin added to the FRESH support bath was used to rapidly gel the fibrinogen in the EB bioink into fibrin to maintain the printed structure. The constructs were cultured for a period of 2 days to allow the EBs to grow and fuse, after which they were differentiated into cardiomyocytes in chemically defined media with CHIR and WNT-C59. Electrophysiology and contractility were examined during spontaneous contraction and under paced field stimulation, showing successful cardiomyocyte differentiation, regions of synchronized contraction, and calcium transients with electrical pacing. Finally, scaffolds were imaged by confocal microscopy for residual structural fibrin, cell generated matrix, cardiac troponin T and myofibril alignment. In total, these results demonstrate that FRESH 3D bioprinted cardiac tissues from EB bioinks followed by in situ, 3D differentiation is a viable strategy. Future work will focus on identifying the optimal day of EB differentiation for forming and printing the bioink and the role of specific reagents on cell type specification and differentiation.

Funding Source: Additional Ventures Cures Collaborative
Keywords: Bioprinting, Embryoid Bodies, Cardiomyocytes

9:55 AM – 10:05 AM

ACOUSTOFLUIDIC SONOPORATION GENE DELIVERY UTILIZING DNA-ENCAPSULATED SUPRAMOLECULAR NANOPARTICLES FOR GENE THERAPIES

Gong, Yao

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Gene therapies that leverage engineered cells to produce a therapeutic effect via gene correction or modification are increasingly offering exciting treatment solutions for patients with cancer or genetic diseases. Accelerating the clinical translation will require the development of new methods for engineering target cell populations rapidly, efficiently, safely, and cost effectively. Here we report an acoustofluidic intracellular delivery technology that enables precise sonoporation of cells as they are passed through a microfluidic channel. The pressure field generated within the microfluidic system is engineered to drive cells to the sidewall of a glass microcapillary, which transiently increases membrane permeability via shear forces to promote uptake of biomolecular cargoes. We have previously applied this acoustofluidic approach to demonstrate the delivery of model expression plasmid cargoes encoding for a non-integrating enhanced green fluorescent protein to umbilical blood CD34+ hematopoietic stem and progenitor cells with 92% cell viability and 20% GFP expression. Here we adapt this platform for non-virally generating chimeric antigen receptor (CAR) T-cell populations via delivery of plasmids designed to encode for expression of a Glypican-3 (GPC3)-targeting CAR and that include a Sleeping Beauty transposon cassette, which we package into supramolecular nanoparticle (SMNP) carriers. Incorporation of therapeutic payloads into SMNPs adds new capabilities for packaging and delivering more complex and multiple cargo types, and we observed ~40% cell and stable integration of the CAR transgene with ~25% CAR expression after two weeks. And the addition of a thermoelectric cooling system improves both the operation lifetime and output consistency of the acoustofluidic platform. To better understand the mechanisms, we are beginning to probe the dynamics of membrane pore formation at both the plasma and nuclear membranes. Altogether, this study represents an initial step toward expanding the library of acoustofluidic-engineered cell products. Leveraging this versatile acous-

tofluidic platform to deliver an increasing array of biomolecular cargoes ultimately will inform strategies for rapidly advancing the generation of future stem cell-based gene therapeutics.

Keywords: Gene delivery, Gene therapy, Acoustofluidics

10:05 AM – 10:15 AM

DEVELOPMENT OF A BIOINFORMATICS-BASED TOOL, NEURITEST, FOR QUALITY CONTROL OF IPSC-DERIVED DOPAMINE NEURON PRECURSORS FOR TRANSPLANTATION

Williams, Roy M.[1], Barken, Derren[2], Bratt-Leal, Andres[3], Deckert, Gerry[2], Lelos, Mariah[4], Loring, Jeanne[5], Müller, Franz[6], Mossman, James[2], Schuldt, Bernhard[6] and Zhang, Ai[7]

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Parkinson disease (PD) is the second most common neurodegenerative disease, affecting more than ten million people worldwide. The progressive loss of dopamine neurons in the substantia nigra that occur in PD cannot be rescued by current therapies. However, evidence indicates that restoring dopamine neurons by transplantation has the potential to alleviate motor symptoms associated with PD. We are developing an autologous neuron replacement approach, using an individual's own iPSCs to generate dopamine neuron precursors for transplantation. We have developed rigorous protocols to meet the challenges associated with manufacturing of autologous cell products reproducibly. A critical tool is a bioinformatics-based predictive assay that uses whole transcriptome RNA sequencing to identify neural precursor cells at the optimal stage for transplantation. This assay, called "NeuriTest," compares the cells' mRNA expression profile to a reference dataset created from validated dopamine neuron precursor cultures that were demonstrated to engraft and restore motor function in a hemiparkinsonian rat model. We have validated NeuriTest with internal and published datasets, demonstrating its utility for both bulk RNAseq, and pseudo-bulk samples generated from scRNAseq data. NeuriTest is a key analytical development toward delivering reproducible and potent autologous cellular therapeutics for people with PD through establishing a systematic, effective and reliable quality control testing system.

Keywords: Parkinsons, autologous, neural progenitor

10:15 AM – 10:35 AM

ENABLING QUALITY-BY-DESIGN (QBD)-DRIVEN MANUFACTURING OF CELL THERAPIES - THE ROLE OF DATA SCIENCE, IN/AT-LINE PROCESS AND PRODUCT ANALYTICS, AND FEEDBACK-CONTROLLED AUTOMATION

Roy, Krishnendu

Georgia Institute of Technology, GA, USA

Cell and cell-based therapies have shown incredible promise in treating, and even functionally curing, previously incurable diseases. However, scalable manufacturing of these "living products" with reproducible and predictable quality while minimizing batch failures and lowering the cost of goods and services is a major barrier for widespread and equitable use of these therapies across the world. In this talk I will present our collective efforts from the NSF ERC on Cell Manufacturing Technologies (CMAT) and related innovation ecosystem to enable quality-driven manufacturing of cell therapies. Specifically, the roles of feedback controlled and process/product analytics-driven automation, data science and AI-enabled discovery of quality attributes and mechanisms of action, and data-driven manufacturing optimization strategies will be discussed.

Keywords: cell manufacturing, quality-by-design, flexible automation, real time process analytics

TRACK: TISSUE STEM CELLS AND REGENERATION (TSC)
PRINCIPLES OF TISSUE AND ORGAN REGENERATION
9:00 AM – 10:45 AM
ROOM 2007
LEVEL 2

9:05 AM – 9:25 AM

TRACING THE DEVELOPMENTAL ORIGIN OF HAIR FOLLICLE STEM CELLS

Fujiwara, Hironobu

RIKEN Center for Biosystems Dynamics Research, Kobe, Japan

Tissue stem cells are generated from an embryonic progenitor population through organ-specific morphogenetic events. Although tissue stem cells are central to organ homeostasis and regeneration, it remains unclear how they are induced during development, mainly owing to the lack of specific markers that exclusively label prospective stem cells. Here, by combining marker-independent long-term 3D live imaging and single-cell transcriptomics, we captured cellular dynamics, cell lineages, and transcriptome changes in the entire epithelium of developing mouse hair follicles. We found that different epithelial lineage precursors were aligned in a 2D concentric manner in the basal layer of the hair placode. Each concentric ring zone acquired unique transcriptomes and telescoped out to form longitudinally aligned 3D cylindrical compartments. Prospective bulge stem cells were derived from the peripheral ring zone of the placode, irrespective of cell division orientation. We also identified 13 gene clusters in which their ensemble expression dynamics drew the entire transcriptional landscape of epithelial lineage diversification, coinciding with cell lineage data. Combining these findings with insect appendage development, we provide a generalized model termed the "telescope model" wherein 2D concentric zones in the placode telescope out to form 3D longitudinally aligned cylindrical compartments.

Keywords: hair follicle stem cells, developmental origin, live imaging, transcriptomics

9:25 AM – 9:35 AM

A MAPK/ERK-DEPENDENT MOLECULAR SWITCH ANTAGONIZES FIBROSIS AND PROMOTES REGENERATION IN SPINY MICE (ACOMYS)

Tomasso, Antonio[1], Bartscherer, Kerstin[1] and Seifert, Ashley[2]

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Regenerative ability diverges enormously across animal phyla and even closely related species respond differently to injury. While most mammals heals wounds with scar tissue, African spiny mice (Acomys cahirinus) regenerate skin and complex musculoskele-

tal structures, including hair follicles, glands, nerves, muscles and cartilage upon injury. However, the mechanisms underlying mammalian tissue regeneration are poorly characterized. The identification of core signaling pathways driving regenerative rather than fibrotic healing in mammals are of a great significance. Here, we show that MAPK/ERK signaling acts as a major hub directing cellular injury responses towards regeneration. Through cellular and molecular analysis of ERK activity, we found that early ERK activation was a conserved feature of wound healing between regenerators (Acomys) and poor regenerators (Mus musculus). However, the duration of MAPK/ERK signaling controlled the diverged scar and regeneration responses. Through RNA profiling, the inhibition of ERK activity revealed that it coordinated the cellular crosstalk in the local microenvironment to form a functional blastema characterized by cell proliferation, a transitional wound epidermis and a pro-regenerative matrisome. Thus, these data indicate that the manipulation of the MAPK/ERK signaling shifted the Acomys regeneration towards a Mus-like fibrotic repair. Loss-of-function experiments prompted us to identify upstream regulators of the MAPK/ERK signaling during regeneration. Conversely, gain-of-function experiments in the normally non-regenerating Mus, demonstrated a capacity of ERK activators to induce a transient regenerative response, including controlled tissue growth, cell proliferation, wound epidermis markers, a pro-regenerative matrisome and the de novo hair follicle formation. Our study demonstrates that cellular ERK activity controls the delicate balance between regeneration and fibrosis in mammals. Ultimately, these findings provide new insights to why some mammals regenerate and others do not. Understanding how the MAPK/ERK signaling orchestrates wound response may open avenues for therapeutic strategies to reverse fibrosis in favor of regeneration.

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Keywords: Mammalian tissue regeneration, Injury response, MAPK/ERK signaling

9:35 AM – 9:45 AM

GLUTAMATE ACTIVATES A PROLIFERATIVE AND ASTROGLIOGENIC PROGRAM IN EPENDYMAL STEM CELLS: IMPLICATIONS FOR REGENERATIVE THERAPEUTIC TRANSLATION

Hachem, Laureen D.[1], Hong, James[2], Velumian, Alexander[2], Mothe, Andrea[2], Tator, Charles[3] and Fehlings, Michael[3]

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The adult spinal cord contains a population of ependymal derived neural stem/progenitor cells (epNSPCs) that are normally quiescent, but are activated to proliferate, differentiate, and migrate after spinal cord injury (SCI). Once activated, epNSPCs serve as critical players in modulating the injury environment and enhancing axon regeneration. However, epNSPC numbers remain insufficient for adequate regeneration in the subacute and chronic injury period. The factors and signaling pathways that regulate spinal cord epNSPC proliferation and differentiation in response to cellular stress and injury remain largely unknown. Elucidating these mechanisms is essential in regulating endogenous neural stem cells and further enhancing their regenerative potential. Glutamate excitotoxicity is a hallmark of SCI, and while toxic to neurons and glia, we recently discovered that excitotoxic levels of glutamate paradoxically lead to activation of epNSPCs and increase their survival and proliferation. Here, we demonstrate that glutamate leads to calcium influx in spinal cord epNSPCs via AMPA receptors. Through a combination of RNAseq, protein analysis and immunohistochemical profiling, we show that this AMPA receptor dependent change in calcium in concert with Notch signaling serves to increase the proliferation of spinal cord epNSPCs via phosphorylated CREB, and induce astrocytic cell fate specification through Hes1 upregulation. Using a clinically relevant in vivo model of SCI we demonstrate that positive allosteric modulation of AMPA receptors subacutely after injury enhances epNSPC proliferation, astrogliogenesis, neurotrophic factor production and promotes neuronal survival and early functional recovery. Our study uncovers an important mechanism by which glutamatergic signaling via AMPA receptors alters the proliferation and phenotype of spinal cord epNSPCs which may be harnessed therapeutically to enhance the regenerative potential of these cells after injury.

Funding Source: This work was supported by grants from the Neurosurgery Research and Education Foundation/Academy of Neurological Surgeons, Physicians' Services Incorporated Foundation, Canadian Institutes of Health Research.
Keywords: ependymal neural stem cells, spinal cord injury, glutamate

9:45 AM – 9:55 AM

G2 STEM CELLS ORCHESTRATE TIME-DIRECTED, LONG-RANGE COORDINATION OF CALCIUM SIGNALING DURING SKIN EPIDERMAL REGENERATION

Moore, Jessica[1], Gao, Feng[1], Matte-Martone, Catherine[1], Du, Shuangshuang[1], Lathrop, Elizabeth[1], Ganesan, Smirthy[1], Shao, Lin[2], Bhaskar, Dhananjay[1], Cox, Andy[1], Hendry, Caroline[1], Rieck, Bastian[3], Krishnaswamy, Smita[1] and Greco, Valentina[1]

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Skin epidermal homeostasis is maintained via constant regeneration by stem cells, which must communicate to balance their self-renewal and differentiation. A key molecular pathway, Ca2+ signaling has been implicated as a signal integrator in developing and wounded epithelial tissues. Yet how stem cells carry out this signaling across a regenerative tissue remains unknown due to significant challenges in studying signaling dynamics in live mice, limiting our understanding of the mechanisms of stem cell communication during homeostasis. To interpret high dimensional signals that have complex spatial and temporal patterns, we combined optimized imaging of Ca2+ signaling in thousands of epidermal stem cells in living mice with a new machine learning tool, Geometric Scattering Trajectory Homology (GSTH). Using a combination of signal processing, data geometry, and topology, GSTH captures patterns of signaling at multiple scales, either between direct or distant stem cell neighbors. Here we show that epidermal stem cells display dynamic intercellular Ca2+ signaling among neighborhoods of up to 10 cells that is surprisingly coordinated and directed through time across a pool of thousands of stem cells. We find that this collective coordination is an emergent property of the stem cell compartment, distinct from excitatory quiescent neuronal tissues. We demonstrate that cycling stem cells, specifically G2 cells, govern homeostatic patterns of Ca2+ signaling. Stem cells in different cell cycle stages dynamically regulate localization of the gap junction component Connexin43 (Cx43). Lastly, we uncouple global from local communication and identify Cx43 as the molecular mediator necessary for connectivity between local signaling neighborhoods. This work provides

resolution in how stem cells at different stages of the cell cycle communicate and how that diversity of phases is essential for tissue wide communication and signaling flow during epidermal regeneration. Our approach provides a framework to investigate stem cell populations and their signaling dynamics, previously not possible.

Keywords: epidermal stem cells, calcium signaling, cell cycle

9:55 AM – 10:05 AM

ACQUISITION OF CELLULAR PLASTICITY IN THE HUMAN LIVER DURING CHRONIC DISEASE PROGRESSION

Gribben, Christopher[1], Galanakis, Vasileios[1], Calderwood, Alexander[1], Allison, Michael[2], Athanasiadis, Emmanouli[3], Mohorianu, Irina[1] and Vallier, Ludovic[1]

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The liver is key to numerous physiological processes, including playing central roles in metabolism and detoxification. Liver disease is on the rise, and this is predicted to create a significant burden on healthcare systems in the coming years. The remarkable ability of the liver to regenerate after acute injury is well established, and an understanding of this process may be important in the design of future therapies. This regenerative property is believed to be driven mainly by hepatocyte proliferation. However, regeneration during chronic injury, especially in human, appear to be more complex. Indeed, studies in animal models have shown that 3 mechanisms can take place: (i) activation of liver stem cells, (ii) dedifferentiation/redifferentiation of adult liver cells and (iii) cellular plasticity between cholangiocytes and hepatocytes. However, whether such mechanisms are at play during progression of chronic human liver disease remains a key question in the field. Here, we examine the progression of non-alcoholic fatty liver disease (NAFLD) towards liver failure by performing single-nuclei transcriptional analysis (snRNAseq) of patient biopsies at different stage of the disease. This approach captured a diversity of liver cell types, with approximately 100,000 nuclei analysed, representing the largest scRNAseq human liver dataset available. Analyses reveal that disease progression is characterised by loss of tissue organisation, with disruption to hepatocyte zonation and expansion of the biliary tree. Evidence of hepatocyte and cholangiocyte plasticity was observed, with cholangiocyte-hepatocyte bi-phenotypic cells identified in the diseased liver. These features of disease were also observed using immunofluorescent staining of tissue sections and 3D cleared-tissue imaging. Cholangiocyte organoids derived from patients with NAFLD-driven liver failure, could be differentiated towards hepatocytes in vitro, indicating this model system could be useful for studying the cholangiocyte-hepatocyte plasticity observed in vivo. Together, this analysis indicates that cellular plasticity could be the main regenerative mechanism existing in chronic liver injury. This knowledge may provide a steppingstone for the development of new therapies.

Funding Source: Open Targets consortium
Keywords: Liver, Plasticity, Regeneration

10:05 AM – 10:15 AM

ABSOLUTE SCALING OF SINGLE-CELL TRANSCRIPTOMES REVEALS PERVASIVE HYPERTRANSCRIPTION IN ADULT STEM AND PROGENITOR CELLS

Kim, Yun-Kyo[1] and Ramalho-Santos, Miguel[2]

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Hypertranscription facilitates biosynthetically demanding cellular state transitions through global upregulation of the nascent transcriptome. Despite its potential widespread relevance, documented examples of hypertranscription remain few and limited predominantly to early development. This limitation is in large part a consequence of modern sequencing approaches, including single-cell RNA sequencing (scRNA-seq), that generally assume similar levels of transcriptional output per cell. Here, we use molecule counting and spike-in normalization to develop absolute scaling of scRNA-seq data. Absolute scaling enables an estimation of total transcript abundances per cell, which we validate by detecting hypertranscription in embryonic stem cells and primordial germ cells. When applied to single-cell atlases of post-natal mouse organs, absolute scaling reveals a remarkable dynamic range in the transcriptional output of mature adult cell types. Notably, we find that hypertranscription is enriched in several multipotent stem and progenitor cell populations, including those of the hematopoietic system, intestine, and skin. In these systems of high cellular turnover, we find that hypertranscription marks cells with multilineage potential and is gradually lost throughout the course of terminal differentiation. Furthermore, we identify hypertranscription as a defining hallmark for regenerative stem cell populations in conditions of tissue injury, which can precede by 1-2 days bursts of proliferation during organ renewal. By dissecting the association between hypertranscription and the stem/progenitor cell state, we reveal that a common set of molecular pathways are associated with adult hypertranscription that are shared with early development, including chromatin remodeling, DNA repair, ribosome biogenesis and translation. Critically, our findings introduce an approach towards maximizing transcriptomic data and unmasking a previously unappreciated biological dimension in single-cell profiling. By applying this methodology across a diverse collection of cell states and contexts, we put forth hypertranscription as a general and dynamic cellular program that is pervasively employed by stem cells during development, organ maintenance and regeneration.

Funding Source: This work was supported by a Whiteside Scholarship (University of Toronto) and a McLaughlin Award (University of Toronto) to YK., CIHR Project Grant 420231, and a Canada 150 Research Chair in Developmental Epigenetics to MRS.
Keywords: single-cell RNA-seq, hypertranscription, regeneration

10:15 AM – 10:35 AM

METABOLIC REGULATION OF ADULT STEM CELL BEHAVIOR IN DROSOPHILA MELANOGASTER

Jones, Leanne, Sênos Demarco, Rafael, Koehler, Chris, Joy, Jery, Clemot, Marie and D'Alterio, Cecilia

Departments of Anatomy and Medicine/Geriatrics, University of California, San Francisco, CA, USA

The capacity of stem cells to self-renew or differentiate has been attributed to distinct metabolic states. We conducted genetic screens targeting regulators of mitochondrial dynamics in both adult intestinal stem cells (ISCs) and germline stem cells (GSCs),

which revealed that mitochondrial fusion is required for male germline stem cell (GSC) maintenance in Drosophila melanogaster. Depletion of Mitofusin (dMfn) or Optic atrophy 1 (Opa1) led to dysfunctional mitochondria, activation of Target of Rapamycin (TOR), and a dramatic accumulation of lipid droplets (LDs). Pharmacologic or genetic enhancement of lipid utilization by the mitochondria decreased LD accumulation, attenuated TOR activation and rescued GSC loss caused by inhibition of mitochondrial fusion. However, the mechanism(s) leading to GSC loss were unclear. TOR activation has been demonstrated to suppress JAK-STAT signaling by stabilizing the JAK-STAT inhibitor SOCS36E. JAK-STAT signaling is critical for regulating stem cell self-renewal in the testis; indeed, we found that SOCS36E levels are higher in early germ cells upon depletion of Mfn or Opa1. Subsequently, we show that activation of the JAK-STAT pathway, but not BMP signaling, is sufficient to rescue loss of GSCs as a result of the block in mitochondrial fusion. Our findings highlight a critical role for mitochondrial fusion and lipid homeostasis in GSC maintenance, providing a framework for investigating the impact of metabolic diseases on stem cell function and tissue homeostasis.

Keywords: Mitochondria, lipid droplets, JAK-STAT, germline stem cells, intestinal stem cells, Drosophila

TRACK: NEW TECHNOLOGIES (NT)
PLENARY VI: TECHNOLOGIES THAT MODEL AND DIRECT EMERGENT CELL BEHAVIORS IN STEM CELL BIOLOGY AND REGENERATION BEHAVIORS
12:45 PM – 2:55 PM
LEVEL 3

12:50 PM – 1:10 PM

SINGLE-CELL RIBOSOME PROFILING

van Oudenaarden, Alexander[1], VanInsberghe, Michael[1], van den Berg, Jeroen[1], Andersson-Rolf, Amanda[2] and Clevers, Hans[2]

[1]Hubrecht Institute-KNAW and University Medical Center, Utrecht, Netherlands, [2]Hubrecht Institute, Utrecht, Netherlands

Single-cell sequencing methods have enabled in-depth analysis of the diversity of cell types and cell states in a wide range of organisms. These tools focus predominantly on sequencing the genomes, epigenomes and transcriptomes of single cells. However, despite recent progress in detecting proteins by mass spectrometry with single-cell resolution, it remains a major challenge to measure translation in individual cells. Here, building on existing protocols, we have substantially increased the sensitivity of these assays to enable ribosome profiling in single cells. Integrated with a machine learning approach, this technology achieves single-codon resolution. We validate this method by demonstrating that limitation for a particular amino acid causes ribosome pausing at a subset of the codons encoding the amino acid. Of note, this pausing is only observed in a sub-population of cells correlating to its cell cycle state. We further expand on this phenomenon in non-limiting conditions and detect pronounced GAA pausing during mitosis. Finally, we demonstrate the applicability of this technique to rare primary enteroendocrine cells. This technology provides a first step towards determining the contribution of the translational process to the remarkable diversity between seemingly identical cells.

Keywords: single-cell sequencing, ribosome profiling, translation

1:10 PM – 1:30 PM

GEOMETRIC AND TOPOLOGICAL APPROACHES TO REPRESENTATION LEARNING IN DEVELOPMENTAL DATA

Krishnaswamy, Smita

Yale University, CT, USA

High-throughput, high-dimensional data has become ubiquitous in the stem cell field. While these large datasets containing thousands of cells hold great potential for understanding developmental trajectories, cellular lineage specifications and cellular decisions,, they also pose new challenges in terms of noise, missing data, measurement artifacts, and the so-called “curse of dimensionality.” In this talk, I will cover data geometric and topological approaches to understanding the shape and structure of developmental data. We will use human embryonic stem cell development in an embryoid body system as a model culture. First, we show how diffusion geometry and deep learning can be used to obtain useful representations of the data that integrate multiple modalities of data, enable denoising, and dimensionality reduction. Next we show how to combine diffusion geometry with topology to extract multi-granular features from the data to assist in differential and predictive analysis. Finally we will show how to learn dynamics from static snapshot data by using a manifold-regularized neural ODE-based optimal transport to understand the continuous dynamics of development. Together, we will show a complete framework for exploratory and unsupervised analysis of single-cell data in order to uncover insights on development and regeneration.

Keywords: Geometric, Topological, Approach

1:30 PM – 1:50 PM

ORGANS ON A CHIP PLATFORM WITH HUMAN TISSUE NICHES LINKED BY VASCULAR FLOW

Vunjak-Novakovic, Gordana[1], Ronaldson-Bouchard, Kacey[2] and Tavakol, Daniel N.[2]

[1]Mikati Foundation Professor of Biomedical Engineering and Medicine, Columbia University, New York, NY, USA, [2]Biomedical Engineering, Columbia University, New York, NY, USA

Human tissues engineered from pluripotent stem cells can be used to recapitulate organ-level functions, such as contractility of the heart or liver metabolism. For physiological relevance, the individual tissues need to maintain their individual phenotypes for weeks to months, while allowed to communicate by secreted factors, extracellular vesicles and circulating cells. To reconcile these conflicting requirements, we developed a platform in which each tissue is maintained in its own optimized niche and linked to other tissues by vascular flow containing circulating cells. The interlinked tissues maintained their molecular, structural and functional phenotypes, allowing long-term studies of tissue development and maturation, systemic diseases and injury in a systemic context. Engineering tissues from ipSCs allows individualized approach to biological and medical research. To illustrate the potential of this technology and discuss some of the current challenges, this talk will provide examples of platforms designed to study (i) systemic effects of drugs, (ii) cancer metastasis and (iii) radiation damage.

Keywords: hiPSC, tissue engineering, organs on a chip, heart, liver, bone marrow, vasculature, human physiology

1:50 PM – 2:10 PM

PROGRAMMING MULTICELLULAR PATTERN FORMATION WITH SYNTHETIC CELL-CELL SIGNALING

Toda, Satoshi

Kanazawa University, Kanazawa, Japan

In developing embryos, cells communicate with each other using various molecules to control the behaviors of cell populations and assemble complex tissue structures. Thanks to recent advances in biological studies and imaging technologies, we have learned molecular players and individual cell behaviors during development. However, cell-cell interactions in vivo are extremely complicated: e.g., signaling molecules interact with many surrounding molecules in addition to receptors and cells dynamically change their own state while exchanging signals. Therefore, it is still unclear how communicating cells organize complex tissue structures robustly. Here, to explore key mechanisms of tissue formation, we have been engineering artificial multicellular model systems using cultured cells that have no ability to self-organize into tissues. We design new cell-cell communication rules there and test multicellular behaviors to understand a logic of how cells organize multicellular structures and patterns. Recently, we have converted a fluorescent protein GFP into an intercellular signaling molecule and designed cell-cell communications based on the secretion and reception of GFP. Using this system, we tested how secreted signaling molecule can generate and regulate multicellular patterns. In this talk, I will introduce our synthetic biology research to create tissue patterning processes and discuss its application to engineer organoids for regenerative medicine.

Keywords: multicellular synthetic biology, morphogen, pattern formation, tissue engineering

2:10 PM – 2:40 PM

ISSCR MOMENTUM AWARD LECTURE: FROM NUCLEOSOMES TO HUMAN FACES: MY JOURNEY IN STEM CELL BIOLOGY

Wysocka, Joanna

Stanford University School of Medicine, Stanford, CA, USA

I am honored to receive the 2022 ISSCR Momentum Award. I've been trained as a chromatin biochemist and became interested in stem cell biology due to my long-held belief that novel gene regulatory mechanisms will reveal themselves during dynamic cell fate transitions. When I was starting my lab, modeling aspects of human development with pluripotent stem cells has just become possible and we've jumped at the opportunity. Using human embryonic stem cells, we demonstrated that simple, combinatorial chromatin signatures are predictive of enhancer position and activity state and thus can be exploited to identify cell type-specific enhancers throughout the genome and to pinpoint regulatory elements that are primed for future activation during differentiation. Enhancers play a privileged role in mediating cell fate transitions and tissue-specific gene expression programs. We have used Cranial Neural Crest Cells (CNCCs) as a paradigm to study how genetic information harbored by enhancers is decoded into a diversity of molecular functions, cellular behaviors and complex morphologies. CNCCs are a transient stem cell population of unusual developmental plasticity and migratory potential that gives rise to most of the craniofacial structures. We pioneered pluripotent stem cell differentiation models that recapitulate human and chimpanzee CNCC formation in vitro, and utilized them – in combination with human facial genetics and in vivo modeling – to understand regulatory mechanisms by which CNCCs produce craniofacial forms that characterize us both as humans and as individuals. Over a third of human congenital malformations are linked to neural crest dysfunction, including over 500 Mendelian-inheritance syndromes with craniofacial manifestations, and a number of non-syndromic, complex diseases. We investigated the mechanisms of multiple craniofacial anomalies associated with mutations of transcriptional and chromatin regulators or non-coding genomic regions. Our studies shed light onto how tissue-specificity arises in these disorders and provided numerous unexpected insights into gene regulation. In my talk, I will discuss these and other discoveries from my lab and highlight most exciting future directions.

Keywords: chromatin, pluripotent stem cells, neural crest

TRACK: CLINICAL APPLICATIONS (CA)
PLENARY VII: CELL AND GENE THERAPY IN THE CLINIC
3:30 PM – 6:00 PM
LEVEL 3

3:50 PM – 4:10 PM

DEVELOPING NEW TRANSFORMING APPROACHES TO GENETIC ENGINEERING OF HEMATOPOIESIS TO BROADEN THE EFFICACY, FEASIBILITY AND SAFETY OF CLINICAL TRANSLATION

Naldini, Luigi

San Raffaele Telethon Institute for Gene Therapy (SR-Tiget) and San Raffaele University, Milan, Italy

Hematopoietic stem cells (HSC) gene therapy (GT) by lentiviral vectors is providing substantial benefit to patients affected by primary immunodeficiencies, hemoglobinopathies and storage disorders. Long-term follow up shows stable hematopoietic reconstitution by high numbers of corrected HSC without signs of clonal expansion or exhaustion, providing a reassuring molecular picture underlying the long-lasting clinical benefit. Precise engineering by gene editing may further improve the safety of HSC GT by achieving in situ gene correction or targeted transgene integration. We reported the first targeted gene editing of human HSC followed by studies highlighting barriers limiting its efficacy and novel strategies overcoming them. Homology-driven repair, however, remains limiting. We now report that the choice of template can increase efficiency and safety of the procedure. Moreover, the emergence of base and prime editors that minimize or bypass the requirement for DNA DSB allows editing single/few mutant nucleotides with limited activation of DNA damage response. Another long-sought goal of HSC GT is to make space for the infused cells without relying on genotoxic conditioning, which entails acute and chronic serious adverse effects. We report that HSC mobilization opens a window of opportunity for engraftment of donor cells, which can effectively outcompete those in the circulation for engraftment in the depleted niches. Competitive advantage results from the rescue in culture of a detrimental impact of mobilizing agents on HSC and can be further enhanced by transient over-expression of engraftment effectors. These findings were obtained in mouse models of diseases to prove their therapeutic potential and in human hematochimeric mice to validate them for human HSC. Overall, our work should advance HSC GT by a combination of transformative approaches leveraging on precision genetic engineering while alleviating the morbidity of the procedure, broadening application to several diseases and patients worldwide.

Keywords: Hematopoietic stem cells, gene therapy, gene editing

4:10 PM – 4:35 PM

JOHN MCNEISH MEMORIAL LECTURE:

RETINAL CELL THERAPY AS A SUSTAINABLE CATEGORIZED MEDICINE

Takahashi, Masayo

Vision Care Inc., Japan

Our goal is to develop cell and gene therapies for outer retinal layer diseases. First, we performed autologous iPS-derived retinal pigment epithelium (RPE) cell sheet transplantation to demonstrate the safe usage of iPS cells from 2013. The cell sheet works still. In an allogeneic transplantation clinical study from 2017, we confirmed that the immune response can be controlled by topical steroids alone if HLA mismatch is avoided, that lead us to the pipeline using HLA partial KO iPS cells. Currently, we expanded our target diseases to RPE impaired diseases and use RPE strips to transplant easily from small holes in our phase 2 like clinical study. To reconstruct outer retinal layer the important challenge is photoreceptor replacement. iPSC-retinal organoid transplantation was conducted last year for two cases of retinitis pigmentosa. Based on these experiences, we believe that we should create therapies for each category of outer retinal diseases. In addition, since replacement therapies are surgical treatments, there is a gap between the end product and the treatment that does not exist in drug development. Therefore, for an ideal treatment, we need to strictly select the right cases for each therapy and prepare clinical methods such as examination tests, surgical techniques and so on. Otherwise, cell therapy will become an expensive gamble. As for cell manufacturing, usually we validate all the apparatus in the facility, but the technique of cell culture is not validated, so that the cell condition differs from culture person to person and education is difficult. For this problem, we put a humanoid robot to do the same manipulation as the tacit technical staff to get stable cell quality always. Cell therapy has many different points compared to small molecule drugs. I will talk about the current status of our project.

Keywords: retina, cell therapy, robot

4:35 PM – 4:55 PM

PATH TO THE DEVELOPMENT OF IPSC-DERIVED OFF-THE-SHELF T AND NK CELLS FOR CANCER IMMUNOTHERAPY

Valamehr, Bob

Fate Therapeutics, Inc, San Diego, CA, USA

Cell-based immunotherapies have shown remarkable promise in the fight against various cancers. The use of induced pluripotent stem cells (iPSCs) to derive immune effector cells offers distinct advantages for immune therapy over existing patient- or donor-derived platforms, not only in terms of scalable and consistent manufacturing, on-demand availability and precision genetic engineering at the clonal level, but also in allowing for the generation of multiple effector cell types each with distinct characteristics. Our iPSC product platform uniquely leverages the use of clonal master iPSC lines that serve as the starting material for the manufacture of multiplexed-engineered, off-the-shelf cell-based cancer immunotherapies that can be fully characterized, stored, and administered on-demand to patients in an outpatient setting. Taking cues from the natural propagation of innate to adaptive effector responses, here I describe the development of multiplexed engineered iPSC-derived chimeric antigen receptor (CAR) natural Killer (iNK) and T (iT) cells, in order to exploit the unique properties of each cell type to achieve both depth and durability of response for hematological malignancies and solid tumors.

Keywords: iPSCs, pluripotent stem cells, natural killer cells, T cells, gene and cell therapy, off-the-shelf, chimeric antigen receptor, genetic engineering

4:55 PM – 5:15 PM

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

Meininger, Gary E.

Vertex Pharmaceuticals, Needham, MA, USA

Type 1 diabetes results from the autoimmune destruction of insulin-producing beta cells in the pancreas. Replacement of beta cells through cadaveric islet transplantation has been shown to restore glucose-responsive insulin production in patients with type 1 diabetes, however, there are limitations on the quantity and quality of available islets. During the past decade, advances in stem cell biology and cell culture have made it possible to reliably differentiate human stem cells into a wide variety of lineages, including islets cells, with high precision and at large-scale. These developments, along with further optimization of differentiation strategies and clinical manufacturing capabilities, have led to the first clinical trial of fully differentiated, stem-cell derived islets cells in patients with type 1 diabetes.

Keywords: #T1D, #type1diabetes, and #SC-islets

5:15 PM – 5:50 PM

KEYNOTE ADDRESS:

BUILDING THE FUTURE OF SCIENCE

Chan, Priscilla

Chan Zuckerberg Initiative, CA, USA

Dr. Priscilla Chan, Co-Founder and Co-CEO of the Chan Zuckerberg Initiative (CZI), will deliver a keynote address on building a future where more people, in more places, are part of scientific progress, as well as highlight CZI-supported efforts to advance the technology and collaborations that are driving discoveries in stem cell research. Dr. Chan will share her journey to medicine, CZI's work to accelerate biomedical science and advance human health, and how new single-cell technologies are enabling exciting research as part of the Human Cell Atlas.

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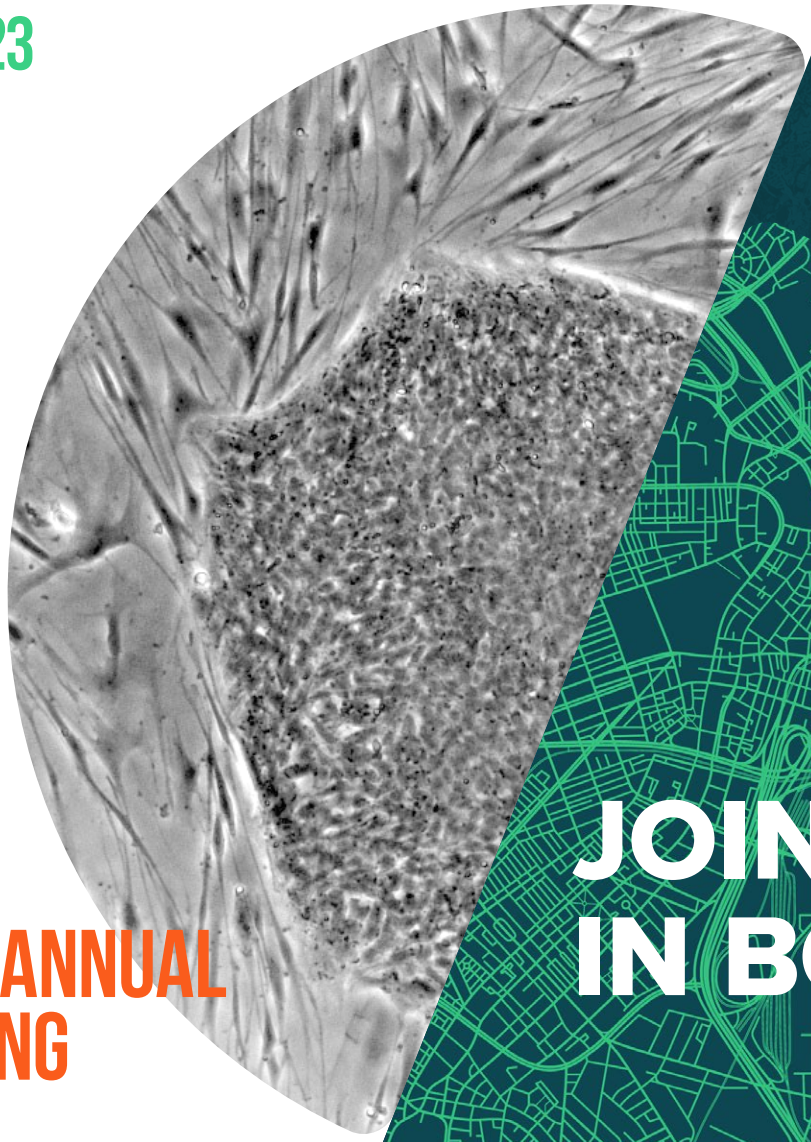

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