CITY OF BOSTON • MASSACHUSETTS

OFFICE OF THE MAYOR
MARTIN J. WALSH

June 2017

Dear Friends,

On behalf of the City of Boston, I would like to extend a warm welcome to all members of the International Society for Stem Cell Research who are visiting our great city to attend the ISSCR 2017 Annual Meeting. For a conference focused on promoting groundbreaking discovery, innovative research, and scientific leadership, I believe the City of Boston is a perfect host.

I am thrilled that the ISSCR will be convening members from all over the world, and invite you all to explore Boston's rich history, dedication to education, and thriving innovation communities. I hope that the City of Boston and all it has to offer will facilitate a productive conference, and will help you to achieve even more advanced research, education, and innovation.

Again, I appreciate your dedication to the City of Boston and wish you a successful meeting.

Sincerely,

Martin J. Walsh
Mayor of Boston

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617-635-4500 • www.boston.gov

Dear Colleagues:

On behalf of the International Society for Stem Cell Research (ISSCR), we are delighted to welcome you to our 15th Annual Meeting, the largest forum for stem cell and regenerative medicine professionals from around the world. It is a pleasure to celebrate the organization's 15th anniversary in Boston, a historic city with scientists and institutions that played a key role in the ISSCR's founding. Boston is a vibrant hub of stem cell research, biotech, and life science research.

A primary goal of our annual meeting is to provide you with an unparalleled array of opportunities to learn about the latest discoveries and scientific breakthroughs from your colleagues and leaders in the field. We have designed a diverse, engaging scientific program that explores all aspects of stem cell science and its translation to the clinic. Our extensive program covers stem cells in development and disease, and highlights the important role this research plays in advancing human health.

You will find an outstanding lineup of international speakers at ISSCR 2017, and we encourage you to attend the Plenary and Concurrent talks, the Focus Sessions, and the named lectures. You will also want to visit the poster hall to meet with researchers, network with colleagues, and discuss advances in science. Many of the program speakers are actively involved in therapy development, and they effectively complement those focused on basic biological research that is leading to new understandings about health and disease.

As the field increasingly moves toward medical applications, ISSCR 2017 is enhancing its clinically-focused programing, with two pre-meeting educational sessions specifically designed for scientists and physicians interested in learning more about how stem cell therapies are developed and moved into the clinic. The Workshop on Clinical Translation, and the Clinical Advances in Stem Cell Research (CASC) program, both on Tuesday, 13 June, reflect where the science is going, and underscore the importance of adhering to ISSCR guidelines as medicines are developed.

The field of stem cell research continues to grow and show promise, and that energy is reflected in our record number of exhibitors this year, many of whom are new. These companies, academic and scientific institutions, publishers, and other exhibitors make our meeting possible, and we encourage you to visit them in the Exhibit Hall and investigate the tools and services they have to offer.

We are proud to announce that the ISSCR journal, Stem Cell Reports, has achieved a 7.0 impact factor, and continues to publish high-quality science every month. Keep us in mind for your next paper submission.

As always, we are grateful for your support of the field and the ISSCR. Thank you for attending ISSCR 2017 -- we believe you'll agree that this year's meeting offers you an unprecedented opportunity to gain a comprehensive understanding of our important and dynamic field.

Sincerely,

Sally Temple
ISSCR President

Elaine Fuchs
2017 Program Chair

For the Harvard Stem Cell Institute, the honor of co-sponsoring this year's ISSCR Annual Meeting is akin to the feeling of satisfaction one enjoys when hosting a multi-generational family reunion. From all corners of the globe, stem cell researchers have assembled in our backyard to share new scientific discoveries, connect with our industry partners, support an emerging generation of young scientists, and huddle together to identify ways to accelerate therapies and cures.

The ISSCR's original leadership team of Len Zon and George Daley hail from pioneering labs in the Boston community. Putting his imprint on future generations of researchers and healers, Daley now leads the Faculty of Medicine at Harvard Medical School, one of the multiple institutions of higher education training the next generation of stem cell researchers in the Boston and Cambridge area. This year, Harvard University's Department of Stem Cell and Regenerative Biology is celebrating its tenth anniversary and is greatly enthused by the number of undergraduates choosing to initiate their careers in the department. These young scholars benefit from access to clinicians and patients in the many Harvard-affiliated hospitals in our vicinity. Tapping into this vibrant talent pool are the leaders in the biomedical/ biopharmaceutical/ biotechnology fields who call this area home: Biogen, GE, Novartis, Sanofi, Shire, Takeda, and Vertex, among others. And providing the adrenalin to these large companies are the many agile and visionary startups that hum in tiny spaces radiating with possibility, supported in turn by the active venture capital community and local incubators and innovation centers.

Each day in the HSCI community is permeated by the aura of potential and promise for those who count on our efforts to mitigate chronic and life-threatening diseases. Patients from around the world who seek treatment in our hospitals provide us with the motivation and encouragement to continue our pursuit in the face of sometimes discouraging outcomes. They may not join us at this meeting but they, too, are vital members of our community. In partnership with the ISSCR, we are ever mindful of our collective challenge and the work that remains to be done. As a family of researchers from around the world gathered together in Boston, let us use this time together to share discoveries, forge new collaborations and renew our joint commitment to accelerating this work to clinical application.

Welcome to Boston – welcome home – and together, let's do our job!

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Cell Research

Cells Tissues Organs

Current Protocols in Stem Cell Biology

Drug Target Review

PLOS ONE

Surrozen, Inc.

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REGISTRATION AND BADGE PICKUP

Pick up your attendee name badge in the registration area in the Boston Convention and Exhibition Center (BCEC), Level 1, North 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, 13 JUNE 14:00 – 18:00
WEDNESDAY, 14 JUNE 7:30 – 20:30
THURSDAY, 15 JUNE 8:15 – 18:30
FRIDAY, 16 JUNE 8:15 – 18:30
SATURDAY, 17 JUNE 8:15 – 18:30

For hotel matters, please visit the housing assistance desk in the registration area WEDNESDAY and THURSDAY and on FRIDAY UNTIL 12:00.

ATTENDEE ORIENTATION

Are you curious to find out how to best navigate through ISSCR 2017? Join us at the BCEC, Level 1, North Lobby for our Attendee Orientation where ISSCR staff and experienced ISSCR members will explain the annual meeting's highlights and facilitate attendee introductions before the meeting kicks off. There will be two scheduled Attendee Orientations:

TUESDAY, 13 JUNE 15:00 – 16:30
WEDNESDAY, 14 JUNE 8:30 – 10:00

THINGS YOU SHOULD KNOW

Internet Access

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

To connect to the Wi-Fi:

1. Enable your wireless and search for open networks in your "Settings"
2. Connect to the network called ISSCR2017
3. Open a web browser
4. When prompted, enter the password: STEMdiff
5. You will then be redirected to the sponsored landing page.

Mobile App

Have the ISSCR 2017 schedule in the palm of your hand. Download the free ISSCR 2017 Mobile App from the Apple Store or Google Play to your smartphone and/or tablet device to have immediate access to many features to enhance your annual meeting program experience:

- Browse or search for scientific content, presenters, exhibitors or events
- Use the People & Networking feature to browse speakers, poster presenters, and attendees who opt in as App Users
- Check the locations of sessions and exhibitors under the maps icon
- Receive important real-time communications from ISSCR
- Build a personalized schedule
- Bookmark exhibitors
- Stay in-the-know and join in on social media with #ISSCR2017 and #GlobalStemCellEvent

Downloading the mobile app is easy! Simply go to the App Store or Google Play and search for "ISSCR 2017" or scan the QR code below to download the mobile app:

Recordings Prohibited

Still photography, video and/or audio taping of the sessions, presentations and posters at the ISSCR 2017 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.

GENERAL INFORMATION

Speaker Ready Room

Speakers must review their uploaded presentations in the Speaker Ready Room (BCEC, Level 2, Room 204B) during the following times:

TUESDAY, 13 JUNE 14:00 – 18:00
WEDNESDAY, 14 JUNE 8:00 – 19:00
THURSDAY, 15 JUNE 8:00 – 19:00
FRIDAY, 16 JUNE 8:00 – 19:00
SATURDAY, 17 JUNE 8:00 – 16:30

Media Office

Credentialed members of the media may use work stations and wireless internet during posted hours in the Media Office (BCEC, Level 2, Room 204A). Please visit the Media Office for media panel details.

WEDNESDAY, 14 JUNE 8:00 – 16:00
THURSDAY, 15 JUNE 8:00 – 16:00
FRIDAY, 16 JUNE 8:00 – 16:00
SATURDAY, 17 JUNE 9:00 – 12:00

Coat Check

For your convenience, you may leave coats and bags at the designated area in BCEC, Level 1, North Lobby.

WEDNESDAY, 14 JUNE 8:00 – 21:00
THURSDAY, 15 JUNE 8:00 – 20:30
FRIDAY, 16 JUNE 8:00 – 20:30
SATURDAY, 17 JUNE 8:00 – 19:00

Food Court & Concession Stand

Attendees can purchase snacks and beverages in the Exhibit & Poster Hall's Food Court, accessible via Level 1, North Lobby. Hours of operation are:

WEDNESDAY, 14 JUNE 15:15 – 18:30
THURSDAY, 15 JUNE 11:00 – 18:00
FRIDAY, 16 JUNE 11:00 – 18:00
SATURDAY, 17 JUNE 11:00 – 16:00

During morning hours when the Exhibit & Poster Hall is closed, a Concession Stand in BCEC, North Lobby will be open on:

TUESDAY FROM 8:00 – 14:00
WEDNESDAY – FRIDAY FROM 8:00 – 17:00
SATURDAY FROM 8:00 – 16:00

BCEC Information Desk

Need help getting around the Boston Convention & Exhibition Center (BCEC)? For directions inside the BCEC, stop by the Public Safety/Information desk located on the east side of the North Lobby. Also, watch for the "Red Coat" guest service ambassadors at each entrance.

Pick up your copy of The BCEC Navigator, a helpful guide to the BCEC at the Information desk located on the east side of the North Lobby on Level 1.

Boston Convention and Visitors Bureau Hospitality Desk

Visit the Boston Convention and Visitors Bureau hospitality desk at the BCEC, Level 1, North Lobby by the main entrance to plan your dining, activities, and tours.

WEDNESDAY, 14 JUNE 13:00 – 18:00
THURSDAY, 15 JUNE 8:30 – 18:00
FRIDAY, 16 JUNE 8:30 – 18:00
SATURDAY, 17 JUNE 8:30 – 18:00

Smoking

Smoking is prohibited in the BCEC convention center.

Lost And Found

Please bring found items to the registration area (BCEC, Level 1, North Lobby). If you lost an item, stop by during registration hours for assistance.

Business Center

A FedEx Office business center is located just off the BCEC, Level 1, North Lobby. The normal business hours are MONDAY - TUESDAY 9:00 - 17:00, WEDNESDAY – FRIDAY 8:00 –18:00 and SATURDAY 8:00 – 19:00. The center does not accept exhibitor freight.

ATM Machines

There are three Citizen's Bank ATM machines, located in: BCEC, Level 1, North Lobby; BCEC, Level 1, Northeast Lobby near the Food Court; and BCEC, Exhibit Level, Southeast Lobby.

Mothers' Room

A private room is available in BCEC, Level 2, Room 255. Please follow onsite signage accordingly. The

Mothers' Room will be open WEDNESDAY, 14 JUNE THROUGH SATURDAY, 17 JUNE FROM 8:00 – 19:00. If you require access outside these hours, please visit the registration area.

Meeting Rooms

Sign up for first-come, first-served ISSCR ad hoc meeting rooms in BCEC, Level 2, Rooms 251, 254A, 254B, 252AB. Sign-up sheets are posted outside each room listing available time slots for each day. Informal seating areas are also available in ISSCR Central, Meet-Up Hubs, and ISSCR Lounge in the Exhibit & Poster Hall.

Parking and Valet

Self-parking is available for BCEC at the South Parking Lot, $17 a day for standard vehicles and $24 a day for oversized vehicles. Keep in mind that there is no 24-hour parking or overnight parking at the BCEC.

Valet service will be available at $30 per day.

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

Message Center

Post messages for friends and colleagues using the message board in the Job Match Lounge located in BCEC, Exhibition Hall A, Exhibit & Poster Hall. Please note we are unable to page meeting delegates. However, the most effective way to reach out to fellow attendees is through the ISSCR 2017 mobile app. Read more on page 1.

Job Opportunities

Post resumes and employment opportunities on the designated board in the Job Match Lounge located in BCEC, Exhibition Hall A, Exhibit & Poster Hall or online in the Job Match directory. Find out more about the brand new ISSCR Job Match opportunity on page 23.

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JOIN US AT THE PRESIDENTIAL SYMPOSIUM, WEDNESDAY, 14 JUNE FOR THE 2017 ISSCR AWARDS PRESENTATIONS

MCEWEN AWARD FOR INNOVATION

The McEwen Award for Innovation, supported by the McEwen Centre for Regenerative Medicine, recognizes original thinking and groundbreaking research pertaining to stem cells or regenerative medicine that opens new avenues of exploration towards the understanding or treatment of human disease or affliction.

The recipient of the 2017 McEwen Award for Innovation is Elaine Fuchs, PhD, Rebecca C. Lancefield Professor at The Rockefeller University, and Investigator, Howard Hughes Medical Institute, U.S., whose research has transformed understanding of skin stem cells and their application to regenerative medicine, genetic syndromes and cancers. She has developed many innovative approaches to analyze skin stem cells and their niches, and to dissect the complex controls that orchestrate how stem cells make and repair tissues and what goes awry in genetic conditions and malignancies.

Dr. Fuchs will present her research in Plenary VI, Tissue Regeneration and Homeostasis, on Saturday, 17 June, 9:00-11:20.

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 investigator in the early part of their independent career in stem cell research.

The 2017 recipient, Jayaraj Rajagopal, MD, Department of Internal Medicine, Center for Regenerative Medicine, Massachusetts General Hospital, Associate Professor, Harvard Medical School, Howard Hughes Faculty Scholar, U.S., has established himself as a young leader in the field of lung stem cells and lung repair, working with both mouse and human models. As a physician-scientist, Dr. Rajagopal has done genetic studies and lineage tracing in the mouse lung, and established a strong research program focused on the repair and regeneration of human lung tissue. His research has provided new insights into the progression of diseases such as asthma, Cystic Fibrosis, COPD, and lung cancers.

Dr. Rajagopal will present his research in Plenary VI, Tissue Regeneration and Homeostasis, on Saturday, 17 June, 9:00-11:20.

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.

George Q. Daley, MD, PhD, Dean, Harvard Medical School, and Professor, Stem Cell Transplantation Program, Boston Children's Hospital & Dana-Farber Cancer Institute, U.S. is this year's recipient of the award. An outstanding physician-scientist and leading public advocate for the responsible ethical oversight of human stem cell research, Dr. Daley has long been involved in promoting and upholding rigorous standards for the field. He initiated and played key roles in the formulation of three sets of ISSCR guidelines, for the Conduct of Human Embryonic Stem Cell Research (2006), the Clinical Translation of Stem Cells (2008), and Stem Cell Research and Clinical Translation (2016), which are in use around the world.

Dr. Daley will present in Plenary Session III, Stem Cells and Cancer, Thursday, 15 June, 9:00-11:20 and in Concurrent Session IVD, Ethics and Regulatory Considerations, Friday, 16 June, 13:15-15:15.

ISSCR TOBIAS AWARD LECTURE

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

Award winner John Dick, PhD, FRS, Canada Research Chair in Stem Cell Biology and Senior Scientist, University Health Network of Canada, Professor, University of Toronto, Canada, and Director, Program in Cancer Stem Cells, Ontario Institute for Cancer Research, has been a leader in the areas of normal stem cell and cancer stem cell biology over the last 30 years, and his discoveries have led to significant advances in cancer biology that have opened new areas of inquiry. By isolating human hematopoietic stem cells, Dr. Dick was able to study cellular and molecular mechanisms that regulate their function, and his method is now widely used by researchers around the world. Notably, Dr. Dick achieved a breakthrough finding that there are intrinsic differences in tumorigenic potential among cancer cells from the same tumor, and he expanded his work to include common solid cancers.

Dr. Dick will present his research in Plenary IV, Chromatin and RNA Biology, on Friday, 16 June, 9:00-11:20.

CONGRATULATIONS TO THE 2017 TRAVEL AWARD WINNERS

2017 ISSCR ZHONGMEI CHEN YONG TRAVEL AWARDS FOR SCIENTIFIC EXCELLENCE

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

Michalis Agathocleous
Yunus Alpagu
Amanda Andersson Rolf
Yaser Atlasi
Muneef Ayyash
Shiran Bar
Andrea Barabino
Raquel Bernad
Semir Beyaz
Charlotta Boiers
Nina Cabezas Wallscheid
Luiz Carlos Caires
Silvia Calpe
Katia Cheaito
Ya-Wen Chen
Hao Chiang
Seung-Ju Cho
Joshua Currie
Thomas Duncan
Ahmed El-Badawy
Carola Endes
Zhuoqing Fang
Iman Fares
Sisi Feng
Dustin Flanagan
Max Friesen
Tomas Gonzalez Hernandez
Shiri Gur-Cohen
Gulben Gurhan
Theodore Ho
Corey Hoffman
Kang-Chieh Huang
Elena Itskovich
Simon Joost
Sophia Kelaini
Yohei Korogi
Marja Koskuvi
Yuta Koui
Meng Li
Qing Li
Zhenrui Li
Jisun Lim
He Ling
Raphael Lis
Guang Liu
Wenxuan Liu
Fernando Lojudice
Carla Lopes
Catherine Lu
Janvie Manhas
Jerome Mertens
Nofar Mor
Carola Maria Morell
Yuki Morimoto
Taiki Nakajima
Mehrnaz Namiri
Bjoern Neumann
Yuzhe Niu
Toshiki Okubo
Meryem Ozgencil
Hetal Pandya
Sarita Panula
Michaela Patterson
Pengxu Qian
Lydia Reinhardt
Anne Robertson
Samuel Rowbotham
Ido Sagi
Jose Sardina
Kotaro Sasaki
Humayoon Satti
Simon Schafer
Michael Segel
Hayden Selvadurai
Mansoureh Shahsavani
Nadav Sharon
Jian Shu
Julianne Smith
Wenqian Song
Ralph Stadhouders
Hannah Stuart
Yogapriya Sundaresan
Hadiseh Taheri
Hiroyuki Tamiya
Marco Terrigno
Julia Tischler
Zuzana Tothova
Kathryn Tremble
Jessalyn Ubellacker
Jessica Vanslambrouck
Sandra Varum
Dan Vershkov
Jingqiang Wang
Curtis Warren
Abraham Weintraub
Ting Wu
Fang-Ju Wu
Mitsutoshi Yamada
Atilgan Yilmaz
Jason Yu
Luis Zurkirchen
Jan Zylicz

Recipients of the PLOS ONE Travel Awards

Nicole Edwards
Jonathan Henninger
Qing Cissy Yu

Recipients of the ISSCR Travel Awards

Sylwia Bobis-Wozowicz
Jose Hernandez-Trejo
Xin Huang
Isabela Pereira
Stephanie Protze
Wenbo Wu

CONGRATULATIONS TO THE ISSCR ABSTRACT MERIT AWARD RECIPIENTS

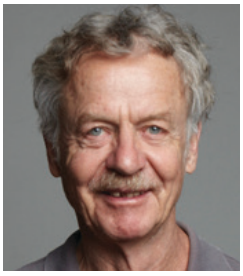
New this year, the ISSCR recognizes outstanding abstracts with the ISSCR Abstract Merit Awards. These awards recognize ISSCR Trainee members who have submitted distinguished abstracts, as judged by the ISSCR abstract reviewers.

Michalis Agathocleous
Yunus Alpagu
Amanda Andersson Rolf
Shiran Bar
Semir Beyaz
Luiz Carlos Caires
Joshua Currie
Iman Fares
Max Friesen
Casey Gifford
Simona Gribaudo
Shiri Gur-Cohen
Jonathan Henninger
Theodore Ho
Biao Huang
Elena Itskovich
Marja Koskuvi
Meng Li
Francois Mercier
Jerome Mertens
Carola Maria Morell
Yuki Morimoto
Bjoern Neumann
Toshiki Okubo
Michaela Patterson
Pengxu Qian
Anne Robertson
Samuel Rowbotham
Ido Sagi
Kotaro Sasaki
Christopher Schlieve
Hayden Selvadurai
Masamitsu Sone
Wenqian Song
Ralph Stadhouders
Zuzana Tothova
Daniel Wagner
Abraham Weintraub
Ole Wiskow
Fang-Ju Wu
Wenbo Wu
Atilgan Yilmaz
Erwei Zuo
Jan Zylicz

A DECADE OF IPSCS FROM DISCOVERY TO CLINIC

WEDNESDAY, 14 JUNE, PLENARY I

RUDOLF JAENISCH, *WHITEHEAD INSTITUTE FOR BIOMEDICAL RESEARCH AND MASSACHUSETTS INSTITUTE OF TECHNOLOGY, U.S.*



Rudolf Jaenisch, MD, is a Founding Member of the Whitehead Institute for Biomedical Research and a Professor of Biology at the Massachusetts Institute of Technology. He generated the first transgenic mice and has explored basic questions such as the role of DNA modification, genomic imprinting, X chromosome inactivation, and the mechanism of nuclear cloning. Major technologies used in the lab are gene-targeting approaches to edit DNA methylation as well as the sequences of target genes. The laboratory is renowned for its expertise in reprogramming cell fate and in using iPS cell technology to model human diseases such as Parkinson's, Alzheimer's and Autism. Dr. Jaenisch is a Member of the National Academy of Sciences and recipient of the first Peter Gruber Foundation Award in Genetics, the March of Dimes Award in Biology and of the United States National Medal of Science. In 2014 he was president of the ISSCR.

SHINYA YAMANAKA, *CENTER FOR IPS CELL RESEARCH & APPLICATION, KYOTO UNIVERSITY, JAPAN AND GLADSTONE INSTITUTES, U.S.*

Shinya Yamanaka, MD, PhD, is the Director of the Center for iPS Cell Research and Application (CiRA) at Kyoto University in Japan and a Senior Investigator at the Gladstone Institutes in the United States. He is most recognized for his discovery of induced pluripotent stem cells (iPSC), which are differentiated cells that have been reprogrammed to the pluripotent state. Since his breakthrough finding, he has been the recipient of prestigious awards including the Albert Lasker Basic Medical Research Award, the 100th Imperial Prize and Japan Academy Prize, the Wolf Prize in Medicine, the ISSCR McEwen Centre Award for Innovation and the Breakthrough Prize in Life Sciences. The significance of iPSC was culminated with Dr. Yamanaka being awarded the Nobel Prize in 2012.

JOANNA WYSOCKA, *STANFORD UNIVERSITY, U.S.*

Joanna Wysocka, PhD, is an Associate Professor in the Department of Chemical and Systems Biology and the Department of Developmental Biology at Stanford University. Research in the Wysocka lab focuses on understanding the mechanistic basis by which covalent histone modifications regulate gene expression patterns during vertebrate development and differentiation. A second major area of interest involves chromatin regulation in embryonic stem cells (ESCs), molecular basis of pluripotency and role of histone methyltransferases in cell fate decisions. Dr. Wysocka is a recipient of numerous awards, including the Searle Scholar Award, W.M. Keck Foundation Distinguished Young Scholar Award, 2010 International Society for Stem Cell Research Outstanding Young Investigator Award, and 2013 Vilcek Prize for Creative Promise.

FEATURED SPEAKERS

ANNE MCLAREN MEMORIAL LECTURE

WEDNESDAY, 14 JUNE, PLENARY I

MAGDALENA ZERNICKA-GOETZ, *UNIVERSITY OF CAMBRIDGE, U.K.*

Magdalena Zernicka-Goetz, PhD, was educated at the University of Warsaw and at the University of Oxford and started her group at the University of Cambridge in 1997 where she is a Professor of Mammalian Development and Stem Cell Biology. She studies the fate determining mechanisms by which cells transit from totipotency through distinct states of pluripotency towards differentiation to build the body. Most recently she established the first 3D platform for development of mouse and human embryos outside the mother as they initiate body formation. This work has been recognized by Zernicka-Goetz's election to EMBO Membership and the Academy of Medical Sciences.

ERNEST MCCULLOCH MEMORIAL LECTURE

WEDNESDAY, 14 JUNE, PLENARY II

MARGARET GOODELL, *BAYLOR COLLEGE OF MEDICINE, U.S.*

Margaret ("Peggy") Goodell, PhD, is a Professor and Director of the Stem Cells and Regenerative Medicine Center at Baylor College of Medicine, in Houston, Texas. Goodell's current research is focused on the fundamental genetic and epigenetic mechanisms that regulate hematopoietic stem cells, and how those regulatory mechanisms go awry in hematologic malignancies, with a particular focus on DNA methylation. Goodell has received the Edith and Peter O'Donnell Award in Medicine in 2011, and the Damashek Prize from the American Society of Hematology in 2012. She serves on the Board of Directors for the Keystone Symposia, is an Associate Editor for Blood, and serves on the editorial boards of Cell Stem Cell and PLoS Biology. Dr. Goodell directs a laboratory of about 15 students and post-doctoral fellows.

WEDNESDAY, 14 JUNE, PLENARY II

SANFORD GREENBERG, *CHAIRMAN, BOARD OF GOVERNORS, JOHNS HOPKINS WILMER EYE INSTITUTE, U.S.*

Blind at 19, Sanford Greenberg graduated Columbia (Phi Beta Kappa), following a Marshall Scholarship at Oxford, received his M.A. and Ph.D. at Harvard and M.B.A. at Columbia. A Johnson White House Fellow; Chairman, Federal Rural Healthcare Corporation; Member, National Science Board; Johns Hopkins Trustee and Chairman of its Wilmer Eye Institute Board; Council Foreign Relations; Fellow, American Academy of Arts and Sciences. His career as inventor, entrepreneur and investor began when he invented the speech-compression machine, later creating the first database tracking antibiotic resistance globally. Furthering his lifelong aspiration, he instituted a prize for research toward ending blindness for all mankind.

KEYNOTE ADDRESS

WEDNESDAY, 14 JUNE, PLENARY II

LAURIE H. GLIMCHER, *DANA-FARBER CANCER INSTITUTE, HARVARD CANCER CENTER AND HARVARD MEDICAL SCHOOL, U.S.*

Laurie H. Glimcher, MD, is President and CEO of Dana-Farber Cancer Institute, Principal Investigator and Director of Dana-Farber/Harvard Cancer Center, and Professor of Medicine at Harvard Medical School. As an immunologist, her primary research interests are elucidating the molecular pathways that regulate the immune system, critical for both the development of protective immunity and for the pathophysiologic immune responses underlying autoimmune, infectious and malignant diseases. She is a Fellow of the American Academy of Arts and Sciences, a Member of the National Academy of Medicine and a Member of the National Academy of Sciences. Dr. Glimcher sits on the Corporate Board of Directors of the Bristol-Myers Squibb Pharmaceutical Corporation and the Waters Corporation.

JOHN MCNEISH MEMORIAL LECTURE

SATURDAY, 17 JUNE, PLENARY VII

ADRIAN THRASHER, *UNIVERSITY COLLEGE LONDON, GREAT ORMOND STREET INSTITUTE OF CHILD HEALTH, U.K.*

Adrian Thrasher, MD, BS, FRCP, MRCPCH, is Professor of Paediatric Immunology and Wellcome Trust Principal Research Fellow at the UCL Institute of Child Health, and Honorary Consultant Paediatric Immunologist at Great Ormond Street Hospital for Children NHS Foundation Trust. He is the Programme Head of the Infection, Immunity and Inflammation Academic Programme at ICH and has a long standing research and clinical interest in development and application of gene therapy. He is Director of the Clinical Gene Therapy Programme, and Theme Leader of the Gene Stem and Cellular Therapies theme of the Biomedical Research Centre, at ICH / GOSH. Thrasher is Principal Investigator on several clinical trials for immunodeficiency and is director of the clinical gene therapy GMP facility, managing a team of trial coordinators, clinical scientists, and quality systems personnel.

His clinical interests are the diagnosis and treatment of patients with primary immunodeficiency. His specialist interests are in the Wiskott-Aldrich Syndrome (WAS), disorders of innate immunity, and Autoimmune Lymphoproliferative Syndrome. His team at ICH/GOSH are conducting trials of somatic gene therapy for various forms of PID including SCID-X1, CGD, ADA-SCID, and WAS. Research interests include the pathophysiology of primary immunodeficiency syndromes especially WAS, the actin cytoskeleton in haematopoietic cells, the development of somatic gene therapy, and thymus transplantation.

FEATURED SPEAKERS

KEYNOTE ADDRESS

SATURDAY, 17 JUNE, PLENARY VII

GEORGE CHURCH, *HARVARD MEDICAL SCHOOL, HARVARD UNIVERSITY AND THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, U.S.*

George Church, PhD, is Professor of Genetics at Harvard Medical School and Professor of Health Sciences and Technology at Harvard and the Massachusetts Institute of Technology (MIT). He is Director of the U.S. Department of Energy Center on Bioenergy at Harvard and MIT and Director of the National Institutes of Health Center of Excellence in Genomic Science at Harvard. Dr. Church is widely recognized for his innovative contributions to genomic science and his many pioneering contributions to chemistry and biomedicine. In 1984, he developed the first direct genomic sequencing method, which resulted in the first commercial genome sequence (the human pathogen, H. pylori). He helped initiate the Human Genome Project in 1984 and the Personal Genome Project in 2005. Dr. Church invented the broadly applied concepts of molecular multiplexing and tags, homologous recombination methods, and array DNA synthesizers.

SCHEDULE AT A GLANCE

REGISTRATION OPEN	
Tuesday, 13 June	14:00 – 18:00
Wednesday, 14 June	7:30 – 20:30
Thursday, 15 June	8:15 – 18:30
Friday, 16 June	8:15 – 18:30
Saturday, 17 June	8:15 – 18:30

EXHIBIT HALL OPEN	
Wednesday, 14 June	15:15 – 20:30
Thursday, 15 June	11:00 – 20:00
Friday, 16 June	11:00 – 20:00
Saturday, 17 June	11:00 – 16:00

TUESDAY, 13 JUNE	
8:30 - 12:00	ISSCR Workshop on Clinical Translation
13:00 - 17:00	Clinical Advances in Stem Cell Research
15:00 - 16:30	Attendee Orientation
18:30 - 20:30	Public Symposium

WEDNESDAY, 14 JUNE	
8:30 - 10:00	Attendee Orientation
9:00 - 12:00	Focus Sessions
11:30 - 12:45	Early Career Group Leader Luncheon
13:00 - 15:15	Plenary I Presidential Symposium: A Decade of iPSCs from Discovery to Clinic
15:15 - 16:00	Refreshment Break
15:15 - 18:30	Poster Set Up
15:15 - 20:30	Exhibit Hall Open
16:00 - 18:10	Plenary II: Organogenesis- Making Tissues and Organs
18:10 – 20:30	Opening Reception
18:30 - 20:30	Poster Session I
21:00 - 00:00	Junior Investigator Social Night

THURSDAY, 15 JUNE	
8:00 - 8:30	Innovation Showcases
8:15 - 9:00	Morning Coffee
9:00 - 11:20	Plenary III: Stem Cells and Cancer
11:00 - 20:00	Exhibit Hall Open
11:15 - 13:15	Poster Set Up

SCHEDULE AT A GLANCE

11:30 - 12:30	Innovation Showcases
11:30 - 13:00	Lunch Break
11:30 - 13:00	Meet the Experts Luncheon
13:15 - 15:15	Concurrent Sessions IA - G
15:15 - 16:00	Meet-up Hubs
15:15 - 16:00	Refreshment Break
16:00 - 18:00	Concurrent Sessions IIA - G
18:00 - 20:00	Poster Session II and Reception

FRIDAY, 16 JUNE	
8:00 - 8:30	Innovation Showcases
8:15 - 9:00	Morning Coffee
9:00 - 11:20	Plenary IV: Chromatin and RNA Biology in Stem Cells
11:00 - 20:00	Exhibit Hall Open
11:15 - 13:15	Poster Set Up
11:30 - 12:30	Innovation Showcases
11:30 - 13:00	Lunch Break
11:30 - 13:00	Meet the Experts Luncheon
13:15 - 15:15	Concurrent Sessions IIIA - G
15:15 - 16:00	Meet-up Hubs
15:15 - 16:00	Refreshment Break
16:00 - 18:00	Plenary V: Stem Cells - Stress, Senescence and Aging
18:00 - 20:00	Poster Session III and Reception

SATURDAY, 17 JUNE	
8:15 - 9:00	Morning Coffee
9:00 - 11:05	Plenary VI: Tissue Regeneration and Homeostasis
11:00 - 16:00	Exhibit Hall Open
11:20 - 13:15	Lunch Break
11:30 - 13:00	Junior Investigator Career Panel Luncheon
13:15 - 15:15	Concurrent Sessions IVA - G
15:15 - 16:00	Refreshment Break
16:00 - 18:30	Plenary VII: Frontiers of Cell Therapy

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- 3D cell culture scaffolds
- Tissue specimen biorepository
- NutriStem™ medium for iPSC
- Differentiation reagents
- Hepato-, Cardio-, Neuronal cells

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Poster Abstract ID #290238 – "Application of Human Patient-Derived Induced Pluripotent Stem Cells (iPSCs) to study the Role of Neurite Inhibition and Mechanisms of Recovery in Alzheimer's Disease", by Prof Stefan Przyborski et al.

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NETWORKING AT A GLANCE

What better way to nurture your research and career than networking? ISSCR 2017 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. ISSCR understands our members' needs and offers various avenues to help scientists foster and strengthen their professional networks. Here is a quick glance at what ISSCR 2017 has to offer.

TUESDAY, 13 JUNE

15:00 – 16:30
Attendee Orientation
BCEC, Level 1, North Lobby

Whether a first-time attendee or an experienced annual meeting regular, join fellow peers as ISSCR staff and engaged ISSCR members walk through the helpful facts about the meeting so you can optimize your ISSCR 2017 experience and work with other attendees to solve a fun challenge. You may even walk away with a prize.

WEDNESDAY, 14 JUNE

8:30 – 10:00
Attendee Orientation
BCEC, Level 1, North Lobby

If you missed Tuesday's orientation, attendees have a second chance to learn how to navigate ISSCR 2017. Whether a first-time attendee or an experienced annual meeting regular, join fellow peers as ISSCR staff and engaged ISSCR members walk through the helpful facts about the meeting so you can optimize your ISSCR 2017 experience and work with other attendees to solve a fun challenge. You may even walk away with a prize.

11:30 – 12:45
Early-Career Group Leader Luncheon – The Review Process and Reality of Getting Published
BCEC, Level 3, Ballroom Lobby

This is a ticketed event that requires pre-registration. To learn more, see page 23.

15:15 – 20:30
Exhibit Hall
BCEC, Exhibition Hall A, Exhibit & Poster Hall

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 24. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

18:30 – 20:30
Poster Session I and Opening Reception
BCEC, Exhibition Hall A, Exhibit & Poster Hall

Sponsored by Medicine by Design/University of Toronto

Browse through 500 posters on Day 1 as you find other attendees interested in the topics of your research while you discover new data and research. Complimentary light snacks and wine/beer available.

21:00 – 00:00
Junior Investigator Networking Social Night
Royale Nightclub, 279 Tremont St, Boston, MA 02116

This is a ticketed event that requires pre-registration. To learn more, see page 24.

THURSDAY, 15 JUNE

11:00 – 20:00
Exhibit Hall
BCEC, Exhibition Hall A, Exhibit & Poster Hall

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 24. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

11:30 – 13:00
Meet the Experts Luncheon
BCEC, Level 3, Ballroom Lobby

This is a ticketed event that requires pre-registration. To learn more, see page 24.

15:15 – 16:00
German Stem Cell Network
Exhibit Hall – Meet-up Hub #1

The German Stem Cell Network (GSCN) invites German scientists to stop by the Meet-up Hub and get information on what is new in the GSCN and discuss your needs and wishes.

15:15 – 16:00
Bedford Research Foundation
Exhibit Hall – Meet-up Hub #2 [Meet-up Hub #2 is supported by the Bedford Research Foundation]

The Bedford Research Foundation is hosting this meet up hub to discuss its findings with stem cell development and Circadian Rhythms. The Foundation is working to determine what role circadian rhythms play in stem cell development, and we are focusing on parthenote stem cells for their ease of genetic modification in this research.

18:00 – 20:00
Poster Session II and Reception
BCEC, Exhibition Hall A, Exhibit & Poster Hall

Browse through 500 posters on Day 2 as you find other attendees interested in the topics of your research while you discover new data and research. Complimentary light snacks and wine/ beer available.

FRIDAY, 16 JUNE

11:00 – 20:00
Exhibit Hall
BCEC, Exhibition Hall A, Exhibit & Poster Hall

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 24. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

11:30 – 13:00
Meet the Experts Luncheon
BCEC, Level 3, Ballroom Lobby

This is a ticketed event that requires pre-registration. To learn more, see page 24.

15:15 – 16:00
Meet the Editors of Stem Cell Reports
Exhibit Hall – Meet-up Hub #1

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

18:00 – 20:00
Poster Session III and Reception
BCEC, Exhibition Hall A, Exhibit & Poster Hall

Browse through 500 posters on Day 3 as you find other attendees interested in the topics of your research while you discover new data and research. Complimentary light snacks and wine/ beer available.

SATURDAY, 17 JUNE

11:00 – 16:00
Exhibit Hall
BCEC, Exhibition Hall A, Exhibit & Poster Hall

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 24. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

11:30 – 13:00
Career Panel Luncheon – Translate Your Idea
BCEC, Level 3, Ballroom Lobby

Sponsored by Stem Cell Program at Boston Children's Hospital

This is a ticketed event that requires pre-registration. To learn more, see page 24.

MOBILE APP GUIDE

Take the first step to a successful networking strategy by reaching out to researchers attending ISSCR 2017 via our free mobile app. To learn how to download the ISSCR 2017 mobile app, refer to page 1. By using this mobile app you can connect directly with other scientists you meet during the annual meeting so you can continue the conversation well after ISSCR is over.

Your Profile

Be sure you create a profile within the ISSCR 2017 mobile app and expand your professional network during the annual meeting.

ISSCR CENTRAL

Meet up with fellow ISSCR members at ISSCR Central. Make this your central meeting location while you collaborate with colleagues, view your email, and establish your meeting agenda.

Learn all that membership in the ISSCR delivers at ISSCR Central:

- ISSCR Hall of Discovery
- Browse through fun facts detailing ISSCR's 15th anniversary
- Meet with a Melbourne representative to learn more about the host city for ISSCR 2018
- Stem Cell Report's commemorative issue

MEET-UP HUBS

Meet and interact with attendees who share a common interest during an attendee-driven Meet-up Hub. These are casual, scheduled meeting times for attendees with a shared interest to meet.

JOB MATCH

This innovative opportunity connects job seekers with principal investigators and industry professionals who are looking to hire. Potential matches can connect virtually prior to the annual meeting and then meet face-to-face in Boston in the BCEC.

Annual meeting attendees can opt in to Job Match at any time, and there is no additional fee. During online registration, job seekers will be asked questions about their expertise, and employers will be asked about their open positions. Visit the Job Match Directory to browse potential matches and filter by geography, field, technical expertise and more. Employers can view CVs of potential matches, and job seekers can view open positions. Make plans to meet potential matches at the annual meeting.

The Job Match Lounge and ISSCR Central will be open in the Exhibit Hall during Exhibit Hall hours. Tables and chairs will be available in these areas on a drop-in basis. Six private meeting rooms will be available on a first come first served basis. Visit www.isscr2017 for details.

EARLY-CAREER GROUP LEADER LUNCHEON

THE REVIEW PROCESS AND REALITY OF GETTING PUBLISHED

WEDNESDAY, 14 JUNE 11:30 – 12:45
BCEC, Level 3, Ballroom Lobby

Discovery keeps us excited, and publishing the discoveries allows us to share that work with others. Publishing also happens to be essential for our career! Yet, on our academic journey, training is focused on executing the most rigorous and exciting science, with very little training on the mechanics of publication and the broader aspects of science communication. Complicating this are the biases that junior investigators may face breaking into the publishing sphere. Take advantage of this unique opportunity to participate in small group discussions with members of the ISSCR Board of Directors, editors of high-impact scientific publications, and members of the ISSCR Junior Investigators Committee.

This is a ticketed event that requires pre-registration.

JUNIOR INVESTIGATOR NETWORKING SOCIAL NIGHT

WEDNESDAY, 14 JUNE 21:00 – 00:00

Trainee members kick off ISSCR 2017 with a bang at the Junior Investigator Networking Social Night. Young investigators from around the world meet, mingle, dance and socialize during this fun-filled night of entertainment taking place at Royale nightclub.

Venue: Royale Nightclub
Address: 279 Tremont St, Boston, MA 02116

What to Expect

21:00 - 22:30	Networking "Meet & Mingle" (light snacks will be provided)
22:30 - 22:40	Thank You from the ISSCR Junior Investigators Committee
22:40 - 00:00	DJ Spins & JIs Dance

This is a ticketed event that requires pre-registration. ISSCR annual meeting badge and photo ID required for entry. Must be age 21 or older to attend. *Transportation will not be provided by ISSCR to the venue.* Attendees are encouraged to use public transportation or taxi service.

MEET THE EXPERTS LUNCHEONS

THURSDAY, 15 JUNE AND FRIDAY, 16 JUNE, 11:30 – 13:00
BCEC, Level 3, Ballroom Lobby

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

Registration is required. A nominal fee applies.

CAREER PANEL LUNCHEON

TRANSLATE YOUR IDEA
Sponsored by Stem Cell Program at Boston Children's Hospital

Boston Children's Hospital
Stem Cell Program

SATURDAY, 17 JUNE, 11:30 – 13:00
BCEC, Level 3, Ballroom Lobby

Junior Investigators are invited to join the ISSCR Junior Investigators Committee and a panel of experts for an in-depth discussion in a casual lunch setting. Registration is required. A nominal fee applies.

Discoveries in stem cell biology at the bench can lead to advances in regenerative medicine in the clinic, and improved therapies for patients. But how does clinical translation work? How can you move your idea from bench to bedside? What does it take to start a company? When is it appropriate to start a company? Come join us for this year's career panel discussion where we will explore this topic. Our panelists represent a diverse set of scientists and physicians who have created their own venture and brought their ideas to the clinic. Come learn how to translate your idea.

MODERATOR
Julia Tischler, PhD
Gurdon Institute Cambridge, U.K.
Member, ISSCR Junior Investigators Committee

PANELISTS
Agnieszka Czechowicz, MD, PhD
Stanford University, U.S.

Luigi Naldini, MD, PhD
San Raffaele Telethon Institute for Gene Therapy, Italy

Trista North, PhD
BIDMC, Harvard Medical School, U.S.

Masayo Takahashi, MD, PhD
RIKEN Center for Developmental Biology, Japan

FOCUS SESSIONS

WEDNESDAY, 14 JUNE 9:00 – 12:00

Focus sessions are parallel, in-depth educational opportunities in science, society and education organized by members and open to all annual meeting attendees. Advance registration is not required. Exact times may vary.

Translational Horizons of Pluripotent Stem Cell Technology

BCEC, Level 2, Room 205A
Presented by BlueRock Therapeutics

BlueRock Therapeutics is a new biotechnology start up funded by Bayer and Versant Ventures, with a translational focus on neurodegenerative disease (Parkinson's) and congestive heart failure disease (CHF). The company platform is based on strong developmental biology from its scientific co-founders, Dr Gordon Keller (Univ Toronto) and Dr Lorenz Studer (Memorial Sloan Kettering).

BlueRock is applying highly innovative tools in building a pluripotent stem cell (iPSC) platform that can deliver cellular therapeutics broadly in degenerative diseases. BlueRock will present their translational approach and emphasize key elements in a successful model for engaging the academic community and young scientists.

AGENDA:

9:00 WELCOME AND INTRODUCTIONS TO THE BLUEROCK TEAM
Emile Nuwaysir, PhD, *CEO*
Robert Deans, PhD, *Chief Technology Officer*
Eric Soller, PhD, *VP Corporate Development*

9:30 BLUEROCK THERAPEUTICS – INTRODUCING OUR MISSION IN TRANSLATIONAL MEDICINE
Robert Deans, PhD, *CTO BlueRock Therapeutics, Cambridge MA*

10:00 TRANSLATING DEVELOPOMENTAL BIOLOGY TO NEW THERAPEUTIC APPLICATIONS
Gordon Keller, PhD, *McEwen Center for Regenerative Biology, Toronto ON*

10:45 SYNTHETIC BIOLOGY IMPACT ON NEXT GENERATION BIOPROCESSING AND CELL DESIGN
Peter Zandstra, PhD, *University of Toronto, Toronto ON*

11:30 PANEL DISCUSSION (speakers and additional invitees)

12:00 CLOSE

Off-the-Shelf Natural Killer Cell Cancer Immunotherapy

BCEC, Level 2, Room 258AB
Presented by Fate Therapeutics

This session will provide an in-depth analysis of the recent progress and therapeutic potential of natural killer (NK) cell immunotherapy and the application of induced pluripotent stem cell (iPSC) technology for the development of transformative, off-the-shelf cellular immunotherapies, including engineered NK cell immunotherapies, for cancer. The speakers will cover topics spanning basic research to clinical development including:

- Overview of NK cell therapy
- Recent advancement in NK cell therapy
- Disruptive potential of iPSC-derived, engineered NK- and T-cell immunotherapies for treatment of cancer

This session is for scientists, clinicians, and product planning professionals interested in stem cell biology, cancer immunotherapy and related fields in capacities spanning basic research, translational medicine and commercialization.

AGENDA:

9:00 WELCOME
Dan Shoemaker, PhD, *Chief Scientific Officer, Fate Therapeutics, Inc.*

9:15 NOVEL STRATEGIES TO ACTIVATE AND TARGET NK CELLS TO TREAT CANCER
Jeff Miller, MD, *Deputy Director, Masonic Cancer Center, Deputy Director, Clinical and Translational Sciences Institute, Director of Cancer Experimental Therapeutics Initiative, University of Minnesota*

10:10 NEW INSIGHTS INTO THE FUNCTIONAL DIVERSIFICATION OF HUMAN NK CELLS
Kalle Malmberg, MD, PhD, *Group Leader of Natural Killer Cell Biology and Cell Therapy, Department of Immunology Oslo University Hospital*

10:40 ADVANCES IN NATURAL KILLER CELL DEVELOPMENT FROM HUMAN PLURIPOTENT STEM CELLS
Dan Kaufman, MD, PhD, *Professor of Medicine, Division of Regenerative Medicine, Director of Cell Therapy, University of California, San Diego*

11:10 HNCD16-NK CELLS: OFF-THE-SHELF IMMUNOTHERAPEUTIC CORNERSTONE APPROACH FOR SOLID AND LIQUID TUMORS
Bob Valamehr, PhD, *Vice President, Cancer Immunotherapy, Fate Therapeutics, Inc.*

11:40 CLOSING REMARKS
Dan Shoemaker, *PhD, Chief Scientific Officer, Fate Therapeutics, Inc.*

Progress of the Cutting-Edge Technologies in Regenerative Medicine

BCEC, Level 2, Room 258C
Presented by Healios K.K.

This session is organized by HEALIOS K.K. (https://www.healios.co.jp/en/) and will provide five hot topics, inspired with "Creation", to highlight remarkable progress in regenerative medicine, which will be "Key" to provide significant benefit to patients suffering from unmet medical needs.

The speakers, global key opinion leaders of selected topics, will cover emerging topics in stem cell-based regenerative medicine.

This session is for scientists and clinicians interested in regenerative medicine with stem cell technologies, and will span basic research, translational medicine, and relevant business strategies.

AGENDA:

9:00 WELCOME AND OPENING REMARKS
Hardy TS Kagimoto, MD, *President & CEO, HEALIOS K.K., Japan*

9:05 CHAIN OF INNOVATIONS - THE FUTURE VISION OF IPS THERAPY
Hardy TS Kagimoto, M.D., *President & CEO, HEALIOS K.K., Japan*

9:40 THE STATE-OF-ART OF HUMAN IPSC-DERIVED ORGAN BUD BASED APPROACHES
Takanori Takebe, MD, *Cincinnati Children's Hospital Medical Center, Yokohama City University, Japan*

10:15 FUNCTIONAL EGGS CREATED IN A DISH FROM MOUSE PLURIPOTENT STEM CELLS
Katsuhiko Hayashi, PhD, *Kyushu University, Japan*

10:50 GLIAL PROGENITOR CELL-BASED TREATMENT OF NEURODEGENERATIVE DISEASE
Steve Goldman, MD, PhD, *University of Rochester and the University of Copenhagen*

11:25 ENGINEERING PLURIPOTENT STEM CELLS TO ESCAPE ALLOGENEIC REJECTION
David Russell, MD, PhD, *CSO and Co-Founder of Universal Cells Inc., University of Washington*

Tools for Basic and Applied Research

BCEC, Level 2, Room 253ABC
Presented by STEMCELL Technologies and Thermo Fisher Scientific

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

1) Selected presentations from Stem Cell COREdinates member labs highlighting disease modeling and cell therapies. (Session Chair: Mark Tomishima, SKI Stem Cell Research Facility)

2) Panel discussion on pluripotent stem cell-based therapies. The panel will include members of groups that are actively developing and manufacturing cell therapies.

This session is for ISSCR members with an interest in pluripotent stem cell applications.

AGENDA

9:00 OVERVIEW OF COREDINATES

9:05 CRYOPAUSE: A NEW METHOD TO IMMEDIATELY INITIATE EXPERIMENTS AFTER CRYOPRESERVATION OF PLURIPOTENT STEM CELLS
Mark Tomishima, *Sloan Kettering Institute*

9:20 TBD
TBD, *STEMCELL Technologies*

9:30 A SCALABLE AND AUTOMATABLE PLATFORM FOR CAS9-CRISPR GENOME EDITING IN HIPSCS
Thorsten Schlaeger, *Boston Children's Hospital*

9:45 A LARGE DIVERSE COLLECTION OF HIPSCS AND DIFFERENTIATED HEPATOCYTE-LIKE CELLS UNCOVER FUNCTIONAL GENETIC VARIATION AT BLOOD LIPID-ASSOCIATED LOCI
Wenli Yang*, University of Pennsylvania*

10:00 THE RAPIDLY EVOLVING TOOLBOX IN THE WORLD OF PLURIPOTENT STEM CELLS: KEEPING IT CURRENT
Deborah French*, Children's Hospital of Philadelphia*

10:15 GENOME ENGINEERING TO INTRODUCE A FLUORESCENT REPORTER INTO HUMAN PLURIPOTENT STEM CELLS TO STUDY CARDIAC DISEASE
Lise Munsie, *CCRM, Thermo Fisher Scientific*

10:30 APPROACHES TO GENERATE CLINICAL GRADE IPS LINES
Laurence Daheron, *Harvard Stem Cell Institute*

10:45-11:00 BREAK

11:00-12:00: PANEL DISCUSSION: STRATEGIES, CHALLENGES AND OPPORTUNITIES FOR PLURIPOTENT STEM CELL-BASED THERAPIES
Session Chair: Stefan Irion, *Sloan Kettering Institute*

Panel:
Robert Millman, JD, *CEO, Semma Therapeutics*

Jeffrey Stern, MD, PhD, *PI/Director of Translational Research/Co-Founder of the Neural Stem Cell Institute*

Eric Roos, *Strategic Alliances Leader, Cell Therapy at Thermo Fisher Scientific*

Neurological Disorders: Transforming the Landscape with hPSC Modeling

BCEC, Level 2, Room 205BC
Presented by WiCell

There are more than 600 diseases and disorders that affect the nervous system, often resulting in dramatic, long-term impact on patents and their families. Research to improve our understanding of and advance our ability to treat neurological disease is essential. Recently there has been an explosion in the number of patient-derived iPS disease model cell lines available to researchers. These model systems can be used to elucidate underlying mechanisms of disease, investigate genetic impact on disease phenotype, screen drug candidates, investigate therapies, and move toward cures. This session will focus on recent advances in the field of neurological disease and disorder using pluripotent stem cell modeling as a tool for investigation. Speakers include those working on specific diseases and disorders (including Parkinson's disease, neuropsychiatric disorders, Alzheimer's disease, ALS, etc.), as well as those working at the stem cell-biomaterial interface to improve disease modeling.

This session is for investigators with a neural focus, and those interested in PSC disease modeling.

AGENDA

9:00 BRAIN ORGANOIDS: OPPORTUNITIES AND LIMITATIONS FOR THE STUDY OF NEURODEVELOPMENTAL ABNORMALITIES
Dr. Thomas Zwaka, *Mt Sinai School of Medicine, USA*

9:25 USING IPSCS TO DISSECT PATHWAYS, DISCOVER NEW THERAPEUTICS AND DEVELOP MODELS FOR LATE ONSET, SPORADIC ALZHEIMER'S DISEASE
Dr. Jessica Young, *University of Washington, USA*

9:50 IDENTIFICATION OF THERAPEUTIC TARGETS FOR ALS USING CHEMICAL AND GENETIC SCREENS ON PATIENT-DERIVED NEURAL CULTURES
Dr. Justin Ichida, *University of Southern California, USA*

10:15 IN VITRO MODEL OF THE HUMAN POSTERIOR CENTRAL NERVOUS SYSTEM
Maria Estevez, *Ashton Laboratory; University of Wisconsin, USA*

10:35-10:45 BREAK

10:45 DIFFERENTIAL ASTROCYTE ACTIVATION INDUCED BY A FAMILIAL ALZHEIMER'S DISEASE MUTATION IN NEURAL CULTURES OF DIFFERENT REGIONAL FATES
Dr. Tracy Young-Pearse, *Brigham and Women's Hospital, USA*

11:10 EFFECTS OF MUTATIONS LINKED TO AUTISM IN ES CELL DERIVED HUMAN NEURONS
Dr. Marius Wernig, *Stanford University, USA*

11:35 TBD
Dr. Lorenz Studer, *Memorial Sloan Kettering, USA*

ETHICAL IMPLICATIONS OF ORGANOID TECHNOLOGY

BCEC, Level 3, Ballroom East
Presented by the ISSCR Ethics Committee

Newly emerging technologies to derive human organoids from pluripotent and adult stem cells as organoids in vitro raise enormous scientific possibilities. Organoids have the potential to impact and modify the entire innovation cycle in biomedical research. Investigating human development and disease and testing compounds directly on human tissue without the need for animal experimentation promises to overcome substantial scientific and ethical limitations of current research methods. As organoids model the development and maintenance of a human organ in vitro, they have the potential to revolutionize biomedical research and to change the drug discovery process. Patient-derived organoids offer possibilities to mimic pathologies of human genetic disorders and develop personalized treatment, be it for hereditary or acquired diseases. Organoids have the potential to impact and modify the entire innovation cycle in biomedical research, including the fields that have been subject of intense ethical debate.

In this session, we will explore the socio-ethical implications of organoid technology. Five speakers will present scientific, ethical and regulatory challenges followed by a moderated debate.

MODERATOR:
Megan Munsie, PhD
Stem Cells Australia/University of Melbourne
Member, ISSCR Ethics Committee

AGENDA

9:00 – 9:05 Introduction & Welcome
Annelien Bredenoord, PhD
University Medical Center Utrecht, Netherlands
Chair, ISSCR Ethics Committee

9:05 – 9:20 The Science Behind Organoid Technology I: Adult Stem Cell-based Organoids
Hans C. Clevers, MD PhD
Hubrecht Institute, Netherlands

9:20 – 9:35 The Ethics of Organoid Biobanking & Transplantation
Annelien Bredenoord, PhD

9:35 – 9:45 Questions & Answers

9:45 – 10:00 The Science Behind Organoid Technology II: Pluripotent Stem Cell-based Organoids
Melissa Little, PhD
Murdoch Children's Research Institute, Australia

10:00 – 10:15 The Ethics of Pluripotent Stem Cell-based Organoids & Gastruloids
Insoo Hyun, PhD
Case Western Reserve University, U.S.
Member, ISSCR Ethics Committee

10:15 – 10:25 Questions & Answers

10:25 – 10:45 Break

10:45 – 11:00 The Science Behind Brain Organoids
Julia Ladewig, PhD
University of Bonn, Germany

11:00 – 11:15 The Ethics of Brain Organoids: A Neurosurgeon's Perspective
Marike Broekman, MD, PhD
Harvard Medical School, U.S.

11:15 – 11:55 Moderated Discussion
Megan Munsie, PhD

11:55 – 12:00 Wrap Up
Megan Munsie, PhD, and Annelien Bredenoord, PhD

FROM THE BENCH TO THE CLINIC: HOW TO MANUFACTURE YOUR CELL PRODUCT

BCEC, Level 3, Ballroom West
Presented by the ISSCR Industry Committee

This focus session will explore the process of cell product manufacturing. Speakers from industry, academics and the FDA will discuss the rigors and pitfalls of the translational process and the key steps in the manufacturing process, including GMP requirements, process development, quality control and product validation. The final presentation will discuss future directions and challenges in a case study in cardiovascular repair.

9:00 – 9:05 Introduction & Welcome
Nils Pfaff, PhD
Bayer, Germany
Member, ISSCR Industry Committee

9:05 – 9:30 Understanding the Rigors and Pitfalls of the Translation Process: A Case Study on the Importance of Manufacturing Process Development
Robert Preti, PhD
Caladrius Biosciences, USA

9:30 – 9:55 GMP Requirements and CMC Submissions
Donald Fink, PhD
U.S. Federal Department of Agriculture (U.S. FDA), USA

9:55 – 10:20 Cell Production: Process Development, Selection and Qualification of Manufacturing Equipment and Materials, and Outsourcing Considerations
Isabelle Rivière, PhD
Memorial Sloan Kettering Cancer Center, USA

10:20 – 10:45 Product Testing and Release Criteria: The Importance of Analytical Method Development and Validation, Including Potency Assays
Beata Surmacz-Cordle, PhD
Catapult Cell and Gene Therapy, UK

10:45 – 10:55 Break

10:55 – 11:20 Future Directions and Challenges: A Case Study of Cardiovascular Repair
Robert Zweigerdt, PhD
Hannover Medical School, Germany

11:20 – 12:00 Moderated Discussion and Wrap Up
Nils Pfaff, PhD

ISSCR 2018

ANNUAL MEETING

MELBOURNE AUSTRALIA

20-23 JUNE

ISSCR2018.ORG

THE GLOBAL STEM CELL EVENT

PROGRAM SCHEDULE

SAVE THE DATE:
20-23 JUNE 2018

The **ISSCR Annual Meeting** brings the stem cell community together to exchange ideas, share insights and advance stem cell research and its application. Join us to engage with the latest science and technologies and envision new possibilities for the field.

Plan now for ISSCR 2018 in Melbourne, Australia.

ENVISION & ENGAGE

Co-sponsored by: ASSCR THE AUSTRALASIAN SOCIETY FOR STEM CELL RESEARCH

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

TUESDAY, 13 JUNE

8:30 – 12:00	**WORKSHOP ON CLINICAL TRANSLATION** *Advance registration required*	Level 2, Room 205ABC
13:00 – 17:00	**CLINICAL ADVANCES IN STEM CELL RESEARCH** *Advance registration required*	Level 2, Room 253A, 253B, and 253C
14:00 – 18:00	**REGISTRATION OPEN**	Level 1, North Lobby
15:00 – 16:30	**ATTENDEE ORIENTATION**	Level 1, North Lobby

WEDNESDAY, 14 JUNE

7:30 – 20:30	**REGISTRATION OPEN**	Level 1, North Lobby
8:30 – 10:00	**ATTENDEE ORIENTATION**	Level 1, North Lobby
	FOCUS SESSIONS	
9:00 – 12:00	**TRANSLATIONAL HORIZONS OF PLURIPOTENT STEM CELL TECHNOLOGY** *Presented by BlueRock Therapeutics*	Level 2, Room 205A
9:00 – 12:00	**OFF-THE-SHELF NATURAL KILLER CELL CANCER IMMUNOTHERAPY** *Presented by Fate Therapeutics*	Level 2, Room 258AB
9:00 – 12:00	**PROGRESS OF THE CUTTING-EDGE TECHNOLOGIES IN REGENERATIVE MEDICINE** *Presented by Healios K.K.*	Level 2, Room 258C
9:00 – 12:00	**TOOLS FOR BASIC AND APPLIED RESEARCH** *Presented by STEMCELL Technologies and Thermo Fisher Scientific*	Level 2, Room 253ABC
9:00 – 12:00	**NEUROLOGICAL DISORDERS: TRANSFORMING THE LANDSCAPE WITH HPSC MODELING** *Presented by WiCell*	Level 2, Room 205BC
9:00 – 12:00	**ETHICAL IMPLICATIONS OF ORGANOID TECHNOLOGY** *Presented by the ISSCR Ethics Committee*	Level 3, Ballroom East

WEDNESDAY, 14 JUNE *(continued)*

9:00 – 12:00	**FROM THE BENCH TO THE CLINIC: HOW TO MANUFACTURE YOUR CELL PRODUCT** *Presented by the ISSCR Industry Committee*	Level 3, Ballroom West
11:30 – 12:45	**EARLY-CAREER GROUP LEADER LUNCHEON** *Advance registration required*	Level 3, Ballroom Lobby
13:00 – 15:15	**PLENARY I PRESIDENTIAL SYMPOSIUM: A DECADE OF HUMAN IPSCS FROM DISCOVERY TO CLINIC** *Sponsored by: Fate Therapeutics* **Chair: Sally Temple** *Neural Stem Cell Institute, U.S.*	Exhibit Level, Exhibition Hall B1
13:00 – 13:05	**OPENING REMARKS**	
13:05 – 13:15	**ISSCR PRESIDENT'S ADDRESS: SALLY TEMPLE**	
13:15 – 13:20	**THE MCEWEN AWARD FOR INNOVATION PRESENTATION TO ELAINE FUCHS**	
13:20 – 13:25	**THE ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR PRESENTATION TO JAYARAJ RAJAGOPAL**	
13:25 – 13:30	**PUBLIC SERVICE AWARD PRESENTATION TO GEORGE Q. DALEY**	
13:30 – 13:35	**ANNOUNCEMENT OF THE ISSCR ZHONGMEI CHEN YONG TRAVEL AWARDS FOR SCIENTIFIC EXCELLENCE**	
13:35 – 14:00	**Magdalena Zernicka-Goetz** *University of Cambridge, U.K.* ANNE MCLAREN MEMORIAL LECTURE: PARTNERSHIP OF EMBRYONIC AND EXTRA-EMBRYONIC STEM CELLS TO BUILD THE IMPLANTING MAMMALIAN EMBRYO IN VIVO AND IN VITRO	
14:00 – 14:25	**Rudolf Jaenisch** *Whitehead Institute for Biomedical Research, U.S.* EPIGENETIC REGULATION, STEM CELLS AND DISEASE RELEVANCE	
14:25 – 14:50	**Shinya Yamanaka** *Center for iPS Cell Research and Application, Japan and Gladstone Institutes, U.S.* RECENT PROGRESS IN IPS CELL RESEARCH AND APPLICATION	
14:50 – 15:15	**Joanna Wysocka** *Stanford University, U.S.* CELLULAR ANTHROPOLOGY: USING IPSCS TO STUDY HUMAN EVOLUTION	
15:15 – 16:00	**REFRESHMENT BREAK**	ISSCR Exhibit & Poster Hall, Exhibition Hall A

WEDNESDAY, 14 JUNE *(continued)*

15:15 – 20:30	**ISSCR EXHIBIT HALL OPEN**	Level 1, Exhibition Hall A
16:00 – 18:10	**PLENARY II: ORGANOGENESIS-MAKING TISSUES AND ORGANS** *Sponsored by: Allen Institute for Cell Science* **Chair: Douglas A. Melton** *Harvard University and Harvard Stem Cell Institute, U.S.*	Exhibit Level, Exhibition Hall B1
16:00 – 16:25	**Margaret A. Goodell** *Baylor College of Medicine, U.S.* ERNEST MCCULLOCH MEMORIAL LECTURE: IMMORTAL HEMATOPOIETIC STEM CELLS AND EPIGENETIC REGULATION	
16:25 – 16:50	**Hans C. Clevers** *Hubrecht Institute, Netherlands* STEM CELL-GROWN ORGANOIDS AS MODELS FOR HUMAN DISEASE	
16:50 – 17:15	**Juergen Knoblich** *Institute of Molecular Biotechnology (IMBA), Austria* CEREBRAL ORGANOIDS: MODELLING HUMAN BRAIN DEVELOPMENT AND TUMORIGENESIS IN STEM CELL DERIVED 3D CULTURE	
17:15 – 17:25	**POSTER TEASERS**	
17:25 – 17:35	**Sanford Greenberg** *Johns Hopkins Wilmer Eye Institute , U.S.* MY PROMISE: END BLINDNESS	
17:35 – 18:10	**KEYNOTE ADDRESS** **Laurie Glimcher** *Dana-Farber Cancer Institute, U.S.* STRESSED OUT: A NOVEL APPROACH TO CANCER IMMUNOTHERAPY	
18:10 – 20:30	**OPENING RECEPTION AND POSTER SESSION I** *Sponsored by: Medicine by Design, University of Toronto* ODD numbered posters present from 18:30-19:30 EVEN numbered posters present from 19:30-20:30	ISSCR Exhibit & Poster Hall, Exhibition Hall A
21:00 – 00:00	**JUNIOR INVESTIGATOR NETWORKING SOCIAL NIGHT** *(Junior Investigator event; advance registration required.)*	Royale Nightclub 279 Tremont St. Boston, MA

THURSDAY, 15 JUNE

INNOVATION SHOWCASES

8:00 – 8:30	**AXOL BIOSCIENCE LTD.** Induced Pluripotent Stem Cell-Derived Endothelial Colony Forming Cells Offer a Robust and Physiologically Relevant Research Tool **Mervin C. Yoder** *Indiana University School of Medicine and Axol Bioscience Ltd.*	Level 2, Room 258C
8:00 – 8:30	**BIOSPHERIX** Total Quality Approach to Cell Incubation and Processing **Kevin Murray** *BioSpherix Medical*	Level 3, Ballroom East
8:00 – 8:30	**LONZA** Enabling hPSC-Based Therapies from Bench Side to Commercialization **Sudha Nair** *Lonza* **Inbar Friedrich Ben-Nun** *Lonza*	Level 3, Ballroom West
8:00 – 8:30	**MILL CREEK LIFE SCIENCES** In Vitro Expansion of Mesenchymal Stem Cells Using Media Supplemented with Unfractionated, Heparin-Free Platelet Lysate **Vanesa Alonso Camino** *Mill Creek Life Sciences*	Level 2, Room 253ABC
8:00 – 8:30	**NIKON CORPORATION** Live Cell Imaging and Morphometric Quantification of Neuronal Degeneration **Lee L. Rubin** *Professor and Director of Translational Medicine Harvard University and the Harvard Stem Cell Institute*	Level 2, Room 205BC
8:00 – 8:30	**THERMO FISHER SCIENTIFIC** Directed Self-Assembly of Inner Ear Organoids from Human Pluripotent Stem Cells **Karl R. Koehler** *Department of Otolaryngology-Head and Neck Surgery, Indiana University School of Medicine*	Level 2, Room 258AB

THURSDAY, 15 JUNE *(continued)*

8:00 – 8:30	**UNION BIOMETRICA, INC.** Automation for Analysis and Handling of Cells and Cell Clusters in Stem Cell Research **Rock Pulak** *Director of Life Science Technologies, Union Biometrica, Inc.*	Level 2, Room 205A
8:15 – 18:30	**REGISTRATION OPEN**	Level 1, North Lobby
8:15 – 9:00	**MORNING COFFEE**	Plenary Hall, Exhibit Level, Exhibition Hall B1
9:00 – 11:20	**PLENARY III: STEM CELLS AND CANCER** **Chair: Leonard I. Zon** *Boston Children's Hospital, U.S.*	Exhibit Level, Exhibition Hall B1
9:00 – 09:25	**George Q. Daley** *Boston Children's Hospital, Harvard Medical School, U.S.* HEMATOPOIETIC STEM CELL DERIVATION FROM PLURIPOTENT STEM CELLS	
9:25 – 09:50	**Connie J. Eaves** *Terry Fox Laboratory, BC Cancer Agency, Canada* INTEGRATED FUNCTIONAL AND MOLECULAR ANALYSES OF INDIVIDUAL HUMAN HEMATOPOIETIC STEM CELLS	
9:50 – 10:15	**Cédric Blanpain** *Université Libre de Bruxelles, Belgium* CANCER CELL OF ORIGIN AND TUMOR HETEROGENEITY	
10:15 – 10:25	**POSTER TEASERS**	
10:25 – 10:50	**Viviane Tabar** *Memorial Sloan Kettering Cancer Center, U.S.* MODELING HISTONE MUTANT BRAIN TUMORS IN PLURIPOTENT STEM CELLS	
10:50 – 11:15	**Sean Morrison** *Children's Research Institute at UT Southwestern, U.S.* THE METABOLIC REGULATION OF STEM CELL FUNCTION AND LEUKEMOGENESIS	
11:00 – 20:00	**ISSCR EXHIBIT HALL OPEN**	Level 1, Exhibition Hall A
11:20 – 13:15	**LUNCH BREAK**	
11:30 – 13:00	**MEET THE EXPERTS LUNCHEON** *(Junior Investigator event; advance registration required.)*	Level 3, Ballroom Lobby

THURSDAY, 15 JUNE *(continued)*

INNOVATION SHOWCASES

11:30 – 12:30	**CELLULAR DYNAMICS INTERNATIONAL, A FUJIFILM COMPANY** Human iPSC-Derived Midbrain Dopaminergic Neurons for Disease Modeling and Cell Therapy **Coby Carlson** *Strategic Marketing Manager, Cellular Dynamics International, a FUJIFILM Company* **Christopher McMahon** *R&D Senior Group Leader, Cellular Dynamics International, a FUJIFILM Company*	Level 2, Room 258C
11:30 – 12:30	**CORNING INC.** Advances in Patient Derived Disease Modeling: From Standardized Reprogramming of iPS Cells to Generation of Human Kidney Organoids **Anna Falk** *Associate Professor, Karolinska Institute* **Benjamin Freedman** *Assistant Professor, University of Washington* **Keith Olsen** *Global Commercial Director, Corning Life Sciences*	Level 3, Ballroom East
11:30 – 12:30	**MILLIPORESIGMA** Technologies to Engineer, Evaluate and Expand Stem Cells to Advance Innovative Therapies **Jason Gustin** *MilliporeSigma* **Darrin Fogg** *MilliporeSigma* **Julie Murrell** *MilliporeSigma*	Level 2, Room 205BC

THURSDAY, 15 JUNE *(continued)*

11:30 – 12:30	**MINERVA BIOTECHNOLOGIES CORP** Primitive Embryonic Growth Factor, $NME7_{AB}$, Induces and Maintains Naïve State in Human Stem Cells Without Karyotype Instability **Cynthia Bamdad** *Minerva Biotechnologies* **Kenneth S. Kosik** *Neuroscience Research Institute, and Department of Cellular Molecular and Developmental Biology University of California, Santa Barbara* **Min-Joon Han** *St. Jude Children's Research Hospital*	Level 3, Ballroom West
11:30 – 12:30	**STEMCELL TECHNOLOGIES INC.** Intestinal and Cerebral Organoids: New Tools to Study Human Development and Diseases **Jordi Guiu Sagarra** *BRIC – Biotech Research & Innovation Center, University of Copenhagen* **Oliver Wüseke** *IMBA – Institute of Molecular Biotechnology*	Level 2, Room 253ABC
11:30 – 12:30	**TAKARA BIO USA, INC.** Footprint-Free Gene Editing Using CRISPR/Cas9 and Single-Cell Cloning of Edited Human iPS Cells **Liz Quinn** *Associate Director of Stem Cell Marketing, Takara Bio USA, Inc.*	Level 2, Room 205A
11:30 – 12:30	**THERMO FISHER SCIENTIFIC** New Monoclonal Antibodies to Defined Cell Surface Proteins on Human Pluripotent Stem Cells **Andrew L. Laslett** *CSIRO Manufacturing, Australian Regenerative Medicine Institute, Monash University*	Level 2, Room 258AB

THURSDAY, 15 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IA: ORGANOIDS AND DISEASE MODELING** Level 2, Room 258AB

Chair: Juergen Knoblich
Institute of Molecular Biotechnology (IMBA), Austria

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Guo-li Ming**
University of Pennsylvania, Philadelphia, PA, U.S.
MODELING NEURAL DEVELOPMENT AND DISEASES USING HUMAN IPSCS

13:45 – 14:00 **Alison L. O'Neil**
Harvard University, U.S.
AMENDING ORGANOID PRODUCTION TO DRUG SCREENING: HIGHLY HOMOGENEOUS HIPSC DERIVED CORTICAL SPHEROIDS PRODUCED IN BULK

14:00 – 14:15 **Cantas Alev**
Center for iPS Cell Research and Application, Japan
MODELING THE HUMAN SEGMENTATION CLOCK WITH PLURIPOTENT STEM CELLS

14:15 – 14:30 **Kihyun Lee**
Memorial Sloan Kettering Cancer Center, U.S.
GENOME EDITING IN HUMAN PLURIPOTENT STEM CELLS REVEALS GATA6 HAPLOINSUFFICIENCY AND A GENETIC INTERACTION WITH GATA4 IN HUMAN PANCREATIC DEVELOPMENT

14:30 – 14:45 **Alena Yermalovich**
Harvard University, U.S.
ENHANCED NEPHROGENESIS THROUGH LIN28-MEDIATED REPROGRAMMING

14:45 – 15:10 **Melissa Little**
Murdoch Childrens Research Institute, Australia
KIDNEY ORGANOIDS IN MODELLING HERITABLE KIDNEY DISEASE

THURSDAY, 15 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IB: PLURIPOTENCY AND IPSC REPROGRAMMING I** Level 3, Ballroom East

Chair: Nissim Benvenisty
Hebrew University, Israel

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Kathrin Plath**
University of California, Los Angeles, School of Medicine, U.S.
COMBINATORIAL BINDING OF TRANSCRIPTION FACTORS IS ESSENTIAL FOR REPROGRAMMING TO PLURIPOTENCY

13:45 – 14:00 **Ralph Stadhouders**
Center for Genomic Regulation (CRG), Spain
KINETICS OF CHANGES IN 3D GENOME STRUCTURE AND GENE EXPRESSION DURING CELLULAR REPROGRAMMING SUGGEST INSTRUCTIVE ROLE OF GENOME TOPOLOGY

14:00 – 14:15 **Miguel A. Esteban**
Guangzhou Institutes of Biomedicine and Health, Chinese Academy of Sciences, China
NCOR/SMRT CO-REPRESSORS CREATE A MOLECULAR BRAKE PAD TO SOMATIC CELL REPROGRAMMING

14:15 – 14:30 **Charles Hernandez**
Yale University, U.S.
CHROMATIN-ASSOCIATED FACTORS OF THE DPPA2/4 FAMILY ARE THE KEY REGULATORS OF CELLULAR REPROGRAMMING

14:30 – 14:45 **Masamitsu Sone**
Center for iPS Cell Research and Application, Japan
HYBRID CELLULAR METABOLISM COODINATED BY ZIC3 AND ESRRB SYNERGISTICALLY ENHANCE SOMATIC CELL REPROGRAMMING

14:45 – 15:10 **Konrad Hochedlinger**
Massachusetts General Hospital, U.S.
ROLE OF SEX CHROMOSOMES AND ENVIRONMENT ON DNA METHYLATION PATTERNS IN PLURIPOTENT STEM CELLS

THURSDAY, 15 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IC: STEM CELLS- STRESS AND AGING** Level 2, Room 258C
Sponsored by: Decibel Therapeutics

Chair: Sean Morrison
Children's Research Institute at UT Southwestern, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Emmanuelle Passegue**
Columbia University, U.S.
AUTOPHAGY, METABOLISM AND AGED HEMATOPOIETIC STEM CELLS

13:45 – 14:00 **Stephanie Xie**
Princess Margaret Cancer Centre, University Health Network, Canada
4HPR ACTIVATES AUTOPHAGY TO PRESERVE HSC FUNCTION DURING HUMAN CORD BLOOD EXPANSION

14:00 – 14:15 **Michael Segel**
University of Cambridge, U.K.
NICHE STIFFNESS UNDERLIES THE AGEING OF OLIGODENDROCYTE PROGENITOR CELLS

14:15 – 14:30 **Albina Ibrayeva**
University of Southern California, CA
ORIGINS OF AGE-RELATED NEUROGENESIS DECLINE

14:30 – 14:45 **Weiqi Zhang**
Institute of Biophysics, Chinese Academy of Sciences, China
INVESTIGATING HUMAN PREMATURE AGING USING STEM CELL MODELS

14:45 – 15:10 **Stefano Piccolo**
Department of Molecular Medicine, University of Padova, Italy
YAP/TAZ AND CELL PLASTICITY: DE NOVO GENERATION OF TISSUE-SPECIFIC SOMATIC STEM/PROGENITOR CELLS BY YAP-MEDIATED REPROGRAMMING OF DIFFERENTIATED CELLS

THURSDAY, 15 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT ID: SINGLE CELL HETEROGENEITY** Level 2, Room 205A

Chair: Richard Young
Whitehead Institute for Biomedical Research, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Tariq Enver**
University College London Cancer Institute, U.K.
SINGLE CELL ANALYSIS OF CLONAL EVOLUTION IN CHILDHOOD LEUKAEMIA REVEALS GENETIC AND EPIGENETIC BOTTLE-NECK SELECTION

13:45 – 14:00 **Heiko Lickert**
Helmholtz Zentrum München, Institute of Diabetes & Regeneration Research, Germany
WNT/PLANAR CELL POLARITY SIGNALING IN THE CRYPT STEM CELL NICHE REGULATES SECRETORY LINEAGE SEGREGATION

14:00 – 14:15 **Daniel Wagner**
Harvard Medical School, U.S.
MAPPING VERTEBRATE DIFFERENTIATION HIERARCHIES WITH HIGH-THROUGHPUT SINGLE-CELL TRANSCRIPTOMICS

14:15 – 14:30 **Ernest Arenas**
Karolinska Institutet, Sweden
DECODING THE DOPAMINERGIC NEUROGENIC NICHE AT A SINGLE CELL LEVEL

14:30 – 14:45 **Maria Kasper**
Karolinska Institutet, Sweden
A SINGLE-CELL ATLAS OF MOUSE SKIN DURING HAIR GROWTH AND REST

14:45 – 15:10 **Barbara Treutlein**
Max Planck Institute for Evolutionary Anthropology, Germany
ENGINEERING CELLS AND TISSUES: INSIGHTS FROM SINGLE-CELL TRANSCRIPTOMICS

THURSDAY, 15 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IE: MUSCLE AND MESENCHYMAL CELLS** Level 2, Room 253ABC

Chair: Thomas A. Rando
Stanford University School of Medicine, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Helen Blau**
Stanford University School of Medicine, U.S.
HIGH-RESOLUTION MAPPING OF MYOGENIC LINEAGE AND EPIGENETIC LANDSCAPE BY SINGLE-CELL MASS CYTOMETRY

13:45 – 14:00 **Chozha Rathinam**
University of Maryland School of Medicine, U.S.
DEFICIENCY OF ENDOPHILINS IMPAIRS MULTILINEAGE HEMATOPOIESIS AND HSC MAINTENANCE DUE TO DEFECTIVE NICHE FUNCTIONS

14:00 – 14:15 **Mingming Zhao**
Center for iPS Cell Research and Application, Kyoto University, Japan
NEW GENERATION MATRIX PROVIDES HIGH EFFICIENT DIFFERENTIATION SYSTEM INDUCING MYOCYTES AND MUSCLE STEM CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS

14:15 – 14:30 **Albert Almada**
Harvard Stem Cell Institute, U.S.
FOS INSTRUCTS EARLY MUSCLE STEM CELL FATE DECISIONS IN RESPONSE TO SKELETAL MUSCLE TRAUMA IN ADULT MICE

14:30 – 14:45 **Jung-Yun Choi**
KAIST, Korea
ACTIVATED TGF-BETA SIGNALING AND DOWNREGULATED BMP SIGNALING CONTRIBUTE TO IMPAIRED OSTEOGENESIS IN CFC SYNDROME-DERIVED IPSCS

14:45 – 15:10 **Simon Mendez-Ferrer**
WT-MRC Cambridge Stem Cell Institute, U.K.
REGULATION OF MESENCHYMAL STEM CELLS IN SPACE AND TIME BY AUTONOMIC NEURAL SIGNALS

THURSDAY, 15 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IF: HEMATOPOIETIC STEM CELLS** Level 2, Room 205BC

Chair: Catriona Jamieson
Moores Cancer Center, University of California, San Diego, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Andreas Trumpp**
DKFZ/ HI-STEM gGmbH, Germany
BRANCHED CHAIN AMINO ACID CATABOLISM CONTROLS HUMAN AML STEM CELLS BY ALTERING THE EPIGENOME

13:45 – 14:00 **Raphael Lis**
Weill Cornell Medicine, U.S.
CONVERSION OF ADULT ENDOTHELIAL CELLS INTO SELF-RENEWING IMMUNE-COMPETENT HAEMATOPOIETIC STEM CELLS

14:00 – 14:15 **Nicola Vannini**
Ludwig Institute at University of Lausanne, Switzerland
NAD BOOSTING STRATEGY ENHANCES STEM CELL FUNCTION BY DECREASING MITOCHONDRIAL MEMBRANE POTENTIAL THROUGH THE ACTIVATION OF MITOCHONDRIAL UNFOLDED PROTEIN RESPONSE (UPR-MT) AND MITOPHAGY

14:15 – 14:30 **Iman Fares**
IRIC, Canada
EPCR EXPRESSION DEFINES THE MOST PRIMITIVE SUBSET OF HUMAN HSPCS THAT IS FUNCTIONALLY REQUIRED FOR THEIR SELF-RENEWAL

14:30 – 14:45 **Lisa Nguyen**
University of Southern California, U.S.
CLONAL COMPENSATION BETWEEN HEMATOPOIETIC STEM CELLS UPON DIFFERENTIATION DEFICIENCY

14:45 – 15:10 **Ido Amit**
Weizmann Institute, Israel
THE POWER OF ONE: IMMUNOLOGY IN THE AGE OF SINGLE CELL GENOMICS

THURSDAY, 15 JUNE *(continued)*

13:15 – 15:15	**CONCURRENT IG: NEURAL STEM CELLS** **Chair: Fiona Doetsch** *University of Basel, Biozentrum, Switzerland*	Level 3, Ballroom West
13:15 – 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 – 13:45	**Arnold Kriegstein** *University of California, San Francisco, U.S.* GENOMIC INSIGHTS INTO HUMAN CORTICAL DEVELOPMENT, LISSENCEPHALY, AND ZIKA MICROCEPHALY	
13:45 – 14:00	**Masashi Fujitani** *Hyogo College of Medicine, Japan* ABNORMAL NEUROGENESIS BY 16P1311 MICRODUPLICATION CAUSES HYPERACTIVITY	
14:00 – 14:15	**Bjoern Neumann** *University of Cambridge, U.K.* INTERVENTIONS TO OVERCOME THE AGE-RELATED DECLINE IN CNS REMYELINATION	
14:15 – 14:30	**Luis Zurkirchen** *University of Zurich, Switzerland* YIN YANG 1 SUSTAINS BIOSYNTHETIC DEMANDS DURING BRAIN DEVELOPMENT IN A DEVELOPMENTAL STAGE-SPECIFIC MANNER	
14:30 – 14:45	**Marlen Knobloch** *University of Lausanne, Switzerland* A FATTY ACID OXIDATION-DEPENDENT METABOLIC SHIFT REGULATES ADULT NEURAL STEM CELL QUIESCENCE	
14:45 – 15:10	**Marianne Bronner** *California Institute of Technology, U.S.* GENE REGULATORY NETWORK UNDERLYING NEURAL CREST DEVELOPMENT	
15:15 – 16:00	**MEET-UP: GERMAN STEM CELL NETWORK**	Meet-up Hub #1
15:15 – 16:00	**MEET-UP: BEDFORD RESEARCH FOUNDATION**	Meet-up Hub #2 (Hub supported by Bedford Research Foundation)
15:15 – 16:00	**REFRESHMENT BREAK**	ISSCR Exhibit & Poster Hall, Exhibition Hall A

THURSDAY, 15 JUNE *(continued)*

16:00 – 18:00 **CONCURRENT IIA: ORGANOIDS AND ORGANOGENESIS** Level 2, Room 205BC

Chair: Melissa Little
Murdoch Childrens Research Institute, Australia

16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**

16:05 – 16:30 **Merixtell Huch**
Wellcome Trust/Cancer Research UK Gurdon Institute, University of Cambridge, U.K.
LIVER ORGANOIDS FOR THE STUDY OF LIVER BIOLOGY AND DISEASE

16:30 – 16:45 **Ya-Wen Chen**
Columbia University, U.S.
A THREE-DIMENSIONAL MODEL OF HUMAN LUNG DEVELOPMENT AND DISEASE FROM PLURIPOTENT STEM CELLS

16:45 – 17:00 **Karl Koehler**
Indiana University School of Medicine, U.S.
DIRECTED SELF-ASSEMBLY OF NEUROSENSORY INNER EAR ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS

17:00 – 17:15 **Julia Ladewig**
University of Bonn, Germany
AN ORGANOID-BASED MODEL OF CORTICAL DEVELOPMENT IDENTIFIES NON-CELL AUTONOMOUS DEFECTS IN ß-CATENIN SIGNALING CONTRIBUTING TO MILLER-DIEKER-SYNDROME

17:15 – 17:30 **Michael Rukstalis**
Pfizer, U.S.
ENDOTHELIN-1 MEDIATES THE SPONTANEOUS CONTRACTION AND EARLY MATURATION OF PLURIPOTENT STEM CELL DERIVED VENTRICULAR CARDIOMYOCYTES

17:30 – 17:55 **Huck-Hui Ng**
Genome Institute Singapore, Singapore
MODELING HUMAN DISEASES USING HUMAN ORGANOID SYSTEMS

THURSDAY, 15 JUNE *(continued)*

16:00 – 18:00 **CONCURRENT IIB: DIRECT REPROGRAMMING AND FATE CONVERSION** Level 3, Ballroom West

Chair: Duanqing Pei
Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, China

16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**

16:05 – 16:30 **Deepak Srivastava**
Gladstone Institutes, U.S.
CELLULAR REPROGRAMMING APPROACHES FOR CARDIOVASCULAR DISEASE

16:30 – 16:45 **Esteban Mazzoni**
New York University, U.S.
A MULTI-STEP TRANSCRIPTIONAL AND CHROMATIN STATE CASCADE UNDERLIES MOTOR NEURON PROGRAMMING FROM EMBRYONIC STEM CELLS

16:45 – 17:00 **Jessica Vanslambrouck**
Murdoch Children's Research Institute, Australia
PIGGYBAC TRANSPOSON-MEDIATED DIRECT TRANSCRIPTIONAL REPROGRAMMING TO NEPHRON PROGENITORS

17:00 – 17:15 **Thomas Moreau**
University of Cambridge, U.K.
MOLECULAR MECHANISMS UNDERLYING HUMAN PLURIPOTENT STEM CELL FORWARD PROGRAMMING TO MEGAKARYOYCTES: FROM BIOLOGY TO TRANSFUSION MEDICINE

17:15 – 17:30 **Samuel Collombet**
Ecole Normale Superieure, France
QUALITATIVE DYNAMICAL MODELLING OF THE REGULATORY NETWORK CONTROLLING BLOOD CELL SPECIFICATION AND REPROGRAMMING

17:30 – 17:55 **Hans Schöler**
Max Planck Institute for Molecular Biomedicine, Germany
INDUCTION OF PLURIPOTENCY WITHOUT OCT4

THURSDAY, 15 JUNE *(continued)*

16:00 – 18:00 **CONCURRENT IIC: STEM CELLS AND EARLY EMBRYOGENESIS** Level 2, Room 253ABC

Chair: Marianne Bronner
California Institute of Technology, U.S.

16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**

16:05 – 16:30 **Ruth Lehmann**
HHMI/Skirball Institute, NYU School of Medicine, U.S.
MECHANISMS AND FUNCTION OF MITOCHONDRIAL INHERITANCE IN GERM LINE STEM CELLS

16:30 – 16:45 **Yue Shao**
University of Michigan, U.S.
BIOENGINEERED IN VITRO MODEL FOR POST-IMPLANTATION HUMAN EMBRYOGENESIS

16:45 – 17:00 **Xin Huang**
Icahn School of Medicine at Mount Sinai, U.S.
THE PLURIPOTENCY FACTOR ZFP281 COORDINATES TRANSCRIPTIONAL AND EPIGENETIC CONTROL OF EPIBLAST MATURATION

17:00 – 17:15 **Guangdun Peng**
Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences, China
LINEAGE SEGREGATION OF POST-IMPLANTATION MOUSE EMBRYO REVEALED BY SPATIAL AND SINGLE CELL TRANSCRIPTOME

17:15 – 17:30 **Vidur Garg**
Memorial Sloan Kettering Cancer Center, U.S.
DISTINCT ROLES OF FGFR1 AND FGFR2 IN FATE ESTABLISHMENT WITHIN THE INNER CELL MASS OF THE MOUSE BLASTOCYST

17:30 – 17:55 **Gordon Keller**
McEwen Centre for Regenerative Medicine, University Health Network, Canada
MODELING HUMAN CARDIOVASCULAR DEVELOPMENT WITH PLURIPOTENT STEM CELLS

THURSDAY, 15 JUNE *(continued)*

16:00 – 18:00 **CONCURRENT IID: GENE MODIFICATION AND GENE EDITING IN STEM CELLS** Level 2, Room 258AB

Chair: Alessandra Biffi
Dana Farber and Boston Children's Hospital, U.S.

16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**

16:05 – 16:30 **Michael Elowitz**
California Institute of Technology, U.S.
THE FUNCTIONAL ROLES AND PERCEPTION HISTORIES OF INTERCELLULAR SIGNALING SYSTEMS

16:30 – 16:45 **Amanda Andersson Rolf**
WT-MRC Cambridge Stem Cell Institute, U.K.
RAPID, ONE-STEP GENERATION OF BIALLELIC CONDITIONAL AND REVERSIBLE GENE KNOCKOUTS

16:45 – 17:00 **Meng Li**
Wellcome Trust Sanger Institute, U.K.
GENETIC DISSECTION OF THE EXIT FROM PLURIPOTENCY IN MOUSE EMBRYONIC STEM CELLS BY CRISPR SCREENING

17:00 – 17:15 **Tomas Gonzalez Fernandez**
Trinity College Dublin, Ireland
MESENCHYMAL STEM CELL FATE FOLLOWING NANOPARTICLE-BASED GENE TRANSFECTION STRONGLY DEPENDS ON THE CHOICE OF DELIVERY VECTOR

17:15 – 17:30 **Casey Gifford**
Gladstone Institute of Cardiovascular Disease, U.S.
OLIGOGENIC INHERITANCE OF FAMILIAL CARDIAC DISEASE INVOLVING MKL2 AND NKX2-5 VARIANTS REVEALED BY DISEASE MODELING

17:30 – 17:55 **Luigi Naldini**
San Raffaele Telethon Institute for Gene Therapy, Italy
ADVANCED GENETIC ENGINEERING OF HEMATOPOIESIS FOR TREATING INHERITED DISEASES

THURSDAY, 15 JUNE *(continued)*

16:00 – 18:00 **CONCURRENT IIE: CARDIAC REGENERATION** Level 2, Room 258C

Chair: Christine Mummery
Leiden University Medical Center, Netherlands

16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**

16:05 – 16:30 **Nadia Rosenthal**
The Jackson Laboratory, U.S.
IMMUNE CONTROL OF REGENERATION

16:30 – 16:45 **Michaela Patterson**
University of Southern California, U.S.
FREQUENCY OF MONONUCLEAR DIPLOID CARDIOMYOCYTES UNDERLIES NATURAL VARIATION IN ADULT HEART REGENERATION

16:45 – 17:00 **Jason Yu**
Wellcome Trust Sanger Institute, U.K.
CRISPR/CAS9 GENOME-WIDE SCREEN IDENTIFYING DMAP1 AS A NEGATIVE REGULATOR OF CARDIAC PROGENITOR REPROGRAMMING FROM MOUSE FIBROBLASTS

17:00 – 17:15 **Agnieszka D'Antonio-Chronowska**
University of California, San Diego, U.S.
CHARACTERIZING GENETIC VARIATION ASSOCIATED WITH CARDIAC-SPECIFIC TRAITS IN HUMAN IPSC-DERIVED CARDIOMYOCYTES

17:15 – 17:30 **Caroline Burns**
Massachusetts General Hospital/Harvard Medical School, U.S.
H3K27ME3 DEPOSITION OVER SARCOMERIC AND ACTINOMYOSIN PROMOTERS IS REQUIRED FOR CARDIOMYOCYTE CYTOKINESIS AND WOUND INVASION DURING ZEBRAFISH HEART REGENERATION

17:30 – 17:55 **Richard Harvey**
Victor Chang Cardiac Research Institute, Australia
NEW WINDOWS INTO MAMMALIAN CARDIAC REPAIR

THURSDAY, 15 JUNE *(continued)*

16:00 – 18:00 **CONCURRENT IIF: ENDODERMAL DERIVATIVES** Level 2, Room 205A

Chair: Carla Kim
Boston Children's Hospital, U.S.

16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**

16:05 – 16:30 **Alireza Rezania**
ViaCyte, Inc., U.S.
DIFFERENTIATING ES CELLS TO MATURE PANCREATIC BETA CELLS IN INCUBATORS

16:30 – 16:45 **Nadav Sharon**
Harvard University, U.S.
SINGLE CELL MRNA SEQUENCING REVEALS THAT PANCREATIC ENDOCRINE DIFFERENTIATION IS SPATIALLY AND TEMPORALLY REGULATED WITHIN A PENINSULAR NICHE

16:45 – 17:00 **M. Cristina Nostro**
McEwen Centre for Regenerative Medicine UHN, Canada
GLYCOCAPTURE PROTEOMICS IDENTIFIES A NOVEL CELL SURFACE MARKER OF HUMAN PANCREATIC PROGENITOR CELLS

17:00 – 17:15 **Kaveh Daneshvar**
Harvard Medical School, Massachusetts General Hospital, U.S.
DIGIT IS A LNCRNA THAT REGULATES DIFFERENTIATION OF EMBRYONIC STEM CELLS INTO DEFINITIVE ENDODERM

17:15 – 17:30 **Qing Li**
Memorial Sloan Kettering Cancer Center, U.S.
DISSECT HUMAN ENDODERM DEVELOPMENT THROUGH A GENOME-WIDE CRISPR SCREEN IN EMBRYONIC STEM CELLS

17:30 – 17:55 **Ludovic Vallier**
Cambridge Stem Cell Institute and Wellcome Trust Sanger Institute, U.K.
FROM HUMAN PLURIPOTENT STEM CELL DERIVED CHOLANGIOCYTES TO BILIARY ORGANOID

THURSDAY, 15 JUNE *(continued)*

16:00 – 18:00 **CONCURRENT IIG: MODELING NEURODEGENERATIVE DISEASE** — Level 3, Ballroom East

Chair: Hideyuki Okano
Keio University, School of Medicine, Japan

16:00 – 16:05 **TOPIC OVERVIEW BY CHAIR**

16:05 – 16:30 **Lawrence Goldstein**
University of California, San Diego, U.S.
USING STEM CELLS TO REVEAL THE SECRETS OF ALZHEIMERS DISEASE

16:30 – 16:45 **Jerome Mertens**
The Salk Institute for Biological Studies, U.S.
AGE-EQUIVALENT AND REJUVENATED INDUCED NEURONS FROM ALZHEIMER PATIENTS TO STUDY AGE-DEPENDENT DISEASE MECHANISMS

16:45 – 17:00 **Nina Makhortova**
Harvard University, Stem Cell and Regenerative Biology, U.S.
SMALL MOLECULE SCREEN FOR MODULATORS OF SURVIVAL OF MOTOR NEURON PROTEIN IN HUMAN MOTOR NEURONS

17:00 – 17:15 **Luiz Carlos Caires**
University of Sao Paulo, Brazil
DISCORDANT TWINS FOR CONGENITAL ZIKA SYNDROME SHOW DIFFERENTIAL ZIKA VIRAL INFECTION IN (HIPSC)-NPCS

17:15 – 17:30 **Gizem Inak**
Max-Delbrueck Center for Molecular Medicine, Germany
FUNCTIONAL AND BIOENERGETIC DEFECTS IN IPSC-DERIVED DOPAMINERGIC NEURONS FROM PATIENTS WITH LEIGH SYNDROME HARBORING SURF1 MUTATIONS

17:30 – 17:55 **Valina Dawson**
Johns Hopkins University School of Medicine, U.S.
CORTICAL CULTURES OF EXCITATORY PROJECTION NEURONS AND INHIBITORY INTERNEURONS TO STUDY CORTICAL FUNCTION AND INJURY

18:00 – 20:00 **POSTER SESSION II AND RECEPTION** — ISSCR Exhibit & Poster Hall, Exhibition Hall A
ODD numbered posters present from 18:00-19:00
EVEN numbered posters present from 19:00-20:00

FRIDAY, 16 JUNE

INNOVATION SHOWCASES

8:00 – 8:30 **ALPHA MED SCIENTIFIC INC.** — Level 2, Room 205BC
High Sensitivity Microelectrode Assay for Stem Cell Derived Neurons

Michael Trujillo
Alpha MED Scientific

Ikuro Suzuki
Tohoku Institute of Technology

Ryan Arant
Alpha MED Scientific

8:00 – 8:30 **BIOLOGICAL INDUSTRIES** — Level 2, Room 205A
Driving Cell Therapies to Market with Key Considerations for Scale-up Manufacturing, Key Partnerships and Serum-free Media Selection

Ohad Karnieli
CEO, Atvio Biotech

8:00 – 8:30 **BIO-TECHNE** — Level 2, Room 253ABC
Win the Race to Discovery: Innovating Stem Cell Research with Cutting-Edge Single-Cell Western and Adult Stem Cell Technologies

Joy Aho
Bio-Techne

Eric Jabbart
Bio-Techne

8:00 – 8:30 **FOUNDATION FOR BIOMEDICAL RESEARCH AND INNOVATION (FBRI)** — Level 2, Room 258AB
Smart Cell Processing: Future of Cell Production

Glyn Stacey
National Institute for Biological Standards and Control

Marc Turner
Scottish National Blood Transfusion Service

Shin Kawamata
Foundation for Biomedical Research and Innovation

8:00 – 8:30 **SONY BIOTECHNOLOGY** — Level 3, Ballroom West
Streamlined Workflow for Sorting Cells with Exchangeable Fluidics Cell Sorter FX500

Deena Soni
Global Marketing Manager, Sony Biotechnology

FRIDAY, 16 JUNE *(continued)*

8:00 – 8:30	**STEMBIOSYS INC** StemBioSys BM-HPME®: A Novel 3-Dimensional Microenvironment to Enhance Mesenchymal Stem Cell Expansion **Sy Griffey** *COO, StemBioSys* **Travis J. Block** *Senior Scientist, StemBioSys*	Level 2, Room 258C
8:00 – 8:30	**THERMO FISHER SCIENTIFIC** Improved DNA, mRNA and Protein Transfection Across Stem Cell Types **James Kehler** *Thermo Fisher Scientific*	Level 3, Ballroom East
8:15 – 18:30	**REGISTRATION OPEN**	Level 1, North Lobby
8:15 – 9:00	**MORNING COFFEE**	Plenary Hall, Exhibit Level, Exhibition Hall B1
9:00 – 11:20	**PLENARY IV: CHROMATIN AND RNA BIOLOGY IN STEM CELLS** **Chair: Shinya Yamanaka** *Center for iPS Cell Research and Application, Japan and Gladstone Institutes, U.S.*	Exhibit Level, Exhibition Hall B1
9:00 – 09:25	**Edith Heard** *Institut Curie, France* THE DEVELOPMENTAL DYNAMICS OF X-CHROMOSOME INACTIVATION	
9:25 – 09:50	**Ling-Ling Chen** *Shanghai Institute of Biochemistry and Cell Biology (SIBS), Chinese Academy of Sciences, China* THE DIVERSITY AND FUNCTION OF LONG NONCODING RNAS	
9:50 – 10:15	**V. Narry Kim** *Seoul National University, Seoul* RNA TAILING IN THE REGULATION OF MATERNAL TRANSCRIPTOME	
10:15 – 10:40	**Richard Young** *Whitehead Institute for Biomedical Research, U.S.* CHROMOSOME NEIGHBORHOODS AND GENE CONTROL IN HEALTH AND DISEASE	
10:40 – 10:50	**POSTER TEASERS**	

FRIDAY, 16 JUNE *(continued)*

10:50 – 10:55	**ISSCR TOBIAS AWARD PRESENTATION TO JOHN DICK**	
10:55 – 11:20	**John Dick** *Princess Margaret Cancer Centre, University Health Network and Department of Molecular Genetics, University of Toronto, Canada* ISSCR TOBIAS AWARD LECTURE: NORMAL AND LEUKEMIC HUMAN HEMATOPOIETIC STEM CELLS: CLONAL ASSAYS MATTER	
11:00 – 20:00	**ISSCR EXHIBIT HALL OPEN**	Level 1, Exhibition Hall A
11:20 – 13:15	**LUNCH BREAK**	
11:30 – 13:00	**MEET THE EXPERTS LUNCHEON** *(Junior Investigator event; advance registration required.)*	Level 3, Ballroom Lobby
	INNOVATION SHOWCASES	
11:30 – 12:30	**10X GENOMICS**	Level 2, Room 205BC
11:30 – 12:30	**ADVANCED CELL DIAGNOSTICS** Visualize the Cellular Localization of RNA Expression in Stem Cells with the RNAscope® ISH Technology **Courtney Anderson** *Senior Scientist, Advanced Cell Diagnostics* **Amnon Sharir** *Assistant Professor, UCSF School of Dentistry*	Level 3, Ballroom East
11:30 – 12:30	**AJINOMOTO CO., INC.** Genome Editing of hPSCs for Accurate Modeling of Human Diseases **Chad Cowan** *Harvard Department of Stem Cell and Regenerative Biology, Massachusetts General Hospital* **Ryuji Morizane** *Brigham and Women's Hospital*	Level 3, Ballroom West
11:30 – 12:30	**IRVINE SCIENTIFIC** Development of Serum Free Media for Mouse and Human Hematopoietic Progenitor Cell Expansion and Maintenance **Vanda S. Lopes** *Senior Scientist, Irvine Scientific* **Jessie H-T Ni** *Chief Scientific Officer, Irvine Scientific*	Level 2, Room 205A

FRIDAY, 16 JUNE *(continued)*

11:30 – 12:30	**MILTENYI BIOTEC GMBH** Novel Surface Markers Specifying hPSC-Derived Anterior Endoderm Subpopulations and PSC Quality Control Using a Novel Quantifiable Differentiation Assay **Heiko Lickert** *Director of the Institute of Diabetes and Regeneration Research, Helmholtz Zentrum München* **Sebastian Knöbel** *Senior Project Manager R&D Stem Cells, Miltenyi Biotec GmbH*	Level 2, Room 258C
11:30 – 12:30	**STEMCELL TECHNOLOGIES INC.** Highly Efficient Single-Cell Human Pluripotent Stem Cell Cloning and Robust Cardiomyocyte Differentiation **Adam Hirst** *STEMCELL Technologies Inc.* **Vincenzo Macri** *STEMCELL Technologies Inc.*	Level 2, Room 253ABC
11:30 – 12:30	**THERMO FISHER SCIENTIFIC** Enabling Modern PSC Workflows and Applications Including Gene Editing, Single Cell Passaging, and Automation **William T. Hendriks** *Harvard Brain Science Initiative, Harvard Medical School* **Duncan E. Crombie** *Centre for Eye Research Australia, University of Melbourne*	Level 2, Room 258AB

FRIDAY, 16 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIA: EMBRYONIC STEM CELLS** Level 2, Room 258AB

Chair: Austin G. Smith
Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute, U.K.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Shangqin Guo**
Yale University, U.S.
MECHANISM OF SOMATIC CELL REPROGRAMMING

13:45 – 14:00 **Abraham Weintraub**
Whitehead Institute Biomedical Research, U.S.
THE 3D GENOME AND TRANSCRIPTIONAL CONTROL

14:00 – 14:15 **Atilgan Yilmaz**
The Hebrew University of Jerusalem, Israel
DEFINING THE ESSENTIALOME OF HUMAN PLURIPOTENT STEM CELLS USING CRISPR/CAS9 SCREENING IN HAPLOID CELLS

14:15 – 14:30 **Florian Merkle**
University of Cambridge, U.K.
NEXT GENERATION SEQUENCING OF OVER 100 HUMAN EMBRYONIC STEM CELLS REVEALS DISEASE-CAUSING MUTATIONS IN MULTIPLE GENES, INCLUDING THE TUMOR SUPPRESSOR P53

14:30 – 14:45 **Sarita Panula**
Karolinska Institutet, Sweden
COMPREHENSIVE CELL-SURFACE PROTEIN PROFILING IDENTIFIES NOVEL MARKERS OF HUMAN NAÏVE AND PRIMED PLURIPOTENT STATES

14:45 – 15:10 **Hongkui Deng**
Peking University, China
DERIVATION OF PLURIPOTENT STEM CELLS WITH IN VIVO EMBRYONIC AND EXTRAEMBRYONIC POTENCY

FRIDAY, 16 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIB: TISSUE REGENERATION AND HOMEOSTASIS** Level 3, Ballroom West

Chair: Jayaraj Rajagopal
MGH Center for Regenerative Medicine, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Fiona Doetsch**
University of Basel, Biozentrum, Switzerland
REGULATION OF ADULT NEURAL STEM CELL DYNAMICS

13:45 – 14:00 **Qing Cissy Yu**
Shanghai Institute of Biochemistry and Cell Biology, China
IDENTIFY VASCULAR ENDOTHELIAL STEM CELLS (VESC) BY THE EXPRESSION OF PROTEIN C RECEPTOR

14:00 – 14:15 **Joshua Currie**
Center for Regenerative Therapies Dresden, Germany
LIVE IMAGING OF AXOLOTL DIGIT REGENERATION REVEALS SPATIOTEMPORAL CHOREOGRAPHY OF DIVERSE CONNECTIVE TISSUE PROGENITOR POOLS

14:15 – 14:30 **Yaron Fuchs**
Technion-Israel Institute of Technology, Israel
CASPASE-3 REGULATES YAP-DEPENDENT ORGAN SIZE AND SKIN REGENERATION

14:30 – 14:45 **Tea Soon Park**
Johns Hopkins School of Medicine, U.S.
IMPROVED VASCULAR DIFFERENTIATION OF HUMAN DIABETIC IPSC FOLLOWING STABLE REVERSION TO A NAÏVE PLURIPOTENT STATE

14:45 – 15:10 **Benjamin Simons**
University of Cambridge, U.K.
DYNAMICS OF MOUSE MAMMARY STEM CELLS DURING BRANCHING MORPHOGENESIS

FRIDAY, 16 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIC: STEM CELL NICHES** Level 2, Room 205A

Chair: Simon Mendez-Ferrer
Fundación CNIC, Spain

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Yi Zeng**
Institute of Biochemistry and Cell Biology, SIBS, Chinese Academy of Sciences, China
PROTEIN C RECEPTOR IN REGULATING MAMMARY STEM CELLS AND BREAST CANCER

13:45 – 14:00 **Joo-Hyeon Lee**
University of Cambridge, U.K.
ANATOMICALLY AND FUNCTIONALLY DISTINCT LUNG MESENCHYMAL POPULATIONS MARKED BY LGR5 AND LGR6

14:00 – 14:15 **Cristina Lo Celso**
Imperial College London, U.K.
BONE MARROW ECOLOGICAL COLLAPSE IN ACUTE MYELOID LEUKEMIA IS MEDIATED BY REMODELING OF ENDOSTEAL VESSELS

14:15 – 14:30 **Shiri Gur-Cohen**
The Rockefeller University, U.S.
EPCR AND TM GUIDE HEMATOPOIETIC STEM CELL HOMING TO THE BONE MARROW INDEPENDENT OF NICHE CLEARANCE

14:30 – 14:45 **Philippos Mourikis**
Institut Mondor de Recherche Biomédicale (IMRB), France
COLLAGEN V MAINTAINS MOUSE MUSCLE STEM CELLS BY CELL-AUTONOMOUS ACTIVATION OF THE CALCITONIN RECEPTOR

14:45 – 15:10 **Tsvee Lapidot**
Weizmann Institute, Israel
METABOLIC REGULATION AND CHEMOTHERAPY RESISTANCE OF BONE MARROW RETAINED HEMATOPOIETIC STEM CELLS: THE ROLE OF REACTIVE OXYGEN SPECIES, MITOCHONDRIA TRANSFER AND NITRIC OXIDE

FRIDAY, 16 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIID: EPIGENETICS AND STEM CELLS** Level 3, Ballroom East
Stanford University, U.S.

Chair: Joanna Wysocka

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Alexander Meissner**
Harvard University, U.S.
MECHANISMS OF EPIGENETIC REGULATION IN STEM CELLS AND DEVELOPMENT

13:45 – 14:00 **Jianlong Wang**
Icahn School of Medicine at Mount Sinai, U.S.
RNA-DEPENDENT CHROMATIN TARGETING OF TET2 FOR ENDOGENOUS RETROVIRUS CONTROL IN MAMMALIAN CELLS

14:00 – 14:15 **Hongjie Yao**
Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, China
RNA-BINDING PROTEIN DDX5 INHIBITS REPROGRAMMING TO PLURIPOTENCY BY MIRNA-BASED REPRESSION OF RYBP AND ITS PRC1-DEPENDENT AND -INDEPENDENT FUNCTIONS

14:15 – 14:30 **Shiran Bar**
The Hebrew University of Jerusalem, Israel
GENOMIC IMPRINTING ABERRATIONS IN HUMAN PLURIPOTENT STEM CELLS ARE DRIVEN BY CELL TYPE AND PARENTAL ORIGIN

14:30 – 14:45 **Amy Chen**
University of California, San Francisco, U.S.
ENHANCER SWITCHING SUBSETS GENE NETWORKS DURING THE TRANSITION FROM NAIVE TO PRIMED PLURIPOTENCY

14:45 – 15:10 **Laurie Boyer**
Massachusetts Institute of Technology, U.S.
TRANSCRIPTIONAL PROGRAMMING AND REPROGRAMMING OF CARDIOMYOCYTE PROLIFERATION

FRIDAY, 16 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIE: EPITHELIAL STEM CELLS** Level 2, Room 258C

Chair: Cédric Blanpain
Université Libre de Bruxelles, Belgium

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Doug Winton**
University of Cambridge, U.K.
USING CLONAL DYNAMICS TO PROBE INTESTINAL STEM CELL PLASTICITY AND SELF RENEWAL

13:45 – 14:00 **Scott Williams**
University of North Carolina at Chapel Hill, U.S.
A POPULATION OF ORAL EPITHELIAL LABEL-RETAINING CELLS RESIDES IN A DISCRETE NICHE IN PALATAL RUGAE RIDGES

14:00 – 14:15 **Lucy Erin O'Brien**
Stanford School of Medicine, U.S.
AUTONOMOUS MOTILITY ENFORCES AN ORDERED SPATIAL DISTRIBUTION OF DROSOPHILA INTESTINAL STEM CELLS

14:15 – 14:30 **Catherine Lu**
The Rockefeller University, U.S.
SPATIOTEMPORAL ANTAGONISM IN MESENCHYMAL-EPITHELIAL SIGNALING IN SWEAT VERSUS HAIR FATE DECISION

14:30 – 14:45 **Ana Pardo-Saganta**
Center for Applied Medical Research (CIMA), Spain
AIRWAY STEM CELLS GOVERN GLOBAL TISSUE RESPONSE TO INJURY

14:45 – 15:10 **Fiona Watt**
King's College London, U.K.
REVERSIBLE TRANSITIONS BETWEEN THE STEM AND DIFFERENTIATED CELL COMPARTMENTS IN MAMMALIAN EPIDERMIS

FRIDAY, 16 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIF: NEW TOOLS FOR STEM CELL RESEARCH** Level 2, Room 205BC

Chair: Arnold R. Kriegstein
University of California San Francisco, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Jacco van Rheenen**
Hubrecht Institute, Netherlands
INTRAVITAL IMAGING REVEALS THE DYNAMIC BEHAVIOUR OF INTESTINAL AND MAMMARY STEM CELLS

13:45 – 14:00 **Matthew Brown**
UW-Madison/Morgridge Institute for Research, U.S.
A NOVEL HUMANIZED MOUSE MODEL INCORPORATING NON-FETAL TISSUE FOR INVESTIGATION OF INDUCED PLURIPOTENT STEM CELL IMMUNOGENICITY

14:00 – 14:15 **William Skarnes**
The Jackson Laboratory, U.S.
BIALLELIC GENOME EDITING OF A REFERENCE HUMAN STEM CELL LINE

14:15 – 14:30 **Christa Haase**
Massachusetts General Hospital, U.S.
IMAGE-GUIDED EXTRACTION OF SINGLE CELLS FROM THE BONE MARROW OF LIVE MICE FOR SPATIALLY-RESOLVED TRANSCRIPTOMIC ANALYSIS

14:30 – 14:45 **Ulrich Elling**
Institute of Molecular Biotechnology (IMBA), Austria
A CONDITIONAL HAPLOID ES CELL BIOBANK FOR FUNCTIONAL GENOMICS

14:45 – 15:10 **Hans-Reimer Rodewald**
German Cancer Research Center (DKFZ), Germany
CRE RECOMBINASE-DRIVEN ENDOGENOUS BARCODING TOWARDS DECONVOLUTION OF HEMATOPOIESIS

FRIDAY, 16 JUNE *(continued)*

13:15 – 15:15	**CONCURRENT IIIG: ROAD TO THE CLINIC I** **Chair: Masayo Takahashi** *RIKEN Center for Developmental Biology, Japan*	Level 2, Room 253ABC
13:15 – 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 – 13:45	**Hardy Kagimoto** *HEALIOS K.K., Japan* HEALIOS CORPORATE STRATEGY TO ADVANCE REGENERATIVE MEDICINE GLOBALLY	
13:45 – 14:00	**Alessandro Prigione** *Max Delbrueck Center for Molecular Medicine (MDC), Germany* HUMAN IPSC-DERIVED NEURAL PROGENITORS ARE AN EFFECTIVE DRUG DISCOVERY MODEL FOR NEUROLOGICAL MTDNA DISORDERS	
14:00 – 14:15	**Elisa Di Pasquale** *National Research Council of Italy, Italy* THE K219T MUTATION IN LMNA GENE PERTURBS CARDIAC FUNCTION THROUGH EPIGENETIC MODULATION OF SCN5A GENE EXPRESSION IN A HUMAN IPSC-BASED CARDIAC MODEL OF LAMINOPATHY	
14:15 – 14:30	**Alfredo Cabrera Socorro** *Janssen Research Development, Belgium* TOWARDS THE STANDARDIZATION OF IPSC TECHNOLOGY FOR DRUG DEVELOPMENT IN NEUROSCIENCE: CHALLENGING DATA REPRODUCIBILITY USING IPSC-DERIVED TAU-MUTANT NEURONS	
14:30 – 14:45	**Zuzana Tothova** *Dana Farber Cancer Institute, U.S.* MODELING THE GENETIC COMPLEXITY OF HUMAN HEMATOLOGIC MALIGNANCIES USING CRISPR GENOME ENGINEERING	
14:45 – 15:10	**Catriona Jamieson** *University of California, San Diego, U.S.* THE ROLE OF RNA PROCESSING DEREGULATION IN BENIGN AND MALIGNANT PROGENITOR AGING	
15:15 – 16:00	**MEET-UP: MEET THE EDITORS OF STEM CELL REPORTS**	Meet-up Hub #1
15:15 – 16:00	**REFRESHMENT BREAK**	ISSCR Exhibit & Poster Hall, Exhibition Hall A

FRIDAY, 16 JUNE *(continued)*

16:00 – 18:00	**PLENARY V: STEM CELLS - STRESS, SENESCENCE AND AGING** **Chair: Elly Tanaka** *Institute of Molecular Pathology, Austria*	Exhibit Level, Exhibition Hall B1
16:00 – 16:15	**ISSCR BUSINESS MEETING**	
16:15 – 16:40	**Thomas Rando** *Stanford University School of Medicine, U.S.* EPIGENETIC MECHANISMS OF STEM CELL AGING AND REJUVENATION	
16:40 – 17:05	**Emi Nishimura** *Tokyo Medical and Dental University, Japan* STEM CELLS ORCHESTRATES HAIR FOLLICLE AGING PROGRAM	
17:05 – 17:30	**Leanne Jones** *University of California, Los Angeles, U.S.* AGE-RELATED CHANGES TO STEM CELLS AND THE STEM CELL NICHE	
17:30 – 17:55	**Leonard Guarente** *Department of Biology and Koch Institute, MIT, U.S.* SIRTUINS, NAD+ AND STEM CELLS	
18:00 – 20:00	**POSTER SESSION III AND RECEPTION** ODD numbered posters present from 18:00-19:00 EVEN numbered posters present from 19:00-20:00	ISSCR Exhibit & Poster Hall, Exhibition Hall A

SATURDAY, 17 JUNE

8:15 – 18:30	**REGISTRATION OPEN**	Level 1, North Lobby
8:15 – 9:00	**MORNING COFFEE**	Plenary Hall, Exhibit Level, Exhibition Hall B1
9:00 – 11:05	**PLENARY VI: TISSUE REGENERATION AND HOMEOSTASIS** **Chair: Urban Lendahl** *Karolinska Institutet, Sweden*	Exhibit Level, Exhibition Hall B1
9:00 – 09:25	**Jayaraj Rajagopal** *MGH Center for Regenerative Medicine, HHMI Faculty Scholar, U.S.* ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE: ISSUE LOGIC IN THE AIRWAY EPITHELIUM: NICHES, NOTCHES, CIRCUITS, HETER0GENEITY, AND PLASTICITY	
9:25 – 09:50	**Peter Reddien** *Whitehead Institute for Biomedical Research, MIT, U.S.* THE CELLULAR AND MOLECULAR BASIS FOR REGENERATION IN PLANARIANS	
9:50 – 10:15	**Valentina Greco** *Yale Stem Cell Center, Yale Medical School, U.S.* TISSUE CORRECTION OF ABERRANT GROWTH PRESERVES HOMEOSTASIS	
10:15 – 10:40	**Constance Cepko** *Harvard Medical School, U.S.* DETERMINATION OF CELL FATE IN THE VERTEBRATE RETINA	
10:40 – 11:05	**Elaine Fuchs** *HHMI, The Rockefeller University, U.S.* MCEWEN AWARD FOR INNOVATION LECTURE: FOUR DECADES OF RESEARCH ON SKIN STEM CELLS	
11:00 – 16:00	**ISSCR EXHIBIT HALL OPEN**	Level 1, Exhibition Hall A
11:20 – 13:15	**LUNCH BREAK**	
11:30 – 13:00	**JUNIOR INVESTIGATOR CAREER PANEL LUNCHEON** *Sponsored by: Stem Cell Program at Boston Children's Hospital* *(Junior Investigator event; advance registration required.)*	Level 3, Ballroom Lobby

SATURDAY, 17 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IVA: PLURIPOTENCY AND IPS CELL REPROGRAMMING II** Level 3, Ballroom East

Chair: Konrad Hochedlinger
Massachusetts General Hospital, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Duanqing Pei**
Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, China
ALTERNATIVE PATH TO PLURIPOTENCY

13:45 – 14:00 **Yuin Han Loh**
Institute of Molecular and Cell Biology, Singapore
SINGLE-CELL CHROMATIN ACCESSIBILITY LANDSCAPES IN CELL FATE REPROGRAMMING

14:00 – 14:15 **Jian Shu**
Broad Institute of MIT and Harvard, U.S.
A CONTINUOUS MOLECULAR ATLAS OF REPROGRAMMING TO IPSCS BY HIGH-THROUGHPUT SINGLE CELL RNA-SEQ

14:15 – 14:30 **Hannah Stuart**
Stem Cell Institute, University of Cambridge, U.K.
SIGNALLING AND TRANSCRIPTIONAL NETWORK INTERPLAY ESTABLISHES THE NAIVE PLURIPOTENT IDENTITY VIA MULTIPLE MECHANISTICALLY DISTINCT ROUTES WITH KEY CONSERVED FEATURES

14:30 – 14:45 **Elisa Narva**
Turku University, Finland
STRONG CONTRACTILE ACTIN FENCE AND CORNERSTONE ADHESIONS DIRECT HUMAN PLURIPOTENT COLONY MORPHOLOGY

14:45 – 15:10 **Kazutoshi Takahashi**
Gladstone Institute of Cardiovascular Disease, U.S.
EARLY HUMAN REPROGRAMMED CELLS ARE MARKED WITH ESRG AND SHOW PROLIFERATION PAUSE REGULATED BY LIN41/P21/RB AXIS

SATURDAY, 17 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IVB: STEM CELLS AND CANCER** Level 2, Room 253ABC

Chair: Valentina Greco
Yale Stem Cell Center, Yale Medical School, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Luis Parada**
Memorial Sloan Kettering Cancer Center, U.S.
GLIOMA STEM CELLLS: ORIGIN AND MOLECULAR FEATURES

13:45 – 14:00 **Francois Mercier**
Massachusetts General Hospital, U.S.
FUNCTIONAL PROFILING OF MURINE LEUKEMIC STEM CELL FITNESS IN VIVO USING COMBINED CRISPR SCREENING AND MODELING OF CLONAL COMPETITION

14:00 – 14:15 **Semir Beyaz**
Harvard Medical School, U.S.
HIGH-FAT DIET DAMPENS IMMUNE SURVEILLANCE OF PREMALIGNANT INTESTINAL STEM CELLS

14:15 – 14:30 **Salvador Aznar-Benitah**
ICREA Researcher, Institute for Research in Biomedicine (IRB Barcelona), Spain
IDENTIFYING AND TARGETING METASTATIC-INITIATING CELLS: A LINK BETWEEN WHAT WE EAT AND METASTASIS

14:30 – 14:45 **Christine Fillmore Brainson**
University of Kentucky, U.S.
LKB1 INACTIVATION DRIVES EPIGENETIC LUNG CANCER LINEAGE SWITCHING FROM DISTINCT CELLS-OF-ORIGIN

14:45 – 15:10 **Philip Beachy**
Stanford University, U.S.
THE STROMAL CELL NICHE FOR EPITHELIAL STEM CELLS: A TEMPLATE FOR ORGAN REGENERATION AND A BRAKE ON MALIGNANCY

SATURDAY, 17 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IVC: GERM CELL DEVELOPMENT** Level 2, Room 258C

Chair: Haifan Lin
Yale University School of Medicine, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Ali Brivanlou**
The Rockefeller University, U.S.
SELF-ORGANIZATION IN SYNTHETIC HUMAN EMBRYOS

13:45 – 14:00 **Di Chen**
University of California, Los Angeles, U.S.
HUMAN PGCLC COMPETENCY DEPENDS ON TFAP2C AND INDUCTION OF CELLS WITH A PRIMITIVE STREAK/MESENDODERM IDENTITY

14:00 – 14:15 **Elena Itskovich**
University of Cambridge, U.K.
BRD4 IS A CONSERVED EPIGENETIC READER THAT PLAYS A KEY ROLE IN MOUSE AND HUMAN PRIMORDIAL GERM CELL SPECIFICATION AND MAINTENANCE

14:15 – 14:30 **Kotaro Sasaki**
Kyoto University, Japan
THE GERM CELL FATE OF CYNOMOLGUS MONKEYS IS SPECIFIED IN THE NASCENT AMNION

14:30 – 14:45 **Fang-Ju Wu**
National Yang-Ming University, Taiwan
BMP8 SUSTAINS SPERMATOGENESIS BY PROMOTING PROLIFERATION AND DIFFERENTIATION OF MOUSE SPERMATOGONIA THROUGH DIFFERENT SMAD PATHWAYS

14:45 – 15:10 **Mitinori Saitou**
Kyoto University, Japan
MECHANISM AND RECONSTITUTION IN VITRO OF GERM CELL DEVELOPMENT IN MICE, MONKEYS, AND HUMANS

SATURDAY, 17 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IVD: ETHICS AND REGULATORY CONSIDERATIONS** Level 2, Room 205A

Chair: Martin Pera
The Jackson Laboratory, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Alta Charo**
University of Wisconsin, U.S.
HUMAN GENOME EDITING: ETHICS AND GOVERNANCE

13:45 – 14:00 **Kirstin Matthews**
Rice University, U.S.
ASSESSING AND ANALYZING THE 14-DAY GUIDELINE ON HUMAN EMBRYO RESEARCH FROM ETHICAL AND POLITICAL AND SCIENTIFIC PERSPECTIVES

14:00 – 14:15 **Kayo Takashima**
The Institute of Medical Science, University of Tokyo, Japan
ETHICAL DISCUSSION ON THE FIRST-IN-HUMAN STUDY OF IPSC-DERIVED RPE WITH AMD: AN ANALYSIS OF THE REVIEW COMMITTEE MEETING MINUTES

14:15 – 14:30 **Zubin Master**
Alden March Bioethics Institute, Albany Medical College, U.S.
THE IMPACT OF CIVIL LAWSUITS ON DIRECT-TO-CONSUMER MARKETING OF STEM CELL INTERVENTIONS

14:30 – 14:45 **Tenneille Ludwig**
WiCell, U.S.
20 YEARS OF HUMAN PLURIPOTENT STEM CELL IMPACT: PATENTS, PUBLICATIONS, AND FUNDING

14:45 – 15:10 **George Q. Daley**
Boston Children's Hospital, Harvard Medical School, U.S.
EMERGING BIOMEDICAL TECHNOLOGY: A BRAVE NEW WORLD

SATURDAY, 17 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IVE: DISEASE MODELING** Level 3, Ballroom West

Chair: Ira Fox
Children's Hospital of Pittsburgh of UPMC, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Leonard Zon**
Boston Children's Hospital, U.S.
PATHWAYS REGULATING STEM CELL INDUCTION, SELF-RENEWAL, AND ENGRAFTMENT

13:45 – 14:00 **Zhexing Wen**
Emory University School of Medicine, U.S.
MODELING ZIKA VIRUS EXPOSURE AND SCREENING THERAPEUTIC COMPOUNDS WITH HUMAN IPSC-DERIVED NEURAL CELLS

14:00 – 14:15 **Brigitte Gomperts**
University of California, Los Angeles, U.S.
USING AN INDUCED PLURIPOTENT STEM CELL MODEL TO UNDERSTAND AND TREAT IDIOPATHIC PULMONARY FIBROSIS

14:15 – 14:30 **Carola Maria Morell**
Wellcome Trust - Medical Research Council Stem Cell Institute, U.K.
A NOVEL 3D IN VITRO APPROACH TO MODEL LIVER DISEASES USING HUMAN INDUCED PLURIPOTENT STEM CELLS

14:30 – 14:45 **Andrea Ditadi**
SR-TIGET, Italy
DISSECTING THE CELLULAR ORIGIN OF DOWN SYNDROME TMD AND AMKL

14:45 – 15:10 **Carla Kim**
Boston Children's Hospital, U.S.
REGULATION OF PROGENITOR CELLS IN THE ADULT LUNG AND IN LUNG CANCER

SATURDAY, 17 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IVF: ROAD TO THE CLINIC II** Level 2, Room 258AB

Chair: Viviane Tabar
Memorial Sloan Kettering Cancer Center, U.S.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Michele De Luca**
Centre for Regenerative Medicine, University of Modena and Reggio Emilia, Italy
EPIDERMAL STEM CELL-MEDIATED COMBINED CELL AND GENE THERAPY FOR EPIDERMOLYSIS BULLOSA

13:45 – 14:00 **Benjamin Reubinoff**
Center for Human Embryonic Stem Cell Research, Goldyne Savad Institute; and Hadassah-Hebrew University Medical Center, Israel
PHASE I/IIA CLINICAL TRANSPLANTATION TRIAL OF HUMAN EMBRYONIC STEM CELL-DERIVED RETINAL PIGMENT EPITHELIUM (OPREGEN®) IN DRY AGE-RELATED MACULAR DEGENERATION: INTERIM RESULTS

14:00 – 14:15 **Shigeo Masuda**
Osaka University Graduate School of Medicine, Japan
ELIMINATING RESIDUAL UNDIFFERENTIATED CELLS FROM HUMAN IPS-DERIVED PRODUCTS BY HEAT SHOCK PROTEIN 90 INHIBITORS

14:15 – 14:30 **Megan Munsie**
University of Melbourne, Australia
IDENTIFYING PATHWAYS TO STEM CELL TREATMENTS AND OPPORTUNITIES TO BUILD ROADBLOCKS: AN ANALYSIS OF THE EXPERIENCES OF PEOPLE WITH SPINAL CORD INJURY

14:30 – 14:45 **Ravi Chandra Yada**
National Institutes of Health, U.S.
GENERATION AND FUNCTIONAL CHARACTERIZATION OF SODIUM IODIDE SYMPORTER TRANSGENIC RHESUS INDUCED PLURIPOTENT STEM CELLS

14:45 – 15:10 **Kia Washington**
University of Pittsburgh, U.S.
TOTAL HUMAN EYE ALLOTRANSPLANTATION: FROM EXPERIMENTAL MODEL TO CLINICAL REALITY

SATURDAY, 17 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IVG: TISSUE ENGINEERING AND CLINICAL APPLICATIONS** Level 2, Room 205BC

Chair: Timothy Allsopp
Consilium Bio Ltd., U.K.

13:15 – 13:20 **TOPIC OVERVIEW BY CHAIR**

13:20 – 13:45 **Molly Shoichet**
University of Toronto, Canada
EXOGENOUS STEM CELL TRANSPLANTATION AND ENDOGENOUS STEM CELL STIMULATION IN THE CENTRAL NERVOUS SYSTEM

13:45 – 14:00 **Christopher Schlieve**
Children's Hospital Los Angeles, U.S.
RESTORATION OF A NEUROEPITHELIAL NETWORK AND NEURON-DEPENDENT MOTILITY IN HUMAN INTESTINAL ORGANOID-DERIVED TISSUE-ENGINEERED SMALL INTESTINE

14:00 – 14:15 **Yibing Qyang**
Yale Stem Cell Center, U.S.
TOWARDS VASCULAR REPAIR USING HUMAN INDUCED PLURIPOTENT STEM CELL-BASED TISSUE-ENGINEERED BLOOD VESSELS

14:15 – 14:30 **Jie Na**
Tsinghua University, China
MESODERM PROGENITOR SELECTION OPTIMIZATION AND 3D MICRONICHE CULTURE ALLOW HIGHLY EFFICIENT ENDOTHELIAL DIFFERENTIATION AND ISCHEMIC TISSUE REPAIR FROM HUMAN PLURIPOTENT STEM CELLS

14:30 – 14:45 **Wolfram Zimmermann**
Georg-August-University Goettingen, Germany
TRANSLATION OF TISSUE ENGINEERED HEART REPAIR

14:45 – 15:10 **Kang Zhang**
Shiley Eye Center, University of California, San Diego, U.S.
LENS REGENERATION USING ENDOGENOUS STEM CELLS WITH GAIN OF VISUAL FUNCTION

SATURDAY, 17 JUNE *(continued)*

15:15 – 16:00	**MEET-UP HUBS**	ISSCR Exhibit & Poster Hall, Exhibition Hall A
15:15 – 16:00	**REFRESHMENT BREAK**	ISSCR Exhibit & Poster Hall, Exhibition Hall A
16:00 – 18:30	**PLENARY VII: FRONTIERS OF CELL THERAPY** *Sponsored by: Burroughs Wellcome Fund* **Chair: Hans C. Clevers** *Hubrecht Institute, Netherlands*	Exhibit Level, Exhibition Hall B1
16:00 – 16:05	**PRESIDENT-ELECT ADDRESS: HANS CLEVERS**	
16:05 – 16:40	**George Church** *Harvard Medical School, U.S.* KEYNOTE ADDRESS: TECHNOLOGIES FOR READING & WRITING OMES	
16:40 – 17:05	**Adrian Thrasher** *UCL Great Ormond Street Institute of Child Health,U.K.* JOHN MCNEISH MEMORIAL LECTURE: EVOLVING GENE THERAPY FOR PRIMARY IMMUNODEFICIENCIES	
17:05 – 17:30	**Olle Lindvall** *University of Lund,Sweden* REPLACING NEURONS BY TRANSPLANTATION IN THE DISEASED HUMAN BRAIN	
17:30 – 17:55	**Masayo Takahashi** *RIKEN Center for Developmental Biology, Japan* RETINAL CELL THERAPY USING IPS CELLS	
17:55 – 18:20	**Douglas A. Melton** *Harvard University and Harvard Stem Cell Institute, USA* MAKING PANCREATIC ISLET CELLS FOR DIABETICS AND DIABETES RESEARCH	
18:20 – 18:30	**POSTER AWARD ANNOUNCEMENTS AND CLOSING REMARKS**	

STEM CELL REPORTS

EDITOR-IN-CHIEF
Christine Mummery, PhD
Leiden University Medical Center

ISSCR's **open-access** journal offering the latest research and technologies across the breadth of stem cell science and its applications to medicine.

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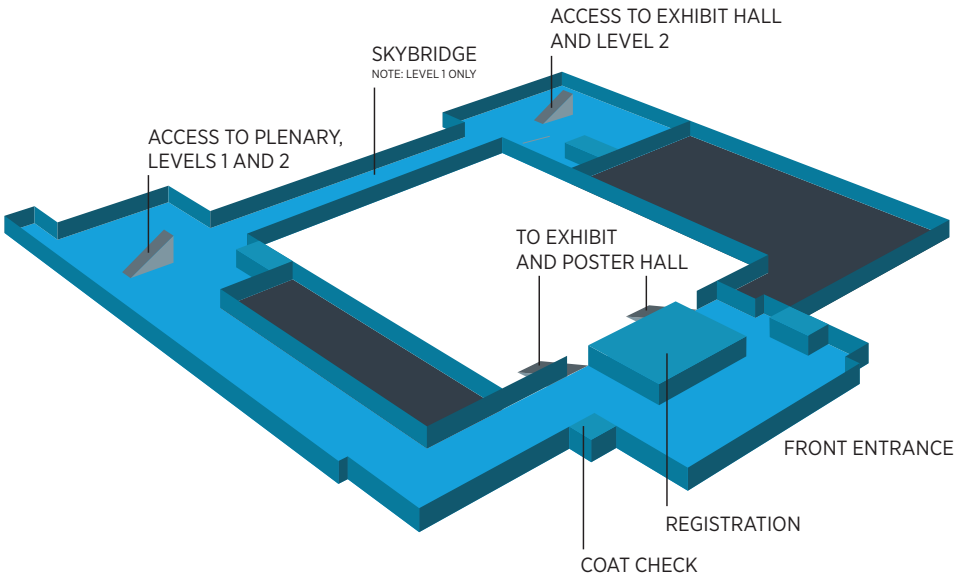
EXHIBIT & POSTER HALL, INNOVATION SHOWCASES

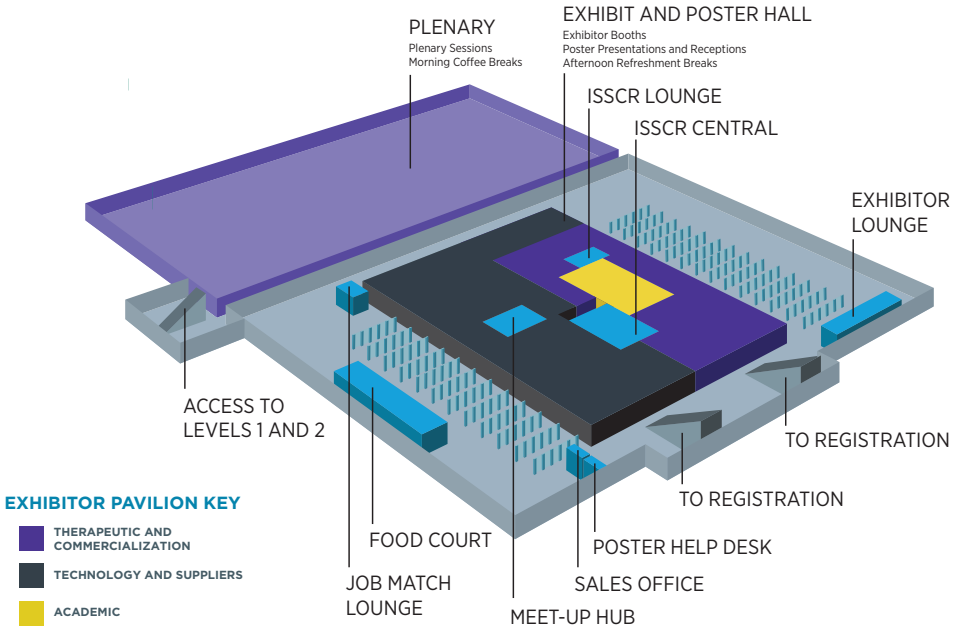
LEVEL ONE

Registration, Exhibit & Poster Hall



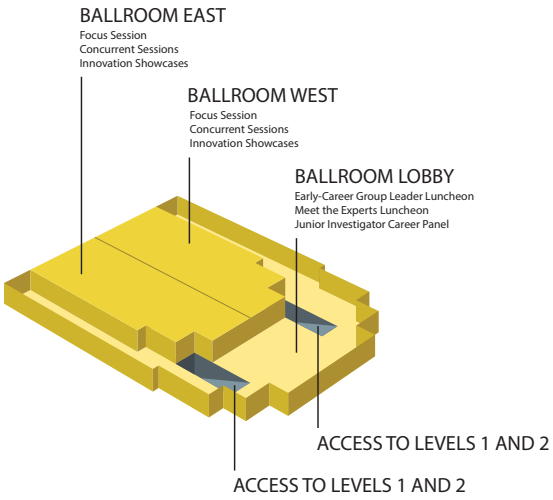
LOWER LEVEL

Plenary Hall, Exhibit and Poster Hall



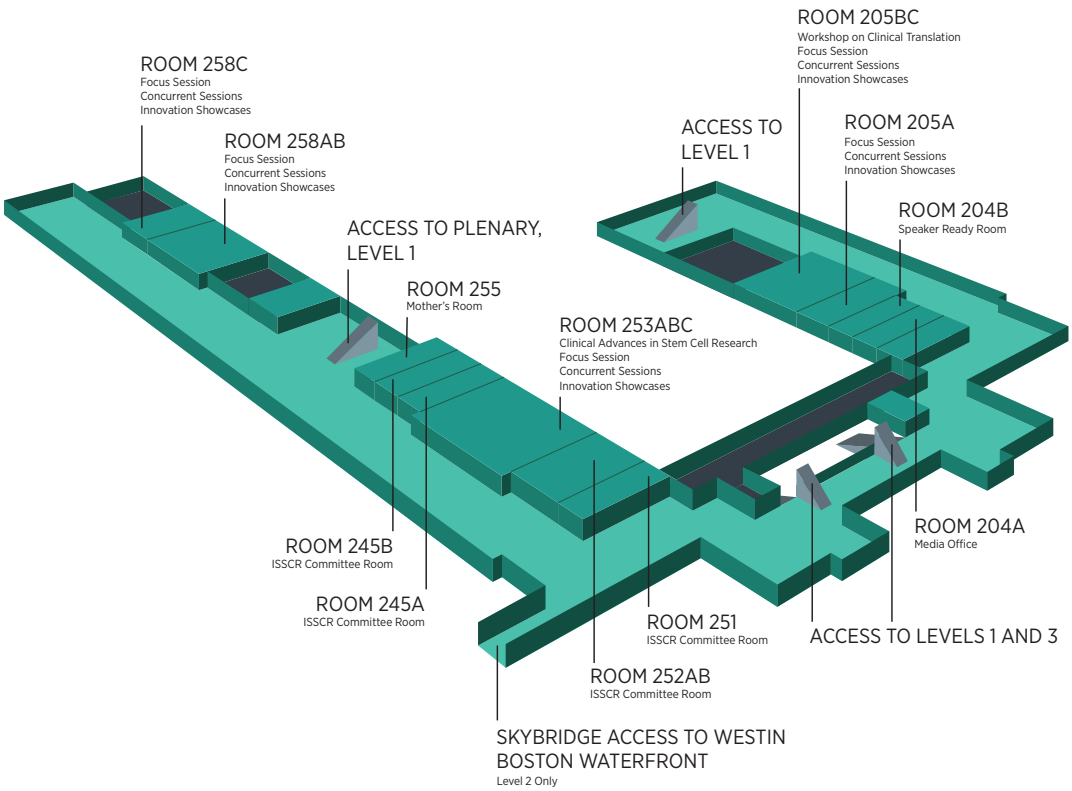
LEVEL THREE

Session Rooms, JI and Early-Career Luncheons, Innovation Showcases



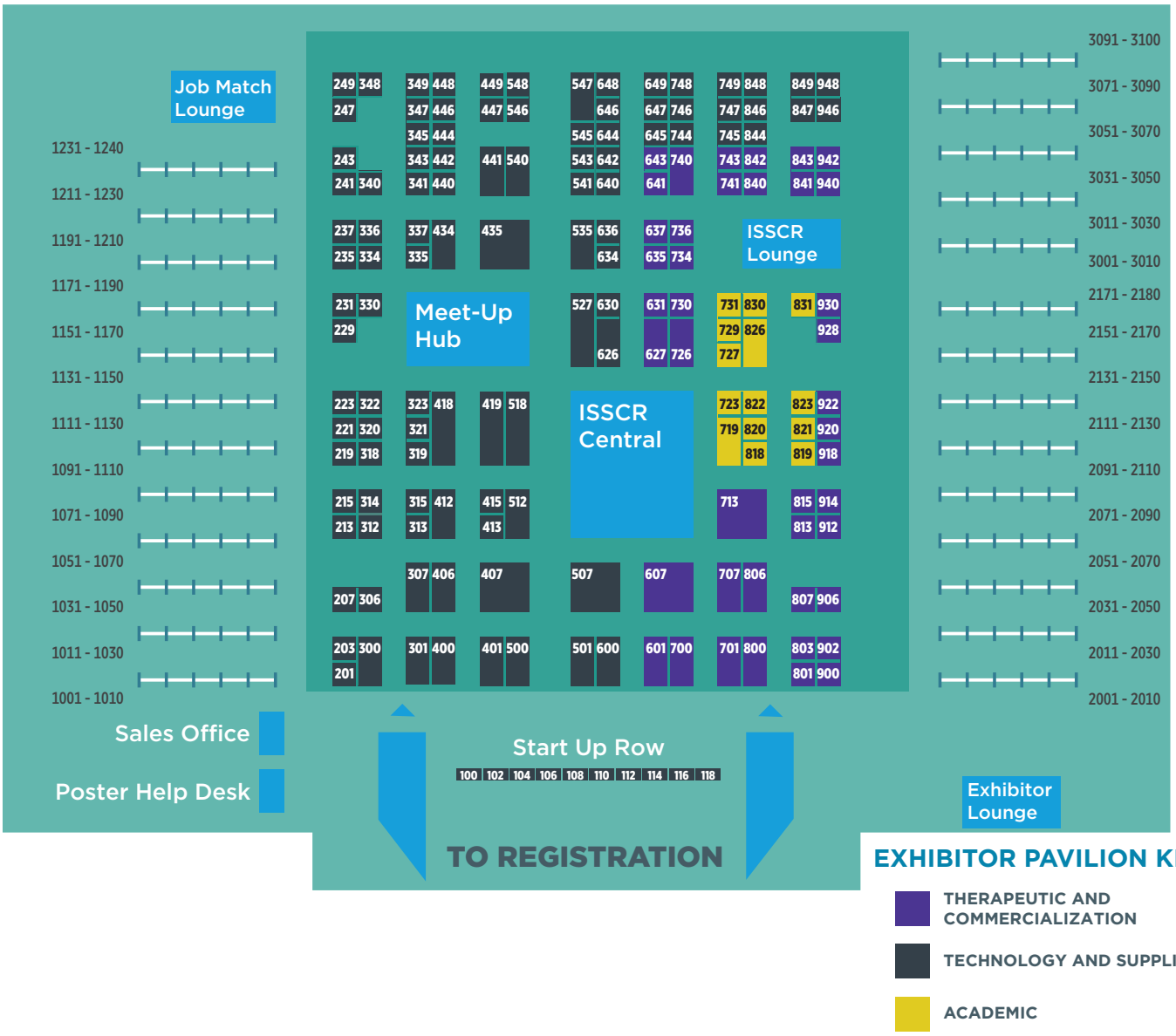
LEVEL TWO

Session Rooms, Committee Rooms, Media Office



BOSTON CONVENTION CENTER, LOWER LEVEL

Exhibit & Poster Hall



EXHIBITOR PAVILION KEY

- THERAPEUTIC AND COMMERCIALIZATION
- TECHNOLOGY AND SUPPLIERS
- ACADEMIC

POSTER BOARDS BY TOPIC

POSTER TOPICS	START NUMBER	END NUMBER
Placenta and Umbilical Cord Derived Cells	1001	1004
Adipose, Musculoskeletal, and Connective Tissue	1005	1024
Cardiac Tissue	1025	1036
Endothelial Cells and Hemangioblasts	1037	1040
Hematopoiesis/Immunology	1041	1060
Pancreas, Liver, Kidney	1061	1073
Epithelial Tissues	1074	1087
Stem Cell Niches	1088	1098
Eye and Retina	1099	1107
Neural Development and Regeneration	1108	1130
Neural Disease and Degeneration	1131	1157
Cancers	1158	1173
Chromatin and Epigenetics	1174	1182
Organoids	1183	1196
Tissue Engineering	1197	1216
Ethical, Legal and Social Issues; Education and Outreach	1217	1223
Clinical Trials and Regenerative Medicine Interventions	1224	1231
Germline, Early Embryo and Totipotency	2001	2004
Pluripotency	2005	2030
Pluripotent Stem Cell Differentiation	2031	2078
Pluripotent Stem Cell: Disease Modeling	2079	2114
Reprogramming	2115	2132
Technologies for Stem Cell Research	2133	2174
LATE-BREAKING	3001	3090

EXHIBITORS, ALPHA BY NAME

COMPANY	STAND NUMBER
10x Genomics	700
Abcam Inc.	401
ABLE/Biott	337
Advanced Cell Diagnostics, Inc.	501
Agilent Technologies, Inc.	203
AIP Publishing	822
Ajinomoto Co., Inc.	412
AllCells, LLC	413
Allen Institute for Cell Science	434
Alpha MED Scientific Inc.	213
ALS Automated Lab Solutions GmbH	415
ALSTEM, Inc.	114
AMSBIO LLC	207
Analytik Jena (formally UVP LLC)	215
Applied StemCell, Inc.	347
Atlas Antibodies AB	442
Axion BioSystems	322
Axol Bioscience Ltd.	334
Azure Biosystems	701
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BD Biosciences	518
Be The Match BioTherapies	841
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BioLamina	300
BioLegend	813
Biological Industries	407
BioMedTech Laboratories, Inc.	630
BioSpherix, Ltd.	306
BioSpherix Medical	807
Biostage, Inc.	842
Bio-Techne	419
BioTek Instruments, Inc.	912
Boston TransTec	102
Brooks Life Science Systems	649
Bulldog Bio	219
CBSET, Inc.	843
Cell Guidance Systems	741
Cell Line Genetics, Inc.	400
Cell Press	719
Cell Signaling Technology	313
Cellara, LLC	444

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COMPANY	STAND NUMBER
CELLINK	106
Cellular Dynamics Intl, a FUJIFILM company	707
Cellular Engineering Technologies Inc.	846
Cell X Technologies	116
The Center for iPS Cell Research and Application (CiRA), Kyoto University	830
ChemoMetec	512
The Company of Biologists	731
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DefiniGEN	541
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The European Collection of Authenticated Cell Cultures	844
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GenScript	546
Greiner Bio-One North America, Inc.	545
HemaCare BioResearch Products & Services	906
Humanzyme, Inc.	321
Illumina	406
IMBA - Institute of Molecular Biotechnology GmbH	646
Instant Systems	640
International Federation for Adipose Therapeutics & Science	743
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Leica Microsystems	243
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Macopharma	636
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COMPANY	STAND NUMBER
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MilliporeSigma	307
Miltenyi Biotec GmbH	435
Minerva Biotechnologies	637
Molecular Devices	319
Multi Channel Systems	747
Nacalai Tesque, Inc.	914
NanoCellect Biomedical	647
NanoEnTek	641
NANOLIVE SA	644
NDRI	940
The New York Stem Cell Foundation Research Institute	727
Nexcelom Bioscience	314
Nikon Corporation	540
Nippi	223
Nipro Corporation	746
Novoprotein Scientific Inc.	335
Olympus	323
On-chip Biotechnologies Co., Ltd.	249
Ontario Institute for Regenerative Medicine	820
Optologix, Inc.	104
Pakair Cargo	745
Panasonic Healthcare Corporation of North America	800
PeproTech, Inc.	713
Prodizen	446
PromoCell GmbH	312
Proteintech Group Inc.	840
RayBiotech Inc.	229
RegMedNet	340
ReproCELL Inc.	626
Roche Custom Biotech	301
RoosterBio Inc.	928
RUCDR Infinite Biologics	823
Sanplatec Corp.	441
Sartorius	740
S-BIO, Sumitomo Bakelite Co., Ltd.	642
School of Life Science and Technology, ShanghaiTech University	831
Selleck Chemicals LLC	247
Shenandoah Biotechnology Inc.	320
Sinfonia Technology Co., Ltd.	349
Sino Biological Inc.	231

EXHIBITORS. ALPHA BY NAME

COMPANY	STAND NUMBER
Society for Neuroscience	821
Sony Biotechnology Inc.	535
Springer Nature	826
StemBioSys, Inc.	315
STEM CELLS Journals	819
STEMCELL Technologies	527
StemCultures	815
StemExpress	744
StemImmune LLC	920
StemoniX	448
Synthego	112
Takara Bio USA, Inc.	601
Takeda Pharmaceutical Company Limited	930
Tecan	918
Thermo Fisher Scientific	507
Thrive Bioscience	500
TOLIMS	118
Trevigen	330
TriFoil Imaging	237
UK Stem Cell Bank	345
Union Biometrica, Inc.	634
UPM-Kymmene Corporation	343
uSTEM s.r.l.	108
Waisman Biomanufacturing	734
WiCell	627
Wiley	729
Worthington Biochemical Corporation	318

ACADEMIC

COMPANY	STAND NUMBER
AIP Publishing	822
Cell Press	719
The Center for iPS Cell Research and Application (CiRA), Kyoto University	830
The Company of Biologists	731
Elsevier	723
Mary Ann Liebert, Inc.	818
The New York Stem Cell Foundation Research Institute	727
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RUCDR Infinite Biologics	823
School of Life Science and Technology, ShanghaiTech University	831
Society for Neuroscience	821
Springer Nature	826
STEM CELLS Journals	819
Wiley	729

START UP ROW

COMPANY	STAND NUMBER
ALSTEM, Inc.	114
Boston TransTec	102
Cell X Technologies	116
CELLINK	106
East River Biosolutions, Inc.	110
Magnetic Insight Inc.	100
Optologix, Inc.	104
Synthego	112
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Allen Institute for Cell Science	434
Alpha MED Scientific Inc.	213

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Instant Systems	640
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Keyence Corporation of America	235
Leica Microsystems	243

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Thrive Bioscience	500
Trevigen	330
TriFoil Imaging	237
UK Stem Cell Bank	345
Union Biometrica, Inc.	634

COMPANY	STAND NUMBER
UPM-Kymmene Corporation	343
Worthington Biochemical Corporation	318

THERAPEUTIC AND COMMERCIALIZATION PAVILION

COMPANY	STAND NUMBER
10x Genomics	700
Be The Match BioTherapies	841
BioSpherix Medical	807
Biostage, Inc.	842
BioTek Instruments, Inc.	912
CBSET, Inc.	843
Cell Guidance Systems	741
Cellular Dynamics Intl, a FUJIFILM company	707
Corning Life Sciences	607
Echo Laboratories	806
Eppendorf	730
Essen Bioscience	736
Genea Biocells US	635
HemaCare BioResearch Products & Services	906
International Federation for Adipose Therapeutics & Science	743
Irvine Scientific	726
MedCision	631
Minerva Biotechnologies	637
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NanoEnTek	641
NDRI	940
Pakair Cargo	745
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PeproTech, Inc.	713
Proteintech Group Inc.	840
RoosterBio Inc.	928
Sartorius	740
StemCultures	815
StemImmune LLC	920
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Tecan	918
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Trevigen, Inc. is focused on the development of products and technologies for cancer research, regenerative medicine, stem cell work, drug discovery, and genetic toxicology. We offer kits and reagents for the study of cancer cell behavior, 3D culture, stem cells, DNA damage & repair, apoptosis, oxidative stress. The company is the recipient of several SBIR grants from the National Institute of Health.

TRIFOIL IMAGING - STAND 237

9457 De Soto Avenue
Chatsworth, CA
91311 U.S.A.
+1 818-709-2468
www.trifoilimaging.com

With a wide variety of systems installed (over 300) TriFoil Imaging drives product innovation in the in-vivo molecular imaging market with the first ever 360° fluorescence imaging (FLECT™) system with integrated X-Ray CT. TriFoil Imaging's technologies enable pharmaceutical companies to reduce costs and standardize analytical techniques across key areas of the drug development/discovery chain.

UK STEM CELL BANK - STAND 345

Blanche Lane, South Mimms
Potters Bar
Herts
EN63QG UK
+44 0-170-764-1000
www.nibsc.org/ukstemcellbank

The UK Stem Cell Bank (UKSCB) provides an international resource for stem cell research, supplying human stem cell lines, both for research and to those wishing to develop cell lines for clinical application. It also has an active programme of precompetitive research in collaboration with academia and industry

UNION BIOMETRICA, INC. - STAND 634

84 October Hill Road
Holliston, MA
01746 U.S.A.
+1 508-893-3115
www.unionbio.com

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

UPM-KYMMENE CORPORATION - STAND 343

Alvar Aallon Katu 1
Helsinki
00101 Finland
+358 204-15-111
www.growdex.com

UPM leads the integration of bio and forest industries into a new, sustainable and innovation-driven products. GrowDex®, a wood-derived hydrogel that physically resembles human ECM, is xeno-free, supports 3D cell growth, spheroid formation and differentiation, is one of these new innovations.
GrowDex® - providing natural solutions for effective cell culture.

USTEM S.R.L. - STAND 108

Corso Stati Uniti 4
Padova
35127 Italy
+39 0-499-64-0155
www.ustemcells.info/

uSTEM s.r.l. is a startup company which uses proprietary microtechnology for reprogramming human cells into iPS. uSTEM service offers fast and unmatched reprogramming efficiency, giving you the chance for high successful rate in reprogramming refractory cells. Our small systems allow you to reprogram your somatic samples starting from only 300 fibroblasts or other cell types. Microscale reprogramming permits high transgene delivery into somatic cells using only few drops of reagents per day compared to traditional methods. uSTEM is aimed at guarantee cost-effective reprogramming allowing you to get pluripotent stem cells even from a large number of patients' samples.

WAISMAN BIOMANUFACTURING - STAND 734

1500 Highland Avenue
Madison, WI
53705 U.S.A.
+1 608-262-9547
www.gmpbio.org

The primary mission of Waisman Biomanufacturing is to deliver efficient translation of scientific discoveries for early stage clinical trials by developing manufacturing processes and quality control methods in conjunction with providing overall product development and regulatory support.

WICELL - STAND 627

504 S. Rosa Road
Suite 101
Madison, WI
53719 U.S.A.
+1 888-204-1782
www.wicell.org

A recognized world leader in pluripotent stem cell banking and characterization, WiCell's stem cell repository includes 1,200+ human iPS and ES cell lines, including disease models and controls, reporter lines, and cGMP material. WiCell's distribution services safeguard your material and eliminate the burden of distribution from your lab. Characterization testing services include G-banded karyotyping, SKY, FISH, SNP/CGH microarray, and identity testing via STR.

WILEY - STAND 729

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Malden, MA
02148 U.S.A.
+1 781-388-8200
www.wiley.com

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

WORTHINGTON BIOCHEMICAL CORPORATION - STAND 318

730 Vassar Avenue
Lakewood, NJ
08701 U.S.A.
+1 800-445-9603
www.worthington-biochem.com

Register to win an iPAD at Worthington! New! Animal/Xeno Free Collagenases, DNAses, RNAses, Celase® GMP and STEMxyme® Collagenase/Neutral Protease Blends. Connect with us to receive our NEW Catalog, Manuals and 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 @ booth #318

THURSDAY, 15 JUNE

AXOL BIOSCIENCE LTD.

Level 2, Room 258C
8:00-8:30

INDUCED PLURIPOTENT STEM CELL-DERIVED ENDOTHELIAL COLONY FORMING CELLS OFFER A ROBUST AND PHYSIOLOGICALLY RELEVANT RESEARCH TOOL

Mervin C. Yoder, *Indiana University School of Medicine and Axol Bioscience Ltd.*

Human iPSC-Derived Endothelial Colony Forming Cells (ECFCs) (Axol Bioscience) are highly expandable and show comparable expression and functionality to primary cells, providing a robust and physiologically relevant tool for use in numerous applications. ECFCs are rare circulating endothelial cells that display a hierarchy of clonal proliferative potential and possess in vivo vessel-forming ability upon implantation. In numerous animal models of disease, human ECFCs have demonstrated the capacity to promote revascularization and reperfusion to injured vascular beds via direct integration and/or through paracrine effects. Human umbilical cord blood is enriched in circulating ECFCs compared to adult peripheral blood. We have recently reported that ECFCs displaying properties similar to cord blood can be obtained from human ESCs and iPSCs. Using defined serum-free culture medium and sequential addition of specific growth factors, we've identified ECFC precursors within 12 days of iPSC differentiation. These iPSC-derived ECFCs display clonogenic proliferative potential and in vivo vessel forming ability similar to cord blood ECFCs and promote vascular repair and regeneration in multiple animal models of human disease.

BIOSPHERIX

Level 3, Ballroom East
8:00-8:30

TOTAL QUALITY APPROACH TO CELL INCUBATION AND PROCESSING

Kevin Murray, *BioSpherix Medical*

Total quality recognizes that for best cell potency, cells need full-time optimization of all critical cell process parameters (O2, CO2, RH, T). Total quality recognizes that all typical negative side effects of machines on cells (particles, heat, vibration, etc.) must be neutralized to make automation compatible with a cell optimized ecosystem, and those machines must be protected from dust, aerosols, and corrosion. Total quality recognizes that each entire cell production line (all manual and automated steps) must be protected from microbial contamination by full-time, absolutely aseptic conditions. Total quality recognizes that all personnel must be fully protected from cells harboring virus, vectors, prion, and other pathogens. Total quality recognizes that scaling up and out must be efficient. Total quality recognizes that cost efficiency is a fundamental quality attribute, critical for commercial. The Xvivo System is a comprehensive, modular, total quality "platform" for cells.

LONZA

Level 3, Ballroom West
8:00-8:30

ENABLING HPSC-BASED THERAPIES FROM BENCH SIDE TO COMMERCIALIZATION

Sudha Nair, *Lonza*

Inbar Friedrich Ben-Nun, *Lonza*

Enabling hPSC-based therapies entails bridging the gap that exists between methods used in research laboratories and those that will be required in manufacturing hPSC based therapies for commercial and clinical use. This gap encompasses requirements such as cell quantity, cell quality, comparability and cost. Process scale-up as well as cGMP manufacturing and regulatory considerations should be taken into account early in the product development. Taking advantage of cell therapy-ready materials such as animal-free reagents and scalable cell culture systems, in combination with real-time in-process controllers, will significantly increase the chances of therapies reaching clinical and commercial success. We will discuss scalable cell culture systems for hPSC expansion going from translational and early clinical phase to late clinical and commercial manufacturing. Our approach is to use a bioreactor based, closed, automated and monitored platform, which allows scalability, high cell numbers and cell quality, facilitating the transition of hPSC-based therapies from the bench side to the clinic and to commercialization.

MILL CREEK LIFE SCIENCES

Level 2, Room 253ABC
8:00-8:30

IN VITRO EXPANSION OF MESENCHYMAL STEM CELLS USING MEDIA SUPPLEMENTED WITH UNFRACTIONATED, HEPARIN-FREE PLATELET LYSATE

Vanesa Alonso Camino, *Mill Creek Life Sciences*

Human platelet lysate (HPL) arose as a xenogeneic-free alternative to FBS to be used as a supplement for in vitro expansion of human Mesenchymal Stem Cells (MSCs) used in clinical applications. Due to the presence

of fibrinogen and coagulation factors, the use of the first generation HPL involves the addition of heparin to the cell culture media to prevent clotting. Heparin is purified and refined from swine according to cGMP methods and is one of the most widely used drugs in humans. MSC cell culture media with heparin have been used all over the world for more than 30 clinical trials. There has been no overt regulatory request for removal of heparin. However; some quality systems have required its removal or replacement from cell culture processes in an effort to remove any form of xenogeneic components. Here we present PLTGold®, an unfractionated product derived from HPL that does not require the addition of heparin. PLTGold® remains clot free and performs equal to the original PLTMax® platelet lysate.

NIKON CORPORATION

Level 2, Room 205BC
8:00-8:30

LIVE CELL IMAGING AND MORPHOMETRIC QUANTIFICATION OF NEURONAL DEGENERATION

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

The ability to generate patient-derived neurons using iPS cell technology provides an exciting opportunity to identify the biological defects that underlie neurodegenerative diseases and to perform screens for new therapeutics. The Rubin lab and Nikon Corporation are collaborating to use the BioStation CT for live cell imaging of disease-relevant neuronal subtypes. For these studies, cell type specific fluorescent reporters are used to identify neurons of interest within heterogenous cultures of differentiated cells. Our comprehensive analysis includes single cell tracking over extended periods of time (up to weeks) paired with detailed measurements of various cell properties like changes in soma size and growth of neurites. This approach has uncovered morphological changes occurring in neurons undergoing stress, providing early signs of impending death. Further, we have used these changes to identify degenerating neurons that can still be fully rescued and to find different treatments that have distinct efficacies and modes of action. These types of studies provide the basis for a physiologically meaningful approach to identifying new therapeutics for neurodegenerative diseases.

THERMO FISHER SCIENTIFIC

Level 2, Room 258AB
8:00-8:30

DIRECTED SELF-ASSEMBLY OF INNER EAR ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS

Karl R. Koehler, *Department of Otolaryngology-Head and Neck Surgery, Indiana University School of Medicine*

We have established a novel inner ear organoid culture system by mimicking the complex signalling dynamics leading to inner ear induction from human PSCs. In 3D culture, we modulated TGF, BMP, FGF, and Wnt signaling to direct the self-assembly of multiple PAX2, PAX8, SOX10, and ECAD-positive otic vesicle-like cysts from homogenous hPSC aggregates. The vesicles developed into multi-chambered organoids with non-sensory and sensory epithelia, reminiscent of the membranous labyrinth of the inner ear. MYO7A+ BRN3C+ hair cells in the sensory epithelia of organoids had Actin-rich hair bundles similar to those on vestibular hair cells in vivo. Using an ATOH1-2A-eGFP cell line and 3D imaging, we detected that 20% of organoids contained hundreds-to-thousands of nascent hair cells with physiological properties similar to native vestibular hair cells. Finally, we found evidence that sensory neurons co-developed and formed ribbon synapses with organoid hair cells. Together, these findings suggest that our organoid culture system could provide a biologically relevant model for investigating human inner ear development and disease.

UNION BIOMETRICA, INC.

Level 2, Room 205A
8:00-8:30

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

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

Cells growing in clusters communicate with each other and behave differently than cells grown as monolayers or in suspension. These interactions are likely to be important for proper function. Union Biometrica Large Particle Flow Cytometers automate the analysis, sorting and dispensing of objects too big or too fragile for traditional cytometers including those studied by stem cell researchers such as embryoid bodies, neurospheres and other spheroids and organoids. This technology provides automation for the analysis and handling of these sample types in multiwell plate format and increases reproducibility by removing some of the day-to-day vari-

ability that can be introduced between researchers and by the same researcher from one day to the next.

THURSDAY, 15 JUNE

CELLULAR DYNAMICS INTERNATIONAL, A FUJIFILM COMPANY

Level 2, Room 258C
11:30-12:30

HUMAN IPSC-DERIVED MIDBRAIN DOPAMINERGIC NEURONS FOR DISEASE MODELING AND CELL THERAPY

Coby Carlson, *Strategic Marketing Manager, Cellular Dynamics International, a FUJIFILM Company*

Christopher McMahon, *R&D Senior Group Leader, Cellular Dynamics International, a FUJIFILM Company*

Parkinson's disease (PD) affects approximately 1% of people over the age of 65 and is the second most common neurodegenerative disorder after Alzheimer's disease. The advent of induced pluripotent stem cell (iPSC) technology now grants us access to previously unattainable cell types in the human brain. In this presentation, we will discuss how stem cells are being used not only to study PD in the lab, but also to develop treatments for PD using cells as therapies. Specifically, we have created an isogenic disease model for PD using human iPSC-derived midbrain dopaminergic neurons and have developed in vitro assays for comparative analysis of mitochondrial bioenergetics, calcium handling, and network-level electrophysiology. In the regenerative medicine space, we are actively manufacturing cGMP HLA "superdonor" iPSC lines for universal utility and will provide an update on our progress in developing iPSC-derived cellular therapies, including our program to treat PD by engrafting human midbrain dopaminergic neurons.

CORNING INC.

Level 3, Ballroom East
11:30-12:30

ADVANCES IN PATIENT DERIVED DISEASE MODELLING: FROM STANDARDIZED REPROGRAMMING OF IPS CELLS TO GENERATION OF HUMAN KIDNEY ORGANOIDS

Anna Falk, *Associate Professor, Karolinska Institute*

Benjamin Freedman, *Assistant Professor, University of Washington*

Keith Olsen, *Global Commercial Director, Corning Life Sciences*

The Nobel-prize discovery of induced pluripotent stem (iPS) cells and the progress made with stem cell culture environments have opened up many opportunities to study and mimic the in vivo environment as well as the possibility to achieve patient derived therapies. Building relevant cellular models is becoming vital to study disease mechanisms, toxicity and regeneration. Here we present solutions and techniques to achieve standardized reprogramming of somatic cells to iPS cells and discuss their transcriptional and functional differences under defined and non-defined conditions. Furthermore, we will present the generation of human kidney organoids from iPS cells for the study of polycystic kidney disease (PKD), a leading cause of kidney failure. These innovative techniques enable researchers to create cellular models to study proliferation, self-renewal, differentiation and functionality, bringing us one step closer to immunocompatible cell therapy.

MILLIPORESIGMA

Level 2, Room 205BC
11:30-12:30

TECHNOLOGIES TO ENGINEER, EVALUATE AND EXPAND STEM CELLS TO ADVANCE INNOVATIVE THERAPIES

Jason Gustin, *MilliporeSigma*

Darrin Fogg, *MilliporeSigma*

Julie Murrell, *MilliporeSigma*

There are many considerations when developing new therapies. Engineering the correct cell lines for discovery, safety and efficacy testing is a key first step. The Cell Design Studio(tm) team specializes in genome engineering to precisely modify patient-derived iPSCs to introduce or correct disease-specific mutations to create isogenic cell models. Innovative technologies for evaluating cells through characterizing and tracking cellular functions facilitates transition of novel therapies to the clinic. Scalable solutions for expanding cell therapies necessitates high quality reagents, closed systems, and reliable expansion systems. Developing manufacturing-ready processes to support industrialization of therapies is best considered early. Learn more about engineering your cells, evaluating your model and expanding your process during the session.

MINERVA BIOTECHNOLOGIES CORP.

Level 3, Ballroom West
11:30-12:30

PRIMITIVE EMBRYONIC GROWTH FACTOR, NME7^{AB}, INDUCES AND MAINTAINS NAÏVE STATE IN HUMAN STEM CELLS WITHOUT KARYOTYPE INSTABILITY

Cynthia Bamdad, *Minerva Biotechnologies*

Kenneth S. Kosik, *Neuroscience Research Institute, and Department of Cellular Molecular and Developmental Biology, University of California, Santa Barbara*

Min-Joon Han, *St. Jude Children's Research Hospital*

NME7^{AB} is a newly discovered embryonic stem cell growth factor that is only present for the first few days of a human blastocyst. Culturing stem cells in minimal media with NME7^{AB} as the only added growth factor causes human stem cells to revert to a naïve state. Later in embryonic development NME7^{AB} is replaced by another NME family member, NME1, which limits pluripotency by changing its multimerization state from active dimer to inactive hexamer. NME7^{AB} may support an early naïve state, while NME1 supports a later naïve-like state. Stem cells cultured in NME7^{AB} or NME1 have stable karyotype for up to 70 passages. Two early users of NME7^{AB} media will present some of their results, which include what could be new defining characteristics of the naïve state. They will also discuss some of their latest research which elucidates some of the earliest decision points in embryonic cell fate decisions and how the naïve state might promote certain cell fates over others.

STEMCELL TECHNOLOGIES INC.

Level 2, Room 253ABC
11:30-12:30

INTESTINAL AND CEREBRAL ORGANOIDS: NEW TOOLS TO STUDY HUMAN DEVELOPMENT AND DISEASES

Jordi Guiu Sagarra – BRIC – Biotech Research & Innovation Center, *University of Copenhagen*

Oliver Wüseke – IMBA - Institute of Molecular Biotechnology

Cell culture models for studying human development have previously been limited to 2-D monolayer cultures derived from primary tissues or human pluripotent stem cells (hPSCs). Recently, the development of 3-D organoid models has enabled significant advances in developmental biology, disease modeling and patient-specific drug screening. Organoids contain progenitor cells and differentiated cell types, and can self-organize into 3-D structures that resemble their in vivo counterparts. Here, we present two of these models: intestinal and cerebral organoids. Adult intestinal epithelial stem cells are located at the bottom of crypts of Lieberkühn. Using a combination of human and mouse intestinal organoids and in vivo fate mapping studies, we describe when, where and how cell fate, and stem cell identity are first established during development. Cerebral organoids derived from hPSCs can generate cell types and cell layers that recapitulate the complex organization of the human cortex. The derived brain tissues model early human fetal brain development and have been used to study diverse brain disorders such as microcephaly, schizophrenia and Zika virus infection.

TAKARA BIO USA, INC.

Level 2, Room 205A
11:30-12:30

FOOTPRINT-FREE GENE EDITING USING CRISPR/CAS9 AND SINGLE-CELL CLONING OF EDITED HUMAN IPS CELLS

Liz Quinn, *Associate Director of Stem Cell Marketing, Takara Bio USA, Inc.*

The combination of two powerful technologies (human induced pluripotent stem [hiPS] cells and precise, footprint-free editing using CRISPR/Cas9) allows for a new level of sophistication in cell biology research and disease model development. The ability to create hiPS cell lines from different donors and to determine the effects of specific mutations created via gene editing within the donor-specific genetic background will enable discoveries with a new level of granularity. However, while the introduction of CRISPR/Cas9 technology has made gene editing easier to achieve (even in hiPS cells), obtaining single-cell clones of edited hiPS cells has been a major bottleneck. Here we show a new workflow using footprint-free editing via efficient delivery of Cas9/sgRNA RNP complexes and single-cell cloning of hiPS cells using a modified DEF-CS culture protocol, results in a high number of edited and expandable hiPS clones that maintain the hallmarks of pluripotency.

THERMO FISHER SCIENTIFIC

Level 2, Room 258AB
11:30-12:30

NEW MONOCLONAL ANTIBODIES TO DEFINED CELL SURFACE PROTEINS ON HUMAN PLURIPOTENT STEM CELLS

Andrew L. Laslett, *CSIRO Manufacturing and Australian Regenerative Medicine Institute, Monash University*

The availability of well-characterised monoclonal antibodies (mAbs) detecting cell-surface epitopes on human pluripotent stem cells (hPSCs) provides useful research tools to investigate the cellular mechanisms underlying human pluripotency and states of cellular reprogramming. Here we describe generation of seven new mAbs that detect cell surface proteins present on primed and naive human ES cells (hESCs) and human iPS cells (hiPSCs), confirming our previous prediction that these proteins were present on the cell surface of hPSCs. The mAbs all show a high correlation with POU5F1 (OCT4) expression and other hPSC surface markers (TRA-160 and SSEA-4) in hPSC cultures and detect rare OCT4 positive cells in differentiated cell cultures. In addition, we report that subsets of the seven new mAbs are also immunoreactive to specific human somatic cell populations. The mAbs reported here should accelerate the investigation of the nature of pluripotency, and enable development of robust cell separation and tracing technologies to enrich or deplete for hPSCs and other human stem and somatic cell types.

FRIDAY, 16 JUNE

ALPHA MED SCIENTIFIC INC.

Level 2, Room 205BC
8:00-8:30

HIGH SENSITIVITY MICROELECTRODE ASSAY FOR STEM CELL DERIVED NEURONS

Michael Trujillo, *Alpha MED Scientific*

Ikuro Suzuki, *Tohoku Institute of Technology*

Ryan Arant, *Alpha MED Scientific*

Stem cell derived neurons can provide insights into mechanisms of the brain, behavior, and disease. Due to the intricate yet subtle activity of stem cell derived neurons, a high fidelity assay is needed to measure and examine their activity. The MED64 is a high fidelity microelectrode array (MEA) platform that is engineered to detect a broad range of action potentials that stem cell derived neurons produce. Our new system, the MED64 Presto, is engineered to provide the high sensitivity that stem cell derived assays require in a multi-well format. Discover the power that high-sensitivity high-throughput MEAs can provide for pain, sensory, and epileptiform stem cell derived neuron assays.

BIOLOGICAL INDUSTRIES

Level 2, Room 205A
8:00-8:30

DRIVING CELL THERAPIES TO MARKET WITH KEY CONSIDERATIONS FOR SCALE-UP MANUFACTURING, KEY PARTNERSHIPS AND SERUM-FREE MEDIA SELECTION

Ohad Karnieli, *PhD, CEO, Atvio Biotech*

In the pursuit to move cell-based therapy forward, the ability to generate a consistent quality cell product remains a challenge. This presentation will explore the challenges in cell manufacturing with a focus on serum-free media selection highlighting a high-performing culture medium - MSC NutriStem® Medium. We will also discuss key considerations for selecting the right platform, technology, and the importance of selecting the right partners in bridging the gap to better processes.

Talking points:

- Challenges in cell therapy manufacturing; focus on process and partnerships
- Industrial platform overview and impact
- Considerations and impact when selecting technology
- Case Study example

BIO-TECHNE

Level 2, Room 253ABC
8:00-8:30

WIN THE RACE TO DISCOVERY: INNOVATING STEM CELL RESEARCH WITH CUTTING-EDGE SINGLE-CELL WESTERN AND ADULT STEM CELL TECHNOLOGIES

Joy Aho, *Bio-Techne*

Eric Jabbart, *Bio-Techne*

Innovation is a catalyst to discovery. At Bio-Techne, we have developed cutting-edge instrumentation and stem cell-based model systems that advance stem cell research, facilitate regenerative medicine, and accelerate drug discovery. In this symposium we first discuss Milo™, our award-winning Single-cell Western platform. Milo is capable of analyzing protein expression in up to 1000 individual stem cells simultaneously. Application data will be presented, including how to utilize Milo to

interrogate stem cell population heterogeneity. Next, we will introduce our new "ground state" adult stem cell-based organ tissue models, which are being developed in partnership with Dr. Frank McKeon and Dr. Wa Xian of Multiclonal Therapeutics. This technology provides a transformative platform to isolate, expand, and differentiate adult stem cells on a clonal level from a broad range of human and rodent epithelial tissues. By enabling scientists to create ex vivo models of healthy and diseased epithelial organs in their own laboratories, this adult stem cell technology has the potential to advance biomarker discovery, drug development, toxicology testing, and disease modeling.

FOUNDATION FOR BIOMEDICAL RESEARCH AND INNOVATION (FBRI)

Level 2, Room 258AB
8:00-8:30

SMART CELL PROCESSING: FUTURE OF CELL PRODUCTION

Glyn Stacey, *National Institute for Biological Standards and Control*

Marc Turner, *Scottish National Blood Transfusion Service*

Shin Kawamata, *Foundation for Biomedical Research and Innovation*

Currently cells are produced manually in huge clean laboratories; the quality of the cells depends on operators and it costs a lot and needs to meet a lot of regulatory requirements. To make a breakthrough in this traditional method, we are introducing our Smart Cell Processing System that comes out of automation and is based on data collecting with many advantages such as quality control and commercial production in the future. This SPC System also has the protocol aiming to be GMP-compliant. In this session, we are presenting what SCP Systems is as users and developers and QC aspects of this system.

SONY BIOTECHNOLOGY

Level 3, Ballroom West
8:00-8:30

STREAMLINED WORKFLOW FOR SORTING CELLS WITH EXCHANGEABLE FLUIDICS CELL SORTER FX500

Deena Soni, *Global Marketing Manager, Sony Biotechnology*

A growing range of applications need that cells be sorted in controlled conditions. In many cases, there is a need to minimize carryover from sample to sample. Here we demonstrate a streamlined approach to sorting of cells without cross-contaminating successive samples using an integrated approach that uses exchanging sorter components that come in direct contact with sample, sterile source of sheath fluid and a biosafety and aerosol management system to enclose the sorter.

STEMBIOSYS INC.

Level 2, Room 258C
8:00-8:30

STEMBIOSYS BM-HPME®: A NOVEL 3-DIMENSIONAL MICROENVIRONMENT TO ENHANCE MESENCHYMAL STEM CELL EXPANSION

Sy Griffey, *COO, StemBioSys*

Travis J. Block, *Senior Scientist, StemBioSys*

StemBioSys, Inc. is a privately-held biomedical company focused on enhancing the growth and delivery of adult stem cells for research, therapeutic or drug discovery applications. Its patented and proprietary technology platforms overcome key obstacles to creating clinically useful stem cell therapies. The centerpiece of these enabling technologies is the HPME® (High Performance Micro Environment) platform. This stem cell derived 3-dimensional microenvironment allows a variety of stem cells to replicate more rapidly, maintain a small cell size, express markers indicative of retained stem cell potency and reduce donor to donor variability beyond that seen with traditional tissue culture substrates. This technology is positioned to transform and improve the methods and cost of growing and delivering various stem cell populations for applications in research, therapeutic and drug discovery.

THERMO FISHER SCIENTIFIC

Level 3, Ballroom East
8:00-8:30

IMPROVED DNA, MRNA AND PROTEIN TRANSFECTION ACROSS STEM CELL TYPES

James Kehler, *Thermo Fisher Scientific*

During this 30-minute session, Dr. James Kehler from Thermo Fisher Scientific will present data on a new transfection reagent optimized for efficient DNA delivery into stem cells. This reagent has been validated to achieve high efficiency delivery of large plasmid DNA (>11 KB) into human Pluripotent Stem Cells (PSC), while supporting their continued proliferation in an undifferentiated state in defined and complex feeder-free culture systems. In addition, it supports the co-delivery of mRNA and protein into stem cells, for applications such as gene-editing. This same reagent can also be used to transfect primary and iPSC-derived Neural Stem Cells

with a broad range of payloads for experimental manipulation. This transformative product offers a simplified alternative to other techniques, electroporation and reagents by supporting DNA, mRNA and protein delivery into a wide range of stem cells using a single reagent. Researchers can readily integrate it into their existing workflows to target, isolate, expand and differentiate stem cell lines for use in basic research and screening programs.

FRIDAY, 16 JUNE

10X GENOMICS

Level 2, Room 205BC
11:30-12:30

ADVANCED CELL DIAGNOSTICS

Level 3, Ballroom East
11:30-12:30

VISUALIZE THE CELLULAR LOCALIZATION OF RNA EXPRESSION IN STEM CELLS WITH THE RNASCOPE® ISH TECHNOLOGY

Courtney Anderson, *Senior Scientist, Advanced Cell Diagnostics*

Amnon Sharir, *Assistant Professor, UCSF School of Dentistry*

Research in the stem cell biology field has demonstrated the remarkable capabilities of these cells to self-renew, differentiate, and reprogram. Yet the field is still burgeoning with studies trying to elucidate stem cell populations, characterize stem cell markers, and identify the signals secreted from stem cells. The exquisite sensitivity and specificity of the RNAscope® in situ hybridization (ISH) technology makes it a powerful technique for molecular identification and characterization of rare stem cell populations in complex tissues that can easily be viewed and quantified with any standard bright-field or fluorescence microscope. The RNAscope® assay can be used to: Identify, characterize, and locate stem cell populations, reveal markers of stem cell maintenance and regeneration, identify long non-coding RNAs in stem cells, and detect stem cell markers when no reliable antibodies are available. In this session we will discuss a variety of applications of the RNAscope® technology in the stem cell field, including the detection of Lgr5+ intestinal stem cells and the visualization and characterization of Wnt-producing cells, among other topics.

AJINOMOTO CO., INC.

Level 3, Ballroom West
11:30-12:30

GENOME EDITING OF HPSCS FOR ACCURATE MODELING OF HUMAN DISEASES

Chad Cowan, *Massachusetts General Hospital*

Ryuji Morizane, *Brigham and Women's Hospital*

Human pluripotent stem cells (hPSCs) offer an unprecedented opportunity for giving rise to a wide range of specific differentiated cell types in which we could explore the mechanisms by which particular diseases arise at the cellular level. Recent advances in genome editing technology of hPSCs have allowed for the generation of more accurate human disease models with specific genetic alterations or correction of mutations in the mutant human induced pluripotent stem cell (hiPSC) lines. In this workshop, we will discuss recent technological advances in genome editing, and their use in human biology and disease research.

IRVINE SCIENTIFIC

Level 2, Room 205A
11:30-12:30

DEVELOPMENT OF SERUM FREE MEDIA FOR MOUSE AND HUMAN HEMATOPOIETIC PROGENITOR CELL EXPANSION AND MAINTENANCE

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

Jessie H-T Ni, *Chief Scientific Officer, Irvine Scientific*

Hematopoietic progenitor cell (HPC) ex vivo expansion is critical, but the ability to generate a consistently quality cell product remains a challenge. A high performing HPC expansion medium closely meeting the clinical quality requirements is an essential component to reach that goal. In this workshop we will share the development of a serum-free expansion medium for mouse HPCs and a serum- and xeno-free formulation for human HPCs. The performance of media was accessed and verified on quality expansions of mouse HPCs derived from young adult bone marrow or human CD34+ cells isolated from cord blood.

MILTENYI BIOTEC GMBH

Level 2, Room 258C
11:30-12:30

NOVEL SURFACE MARKERS SPECIFYING HPSC-DERIVED ANTERIOR ENDODERM SUBPOPULATIONS AND PSC QUALITY CONTROL USING A NOVEL QUANTIFIABLE DIFFERENTIATION ASSAY

Heiko Lickert, *Director of the Institute of Diabetes and Regeneration Research, Helmholtz Zentrum München*

Sebastian Knöbel, *Senior Project Manager R&D Stem Cells, Miltenyi Biotec GmbH*

Specified anterior endoderm subpopulations (ADE) give rise to thymus, lung, liver and pancreatic progenitors during embryogenesis. Currently, no surface markers are available to distinguish these different ADE subpopulations during pluripotent stem cell (hPSCs) differentiation. In order to identify novel surface markers that detect specified ADE populations already at endoderm stage, we screened a library of 330 antibodies. We identified two novel surface markers distinguishing pancreatic and liver progenitors already at the ADE stage. Importantly, re-aggregated pancreatic progenitors in cluster differentiation towards monohormonal insulin-producing β-like cells isolated using the identified marker perform superior when compared to published protocols. In the second talk we introduce a quantifiable differentiation assay for hPSC qualification. The assay is based on standardized complete media that support directed differentiation into all three germ layers. Analysis can be performed by immunohistochemistry or quantitative flow cytometry. Lastly, we present an automated process for hPSC expansion and differentiation into mesencephalic dopaminergic progenitors on the CliniMACS Prodigy® and introduce a novel marker panel for quality control of the differentiated cell product.

STEMCELL TECHNOLOGIES INC.

Level 2, Room 253ABC
11:30-12:30

HIGHLY EFFICIENT SINGLE-CELL HUMAN PLURIPOTENT STEM CELL CLONING AND ROBUST CARDIOMYOCYTE DIFFERENTIATION

Adam Hirst, *STEMCELL Technologies Inc.*

Vincenzo Macri, *STEMCELL Technologies Inc.*

Recent advances in gene-editing techniques have led to more accessible and cost-effective methods to produce edited human pluripotent stem cell (hPSC) lines. However, low single-cell cloning efficiency (typically < 1%) remains a major limitation of this technology. To address this challenge, we developed a novel hPSC cloning supplement, CloneR™, that yields single-cell cloning efficiencies of 20-40% in mTeSR™1 and TeSR™-E8™ across multiple matrices. Gene-edited hPSC clones can be differentiated to specific cell types for disease modelling, drug discovery, or toxicology screening purposes. The production and processing of hPSC-derived cardiomyocytes (hPSC-CMs) is both variable and cumbersome. To overcome this, we have developed an optimized workflow for hPSC-CM-based research, including cardiomyocyte differentiation, maintenance, dissociation, freezing, and support reagents. These STEMdiff™ Cardiomyocyte products facilitate reproducible and robust production and simple processing to yield high-quality hPSC-CMs (>80% cTNT+ and >1x106 hPSC-CMs/well of a 12-well plate). In summary, this tutorial will highlight hPSC gene-editing and cardiac differentiation workflows using the CloneR™ Supplement and the STEMdiff™ Cardiomyocyte product line.

THERMO FISHER SCIENTIFIC

Level 2, Room 258AB
11:30-12:30

ENABLING MODERN PSC WORKFLOWS AND APPLICATIONS INCLUDING GENE EDITING, SINGLE CELL PASSAGING, AND AUTOMATION

William T Hendriks, *Harvard Brain Science Initiative, Harvard Medical School*

Duncan E. Crombie, *Centre for Eye Research Australia, University of Melbourne*

Several practical considerations hinder the development of PSC-derived models to enable insight into disease mechanisms and provide cell models for drug discovery. In this session, Dr. William Hendriks will discuss challenges in working with patient-derived PSCs, and in the CRISPR/Cas9 editing of such lines. Patient-derived lines often demonstrate decreased survival after thawing, and the transfection, recovery, and clonal isolation of edited lines can be bottlenecks to creating disease models. Dr. Hendriks will discuss the use of StemFlex™ media in addressing these challenges when creating lines used to model dystonia-parkinsonism linked to PARK7 and DYT1 mutations. To address the labor-intensive nature of PSC culture, and to minimize variability, Dr. Duncan Crombie will discuss the development of an automated platform to enable PSC production. Here, incorporation of StemFlex™ media has improved consistency of cell morphology, and supported more robust recovery of cells after automated passaging. Together, these advantages are contributing to a system that will support high-throughput analyses of human iPSCs and their derivatives for the study of blinding eye diseases.

INTERNATIONAL 2017 SYMPOSIA

GUANGZHOU CHINA 2017

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STEM CELLS: THE NEXT GENERATION

KEYNOTE SPEAKER

Rudolf Jaenisch
Whitehead Institute for Biomedical Research, US

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SPEAKER ABSTRACTS

WEDNESDAY, 14 JUNE, 13:00 – 15:15

PLENARY I PRESIDENTIAL SYMPOSIUM: A DECADE OF HUMAN IPSCS FROM DISCOVERY TO CLINIC

Exhibit Level, Exhibition Hall B1
Sponsored by Fate Therapeutics

13:35 – 14:00

ANNE MCLAREN MEMORIAL LECTURE: PARTNERSHIP OF EMBRYONIC AND EXTRA-EMBRYONIC STEM CELLS TO BUILD THE IMPLANTING MAMMALIAN EMBRYO IN VIVO AND IN VITRO

Zernicka-Goetz, Magdalena

University of Cambridge, U.K.

Mammalian embryogenesis requires intricate interactions between embryonic and extra-embryonic tissues to orchestrate and coordinate morphogenesis with changes in developmental potential. In both mouse and human embryos the first most dramatic series of morphogenetic transformations in embryo architecture and potency is initiated during embryo implantation into the body of the mother. Despite its major importance, an understanding of embryo remodeling during the implantation stage has been lacking, due to the embryo's inaccessibility within the mother. Motivated to understand this process, we have established a system permitting mouse and human embryogenesis beyond implantation in vitro. This allowed us to reveal steps of architectural remodelling and the importance of embryonic and extra-embryonic partnership in this process. Building upon this knowledge, we have attempted to mimic successive steps of this partnership with stem cells in vitro. To achieve this, we have combined mouse embryonic stem cells (ESCs) and extra-embryonic trophoblast stem cells (TSCs) in a 3D scaffold of extra-cellular matrix (ECM) that allowed us to generate structures whose morphogenesis is remarkably similar to natural embryos. By using genetically-modified stem cells and specific inhibitors, we show that embryogenesis of ESC- and TSC-derived embryos, ETS-embryos, depends on crosstalk involving Nodal signalling. When ETS-embryos develop further, they spontaneously initiate expression of mesoderm and primordial germ cell markers asymmetrically on the embryonic - extra-embryonic border, in response to Wnt and BMP signalling. This study demonstrates that enabling crosstalk between embryonic and extra-embryonic stem cells in a 3D ECM scaffold is sufficient to trigger self-organization recapitulating spatio-temporal events and leading to faithful reconstruction of embryo architecture and patterning. This stem cell model of mammalian embryogenesis, in combination with genetic manipulations, might provide a powerful platform to dissect physical and molecular mechanisms that mediate natural embryogenesis.

14:00 – 14:25

EPIGENETIC REGULATION, STEM CELLS AND DISEASE RELEVANCE

Jaenisch, Rudolf, Liu, Shawn, Stelzer, Yonatan, Markoulaki, Styliani, Song, Yuelin, Ji, Xiong, Young, Richard and Wu, Hao

Whitehead Institute for Biomedical Research, Cambridge, MA, U.S.

The development of the iPS cell technology has revolutionized our ability to study development and diseases in defined in vitro cell culture systems. Epigenetic regulation is an crucial mechanism of normal development and epigenetic misregulation may lead to disease. Current methods to quantify DNA methylation provide only a static "snap shot" of DNA methylation, thus precluding to detect methylation changes in real-time methylation during cell fate changes. We have established a new approach that enables monitoring loci-specific DNA methylation dynamics at single-cell resolution. In addition we have developed a DNA methylation editing toolbox based on the fusion of either the catalytic domain of Tet1 or Dnmt3a protein with a catalytic inactive Cas9 to achieve targeted DNA methylation editing. This system allows for the precise de-methylation of methylated and de novo methylation of un-methylated genomic loci and can be used to reverse silencing of genes involved in disease.

14:25 – 14:50

RECENT PROGRESS IN IPS CELL RESEARCH AND APPLICATION

Yamanaka, Shinya

Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan

Induced pluripotent stem cells (iPSCs) can proliferate almost indefinitely and differentiate into multiple lineages, giving them wide medical application. As a result, they are being used for new cell-based therapies, disease models and drug development around the world. We are establishing technologies for the efficient generation of safe iPSCs. The original iPSCs were made from the retroviral transduction of four genes, Oct3/4, Sox2, c-Myc and Klf4. We have since reported an integration-free method using episomal vectors that does not cause chromosomal damage and proposed using L-Myc as an alternative to oncogenic c-Myc to reduce the risk of tumorigenicity. We have also developed a recombinant laminin-based matrix and developed a culture medium free of animal-derived constituents (xeno-free) to generate iPS cells that satisfy regulatory requirements for medical practice. In 2014, the world's first clinical study using iPSCs began for the treatment of age-related macular degeneration, and two years later indications are the transplant of an autologous iPSC-derived RPE cell sheet in a patient was a success. iPSC studies have also made major progress for other disorders, giving expectation that iPSC-based regenerative medicine will be widely used in the near future. To push these efforts, we are proceeding with the iPSC Stock Project for

Regenerative Medicine in which clinical-grade iPSC clones are being established from donors with homologous HLA haplotypes, which are associated with decreased immune response and less risk of transplant rejection. Allogeneic transplants using the iPSC stock will be conducted in Japan within the next few years. Other applications of iPSCs are drug screening, toxicity studies and disease modeling. Additionally, iPSCs may be resourceful for preventative measures, as they make it possible to predict the patient condition and provide preemptive treatment. Finally, accumulating evidence is demonstrating the benefits of iPSCs in drug repositioning.

14:50 – 15:15

CELLULAR ANTHROPOLOGY: USING IPSC TO STUDY HUMAN EVOLUTION

Wysocka, Joanna

Stanford University, Stanford, CA, U.S.

Discovery and characterization of induced pluripotent stem cells (iPSC) furthered our understanding of fundamental mechanisms underlying cell fate establishment, cellular plasticity, differentiation and disease and offered promising, patient-tailored therapeutic avenues. It is less well appreciated, however, that iPSC can also provide invaluable tools to study human evolution. I will discuss an approach we termed 'cellular anthropology' in which in vitro differentiation models using hominid iPSCs can be effectively applied to studies of both basic physiology as well as evolutionary questions. In particular, I will focus on how sequence changes in cis-regulatory elements such as enhancers can influence gene regulatory programs and in turn give rise to morphological divergence.

WEDNESDAY, 14 JUNE, 16:00 – 18:10

PLENARY II: ORGANOGENESIS- MAKING TISSUES AND ORGANS

Exhibit Level , Exhibition Hall B1

Sponsored by: Allen Institute for Cell Science

16:00 – 16:25

ERNEST MCCULLOCH MEMORIAL LECTURE: IMMORTAL HEMATOPOIETIC STEM CELLS AND EPIGENETIC REGULATION

Goodell, Margaret A.

Baylor College of Medicine, Houston, TX, U.S.

Hematopoietic stem cells (HSCs) sustain blood production through decades of life due to their capacity to both self-renewal and differentiate. Numerous genetic factors can influence the capacity of individual HSCs to regenerate the blood, with epigenetic regulators recently emerging as particularly important over time. Loss of DNA methyltransferase 3A (DNMT3A) can promote HSC self-renewal in the mouse, and mutations in DNMT3A are associated with clonal advantage in aging humans. We now show that loss of DNMT3A can lead to HSC immortalization with indefinite expansion capacity but no overt malignant transformation. Epigenetic features of normal HSCs are exacerbated with marked loss of DNA methylation associated with key self-renewal genes. A subset of gene previously linked to cancer become highly expressed, suggesting their mechanistic link to self-renewal. Concurrently, regions of normally silent chromatin become extremely hypermethylated. We surmise that these features lock in the self-renewal program. Potential interactions with other epigenetic regulators as well as implications for chromatin organization will be discussed. Together, these finding lend insight into key determinants of self-renewal distinct from differentiation and malignant transformation.

16:25 – 16:50

STEM CELL-GROWN ORGANOIDS AS MODELS FOR HUMAN DISEASE

Clevers, Hans

Hubrecht Institute, Utrecht, Netherlands

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined Lgr5 as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of Lgr5 in cycling, columnar cells at the crypt base. Using lineage tracing experiments in adult mice, we found that these Lgr5+ve crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that they represent the stem cell of the small intestine and colon. Lgr5 was subsequently found to represent an exquisitely specific and almost 'generic' marker for stem cells, including in hair follicles, kidney, liver, mammary gland, inner ear tongue and stomach epithelium. Single sorted Lgr5+ve stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the Lgr5+ve stem cells of human stomach, liver, pancreas, prostate and kidney. Using CRISPR/Cas9 technology, genes can be efficiently modified in organoids of various origins.

16:50 – 17:15

CEREBRAL ORGANOIDS: MODELLING HUMAN BRAIN DEVELOPMENT AND TUMORIGENESIS IN STEM CELL DERIVED 3D CULTURE

Knoblich, Juergen

IMBA-Institute of Molecular Biotechnology, Vienna, Austria

The human brain is unique in size and complexity, but also the source of some of the most devastating human diseases. While many of these disorders have been successfully studied in model organisms, recent experiments have emphasized unique features that cannot easily be modeled in animals. We have therefore developed a 3D organoid culture system derived from human pluripotent stem cells that

recapitulates many aspects of human brain development. These cerebral organoids are capable of generating several brain regions including a well-organized cerebral cortex. With intriguing precision, they recapitulate key brain morphogenetic events like the formation of distinct progenitor and differentiation zones, the generation of neuronal subclasses with distinct layer identities and the establishment of coordinated neuronal activity. We have used patient specific iPS cells to model microcephaly, a human neurodevelopmental disorder that has been difficult to recapitulate in mice. This approach reveals premature neuronal differentiation with loss of the microcephaly protein CDK5RAP2, a defect that could explain the disease phenotype. More recently, we have developed organoid based models for long distance interneuron migration between distinct areas of the human brain which we are using for modeling neuropsychiatric disorders. Our data describe an in vitro approach that recapitulates development of even the most complex organ and can be used to gain insights into disease mechanisms.

17:25 - 17-35

POSTER TEASERS

W-2113

MODELING CYSTIC FIBROSIS FOR DRUG-PROFILING ON HEPATIC-BILIARY ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS

Ogawa, Mina
McEwen Centre for Regenerative Medicine, ON, Canada

W-2003

LOSS OF P66SHC ACCELERATES THE CELL CYCLE AND THE ONSET OF GATA4 EXPRESSION IN MOUSE BLASTOCYSTS

Edwards, Nicole A.
Western University, ON, Canada

W-1165

CHEMICAL SCREENING IN ZEBRAFISH EMBRYO CULTURES IDENTIFIES RETINOIC ACID AS A TRANSCRIPTIONAL SUPPRESSOR OF MYB AND LEADS TO A NEW TREATMENT FOR MYB-DRIVEN ADENOID CYSTIC CARCINOMA

Mandelbaum, Joseph
Boston Children's Hospital, MA, U.S.

W-1064

SCALABLE GENERATION OF FUNCTIONAL AND TRANSPLANTABLE HEPATIC CELLS FROM HUMAN ENDODERM STEM CELLS

Feng, Sisi
Shanghai Institutes for Biological Sciences, CAS, China

W-2133

PRECISE GENE EDITING OF HUMAN STEM CELLS USING NOVEL NANOPARTICLES CONTAINING CRISPR NUCLEASES WITH DNA REPAIR TEMPLATES

Carlson-Stevermer, Jared
University of Wisconsin-Madison, WI, U.S.

17:35 – 18:10

KEYNOTE ADDRESS: STRESSED OUT: A NOVEL APPROACH TO CANCER IMMUNOTHERAPY

Glimcher, Laurie H.
Dana-Farber Cancer Institute, Boston, MA, U.S.

Cancer cells induce a set of adaptive response pathways to survive in the face of stressors due to inadequate vascularization1. One such adaptive pathway is the unfolded protein (UPR) or endoplasmic reticulum (ER) stress response mediated in part by the ER-localized transmembrane sensor IRE1 and its substrate XBP1. We have shown that the transcription factor XBP1 promotes intrinsic tumor growth directly in the setting of triple negative breast cancer, and now have established that this signaling pathway also regulates the host anti-tumor immune response. Dendritic cells (DCs) are required to initiate and sustain T cell-dependent anti-cancer immunity. However, tumors often evade immune control by crippling normal DC function. Constitutive activation of XBP1 in tumor-associated DCs (tDCs) drives ovarian cancer (OvCa) progression by blunting anti-tumor immunity. XBP1 activation, fueled by lipid peroxidation byproducts, induced a triglyceride biosynthetic program in tDCs leading to abnormal lipid accumulation and subsequent inhibition of tDC capacity to support anti-tumor T cells. Accordingly, DC-specific XBP1 deletion or selective nanoparticle-mediated XBP1 silencing in tDCs restored their immunostimulatory activity in situ and extended survival by evoking protective Type 1 anti-tumor responses. Targeting the ER stress response should concomitantly inhibit tumor growth and enhance anti-cancer immunity, thus offering a unique approach to cancer immunotherapy.

THURSDAY, 15 JUNE, 9:00 – 11:20

PLENARY III: STEM CELLS AND CANCER

Exhibit Level , Exhibition Hall B1

9:00 – 9:25

HEMATOPOIETIC STEM CELL DERIVATION FROM PLURIPOTENT STEM CELLS

Daley, George Q.

Boston Children's Hospital and Harvard Medical School, Boston, MA, U.S.

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. While current protocols for directing hematopoietic differentiation faithfully recapitulate myeloid lineages, and there have been encouraging reports of NK, B and T cell development, recapitulating the various stages of hematopoietic ontogeny and producing bona fide hematopoietic stem cells (HSC) has proven elusive. Novel strategies to achieve the production of specific hematopoietic lineages, and to achieve the ultimate goal of HSC derivation will be discussed, alongside illustrations of the utility of ESC/iPSC in disease modeling.

9:25 – 9:50

INTEGRATED FUNCTIONAL AND MOLECULAR ANALYSES OF INDIVIDUAL HUMAN HEMATOPOIETIC STEM CELLS

Eaves, Connie J., Knapp, David, Hammond, Colin, Wang, Fangwu, Aghaeepour, Nima, Miller, Paul, Van Loenhout, Marijn, Hui, Tony, Moksa, Michelle, VanInsberghe, Michael, Pellacani, Davide, Humphries, Keith, Bendall, Sean, Nolan, Garry, Hirst, Martin and Hansen, Carl

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

Understanding the process of human hematopoiesis has historically drawn heavily on results obtained in mice but has often lagged behind because of the lack of analogous experimental syngeneic transplantation assays or lineage tracing strategies. Recent experiments in mice have introduced major conceptual changes in the original generic hierarchical model of the cellular changes that underpin the earliest stages of hematopoiesis through the demonstration using single cell analyses that changes in the self-renewal, lineage competence and proliferation state of the more primitive cells are not necessarily coordinately regulated. These revelations have led to an appreciation that current methods to isolate cells based on surface phenotypes still mask considerable heterogeneity in the types of blood cells that can be produced and these differences are exacerbated during development, aging and exposure to abnormal stimuli. We now provide new evidence that a similar paradigm applies to human hematopoiesis. This was first revealed from multidimensional analyses of the expression of several signaling intermediates, transcription factors, and cell cycle regulators measured simultaneously by mass cytometry of single human CD34+ cord blood cells with defined surface phenotypes. Based on these findings, we have been able to identify a novel subset of CD33+ cells within the CD34+CD38-CD45RA-CD90+CD49f+ population that exclusively possesses durable blood cell output capacity as shown in clonally tracked transplants generated in serially transplanted immunodeficient mice. These findings set the foundation for a new era of unbiased approaches to defining the intrinsic and extrinsic mechanisms that control normal human hematopoiesis both physiologically and when manipulated ex vivo.

9:50 – 10:15

CANCER CELL OF ORIGIN AND TUMOR HETEROGENEITY

Blanpain, Cédric

Université Libre de Bruxelles, Belgium

Different theories have been proposed to explain tumour heterogeneity including the cancer cell of origin. Here, we developed new genetically engineered mouse models allowing lineage tracing together with oncogenic activation in different cell lineages of the skin epidermis and the mammary gland and assessed whether the cancer cell of origin controls tumour heterogeneity. I will present evidence that the cancer cell of origin controls tumour heterogeneity and the underlying molecular mechanisms by which the cancer cell of origin control tumor differentiation, stemness, EMT, resistance to therapy and metastasis in primary tumors. These results have important implications for our understanding of the mechanisms controlling tumor heterogeneity and the development of new strategies to block tumor initiation, progression, metastasis and resistance to therapy.

10:15 – 10:25

POSTER TEASERS

T-1044

AUTOPHAGY MAINTAINS THE METABOLISM AND FUNCTION OF YOUNG AND OLD HEMATOPOIETIC STEM CELLS

Ho, Theodore T.

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

T-1047

TRANSITION OUT OF HSC DORMANCY BY A CONTINUOUS UPREGULATION OF METABOLISM IS CONTROLLED VIA RETINOIC ACID

Cabezas-Wallscheid, Nina

German Cancer Research Center, Germany

T-1178

SIRT1 REGULATES EPIGENETIC STABILITY AND DIFFERENTIATION POTENTIAL OF EMBRYONIC STEM CELLS BY ANTAGONIZING DNMT3L

Lim, Jisun
Ulsan University College of Medicine, Korea

T-1183

LGR5-POSITIVE SUPPORTING CELLS IN THE COCHLEA: REPLACEMENT OF HAIR CELLS IN RESPONSE TO WNT

Chiang, Hao
Harvard Medical School, MA, U.S.

T-1179

CONCURRENT EPIGENETIC REPROGRAMMING OF THE 3D CHROMATIN LANDSCAPE IN GROUND STATE PLURIPOTENCY

Atlasi, Yaser
Radboud UMC, Netherlands

10:25 – 10:50

MODELING HISTONE MUTANT BRAIN TUMORS IN PLURIPOTENT STEM CELLS

Tabar, Viviane, Funato, Kosuke, Smith, Ryan C. and Yang, Yanhong

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

Brain tumors bearing histone mutations occur in young patients and exhibit exquisite spatiotemporal specificity. H3K27M tumors occur exclusively in the midline from thalamus to pons, while H3G34R/V tumors occur in young adults in the cortex. These mutations are often paired with receptor tyrosine kinase amplifications or mutations, adding further regional specificity. Neural precursors (NPCs) arising from pluripotent stem cells (hPSC) offer an excellent platform for modeling these tumors. We have generated brain tumor models in hPSC-derived NPCs with appropriate regional patterning, leading to greater insight into the biology of histone mutation-driven oncogenesis, and to the development of platforms for drug discovery.

10:50 – 11:15

THE METABOLIC REGULATION OF STEM CELL FUNCTION AND LEUKEMOGENESIS

Morrison, Sean J., and Agathocleous, Michalis

Children's Research Institute at UT Southwestern, Dallas, TX, U.S.

We have developed methods that make it possible to perform metabolomics in rare cell populations isolated directly from tissues. We have applied these approaches to the hematopoietic system to test whether there are metabolic differences between stem cells and other hematopoietic progenitors. We found that all hematopoietic stem and progenitor cell populations have clearly distinct metabolic signatures and that stem cells differ from restricted progenitors in terms of multiple metabolites that have not previously been implicated in the regulation of stem cell function. It is known that stem cell fate can be influenced by metabolite levels in culture but it is unknown to what extent physiological variations in metabolite levels within normal tissues regulate stem cell function in vivo. We thus set out to test whether the metabolic differences between hematopoietic stem cells (HSCs) and restricted progenitors regulate stem cell fate in vivo. We found in particular that ascorbate levels were highest in HSCs and declined with differentiation. Depletion of ascorbate in mice to a level observed in some humans increased HSC frequency and function as a result of reduced Tet2 function, a dioxygenase tumor suppressor. This allowed haematopoietic stem/progenitor cells with Flt3ITD leukaemic mutations to outcompete wild-type cells in an ascorbate-depleted, but not in an ascorbate-replete, environment and accelerated leukaemogenesis by Flt3ITD; Tet2+/- cells. Ascorbate thus accumulates within HSCs to promote Tet function, limiting HSC frequency and suppressing leukaemogenesis. Our data raise the possibility that human that develop clonal hematopoiesis as they age might be at increased risk of progressing to leukemogenesis if they have low ascorbate diets.

THURSDAY, 15 JUNE, 13:15 – 15:15

CONCURRENT IA: ORGANOIDS AND DISEASE MODELING

Level 2, Room 258AB

13:20 – 13:45

MODELING NEURAL DEVELOPMENT AND DISEASES USING HUMAN IPSCS

Ming, Guo-li

University of Pennsylvania, Philadelphia, PA, U.S.

Three dimensional (3D) cerebral organoid cultures from human iPSCs have been recently developed to recapitulate the cytoarchitecture of the developing brain. This system offers unique advantages in understanding molecular and cellular mechanisms governing embryonic neural development and in modeling congenital neurodevelopmental disorders, such as microcephaly. We have improved the organoid technology and developed a protocol to produce forebrain-specific organoids derived from human iPSCs using a novel miniaturized spinning bioreactor that recapitulate the human embryonic cortical development. ZIKV, a mosquito-borne flavivirus, has re-emerged as a major public health concern globally because ZIKV causes congenital defects, including microcephaly, and is also associated with Guillain-Barré syndrome in infected adults. We found that ZIKV exhibit specific tropism towards human neural

progenitor cells and results in cell death and defects in neural development. I will discuss our recent work in further dissecting the molecular mechanisms underlying the ZIKV pathogenesis and microcephaly.

13:45 – 14:00

AMENDING ORGANOID PRODUCTION TO DRUG SCREENING: HIGHLY HOMOGENEOUS HIPSC DERIVED CORTICAL SPHEROIDS PRODUCED IN BULK

O'Neil, Alison[1], Rapino, Francesca[1], Collins, Jesse[2], Heyman, John[2], Bortolin, Laura[3], Goldman, Melissa[3], Weitz, David[2], McCarroll, Steven[3], and Rubin, Lee[1]

[1]Stanley Center for Psychiatric Disease Research, SCRB, Harvard University, MA, U.S., [2]SEAS, Harvard University, MA, U.S., [3]Department of Genetics, Harvard Medical School, MA, U.S.

Human stem cell derived organoids have emerged as a prominent and useful tool to research the development and microanatomy of whole human organs in vitro. Relevant anatomical features and cell types are at least partially recapitulated in organoids and thus they can be used to more completely model human disease. Interestingly, when growing most types of organoids they must be embedded in a gel-like matrix to give them organizational cues for their proper formation. This embedding is typically done manually, which severely limits the scale on which research can be conducted and may be a source of the organoid-to-organoid variability that is generally observed. To address some of these limitations, we have brought together two technologies for the high-throughput production of homogeneous cortical spheroids. As a first application, we have harnessed our 3D spinning bioreactor culture system to produce thousands of homogeneous cortical spheroid precursors from human iPSCs via suspension mediated cellular aggregation. At the appropriate time, these precursor spheres are quickly embedded into individual droplets of custom alginate gel at the rate of about 100 droplets per minute using an engineered droplet maker. Once encapsulated in gel, the precursor spheres are further differentiated to mature cortical organoids, again in 3D spinning culture. Our cortical spheroids produce several different cortical layer neuron sub-types, and are relatively homogeneous in size and in the percentage of each neuron sub-types found per spheroid. This high level of homogeneity, along with a large quantity of material, enables us to begin to study psychiatric disease and other phenotypes in this more in vivo-like human model.

Funding Source: The authors thank the Stanley Center for Psychiatric Disease at the Broad Institute for funding.

14:00 – 14:15

MODELING THE HUMAN SEGMENTATION CLOCK WITH PLURIPOTENT STEM CELLS

Alev, Cantas[1], Matsuda, Mitsuhiro[2], Maya, Uemura[1], Yamanaka, Yoshihiro[1], Osawa, Mitsujiro[1], Saito, Megumu[1], Ikeya, Makoto[1], Yoshitomi, Hiroyuki[1], Toguchida, Junya[1], Yamamoto, Takuya[1], Woltjen, Knut[1] and Ebisuya, Miki[2]

[1]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan, [2]RIKEN Quantitative Biology Center (QBiC), Kobe, Japan

We recently succeeded with the step-wise in vitro induction of murine and human presomitic mesoderm (PSM) from pluripotent stem cells (ESCs/iPSCs). Aiming to model different aspects of somitogenesis we focused initially on the establishment of an in vitro model of the segmentation clock, combining step-wise induction of human and mouse PSM from ES and/or iPS cells, with in vitro quantitative measurement of oscillatory gene expression activity. For this purpose we established piggyBac-based promoter-driven luciferase reporter lines of core oscillatory genes (e.g. HES7) and used in vitro luminescence time-lapse imaging to visualize oscillatory gene expression in induced PSM samples and their 3D aggregates. Utilizing our pluripotent stem cell based in vitro approach we quantified and determined the period of the human and mouse segmentation-clock. We furthermore showed that oscillating foci are forming in vitro in a self-organizing manner. CRISPR/Cas9-based genome engineering was further utilized to establish knock-out reporter-lines lacking selective members of the putative gene network underlying oscillatory gene expression. Bioluminescence time-lapse imaging of human knock-out line-derived PSM samples revealed significant alterations in oscillatory gene expression activity. Overall, our work revealed key features and parameters of the human and murine segmentation clock, and represents a successful example of modeling defined aspects of embryonic development and disease with pluripotent stem cells.

14:15 – 14:30

GENOME EDITING IN HUMAN PLURIPOTENT STEM CELLS REVEALS GATA6 HAPLOINSUFFICIENCY AND A GENETIC INTERACTION WITH GATA4 IN HUMAN PANCREATIC DEVELOPMENT

Lee, Kihyun[1], Shi, Zhong-Dong[2] and Yang, Dapeng[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, U.S., [2]InVitro Cell Research, LLC, New York, NY, U.S.

Human disease phenotypes associated with haploinsufficient gene requirements are often not recapitulated well in animal models. We have investigated the association between human GATA6 haploinsufficiency and a wide-range of clinical phenotypes that include neonatal and adult-onset diabetes using CRISPR/Cas9-mediated genome editing coupled with human pluripotent stem cell (hPSC) directed

differentiation. We found that loss of one GATA6 allele specifically affects the differentiation of human pancreatic progenitors from the early PDX1+ stage to the more mature PDX1+NKX6.1+ stage, leading to an impaired formation of glucose- responsive ß-like cells. In addition to this GATA6 haploinsufficiency, we also identified dosage-sensitive requirements for GATA6 and GATA4 in the formation of both definitive endoderm and pancreatic progenitor cells. Our work expands the application of hPSCs from studying the impact of individual gene loci to the investigation of multigenic human traits and establishes an approach for identifying genetic modifiers of human disease.

14:30 – 14:45

ENHANCED NEPHROGENESIS THROUGH LIN28-MEDIATED REPROGRAMMING

Yermalovich, Alena V.[1], Osborne, Jihan[2], Sousa, Patricia[2], Combes, Alexander[3], Chen, Michael[2], Urbach, Achia[4], Little, Melissa[5] and Daley, George[2]

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Kidney disease represents a major public health issue in large part because nephrons, which are responsible for the filtration function of the kidney, form only during development in utero, and reach completion at approximately 34-36 weeks of gestation. Therefore, children who are born prematurely or suffer from malnutrition, disease, trauma, or surgical ablation have a reduced number of nephrons, or "nephron endowment." Because new nephrons never form in the extrauterine environment, children with a compromised nephron endowment are at increased risk of hypertension and development of cardiovascular and renal diseases as well as insulin resistance and Type 2 diabetes in later life. In this study we have discovered that regulated expression of the Lin28 gene, which we have previously linked to stem cell and tissue metabolism and enhanced wound healing, prolongs kidney development and activates formation of new nephrons, the functional unit of the kidney. Our studies of normal kidney development reveal expression of Lin28b around the middle of gestation when new nephrons are forming, after which Lin28b is silenced. If we provide a brief additional pulse of Lin28b expression in a kidney-specific and temporally defined manner in our transgenic mouse, we prolong the period of nephrogenesis and a mouse pup is born with 2 fold increased endowment of nephrons. Moreover, the transgenic mice have significantly increased kidney function as measured by filtration rate and creatinine levels relative to littermate controls. In addition, we have linked the activity of Lin28b to its ability to modulate the production of a class of small non-coding microRNAs called let-7 during kidney development. This interaction is potentially druggable by small molecule or anti-miR (a nucleic acid that blocks let-7), which might suffice to act like the endogenous Lin28 protein. Several studies have attempted to emulate nephron formation in vitro by the directed differentiation of pluripotent stem cells towards renal progenitor fate. However, anatomically complicated organs like the kidney are particularly challenging for stem cell-based therapies. This project envisions a new strategy to prolong the period of nephrogenesis in newborns and holds great promise for people suffering from kidney disease.

Funding Source: The NCI Predoctoral to Postdoctoral Fellow Transition Award (F99/K00), The National Institutes of Health

14:45 – 15:10

KIDNEY ORGANOIDS IN MODELLING HERITABLE KIDNEY DISEASE

Little, Melissa, Forbes, Tom, Hoden, Sara, Ghobrial, Irene, Hale, Lorna, Er, Pei Xuan, Lawlor, Kynan, Simons, Cas, Patel, Chirag, Trnka, Peter, Mallett, Andrew, Phipson, Belinda and Oshlack, Alicia

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

Genetic kidney disease accounts for 10% of adults and 50% of children with end stage kidney disease based on evidence of inheritance within a family. Advances in Next Generation sequencing have improved diagnosis rates for such families, however, a causative gene is identified in only 40% of cases. While novel potential causative gene associations are being identified, such variants of unknown significance require functional validation. The use of induced pluripotent stem cells (iPSC) is one approach that has the potential to determine the functional significance of previously un-described gene variants. We have developed a protocol for the successful differentiation of human pluripotent stem cells to a kidney organoid (1). This results in the formation of a complex organoid containing all cellular components anticipated for a trimester 1 human kidney. We are now investigating the capacity to model genetic kidney disease using organoids containing mutations in known and novel genes associated with kidney disease. This presentation will discuss a proof of concept for the utility of organoids in modelling heritable kidney disease from clinical identification through trio exome sequencing to identify a causative gene, derivation of patient and corrected patient iPSC and the validation of a corrected phenotype. It will also discuss the challenges of the model itself and the development of characterisation approaches tailored for the study of distinct kidney disease types, including nephronophthisis, proximal tubulopathies and glomerulopathies.

THURSDAY, 15 JUNE, 13:15 – 15:15

CONCURRENT IB: PLURIPOTENCY AND IPS CELL REPROGRAMMING I

Level 3, Ballroom East

13:20 – 13:45

COMBINATORIAL BINDING OF TRANSCRIPTION FACTORS IS ESSENTIAL FOR REPROGRAMMING TO PLURIPOTENCY

Plath, Kathrin

University of California, Los Angeles School of Medicine, Los Angeles, CA, U.S.

Transcription factor-induced reprogramming of somatic cells to induced pluripotent stem cells (iPSCs) is a process by which a differentiated cell is re-wired to an ESC-like state. Conceptually, reprogramming processes can be divided into two major steps: the decommissioning of the somatic program, where the transcriptional network of the starting somatic cell is shut down, and target program establishment, where a new transcriptional program corresponding to the desired end state is assembled. Our focus lies on deciphering the mechanisms by which the four Yamanaka reprogramming factors (Oct4, Sox2, Klf4 and cMyc) induce these events during reprogramming to pluripotency, particularly how they achieve the reorganization of the enhancer landscape. We believe that understanding the role of the reprogramming factors at a mechanistic level is integral to our ability to modulate expression states and cell identity. Our approach is three-fold. First, we have mapped where the reprogramming factors bind at different stages of the reprogramming process in relation to chromatin states. Second, we have performed functional studies where additional transcription factors are co-expressed with OSKM or only one reprogramming factor is induced. Third, we are applying RNA seq approaches to understand the path towards pluripotency. Our work is beginning to discern the mechanisms by which the Yamanaka factors inactivate somatic enhancers and select pluripotency enhancers.

13:45 – 14:00

KINETICS OF CHANGES IN 3D GENOME STRUCTURE AND GENE EXPRESSION DURING CELLULAR REPROGRAMMING SUGGEST INSTRUCTIVE ROLE OF GENOME TOPOLOGY

Stadhouders, Ralph[1], Vidal, Enrique[1], Serra, François[3], Le Dily, François[1], Quilez, Javier[1], Gomez, Antonio[1], Collombet, Samuel[3], Berenguer, Clara[1], Cuartero, Yasmina[2], Di Stefano, Bruno[4], Hecht, Jochen[1], Beato, Miguel[1], Marti-Renom, Marc[2] and Graf, Thomas[1]

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Previous studies have shown that chromosomes are folded in a cell-type specific manner, raising the possibility that genome topology has an instructive role in determining cellular identity. This question remains to be resolved, as so far only discrete cell states have been studied in a comprehensive genome-wide fashion. Here we determined the relationship between genome topology, chromatin state and gene expression dynamics by analyzing an efficient cellular reprogramming system at 7 timepoints - all representing homogeneous populations. Our system employs the transient overexpression of C/EBPß to render B cells highly sensitive to rapid and deterministic reprogramming into induced pluripotent stem cells (iPSCs) by the Oct4-Sox2-Klf4-Myc (OSKM) transcription factors. Transcriptome and epigenome analyses using RNA-Seq, ChIP-Seq and ATAC-Seq showed that OSKM rapidly primes pluripotency-associated enhancers for activation to establish the iPSC identity. High-resolution in-situ HiC revealed that reprogramming involved a stepwise but not always linear reorganization of chromosome folding at the level of subnuclear compartmentalization, genome insulation into topologically associated domains (TADs) and chromatin loop formation. As somatic cell identity was erased, topological features specific to iPSCs emerged, including reduced compartmentalization and TAD-enforced transcriptional co-regulation - likely contributing to the malleable state of the pluripotent epigenome. Transcriptome rewiring was dynamically coupled to changes in genome compartmentalization and TAD structure, often exhibiting strikingly similar kinetics. Surprisingly, we also frequently observed topological alterations preceding transcriptional changes, suggesting a role for chromosome folding in regulating gene expression. Furthermore, we found that Oct4 induces rapid architectural changes that include alterations in TAD insulation and the establishment of inter-TAD crosstalk connecting gene regulatory elements in 3D. Together, our data reveal a highly dynamic transcription factor-driven interplay between gene expression, chromatin state and genome topology,

suggesting that chromosomal architecture has an instructive role in gene regulation and cell fate decisions.

Funding Source: This work is funded by an ERC Synergy Grant ("4D-Genome", to M.B., M.M-R. and T.G.), an EMBO Long-term Fellowship (ALTF 1201-2014, to R.S.) and a Marie Curie Individual Fellowship (H2020-MSCA-IF-2014, to R.S.).

14:00 – 14:15

NCOR/SMRT CO-REPRESSORS CREATE A MOLECULAR BRAKE PAD TO SOMATIC CELL REPROGRAMMING

Esteban, Miguel A.[1], Li, Wenjuan[2] and Hutchins, Andrew P.[3]

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The reprogramming of somatic cells to induced pluripotent stem cells requires the intimate cooperation between the exogenous transcription factors and transcriptional co-regulators to remodel the epigenetic environment, but how this interplay is regulated remains yet poorly understood. We became interested in studying the role of a well-known co-repressor complex, NCoR/SMRT-HDAC3, which has fundamental roles in development and adult physiology, in somatic cell reprogramming. We have demonstrated that NCoR/SMRT co-repressors bind to pluripotency loci to create a barrier to reprogramming with the 4 Yamanaka factors (OCT4, SOX2, KLF4, and c-MYC), and consequently, suppressing NCoR/SMRT significantly enhances reprogramming efficiency and also accelerates the kinetics. The core epigenetic subunit of the NCoR/SMRT complex, HDAC3, executes the detrimental effects of NCoR/SMRT on pluripotency loci by inducing their selective histone deacetylation. Moreover, although recruitment of NCoR/SMRT-HDAC3 to pluripotency loci is facilitated by all 4 exogenous factors, the main responsible is c-MYC, and therefore, c-MYC is beneficial for the early phase of reprogramming but deleterious afterwards. Overall, we uncover a new fundamental roadblock of reprogramming and propose a dual role for c-MYC in this process. We also propose that recruitment of NCoR/SMRT-HDAC3 may contribute to explain the repressor function of c-MYC in other contexts.

Funding Source: National Natural Science Foundation of China (31371513, 31671537); The National Key Research and Development Program of China (2016YFA0100102); National Basic Research Program of China (2016YFA0100701)

14:15 – 14:30

CHROMATIN-ASSOCIATED FACTORS OF THE DPPA2/4 FAMILY ARE THE KEY REGULATORS OF CELLULAR REPROGRAMMING

Hernandez, Charles[1], Wang, Zheng[2], Lee, Yu-Wei[2], Dambrot, Cheryl[2], Strino, Francesco[2], Kluger, Yuval[2] and Ivanova, Natalia[1]

[1]Genetics, Yale University, New Haven, CT, U.S., [2]Yale University, New Haven, CT, U.S.

Following seminal discovery by Takahashi and Yamanaka, pluripotency can now be induced in somatic cells by expression of OSKM factors. While the technology is being increasingly utilized to produce iPSCs, its mechanistic understanding remains incomplete. In particular, the process of epigenetic remodeling, shown to be a major rate-limiting step of the reprogramming process, remains poorly characterized. Recent work in the field identified a set of predictive markers (Utf1, Esrrb, Lin28 and Dppa2) whose expression labels the rare cells which have higher probability of becoming iPSCs. We show that Dppa2 and its close homolog Dppa4 are the essential components of the chromatin remodeling network and govern the transition to pluripotency. Dppa2/4 are induced in pre-iPSCs and are required for generation of iPSCs. Ectopic expression of single Dppa2/4 transgene in OSKM-MEFs significantly increases the number of iPSC colonies compared to OSKM alone. Expression of both Dppa2 and Dppa4 (Dppa2/4-OE) results in additional and drastic increase in colony numbers. In a single-cell assay, more that 75% of Dppa2/4-OE MEFs give rise to Nanog+ iPSCs compared to less than 2% in the OSKM cultures. The emergence of reprogramming intermediates is also greatly accelerated, resulting in formation of fully-reprogrammed iPSCs in 2-4 days. Dppa2/4-OE iPSCs exhibit correct pattern of pluripotency marker expression and robustly generate germline-competent chimeric mice by blastocyst injection and tetraploid complementation. Importantly, overexpression of DPPA2/4 drastically improves both the efficiency and the kinetics of human iPSC generation. Mechanistically, Dppa2 and Dppa4 function as a dimer that recognizes a conserved DNA motif at the promoters and intergenic regions located within large H3K9me3 heterochromatin domains. Biochemical and bioinformatics analyses revealed that Dppa2/4 binding leads to the recruitment of several chromatin remodeling complexes, gain of H3K4me3 marks, and erasure of H3K9me3 marks, increase in DNA accessibility and rapid activation of endogenous pluripotency network. Our findings reveal a novel mechanism responsible for generation of accessible chromatin during reprogramming and provides a useful strategy to enhance iPSC generation for clinical and research use.

14:30 – 14:45

HYBRID CELLULAR METABOLISM COODINATED BY ZIC3 AND ESRRB SYNERGISTICALLY ENHANCE SOMATIC CELL REPROGRAMMING

Sone, Masamitsu and Yamamoto, Takuya

Center for iPS Cell Research and Application (CiRA), Kyoto, Japan

In the process of somatic cell reprogramming into both naïve and primed pluripotent stem cells (PSCs), cells become much more dependent on glycolysis than their original somatic cells. In addition, it has been recently reported that activation of not only the glycolysis pathway but also the OXPHOS pathway is essential for somatic cell reprogramming even though these metabolic pathways act antagonistically. Therefore, the balance between these two pathways should be strictly controlled during reprogramming, and disproportionate activation of these pathways might abrogate the acquisition of pluripotency. However, the molecular basis for establishing the appropriate balance of this hybrid cellular metabolism is completely unknown. In this study, we demonstrate that the introduction of Zic3 and Esrrb along with OSK into somatic cells synergistically enhances the reprogramming into naïve iPSCs by coordinating the glycolysis and OXPHOS metabolic pathways. Our transcriptome and ChIP-seq analyses reveal that Zic3 is an important partner of Esrrb in the upregulation of glycolysis-related genes. Further, our metabolome analysis shows that Zic3 and Esrrb activate glycolysis and the pentose phosphate pathway in an accommodating manner. At the same time, overexpression of Zic3 represses mitochondrial activity, presumably because activated glycolysis deprives the OXPHOS pathway of its metabolic substrate, whereas Esrrb activates OXPHOS-related genes and reconstructs the mitochondrial architecture. Therefore, Esrrb reactivates Zic3-mediated reduced OXPHOS activity when simultaneously introduced with Zic3 during reprogramming. Moreover, we also show that other OXPHOS activators, such as Pgc1a can enhance reprogramming synergistically with Zic3. Additionally, Esrrb powerfully converts mouse EpiSCs into naïve iPSCs, and Pgc1a partially mimics it. These data indicate that the function of Esrrb could be substituted at least in part by the activation of OXPHOS. In summary, our results demonstrate that metabolic shift is controlled by sophisticated coordination of TFs in somatic cell reprogramming into naïve pluripotency.

14:45 – 15:10

ROLE OF SEX CHROMOSOMES AND ENVIRONMENT ON DNA METHYLATION PATTERNS IN PLURIPOTENT STEM CELLS

Hochedlinger, Konrad

Massachusetts General Hospital, Boston, MA, U.S.

I will share recent data from our lab on the role of sex chromosomes and culture conditions on DNA methylation and developmental potential of pluripotent stem cells.

THURSDAY, 15 JUNE, 13:15 – 15:15

CONCURRENT IC: STEM CELLS- STRESS AND AGING

Level 2, Room 258C

Sponsored by: Decibel Therapeutics

13:20 – 13:45

AUTOPHAGY, METABOLISM AND AGED HEMATOPOIETIC STEM CELLS

Passegué, Emmanuelle

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

Hematopoietic stem cell (HSC) activation is accompanied by mitochondria activation and a shift in metabolic activity from glycolysis to OXPHOS, which provides energy and increases the production of ROS and other mitochondrial metabolites that can act both as signaling molecules and substrates/co-activators for epigenetic enzymes. Metabolically activated HSCs are poised to undergo lineage priming and produce different lineage-biased multipotent progenitors (MPP). However, activated HSCs must also return to quiescence to maintain the stem cell pool. In this context, autophagy plays an essential role by clearing activated mitochondria to allow OXPHOS-driven HSCs to efficiently revert to a mostly glycolysis-based quiescence metabolism. Without autophagy, HSCs display an overactive OXPHOS-driven metabolism that promotes myeloid-biased differentiation and loss of stemness, likely as a direct consequence of epigenetic reprogramming. This role of autophagy becomes even more important with age as the inability of about two-thirds of aged HSCs to activate autophagy results in an overactive OXPHOS metabolism that impairs self-renewal, promotes proliferation and myeloid differentiation, and contributes to replication stress. These unhealthy aged HSCs drive most of the aging blood phenotypes. In contrast, about one-third of aged HSCs activate autophagy, control their metabolic activity, and are the fittest old stem cells that retain functional abilities in an adverse aging bone marrow microenvironment. We are now exploring the mechanisms responsible for this differential induction of autophagy in aged HSCs, and testing whether interventions aimed at re-activating autophagy in unhealthy autophagy-inactivated aged HSCs will improve the health of the old blood system.

13:45 – 14:00

4HPR ACTIVATES AUTOPHAGY TO PRESERVE HSC FUNCTION DURING HUMAN CORD BLOOD EXPANSION

Xie, Stephanie Zhi-Juan[1], Garcia-Prat, Laura[1], Laurenti, Elisa[1], Ferrari, Robin[1], Nakayama, Naoya[1], Patel, Ishita[1], Lee, Esther[1], Gan, Olga[1], Murison, Alex[2], Medina, Tiago[2], Lupien, Mathieu[2] and Dick, John[3]

[1]Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada, [2]Department Medical Biophysics, University of Toronto, Canada, [3]Princess Margaret Cancer Centre, University Health Network, Department of Molecular Genetics, University of Toronto, Canada

Clinically, single cord blood (CB) units do not contain enough short (ST) and long term (LT) hematopoietic stem cells (HSC) to enable HSC transplant (HSCT) into adult recipients, prompting the development of ex vivo CB expansion methods. Numerous conditions yield ST-HSC/progenitor expansion, but LT-HSC expansion is neither robust nor reliable. LT-HSC have properties distinct from those of ST-HSC and more committed progenitors, including altered cell cycle properties, stress responses and metabolism. Current strategies to expand primitive CD34+ cells in the presence of cytokines disrupt many of these HSC properties, leading to release from quiescence, increased reactive oxygen species (ROS) and activation of stress responses. Autophagy is an essential process for protection of mouse LT-HSC from metabolic stress and aging. Therefore, we asked if activation of autophagy in human CB with the pleiotropic retinoid fenretinide/N-(4-hydroxyphenyl) retinamide (4HPR) would improve LT-HSC function following ex vivo expansion regimens. 4HPR increases LC3 cleavage and autophagy as detected by CYTO-ID, selectively in primitive CD34+CD38- but not more committed CD34+CD38+ cells, under cytokine-rich culture conditions or upon short-term cytokine withdrawal. Treated cells exhibit decreased ROS and mitochondrial membrane potential, reflective of the metabolic state of quiescent HSC. In ex vivo culture, 4HPR treatment for 8 d alone or in combination with known CB ex vivo expansion agents SR1 or UM171 remarkably limits the expansion of CD34+CD45RA+ committed progenitors while preserving immunophenotypic LT- and ST-HSC. 4HPR induces changes to chromatin accessibility that are distinct from those induced by SR1 or UM171 as measured by ATAC-seq. Importantly, in limiting dilution serial transplantation assays, the frequency of LT-HSC was increased by ex vivo 4HPR treatment compared to controls, and doubled when 4HPR was added to SR1+UM171 treatment compared to SR1+UM171 treatment alone. Here, we describe a previously unrecognized function of 4HPR in preserving human LT-HSC function while still allowing ex vivo expansion of ST-HSC and progenitors. We propose that upregulation of autophagy in primitive CB cells with 4HPR as a novel strategy to improve clinical HSCT outcome.

Funding Source: Medicine by Design; CIHR, TFRI

14:00 – 14:15

NICHE STIFFNESS UNDERLIES THE AGEING OF OLIGODENDROCYTE PROGENITOR CELLS

Segel, Michael S.[1], Weber, Isabell[2], Hill, Myfanwy[1], Neumann, Björn[1], Franze, Kristian[2], Franklin, Robin[3] and Chalut, Kevin[1]

[1]Stem Cell Institute, University of Cambridge, U.K., [2]Physiology, Development, and Neuroscience, University of Cambridge, U.K., [3]WT MRC Stem Cell Institute, University of Cambridge, U.K.

Like many adult stem cell populations, the function of the central nervous system's oligodendrocyte progenitor cell (OPC) is impaired with ageing. Importantly, the number of OPCs does not change with age, yet aged OPCs have a marked decline in their capacity to proliferate and differentiate into myelinating oligodendrocytes. As progenitor cells' microenvironments are known to affect their function, we have focused on better understanding how the brain microenvironment changes with ageing. We have found that the CNS stiffens by 3-5 fold with ageing. Moreover, isolated aged OPCs put on biological and synthetic scaffolds that recapitulate the stiffness of the young brain are rejuvenated in terms of their proliferation and differentiation rates, and in terms of their gene expression profiles. Small molecules overriding the mechanosensitivity of OPCs accelerate re-myelination in vivo. Finally, we have shown that the nuclear lamina are the downstream effectors of OPC mechanosensitivity. Indeed, it is unlikely that a stiffening environment alone causes OPC ageing. However, we believe that replicative stress, DNA instability, and a loss of proteostasis, in addition to the stiffening progenitor cell niche feed-forward progressively and that it is this combination of factors that ultimately cause the ageing of the CNS.

Funding Source: Biotechnology and Biological Sciences Research Council (BBSRC), MS Society

14:15 – 14:30

ORIGINS OF AGE-RELATED NEUROGENESIS DECLINE

Ibrayeva, Albina[1] ,Pu, Elbert[1] , Krieger, Teresa G.[2], Stadel, Ryan[3], Berg, Daniel[3], Ming, Guo-li[3], Simons, Benjamin D.[2], Song, Hongjun[3], Bonaguidi, Michael[1]

[1]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, Zilkha Neurogenetic Institute, Department of Stem Cell Biology and Regenerative Medicine W. M. Keck School of Medicine, University of Southern California, CA, U.S., [2]Cavendish Laboratory, Department of Physics, University of Cambridge, U.K., [3]Institute for Cell Engineering, Department of Neurology, Johns Hopkins University School of Medicine, CA, U.S.

Equilibrium between self-renewal and cell differentiation is preserved by endogenous stem cells in most tissues through late life. However, neurogenesis in the adult rodent hippocampus diminishes significantly by middle age of un-

clear origins. By using in vivo single cell linage tracing and computational reconstruction, we identify two radial glia-like (RGL) neural stem cell (NSC) populations. These cells differentially contribute to cell production under physiological and injury conditions in the young adult. During aging, these cohorts serve as short-term and 'long-term' NSCs. Long-term RGL behaviors change in attempt to restore homeostasis during aging. Yet, loss of NSC homeostasis is ultimately driven by increased RGL quiescence and slowing expansion rate. Our study elucidates cellular origins of neurogenesis decline and may serve as a new mammalian stem cell model to study early-onset cellular aging.

Funding Source: Bolashak Fellowship to A.I. NIH (NS080913) to MAB

14:30 – 14:45

INVESTIGATING HUMAN PREMATURE AGING USING STEM CELL MODELS

Zhang, Weiqi[1], Liu, Guanghui[1] and Qu, Jing[2]

[1]Institute of Biophysics, Chinese Academy of Sciences, Beijing, [2]Institute of Zoology, Beijing, China

Werner syndrome (WS) and Hutchinson-Gilford progeria syndrome (HGPS) are rare premature aging disorder, which mainly affect tissues derived from mesoderm. We have recently developed a novel human WS model using WRN-deficient human mesenchymal stem cells (MSCs) , which could recapitulates many phenotypic features of WS. HGPS is caused by constitutive production of progerin, a mutant form of the nuclear architectural protein lamin A, leading, through unknown mechanisms, to diverse morphological, epigenetic, and genomic damage and to mesenchymal stem cell (MSC) attrition in vivo. Using a stem cell model, we found that impaired activity of the NRF2 antioxidative pathway is a driver mechanism in HGPS and reactivation of NRF2 decreases oxidative stress and reverses cellular HGPS defects. Based on a screen of a number of chemicals, here we found that combination of three compounds could exerts high efficient rescue for many features in premature aging, including cell growth arrest, increased reactive oxygen species levels, telomere attrition, excessive secretion of inflammatory factors, as well as disorganization of nuclear lamina and heterochromatin. Our results identify a rejuvenating cocktail for WS and HGPS MSCs, which holds the potential of being applied as a novel type of treatment of premature aging.

14:45 – 15:10

YAP/TAZ AND CELL PLASTICITY: DE NOVO GENERATION OF TISSUE-SPECIFIC SOMATIC STEM/PROGENITOR CELLS BY YAP-MEDIATED REPROGRAMMING OF DIFFERENTIATED CELLS

Piccolo, Stefano, Panciera, Tito, Azzolin, Luca and Fujimura, Atsushi

Department of Molecular Medicine, University of Padova, Italy

The ability to induce autologous tissue-specific stem cells in culture could have a variety of applications in regenerative medicine and disease modeling. We found that transient expression of exogenous YAP in primary differentiated mouse cells can induce conversion to a tissue-specific stem/progenitor cell state. YAP-induced stem/progenitor cells show molecular and functional properties overlapping to endogenous stem cells. YAP-induced stem cells do not require continuous supply of exogenous YAP and rather rely on endogenous YAP/TAZ, suggesting the existence of self-sustaining gene-network for the somatic stem cell state shared by different lineages. Endogenous YAP/TAZ function is also essential for self-renewal of endogenous stem cells in culture, to grow and expand organoids from many tissue sources and, in vivo, for tissue regeneration and cancer.

THURSDAY, 15 JUNE, 13:15 – 15:15

CONCURRENT ID: SINGLE CELL HETEROGENEITY

Level 2, Room 205A

13:20 – 13:45

SINGLE CELL ANALYSIS OF CLONAL EVOLUTION IN CHILDHOOD LEUKAEMIA REVEALS GENETIC AND EPIGENETIC BOTTLENECK SELECTION

Enver, Tariq, Turati, Virginia, Guerra-Assuncao, J Alfonso, Ambrose, John C, Brown, John, Hubank, Mike, Lynch, Mark, Gaal, Bernadette, Herrero, Javier, Jacobsen, Sten E and Conde, Lucia

University College London Cancer Institute, London, U.K.

While intratumor heterogeneity has been long recognized, its biological and clinical significance is not well understood. To determine the relative contribution of different sources of heterogeneity to therapeutic resistance in childhood acute lymphoblastic leukemia (cALL), we have developed a mouse model that affords longitudinal analysis of subclonal dynamics. By assessing the reproducibility of independent outcomes, one can distinguish between deterministic and stochastic mechanisms of selection during therapy. We use a combination of single cell assays to track the fate of individual clones. Using multicolor-FISH, we show that, while treatment of ALL results in a striking reduction in leukemic burden, the overall extent of genetic diversity is largely unaffected. We have subsequently adapted PicoPLEX WGA to the Fluidigm C1 platform to produce high resolution single-cell copy number maps. WGS data dissect heterogeneity in greater detail, revealing the coexistence of clones carrying the same lesion but distinct breakpoints, formally proving convergent evolution of cALL. Bulk transcriptome analysis of treated and untreated cells reveals that resistant cells have features characteristic of more primitive hematopoietic cells, including concomitant up-regulation

of hematopoietic stem and lympho-myeloid progenitor markers. Functional analysis shows that chemotherapy enriches for cells with tumor initiating potential. At the single cell level, the treatment naïve population displays higher transcriptional variance both across cells and genes. Importantly, a rare population of untreated cells appears to bear resistance potential. Using a novel algorithm for analysis of gene expression networks in single cells - SCENT - we can assign treated and untreated populations based on transcriptional entropy - a surrogate for cellular potential in a 'Waddingtonian' landscape. All together the data suggest that genetic heterogeneity in cALL arises through independent acquisition of copy number alterations affecting the same gene or genes within a pathway, thereby resulting in convergent phenotypic evolution; resistance is instead likely driven by a pre-existing population of immature cells with a distinct global gene expression signature and higher tumor propagating potential.

13:45 – 14:00

WNT/PLANAR CELL POLARITY SIGNALING IN THE CRYPT STEM CELL NICHE REGULATES SECRETORY LINEAGE SEGREGATION

Lickert, Heiko

Helmholtz Zentrum München, Institute of Diabetes and Regeneration Research, Neuherberg, Germany

A detailed understanding of intestinal stem cell (ISC) self-renewal and differentiation is required for better treatment options for a variety of chronic intestinal diseases, however, current models of the ISC lineage hierarchy and segregation are still under debate. Here we report the identification of Lgr5+ ISCs that express Flattop (Fltp), a Wnt/planar cell polarity (PCP) reporter and effector gene. Functional analysis and lineage tracing reveals that Wnt/PCP activated Fltp+ ISCs committed to either enteroendocrine or Paneth cells in vivo, while retaining self-renewal and multi-lineage capacity in vitro. Surprisingly, canonical Wnt/catenin- and non-canonical Wnt/PCP-activated Lgr5+ ISCs are indistinguishable by the expression of stem-cell signature or secretory lineage-specifying genes, suggesting that lineage commitment and cell-cycle exit is triggered at the post-transcriptional level by polarity cues. Using computational determination of a pseudotime from targeted single cell gene expression analysis allowed us to reconstruct the ISC differentiation path into enteroendocrine and Paneth cells. Strikingly, both lineages are directly recruited from ISCs via unipotent transition states, excluding the existence of formerly predicted bi- or multipotent secretory progenitors. Transitory cells to the Paneth fate are characterized by label-retention and co-expression of stem cell and secretory lineage genes, indicating that these cells are the previously described Lgr5+ label-retaining cells (LRCs). Taken together, we identified the Wnt/PCP pathway as a new niche signal and polarity cue regulating stem cell fate. Active Wnt/PCP signaling represents one of the earliest events in ISC lineage commitment towards the Paneth and enteroendocrine cell fate, preceding lateral inhibition and expression of secretory lineage-specifying genes. Thus, our findings redefine the mechanisms underlying ISC lineage hierarchy and segregation and provide a better understanding of niche signals.

Funding Source: Helmholtz Alliance ICEMED ; Helmholtz Society; Helmholtz Portfolio Theme 'Metabolic Dysfunction and Common Disease; German Research Foundation and German Center for Diabetes Research (DZD e.V.).

14:00 – 14:15

MAPPING VERTEBRATE DIFFERENTIATION HIERARCHIES WITH HIGH-THROUGHPUT SINGLE-CELL TRANSCRIPTOMICS

Wagner, Daniel E., Megason, Sean and Klein, Allon

Harvard Medical School, Boston, MA, U.S.

This project addresses a longstanding goal of developmental biology: to map the detailed molecular events beginning with the expansion of pluripotent blastomeres to the differentiation of all mature cell types in the body. To date, many key molecular components and cell types have been catalogued through the use of genetic screens, perturbations, and fate mapping. However, a precise understanding of how cells choose their final identities requires deeper examinations of transitional states in development. Here, we use high-throughput single-cell transcriptomics to deliver a quantitative map of early vertebrate development (in vivo), using the zebrafish as a model. Single-cell suspensions were generated from dissociated zebrafish embryos from 7 timepoints spanning the first 24 hours post-fertilization. Over 35,000 individual cells were then encapsulated using a microfluidic droplet-based barcoding platform and analyzed by single-cell RNAseq. Established dimensionality reduction and clustering analyses revealed a comprehensive atlas of cell states, which increased in complexity over developmental time. In total, we annotated over 194 cell states (representing both stable cell types as well as dynamic processes) using data from the ZFIN gene expression database. Furthermore, we developed a quantitative strategy for inferring cell state progression over time and constructed a cell state "tree" for development. This tree recapitulates a branching pattern: cells initially expressing early pluripotency markers give rise to distinct germ layers, and progressively discrete tissue-specific compartments. In addition to providing a rich resource for gene discovery, our data also reveal several novel cell types, and elucidate a previously unknown lineage branching event.

Funding Source: DEW is an HHMI fellow of the Life Sciences Research Foundation.

14:15 – 14:30

DECODING THE DOPAMINERGIC NEUROGENIC NICHE AT A SINGLE CELL LEVEL

Arenas, Ernest[1], Toledo, Enrique[2], La Manno, Gioele[2], Gyllborg, Daniel[2], Islam, Saiful[2], Villaescusa, J. Carlos[2] and Linnarsson, Sten[2]

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The development of midbrain dopaminergic (mDA) neurons requires the interaction of multiple transcription factors and signaling pathways. These factors are coordinated over time and space in complex microenvironments or niches where stem/progenitor cells reside. One of the most critical components of such niches is the radial glia. In the developing mouse ventral midbrain, radial glia has been found to be a neurogenic cell type capable of giving rise to mDA neurons. Surprisingly, in a recent single-cell RNA-sequencing analysis of the developing mouse midbrain, we found three different types of molecularly distinct radial glia (Rgl1-3) emerging progressively from E11.5 to E13.5, during mDA neurogenesis. This finding raised several important questions as to the function of each of the three radial glia cell types: Which of them is neurogenic? Do they express cell extrinsic factors capable of regulating neurogenesis? How are cell intrinsic and extrinsic factors spatially and temporally integrated in this neurogenic niche? What is the cellular microenvironment in which mDA neurogenesis takes place? By analyzing the transcriptome of the mouse ventral midbrain at a tissue and single-cell level during mDA neurogenesis and performing a system biology analysis we found that the three radial glia types (Rgl1-3) contribute to different aspects of mDA neurogenesis. Rgl3 was found to express most extracellular matrix components and ligands for multiple signaling pathways controlling mDA neuron development, such as Wnt, Shh and Fgf. On the other hand, Rgl2 expresses most receptors for these pathways and transcription factors such as Pax6 and Tcf7l1, which regulate progenitor maintenance. Finally, Rgl1 was found to express few ligands and multiple receptors for developmental signaling pathways as well as several transcription factors of the basic-helix-loop-helix family, some of which are known to control neurogenesis, such as Ascl1 and Tcf family members. These transcription factors are currently being investigated for their capacity to promote mDA neurogenesis in vitro and in vivo. In sum, we hereby identify Rgl1 is a neurogenic cell type and uncover how molecularly distinct radial cell types utilize multiple cell extrinsic and intrinsic factors in a temporally defined manner to control and promote mDA neurogenesis.

Funding Source: Swedish Research Council (VR:2011-3116, 2011-3318, 2016-01526), Swedish Foundation for Strategic Research (SRL program), EU-FP7 programs (NeuroStemcellRepair and DDPDGENES), KI and Hjärnfonden (FO2013:0108, FO2015:0202).

14:30 – 14:45

A SINGLE-CELL ATLAS OF MOUSE SKIN DURING HAIR GROWTH AND REST

Kasper, Maria[1], Sun, Xiaoyan[1], Joost, Simon[1], Sivan, Unnikrishnan[1], Jacob, Tina[1], Annusver, Karl[1] and Sandberg, Rickard[2]

[1]Karolinska Institutet, Huddinge, Sweden, [2]Karolinska Institutet, Stockholm, Sweden

The homeostasis of the skin is characterized by cycles of hair growth (anagen), regression (catagen) and rest (telogen), and involves a delicate interplay of epithelial cells and their dermal microenvironment. This makes skin an excellent model system for tissue regeneration and stem cell research. Here, we used single-cell gene expression analysis of more than 6000 cells to systematically determine the full repertoire of cells in the mouse skin during hair growth and rest. Analyses revealed a complex cellular composition consisting of more than 60 distinct populations of epithelial, fibroblast and fibroblast-like, immune, vascular and neuronal cells. Intriguingly, we captured more than 25 known and novel hair follicle populations during anagen, which enabled us to computationally reconstruct the hair follicle differentiation during hair growth. In addition, we found clear differences between anagen and telogen skin in the abundance, identity and gene expression of most dermal cell populations. We also identified a striking heterogeneity of fibroblasts and fibroblast-like cells in the dermis and provide robust gene expression signatures from difficult to purify, or rare populations such as dermal sheath cells or perineural fibroblasts. In summary, we provide one of the first single-cell gene expression datasets that includes both epithelium and microenvironment of a mammalian organ and use it to gain new insights into the molecular and temporal composition of the mouse skin.

14:45 – 15:10

ENGINEERING CELLS AND TISSUES: INSIGHTS FROM SINGLE-CELL TRANSCRIPTOMICS

Treutlein, Barbara

Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

Engineering specific cell types and complex tissues in vitro is an important goal for regenerative medicine. I will present two projects using single cell transcriptomics to understand mechanisms underlying cell fate programming in 2-D cell cultures and 3-D organoids. The first part focuses on cerebral organoids, three-dimensional cultures of human cerebral tissue derived from pluripotent stem cells. We use single-cell RNA-seq to dissect and compare cell composition and progenitor-to-neuron lineage relationships in human cerebral organoids and fetal neocortex in order to find out how well these in vitro systems recapitulate neural progenitor cell proliferation and neuronal differentiation programs observed in vivo. We identify cells in the cerebral organoids that derived from regions resembling the fetal neocortex and find that these cells use gene expression programs remarkably similar to those of the fetal tissue. We then extend this study to compare cells from human organoids with those from chimpanzee organoids to find features of corticogenesis that are unique to humans. In the second part, we analyze the direct reprogramming of fibroblasts to induced neuronal cells. We deconstruct heterogeneity at multiple time points in order to reconstruct the reprogramming path in high resolution. Surprisingly, we identify a competing myogenic program that emerges when using a single transcription factor (Ascl1), but this alternative fate is repressed by a combination of three factors (Ascl1, Brn2, Myt1l). Our analysis highlights major inefficiencies in the direct reprogramming process. In summary,

these data provide an approach to systematically analyze and improve cell and tissue engineering.

THURSDAY, 15 JUNE, 13:15 – 15:15

CONCURRENT IE: MUSCLE AND MESENCHYMAL CELLS

Level 2, Room 253ABC

13:20 – 13:45

HIGH-RESOLUTION MAPPING OF MYOGENIC LINEAGE AND EPIGENETIC LANDSCAPE BY SINGLE-CELL MASS CYTOMETRY

Blau, Helen M., Porpiglia, Ermelinda and Yucel, Nora

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

Muscle regeneration is a dynamic process during which cell state and identity change over time. A major roadblock has been a lack of tools to resolve a myogenic progression in vivo. Here we capitalize on a transformative technology, single-cell mass cytometry (CyTOF), to identify in vivo skeletal muscle stem cell and previously unrecognized progenitor populations that precede differentiation. X-shift clustering analysis combined with single-cell force directed layout visualization of the myogenic compartment provides a high-resolution lens that reveals a molecular signature of the activated stem cell state and a myogenic trajectory during regeneration. Further, we use CyTOF to capture the dynamics of histone acetylation, at the single-cell level, upon muscle injury. We identify a metabolic driver, pyruvate dehydrogenase (PDH), which directs the flux of glucose to fuel histone acetylation. Pharmacological or genetic activation of PDH results in increased histone acetylation and impedes regeneration. Our studies provide the first CyTOF-driven identification of stem and progenitor cells and their metabolic regulation in skeletal muscle regeneration, paving the way for the elucidation of the regulatory networks that underlie cell-state and epigenetic transitions in muscle diseases and aging.

13:45 – 14:00

DEFICIENCY OF ENDOPHILINS IMPAIRS MULTILINEAGE HEMATOPOIESIS AND HSC MAINTENANCE DUE TO DEFECTIVE NICHE FUNCTIONS

Rathinam, Chozha V.[1] and Thummar, Keyur[2]

[1]*Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD, U.S.,* [2]*University of Maryland School of Medicine, Baltimore, MD, U.S.*

The organization and functions of the Bone marrow (BM) Niche are crucial for hematopoiesis. Indeed, deregulated molecular pathways can contribute to a dysfunctional niche that will induce hematologic disorders, including leukemia. BM Niche is composed of a variety of cell types, including Mesenchymal Stem/Stromal Cells (MSCs), Osteoblasts, Adipocytes, Fibroblasts, Schwann Cells and Perivascular stromal cells. While the cellular constituents of the BM niche began to unfold, molecular mechanisms that control the functions of BM Niche remain largely unknown. During our analysis of mice that are deficient for Endophilin 1 and Endophilin 2, we observed that Endophilins 1 and 2 double knockout (DKO) mice developed pancytopenia, severe reduction in size and cellularity of hematopoietic organs, and exhibited postnatal lethality. Analysis of hematopoietic compartments in Endophilins deficient mice indicated strikingly reduced frequencies of hematopoietic stem and progenitor cells (HSPCs) and of lineage committed progenitors, due to diminished proliferation and increased cell death. Reciprocal bone marrow transplantation experiments and in-vitro culture studies suggested that the hematopoietic defects are caused by cell-extrinsic mechanisms. Mechanistic studies identified that Endophilins deficiency caused decreased levels of key hematopoietic cytokines, including SCF and TPO, in the serum. Interestingly, Endophilins deficient bone marrow contains increased frequencies of MSCs (CD45-Ter119-CD31-CD140a+Sca1+CD90+). Further analysis of endophilins mutant MSCs exhibited hyperproliferation, altered ex-vivo expansion kinetics, augmented adipocyte and reduced osteolineage differentiation, decreased expression levels hematopoietic cytokines and defective abilities to support hematopoiesis. Biochemical and imaging studies identified hyper-phosphorylation of ERK1/2 and sustained ERK signaling in endophilins mutant MSCs, possibly due to prolonged intracellular persistence of signaling endosomes. Finally, blocking ERK signals in DKO MSCs improved HSC maintenance, both in-vivo and in-vitro. These data suggest that Endophilins play an indispensable role in maintaining the cellular and functional integrity of the BM niche.

14:00 – 14:15

NEW GENERATION MATRIX PROVIDES HIGH EFFICIENT DIFFERENTIATION SYSTEM INDUCING MYOCYTES AND MUSCLE STEM CELLS FROM HUMAN INDUCED PLURIPOTENT STEM CELLS

Zhao, Mingming[1], Sekiguchi, Kiyotoshi[2] and Sakurai, Hidetoshi[3]

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Stepwise culture strategy for developing human induced pluripotent stem cells (hiPSCs) to myocytes and skeletal muscle stem cells in vitro has been established by our group. However, this strategy shows relatively lower efficiency, and cells are cultured on the undefined factors containing Matrigel which is unlikely to be permitted for clinical use. Here we describe a system for differentiating hiPSCs on the new generation matrix, which is a recombinant form of a laminin-421 E8 fragment conjugated to the heparan

sulfate attachment domain of perlecan. In this system, heparan sulfate, which is capable of binding to heparin-binding growth factors, remarkably increased the marker genes expression of primitive streak, paraxial mesoderm, dermomyotome and skeletal muscle progenitors, and increased myocytes population. When treated differentiated cells with trypsin, myocytes on the new generation matrix showed trypsin resistance, maintaining cellular homogeneity with approximately 93% MyoD1-positive cells. Furthermore, the new generation matrix increased skeletal muscle stem cell population (Pax7-positive) in mature muscle cells derived from hiPSCs. By using this xeno-free matrix, we established a highly efficient differentiation system for hiPSCs induced myocytes and muscle stem cells, thus providing infinite source for disease modeling and regenerative medicine.

14:15 – 14:30

FOS INSTRUCTS EARLY MUSCLE STEM CELL FATE DECISIONS IN RESPONSE TO SKELETAL MUSCLE TRAUMA IN ADULT MICE

Almada, Albert E.[1], Gonzalez, Alfredo[2], Price, Feodor[2], Maesner, Claire[2] and Wagers, Amy[2]

[1]Harvard Stem Cell Institute, Cambridge, MA, U.S., [2]Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, U.S.

Satellite cells are resident muscle stem cells that respond to local stimuli in injured muscle to replace and regenerate damaged muscle fibers. Upon muscle insult, satellite cells become activated, proliferate, and then differentiate to fuse with recovering myofibers. A portion of proliferating satellite cells undergo self-renewal, ensuring the capacity to respond to future muscle injuries. Self-renewal remains an obscure stage of the satellite cell life cycle, including the timing of self-renewing cell fate decisions and the mechanism(s) that thwart further commitment and differentiation of activated satellite cells. While hunting for novel molecular effectors of the satellite cell fate, we identified Fos as a transcription factor highly expressed by freshly isolated (non-dividing) satellite cells from uninjured muscle that is down-regulated in (highly proliferative) satellite cells from previously injured muscle. Our subsequent flow cytometry and western blot analyses show that Fos protein is expressed in approximately half of all satellite cells isolated from uninjured mice. Using an ex vivo single fiber culture system and an in vivo injury paradigm, we find that Fos is induced in Pax7-expressing satellite cells within the first few hours of activation. Forced Fos expression in satellite cells and their early progeny in culture reduce the mRNA levels of myogenic commitment genes, MyoD and MyoG, and disrupt terminal differentiation. Conversely, genetic deletion of Fos in Pax7-expressing satellite cells in vivo leads to enhanced muscle repair and recovery in the short term, suggesting that loss of Fos function in satellite cells favors their differentiation and contribution to regenerating fibers at the expense of self-renewal. Collectively, our results support the hypothesis that Fos restricts myogenic lineage progression in a portion of newly activated satellite cells, as a mechanism to ensure some progenitors self-renew to maintain the muscle stem cell pool.

14:30 – 14:45

ACTIVATED TGF-BETA SIGNALING AND DOWNREGULATED BMP SIGNALING CONTRIBUTE TO IMPAIRED OSTEOGENESIS IN CFC SYNDROME-DERIVED IPSCS

Choi, Jung-Yun[1], Han, Kyu-Min[2], Kim, Dongkyu[3], Lee, Beom-Hee[4], Choi, Jin-Ho[4], Yoo, Han-Wook[4] and Han, Yong-Mahn[1]

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Cardio-facio-cutaneous syndrome (CFC syndrome; OMIM 115150) is a genetic disorder caused by mutations in RAS/MAPK signaling pathway. CFC syndrome patients have a variety of developmental defects including cardiac disorders, cutaneous anomalies, and bone malformations. Although RAS/MAPK pathway plays important roles in the embryonic development, little is known about which signaling pathway is involved in the defective bone development of most CFC syndrome patients. Here, we report that activated TGF-beta signaling and down-regulated BMP signaling might be responsible for impaired osteogenesis in CFC syndrome during early bone development. CFC-iPSCs were generated from dermal fibroblasts of a patient carrying c.770A>G mutation on BRAF. Though CFC-iPSCs were normally differentiated into mesenchymal stem cells (CFC-MSCs), CFC-MSCs failed to develop into mature osteoblasts. CFC-MSCs exhibited aberrant expression of osteogenic genes, reduced alkaline phosphatase activity, and low mineralizing capacity during osteogenesis as compared to wild type (WT)-MSCs. Moreover, in addition to activated ERK due to BRAF gain-of-function mutation, increased TGF-beta signaling and decreased BMP signaling was observed in CFC-MSCs during osteogenesis. In WT-MSCs, intentional activation of ERK/TGF-beta signaling and inhibition of BMP signaling, respectively, recapitulated impaired osteogenesis of CFC-MSCs. Inversely, defective osteogenesis of CFC-MSCs was partially rescued by ERK/TGF-beta inhibitors and BMP agonist, respectively. In addition, we found that enhanced TGF-beta signaling, resulted from activated ERK, down-regulated BMP signaling in osteogenesis of CFC-MSCs. Our findings indicate that ERK signaling as well as TGF-beta and BMP signaling are involved in defective bone development in CFC syndrome.

14:45 – 15:10

REGULATION OF MESENCHYMAL STEM CELLS IN SPACE AND TIME BY AUTONOMIC NEURAL SIGNALS

Mendez-Ferrer, Simon, Garcia-Garcia, Andres, Korn, Claudia, Garcia-Fernandez, Maria, Fielding, Claire, Isern, Joan, Martin-Perez, Daniel, Lau, Winnie WY, Diamanti, Evangelia, del Toro, Raquel, Skepper, Jeremy N, Sendtner, Regine, Sendtner, Michael, Green, Anthony R, Gottgens, Bertie and Airaksinen, Matti

WT-MRC Cambridge Stem Cell Institute, Cambridge, U.K.

The microenvironment for hematopoietic stem cells (HSCs) in the bone marrow (BM) includes many different cell types that dynamically regulate distinct HSC functions, such as quiescence, maintenance, activation, proliferation, differentiation and migration. However, how these niches coordinate the various stem cell activities with organismal demands remains unclear. We hypothesized that a master regulator of tissue homeostasis, the autonomic nervous system, might orchestrate different HSC responses in this complex microenvironment to meet physiological demands. Here we describe novel neural signals that regulate different stem cell functions in separate niches during circadian time cycles. In early postnatal mice, a subset of bone-associated sympathetic nerve fibers switch from noradrenergic to cholinergic fate and promote BM colonization by HSCs. This is mediated through induction of the key HSC chemokine Cxcl12 in the developing BM. In adult mice, sympathetic cholinergic nerve fibers activate nicotinic receptors and induce Cxcl12 expression in bone-associated nestin+ mesenchymal stem cells, promoting HSC quiescence and long-term maintenance. In contrast, other cholinergic signals antagonize BM sympathetic noradrenergic activity during the resting period, indirectly regulating beta3-adrenergic-receptor-dependent circadian HSC trafficking through sinusoidal niches. Therefore, the sympathetic nervous system can simultaneously promote two opposing processes (stem cell activation and mobilization vs. induction of stem cell quiescence) through different neurotransmitters in separate niches. This might allow to rapidly and locally align stem cell function with organismal demands. Since the autonomic nervous system is a master regulator of stress responses in vertebrates, this regulation might allow the overall stem cell population respond to stress while preventing stem cell attrition/exhaustion, by respectively promoting stem cell activation and quiescence in separate niches.

THURSDAY, 15 JUNE, 13:15 – 15:15

CONCURRENT IF: HEMATOPOIETIC STEM CELLS

Level 2, Room 205BC

13:20 – 13:45

BRANCHED CHAIN AMINO ACID CATABOLISM CONTROLS HUMAN AML STEM CELLS BY ALTERING THE EPIGENOME

Trumpp, Andreas, Raffel, Simon, Falcone, Mattia, Kneisel, Niclas and Radlwimmer, Bernhard

DKFZ/ HI-STEM gGmbH, Heidelberg, Germany

The branched chain amino acid (BCAA) pathway and high levels of BCAA transaminase 1 (BCAT1) have recently been associated with aggressiveness in several cancer entities. However, the mechanistic role of BCAT1 in this process remains uncertain. By performing high-resolution proteomic analysis of functionally defined human acute myeloid leukaemia (AML) stem cell (LSC) and non-LSC populations, we found the BCAA pathway enriched and BCAT1 overexpressed in LSCs. We show that BCAT1, which transfers a-amino groups from BCAAs to a-ketoglutarate (aKG), is a critical regulator of intracellular aKG homeostasis. Next to its role in the tricarboxylic acid (TCA) cycle a a KG is an essential co-factor for aKG-dependent dioxygenases such as EGLN1 and the TET family of DNA demethylases. Knockdown (KD) of BCAT1 in leukaemia cells caused accumulation of aKG resulting in HIF1 protein degradation mediated by EGLN1. This resulted in a growth and survival defect and abrogated leukaemia-initiating potential. In contrast, overexpression (OE) of BCAT1 in leukaemia cells decreased intracellular a a KG levels and caused DNA hypermethylation. BCAT1high AMLs are associated with poor prognosis and display a DNA hypermethylation phenotype similar to patient leukemias mutant for the Isocitrate Dehydrogenase (IDHmut), in which TET2 is inhibited by the oncometabolite 2-hydroxyglutarate. In summary, BCAT1 reduces dioxygenase activity by limiting intracellular aKG, thus linking BCAA catabolism to HIF1a stability and regulation of the epigenomic landscape.

13:45 – 14:00

CONVERSION OF ADULT ENDOTHELIAL CELLS INTO SELF-RENEWING IMMUNE-COMPETENT HAEMATOPOIETIC STEM CELLS

Lis, Raphael[1], Karrasch, Charles[1], Poulos, Micheal[1], Kunar, Balvir[1], Redmond, David[1], Barcia Duran, Jose Gabriel[1], Ginsberg, Micheal[2], Schachterle, William[1], Xiang, Jenny[1], Rafii Tabrizi, Arash[3], Shido, Koji[1], Speck, Nancy[4], Elemento, Olivier[1], Butler, Jason[1], Scandura, Joseph[5] and Rafii, Shahin[1]

[1]Weill Cornell Medicine, New York, NY, U.S., [2]Angiocrine Biosciences, San Diego, CA U.S., [3]Weill Cornell Medicine-Qatar, Doha, Qatar, [4]University of Pennsylvania, Philadelphia, PA, U.S., [5]Weill Cornell Core, New York, NY U.S.

The molecular pathways and microenvironmental cues that choreograph the transition of endothelial cells (ECs) into true engraftable haematopoietic stem cells (HSCs) remain undefined. This is due to lack of models to recreate the ephemeral transition from endothelial to haemogenic cells and subsequently to HSCs. Here, we have developed a sequential in vitro model in which by precise conditional on-off expression of transcription factors: FosB, Gfi1, Runx1, and Spi1 (FGRS; and re-establishing a proper inductive vascular niche for 28 days, we could reprogram adult mouse ECs into self-renewing HSCs (rEC-HSCs). From day 0-8 (induction phase), FGRS are conditionally expressed in adult non-lymphatic ECs isolated from Runx1-IRES-GFP reporter mice and co-cultured with vascular niche. At specification phase (day 8-20), FGRS-transduced VEcad+Runx1-CD45- ECs switch on the endogenous expression of Runx1, initiating haematopoietic program and silencing EC fate in VEcad+Runx1+CD45+ cells, setting the stage for full commitment to VEcad-Runx1+CD45+ haematopoietic stem and progenitor cells (rEC-HSPCs). During expansion phase

(day 20-28), vascular niche cells promote propagation of a large number of haematopoietic cells, at which time expression of exogenous FGRS is turned off. Subsets of rEC-HSPCs are endowed with distinctive features of rEC-HSCs, including single cell clonal and limiting-dilution multi-lineage reconstituting potential, ability to serially re-establish bone marrow HSPC compartments, reconstitute adaptive immune function in Rag1-/- mice, and long-term self-renewal capacity. Employing Runx1-IRES-GFP reporter mouse enabled deconvolution of stage-specific pathways involved in generation of engraftable rEC-HSCs. Inhibition of Tgfß signaling along with activation of Bmp and Cxcl12 pathways reinforced the induction phase. Cxcr4 deficient ECs failed to undergo conversion to rEC-HSPCs, indicating that Cxcl12 signaling is essential for specification and expansion phases. This reprogramming strategy will help to decipher pathways involved in transition of ECs into haematopoietic cells. Our approach facilitates devising strategies to reprogram adult ECs into abundant autologous HSCs amenable to genetic modification for treatment of genetic and acquired haematological disorders.

14:00 – 14:15

NAD BOOSTING STRATEGY ENHANCES STEM CELL FUNCTION BY DECREASING MITOCHONDRIAL MEMBRANE POTENTIAL THROUGH THE ACTIVATION OF MITOCHONDRIAL UNFOLDED PROTEIN RESPONSE (UPR-MT) AND MITOPHAGY

Vannini, Nicola[1], Campos, Vasco[2], Ragusa, Simone[3], Stefanidis, Evangelos[4], Ryu, Dongreyol[2], Girotra, Mukul[2], Semilietof, Aikaterini[4], Yersin, Yannick[2], Panopoulos, Evangelos[2], Tauzin, Loic[2], Pirinen, Eija[2], Petrova, Tatiana[3], Vanhecke, Dominique[4], Coukos, George[4], Auwerx, Johan[2], Lutolf, Matthias[2] and Naveiras, Olaia[2]

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Cellular metabolism is recently emerging as a potential regulator of stem cell fate constituting a crucial regulator of the HSC pool. We have previously demonstrated that mitochondrial activity is a functional predictor of HSC engraftment and fate. Indeed, we found that overall function of the hematopoietic progenitor and stem cell compartment can be resolved by mitochondrial activity alone, as illustrated by the fact that cells having low mitochondrial activity (TMRMlow) can provide efficient long-term engraftment, while those having high mitochondrial activity (TMRMhigh) cannot engraft in lethally irradiated mice. Here we show that the modulation of mitochondrial metabolism, through the administration of the newly developed NAD booster agent nicotinamide riboside (NR) expands the hematopoietic progenitor compartments and maintains LT-HSC pool in vivo. NR improves stem cell function by decreasing mitochondrial membrane potential via activation of unfolded protein response (UPRmt) and mitophagy specifically in LT-HSCs. Moreover, NR-induced hematopoietic progenitor cells expansion dramatically improves the survival and accelerates blood recovery of HSC-transplanted mice. Our work establishes for the first time a link between HSC self-renewal- UPRmt-mitophagy and unveils the potential of NR to enhance the outcome of patients suffering from bone marrow insufficiency.

Funding Source: European Hematology Association; Fundacio JOSEP CARRERAS contra la leucemia; Pierre Mercier; Swiss National Science Foundation

14:15 – 14:30

EPCR EXPRESSION DEFINES THE MOST PRIMITIVE SUBSET OF HUMAN HSPCS THAT IS FUNCTIONALLY REQUIRED FOR THEIR SELF-RENEWAL

Fares, Iman, Chagraoui, Jalila, lehnertz, Bernard lehnertz, MacRae, Tara MacRae, Tomellini, Elisa, Mayotte, Nadine and Sauvageau, Guy

IRIC, Montreal, QC, Canada

Human hematopoietic stem/progenitor cells (HSPCs) represent a rare population which has the ability to differentiate to all blood lineages and to self-renew. Lack of tools required to purify such rare cells to high enough levels precludes studies that dissect the molecular basis of HSPC self-renewal. We have previously developed the pyrimido-indole derivative UM171 with the unique ability to stimulate expansion of human HSC ex vivo. Transcription profiling of UM171-expanded cells show the upregulation of Endothelial Protein C Receptor (EPCR), a known surface antigen of mouse HSPCs. We hypothesized that EPCR expression might also be selectively associated with human HSC activity in UM171 expansion conditions. To validate this observation we performed in vitro and in vivo functional assays and showed that only EPCR+ cell fraction exhibits a robust multi-lineage differentiation and serial reconstitution potential. Knockdown of EPCR compromised the HSPC reconstitution ability suggesting that EPCR is not only marker for the highly self-renewing HSPC but also essential for their function. Identifying surface makers that enrich for cultured human HSC such as EPCR would allow a better understanding of HSC self-renewal mechanism that in turn facilitate manipulating and expansion of human HSC ex vivo for clinical applications.

14:30 – 14:45

CLONAL COMPENSATION BETWEEN HEMATOPOIETIC STEM CELLS UPON DIFFERENTIATION DEFICIENCY

Nguyen, Lisa[1] and Lu, Rong[2]

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In most organ systems, regeneration is a coordinated effort that involves many stem cells, but little is known about how individual stem cells compensate for the functional deficiencies of other stem cells. We hypothesize that

HSCs heterogeneously compensate for blood deficiency. We tracked mouse HSCs in vivo using a single-cell tracking technology that we had previously developed. We found that individual HSCs heterogeneously compensate for the lymphopoiesis deficiencies of other HSCs by increasing their clonal expansion and altering their lineage bias. This compensation rescues the overall blood supply and influences blood cell types outside of the deficient lineages in distinct patterns. We identified the molecular regulators and signaling pathways associated with this HSC coordination using RNA sequencing. To further investigate the dynamics of HSC coordination, we employed a genetically modified mouse model that expresses simian diphtheria toxin (DT) receptor under the control of the CD11b promoter. Monocytes derived from this mouse line can be ablated upon DT administration. We co-transplanted HSCs derived from normal and genetically modified mice, then conditionally ablated the monocyte population repeatedly, and assayed the temporal responses of individual unperturbed HSCs. We hypothesize that individual HSCs can heterogeneously adapt their differentiation programs to restore the unbalanced blood system. Our time-course analysis revealed that a distinct subset of highly differentiating HSC clones responded quickly and persistently to the blood perturbations. We also identified several other significant temporal profiles that indicate remarkable heterogeneity of HSCs in response to changes in the blood system. Together, these data suggest that differentiation compensation is a deterministic feature of HSCs that is independent of their normal differentiation program. Our findings suggest that stem cells interact with each other and form a coordinated cellular network that is robust enough to withstand minor functional disruptions. Individual HSCs distinctly adapt their differentiation bias to compensate for deficient HSCs and specifically overproduce undersupplied cell types.

Funding Source: National Institutes of Health R00-HL113104; University of Southern California Startup Fund

14:45 – 15:10

THE POWER OF ONE: IMMUNOLOGY IN THE AGE OF SINGLE CELL GENOMICS

Amit, Ido

Weizmann Institute, Rehovot, Israel

Immune cell functional diversity is critical for the generation of the different regulator and effector responses required to safeguard the host against a broad range of threats such as pathogens and cancer, but also from attacking its own healthy cells and tissues. In multi cellular organisms, dedicated regulatory circuits control cell-type diversity and responses. The crosstalk and redundancies within these circuits and substantial cellular plasticity and heterogeneity pose a major research challenge. Over the past few years, we have developed a collection of innovative single-cell technologies, which provide unprecedented opportunities to draw a more accurate picture of the various cell types and underlying regulatory circuits, including basic mechanisms, transitions from normal to disease states and response to therapies. I will discuss some of our discoveries and how they change the current dogma in immune regulation as well novel technologies that combine single cell RNA-seq with CRISPR pooled screens and demonstrate the power of these approaches to probe and infer the wiring of mammalian circuits, fundamental to future engineering of immune cells towards desired responses, including immunotherapy.

THURSDAY, 15 JUNE, 13:15 – 15:15

CONCURRENT IG: NEURAL STEM CELLS

Level 3, Ballroom West

13:20 – 13:45

GENOMIC INSIGHTS INTO HUMAN CORTICAL DEVELOPMENT, LISSENCEPHALY, AND ZIKA MICROCEPHALY

Kriegstein, Arnold R., Pollen, Alex, Nowakowski, Tomasz, Bershteyn, Marina and Di Lullo, Elizabeth

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

Radial glia, the neural stem cells of the neocortex, are located in two niches: the ventricular zone and outer subventricular zone. Although outer subventricular zone radial glia (oRG) appear to generate the majority of human cortical neurons, their molecular features remain elusive. We have begun to sequence mRNA from single human progenitor cells for unbiased classification of cell identity and for detection of activated signaling pathways. By analyzing gene expression across single cells, we find that oRG cells preferentially express genes related to extracellular matrix formation, migration, and stemness, and we relate these genes to the position, morphology, and behaviors previously used to classify these cells. Many of these genes are involved in growth factor signaling and self-renewal pathways, suggesting that outer radial glia cells establish a self-sustaining proliferative niche in the OSVZ. Using single cell clonal lineage analysis, we find that oRG cells can generate hundreds of daughter neurons of deep and upper layer identity, establishing the extensive proliferative and neurogenic capacity of this cell type. Finally, by using novel markers that reveal the morphology of oRG or ventricular radial glia cells selectively, we find that oRG cells form the primary scaffold for migration of neurons to the cortical plate during mid- and late-phases of cortical neurogenesis. More generally, we have expanded this approach to identify the genes and pathways distinguishing diverse cell types during cortical development. These molecular insights have already informed a novel model of primate corticogenesis, suggested a relationship between oRG cells and brain tumors, provided insights into the specific cell types affected by genetic forms of lissencephaly, and have helped identify the mechanism of Zika virus microcephaly.

13:45 – 14:00

ABNORMAL NEUROGENESIS BY 16P1311 MICRODUPLICATION CAUSES HYPERACTIVITY

Fujitani, Masashi[1], Noguhi, Koichi[2] and Yamashita, Toshihide[3]

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Chromosome 16p13.11 microduplication is a risk factor associated with various neurodevelopmental disorders such as attention-deficit/hyperactivity disorder, intellectual disabilities, developmental delay, and autistic spectrum disorder or neurodevelopment-related disorder, schizophrenia. The underlying molecular mechanism of this genetic variation remained unknown, but its core genetic locus—conserved across mice and humans—contains seven genes. Here, we generated bacterial artificial chromosome-transgenic mice carrying a human 16p13.11 locus, and these mice showed the abnormal neurogenesis and behavioral hyperactivity phenotype. We identified miR-484 and Marf1, RNase domain containing RNA-binding protein as the responsible genes, not Nde1 or Fopnl by a combination of expression and functional analyses including in utero electroporation method. miR-484 and Marf1 were expressed during active cortical neurogenesis, and overexpression of miR-484 or Marf1 decreased proliferation and increased neural progenitor differentiation in vivo. To investigate each signaling cascade, luciferase screening identified the 3′ untranslated region of protocadherin-19 (Pcdh19) as a target of miR-484. The effect of miR-484 on neurogenesis was rescued by ectopic PCDH19 expression. Moreover, RIP (RNA immunoprecipitation)-Chip analysis identified Marf1 targets. Taken together these results, we assumed that miR-484 and Marf1 synergistically promoted neurogenesis by inhibiting their own targets. Dysregulation of neurogenesis by imbalanced miR-484/PCDH19 and Marf1/(target) expression contribute to the pathogenesis of 16p13.11 microduplication syndrome.

14:00 – 14:15

INTERVENTIONS TO OVERCOME THE AGE-RELATED DECLINE IN CNS REMYELINATION

Neumann, Bjoern[1], Baror, Roey[1], vanWijngaarden, Peter[2] and Franklin, Robin[1]

[1]WT MRC Stem Cell Institute, University of Cambridge, U.K., [2]Centre for Eye Research and Department of Ophthalmology, University of Melbourne, Australia

Remyelination depends on a population of adult multipotent progenitor cells, called oligodendrocyte progenitor cells (OPCs) that give rise to remyelinating oligodendrocytes. Like all regenerative processes, remyelination progressively slows with increasing age. Consequently, axons remain demyelinated, rendering them vulnerable to irreversible degeneration, which eventually contributes to the accumulation of disability in patients suffering from chronic demyelinating diseases, such as multiple sclerosis (MS). The rate limiting step for remyelination in aged individuals is the maturation of OPCs into oligodendrocytes. Based on these findings recent efforts have focused on the development of interventions that prompt OPCs to differentiate. However, since these compounds were found using exclusively OPCs from newborn animals it remains elusive whether aged OPCs are actually able to respond to such signals. Here we report that OPCs undergo inherent changes with ageing that contribute to the loss of their ability to differentiate. Moreover, unlike what was previously thought, aged OPCs do not remain responsive to pro-differentiation signals. Using alternate day fasting, a known intervention to ameliorate the effects of ageing, we were able to restore the remyelination potential of aged animals. Mechanistically, this involved the molecular rejuvenation of aged OPCs and amelioration of ageing hallmarks, such as DNA damage. By exposing aged OPCs to metformin we were able to phenocopy the effects of fasting in vitro and in vivo. Lastly, we demonstrated that metformin treated aged OPCs additionally responded to pro-differentiation compounds like their younger counterparts, which highlights the potential for synergistic effects of rejuvenation and pro-differentiation approaches. Our results suggest that the successful implementation of remyelination therapies will require both understanding and overcoming the effects of ageing on OPCs, as well as finding ways to modulate extrinsic factors to generate a permissive environment for regeneration. Finally, our data stress the importance to use aged cells and animals to identify new therapies for the treatment of chronic degenerative diseases that last for decades or only establish late in life.

Funding Source: MS Society U.K.

14:15 – 14:30

YIN YANG 1 SUSTAINS BIOSYNTHETIC DEMANDS DURING BRAIN DEVELOPMENT IN A DEVELOPMENTAL STAGE-SPECIFIC MANNER

Zurkirchen, Luis[1], Varum, Sandra[1], Giger, Sonja[2], Klug, Annika[1], Haeusel, Jessica[1], Zemke, Martina[1], Cantu, Claudio[1], Zamboni, Nicola[3], Basler, Konrad[1] and Sommer, Lukas[1]

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Cerebral cortex development is a dynamic process in an ever-changing environment. Neural progenitor cells (NPCs) of different developmental stages need to fulfil specific tasks while adapting to rapidly changing surroundings, both of which create distinct demands for biosynthesis in NPCs. How the biosynthetic needs of NPCs are regulated on a transcriptional level, however, remains elusive. The transcription factor Yin Yang 1 (Yy1) has been shown to have context-dependent effects on many cellular processes, including metabolism, during tissue development and homeostasis of vertebrates. Whether Yy1 regulates cortex development and by which potential mechanisms has not been addressed yet. Here, we set out to investigate the role of Yy1 during cerebral cortex development in mice. Dor-

sal cortex-specific ablation of Yy1 before the onset of embryonic neurogenesis resulted in microcephaly due to the depletion of the NPC pool. Loss of Yy1 induced transient G1/S phase cell cycle arrest and p53-dependent cell death at embryonic day 12.5. Despite its constitutive expression, however, deletion of Yy1 after the onset of neurogenesis did neither influence proliferation nor cell survival. A combination of genome-wide expression profiling and global mapping of Yy1 binding regions identified various biosynthetic pathways to be controlled by Yy1. Genes involved in energy metabolism, nucleotide synthesis, subunits of the electron transport chain and protein translation were regulated by Yy1. Likewise, metabolomic profiling revealed downregulation of metabolites of many central metabolic pathways upon knockdown of Yy1 in isolated cortical NPCs. Furthermore, ablation of Yy1 impaired mitochondrial bioenergetics in a stage-dependent manner. Our results unravel a novel role for Yy1 as a stage-dependent regulator of brain size. By sustaining metabolism and protein translation, Yy1 maintains the increased biosynthetic demands of fast proliferating NPCs at early stages of cortex development.

14:30 – 14:45

A FATTY ACID OXIDATION-DEPENDENT METABOLIC SHIFT REGULATES ADULT NEURAL STEM CELL QUIESCENCE

Knobloch, Marlen[1], Pilz, Gregor[2], Ghesquière, Bart[3], Kovacs, Werner[4], Wegleiter, Thomas[2], Moore, Darcie[5], Hruzova, Martina[2], Zamboni, Nicola[6], Carmeliet, Peter[7] and Jessberger, Sebastian[2]

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Neural stem/progenitor cells (NSPCs) generate new neurons throughout life in distinct regions of the mammalian brain. Adult neurogenesis is important for tissue homeostasis and physiological brain function, and disturbed neurogenesis has been associated with diseases such as major depression and epilepsy. A tight regulation of NSPC quiescence and proliferation is crucial to ensure life-long neurogenesis and prevent exhaustion or uncontrolled growth of the stem cell pool. What regulates this delicate balance is not fully understood. Here we show that the rate of lipid breakdown via fatty acid oxidation (FAO) defines quiescence vs. proliferation in NSPCs. Quiescent NSPCs show high expression of the key enzymes regulating FAO, such as for instance carnitine palmitoyltransferase 1a (Cpt1a). Pharmacological inhibition and conditional deletion of Cpt1a in vitro and in vivo leads to altered NSPC behavior, reducing stem cell maintenance and proper neurogenesis. Strikingly, experimental manipulation of a single metabolite that regulates levels of FAO, is sufficient to induce exit from quiescence and to enhance NSPC proliferation. Thus, the data presented here define a metabolically controlled mechanism of quiescence behavior and reveal an instructive role for fatty acid metabolism in regulating NSPC activity.

14:45 – 15:10

GENE REGULATORY NETWORK UNDERLYING NEURAL CREST DEVELOPMENT

Bronner, Marianne E.

California Institute of Technology, Pasadena, CA, U.S.

The neural crest is a multipotent stem cell population, unique to vertebrates, that contributes to a wide variety of derivatives including cartilage and bone of the face, sensory and autonomic ganglia of the peripheral nervous system, the adrenal medulla, and pigmentation of the skin. Neural crest progenitors arise at the neural plate border, between neural and non-neural ectoderm, and, after neurulation, reside within the dorsal aspect of the central nervous system. They then delaminate from the neural tube, and migrate extensively, often to distant locations, and their migratory pathways are thought to influence their subsequent choice of cell fate. We have proposed and tested a gene regulatory network (GRN) that underlies the complex process of neural crest formation. I will discuss our exploration of GRN differences along the body axis, focusing on neural crest cells from distinct axial levels: cranial, vagal and trunk. By using axial level specifier neural crest enhancers, we have isolated pure neural crest populations by fluorescence activated cell sorting, for use in RNA-seq. The resultant transcriptome analysis has revealed numerous transcription factors and signaling molecules that are specific to neural crest subpopulations. Using loss-of-function approaches, we are evaluating the position of these genes in the neural crest GRN to elaborate connections in the regulatory circuitry. Finally, we are using GRN data to reengineer the neural crest cells, and reprogram them to a new identity. The genes and genetic subcircuits we discover may be useful targets for therapeutic intervention and for guiding directed differentiation of neural crest stem cells into particular derivatives.

THURSDAY, 15 JUNE, 16:00 – 18:00

CONCURRENT IIA: ORGANOIDS AND ORGANOGENESIS

Level 2, Room 205BC

16:05 – 16:30

LIVER ORGANOIDS FOR THE STUDY OF LIVER BIOLOGY AND DISEASE

Huch, Merixtell

Wellcome Trust/CRUK Gurdon Institute University of Cambridge, U.K.

Despite the enormous replication potential of the liver, there are currently no culture systems available that sustain hepatocyte replication in vitro. Hepatocytes can be maintained in culture for a few days. However, they lose their hepatocyte phenotype and function almost immediately, thus precluding its application for cell therapy treatments. We have recently developed a mouse liver organoid culture system that allows the long-term expansion of mouse liver cells in vitro. Here, we will show first, how this culture system allows us to study the activation of quiescent liver cells into self-sustaining and highly proliferative mouse liver progenitors. Second, we will also show how we have transferred our mouse liver organoid culture system to study human liver biology and human liver disease. We will describe that this culture system allows the long-term expansion of adult human liver cells (>3 months) from small human donor biopsies. The human expanded cells are highly stable at the chromosome and structural level, while single base changes occur at very low rates. The cells can be converted into functional hepatocytes in vitro and upon transplantation in vivo. Organoids derived from a variety of liver diseases, from monogenic liver diseases such as Alpha-1 Antitrypsin, to complex genetic diseases such as cancer, mirror in vitro the epithelial counterpart of the associated pathologies and are amenable for drug screening platforms. Thus, long-term expansion of primary adult liver cells opens up experimental avenues for disease modeling, regenerative medicine, toxicology studies and gene therapy.

16:30 – 16:45

A THREE-DIMENSIONAL MODEL OF HUMAN LUNG DEVELOPMENT AND DISEASE FROM PLURIPOTENT STEM CELLS

Chen, Ya-Wen[1], Huang, Sarah Xuelian[1], Rodrigues Toste de Carvalho, Ana[1], Ho, Siu-Hong[1], Islam, Mohammad[1], Volpi, Stefano[2], Notarangelo, Luigi[2], Ciancanelli, Michael[3], Casanova, Jean-Laurent[3], Bhattacharya, Jahar[1], Liang, Alice F.[4], Palermo, Laura[1], Porotto, Matteo[1], Moscona, Anne[1] and Snoeck, Hans-Willem[1]

[1]Columbia University, New York, NY, U.S., [2]Harvard Medical School, Boston, MA, U.S., [3]The Rockefeller University, New York, NY, U.S., [4]New York University Langone Medical Center, New York, NY, U.S.

Currently, the only way to replace lung tissue is to perform lung transplantation, which achieves only 10 to 20% survival at 10 years and is hampered by a severe shortage of donor organs. The ability to generate lung tissue in vitro in three dimensions (3D) using human pluripotent stem cells (hPSCs) would open novel avenues for the study of human development, disease modeling, drug screening, and ultimately regenerative medicine for lung disease. Organoids have been defined as in vitro generated 3D structures containing multiple cell types that are organized similar to an organ and recapitulate at least some specific organ function. We previously reported a strategy to differentiate hPSCs in 2D through sequential developmental steps from definitive endoderm to anterior foregut endoderm, lung progenitors, and, lung and airway epithelial cells. Based on this strategy, we developed a 3D human lung organoid model that recapitulates key features of lung development and allows disease modeling. We generated lung bud organoids (LBOs) from hPSCs that contain mesoderm and pulmonary endoderm and develop into branching airway and early alveolar structures after xenotransplantation and in 3D Matrigel culture. This model allowed recapitulation in vitro of fibrosis in hPSCs with engineered mutation in HPS1, which underlies an early-onset form of idiopathic pulmonary fibrosis, an intractable interstitial lung disease of unclear pathogenesis. Furthermore, infection in vitro with respiratory syncytial virus (RSV), which causes small airway obstruction and bronchiolitis in infants, led to swelling, detachment and shedding of infected cells into the organoid lumens, similar to what has been observed in human lungs. LBOs recapitulate human lung development up to the second trimester of gestation, and constitute the first model where a fibrotic disease that can be recapitulated in vitro, thus providing a novel avenue to gain insights into pathogenesis. In addition, we could reproduce the morphological features of RSV infection, for which there is currently no model that reproduces human infection. This work indicates that LBOs will be an invaluable tool for the study of human development and for lung disease modeling.

16:45 – 17:00

DIRECTED SELF-ASSEMBLY OF NEUROSENSORY INNER EAR ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS

Koehler, Karl R.[1], Nie, Jing[2], Lee, Jiyoon[2], Hashino, Eri[2], Longworth-Mills, Emma[2], Liu, Xiao-Ping[3] and Holt, Jeffery[4]

[1]Department of Otolaryngology-Head and Neck Surgery, Indiana University School of Medicine, Indianapolis, IN, U.S., [2]Indiana University School of Medicine, Indianapolis, IN, U.S., [3]Johns Hopkins University, Baltimore, MD, U.S., [4]Boston Children's Hospital, Boston, MA, U.S.

The human inner ear contains ~75,000 sensory hair cells that detect sound or movement via mechanosensitive hair bundles and transmit signals to the brain via specialized sensory neurons. Inner ear sensory cells derived from pluripotent stem cells would provide a valuable model for drug testing or cell therapy, yet defined differentiation approaches remain elusive. Our group has established a stepwise method for generating inner ear organoids, with functioning hair cells, from human pluripotent stem cells. In a 3D culture system, we modulated TGF, BMP, FGF, and Wnt signaling to direct the self-organization of multiple PAX2, PAX8, SOX10, and ECAD-positive otic vesicle-like cysts from a homogenous cell aggregate. Over a 60-day period, the vesicles developed into multi-chambered organoids with non-sensory and sensory epithelia, reminiscent of the membranous labyrinth of the inner ear. MYO7A+ BRN3C+ hair cells in the sensory epithelia of organoids had Actin-rich hair bundles similar to those on vestibular hair cells in vivo. To detect newborn hair cells, we used CRISPR/Cas9 gene editing to produce a novel ATOH1-2A-eGFP cell line. Using this cell line, we demonstrated that derived hair cells have physiological properties similar to native vestibular hair cells. Finally, we discovered that sensory neurons co-developed and formed ribbon synapses with organoid hair cells, mimicking formation of the sensorineural circuit of the inner ear. Thus, our organoid culture system should provide a powerful tool for investigating mechanisms of human inner ear development and drug discovery.

Funding Source: This work was supported by National Institute of Health grants R01 DC013294 (E.H. and J.R.H.), R03 DC015624 (K.R.K.), and an Indiana Clinical and Translational Sciences Institute Core Grant (NIH UL1 TR001108; K.R.K).

17:00 – 17:15

AN ORGANOID-BASED MODEL OF CORTICAL DEVELOPMENT IDENTIFIES NON-CELL AUTONOMOUS DEFECTS IN BETA-CATENIN SIGNALING CONTRIBUTING TO MILLER-DIEKER-SYNDROME

Ladewig, Julia, Iefremova, Vira, Manikakis, George, Krefft, Olivia, Jabali, Ammar, Weynans, Kevin, Wilkens, Ruven, Marsoner, Fabio, Brändl, Björn, Müller, Franz-Josef and Koch, Philipp

Institute of Reconstructive Neurobiology, University of Bonn, Germany

Miller-Dieker-Syndrome (MDS) represents a severe malformation of cortical development caused by a heterozygous deletion of chromosome 17p13.3 involving the genes LIS1 and YWHAE (coding for 14.3.3ε). Here we used patient-specific forebrain-type organoids to identify pathological changes associated with MDS. We demonstrate that patient-derived organoids show a significant reduction in size resulting from a switch of ventricular zone radial glia cells (vRGCs) from symmetric to asymmetric cell division. This was associated with alterations in the organization of vRGCs' microtubule networks, a disruption of the architecture of the cortical niche and altered expression of cell adhesion molecules, leading to a non-cell autonomous disturbance of the N-cadherin/ß-catenin signaling axis. Reinstallation of active ß-catenin signaling rescues division modes and ameliorates growth defects. Our data highlight a new role of LIS1 and 14.3.3ε in maintaining the cortical niche suggesting that organoid-based systems serve as promising models to analyze complex cell-cell interactions in vitro.

17:15 – 17:30

ENDOTHELIN-1 MEDIATES THE SPONTANEOUS CONTRACTION AND EARLY MATURATION OF PLURIPOTENT STEM CELL DERIVED VENTRICULAR CARDIOMYOCYTES

Rukstalis, Michael, Ji, Lin, Loi, Sally, Schulz, Natalie Grace, Ramos-Zayas, Rebeca, Zhao, Yang and Sartoretto, Juliano

Pfizer, Cambridge, MA, U.S.

Human pluripotent stem cell-derived cardiomyocytes (hPSC-CMs) are structurally and functionally immature, limiting their widespread application in disease modeling and drug discovery. We hypothesized that this lack of maturation was derived, in part, from the absence of early critical signals required for cardiomyocyte specification and development. To test this hypothesis we developed a rigorous chemically defined 3D organoid cardiomyocyte cell differentiation platform to synchronously direct pluripotent stem cells through each stage of heart development in a reproducible and predictable manner. Using this platform to probe the fundamental signaling pathways during cardiomyocyte formation, we identified the critical importance of Endothelin-1 signaling in the induction of spontaneous

contraction and early maturation events of ventricular myocytes. Endothelin-1 is sufficient to enhance expression of the ventricular myosin light chain (MYL2) by over 150-fold, promote myosin heavy chain switching from the MYH6 to MYH7, and induce expression of the PKA-sensitive adult cardiac Troponin I (TNNI3). These early maturation events are mediated primarily through the Endothelin B receptor (ETBR), which is transiently expressed during early cardiomyocyte differentiation. The ETBR-specific agonist Endothelin-3 can recapitulate the gene expression changes seen with Endothelin-1, and the effects of Endothelin-1 can be blocked with the ETRB antagonist BQ-788 but not with the ETRA antagonist BQ123. Finally, a continual tone of Endothelin-1 signaling is required to maintain robust expression of MYL2 and TNNI3 in differentiated cardiomyocytes, as removal of Endothelin-1 signaling results in the rapid decrease of gene expression back to basal levels and a loss of a highly differentiated phenotype. We conclude that Endothelin signaling is a critical driver of early cardiomyocyte differentiation, and the appropriate application of Endothelin-1/3 in the cardiomyocyte differentiation protocol significantly enhances in vitro ventricular myocyte maturation.

17:30 – 17:55

MODELING HUMAN DISEASES USING HUMAN ORGANOID SYSTEMS

Ng, Huck-Hui

Genome Institute Singapore, Singapore

One of the greatest limitations in understanding human diseases is the lack of in vitro models that can recapitulate features and functions of human organs. The human organs are comprised of multiple cell-types forming an unique architecture. To develop new understanding of human diseases, our laboratory generates in vitro organoid systems using novel culture methodologies. Parkinson's disease (PD) is a progressive movement disorder, characterized by a selective loss of dopaminergic (DA) neurons in substantia nigra pars compacta (SNpc). Numerous studies of PD genetics have identified genes associated with the disease. The effects of these mutations are not fully understood due to the lack of advanced experimental in vitro systems to model the progressive manifestation of PD. To this end, our group recently established a new protocol to generate 3D human midbrain-like organoids from human pluripotent stem cells that recapitulate features of the midbrain, including the production of neuromelanin, which is concentrated in mDA neurons of SNpc and mature mDA neurons. The 3D environment therefore appears to generate the niche to support the maturation of mDA neurons. This provides a unique opportunity to experimentally model PD pathology in vitro by looking at how mutations in PD-associated genes are correlated with dysfunction of mitochondria lead to synucleinopathies/tauopathies and neuronal toxicity in DA neurons. The midbrain-like organoids provide a new avenue for the investigation of human midbrain biology and modeling of PD.

THURSDAY, 15 JUNE, 16:00 – 18:00

CONCURRENT IIB: DIRECT REPROGRAMMING AND FATE CONVERSION

Level 3, Ballroom West

16:05 – 16:30

CELLULAR REPROGRAMMING APPROACHES FOR CARDIOVASCULAR DISEASE

Srivastava, Deepak

Gladstone Institutes, San Francisco, CA, U.S.

Heart disease is a leading cause of death in adults and children. We, and others, have described complex signaling, transcriptional and translational networks that guide early differentiation of cardiac progenitors and later morphogenetic events during cardiogenesis. We utilized a combination of major cardiac regulatory factors to induce direct reprogramming of cardiac fibroblasts into cardiomyocyte-like cells with global gene expression and electrical activity similar to cardiomyocytes. The in vivo efficiency of reprogramming into cells that are more fully reprogrammed was greater than in vitro and resulted in improved cardiac function after injury in mice and in pigs. Single cell RNA-sequencing has revealed how heterogeneity of the reprogramming process may inhibit efficiency and could be manipulated. We have identified chemical inhibitors of the Wnt and Tgf-beta pathways that improve efficiency, quality and speed of gene-mediated direct cardiac reprogramming in vitro and in vivo. The small molecules appear to increase accessibility of the reprogramming factors to their DNA-binding sites by opening chromatin at those sites genome-wide. To promote translation, we have identified a novel adeno-associated virus that has tropism for human cardiac fibroblasts and this virus can effectively deliver the human reprogramming factors to reprogram in vivo. 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.

16:30 – 16:45

A MULTI-STEP TRANSCRIPTIONAL AND CHROMATIN STATE CASCADE UNDERLIES MOTOR NEURON PROGRAMMING FROM EMBRYONIC STEM CELLS

Mazzoni, Esteban O.[1], Velasco, Silvia[1], Ibrahim, Mahmoud[2], Kakumanu, Akshay[3], Garipler, Gorkem[1], Aydin, Begum[1], AlSayegh, Mohamed[1], Hirsekorn, Antje[2], Abdul-Rahman, Farah[1], Satija, Rahul[4], Ohler, Uwe[2] and Mahony, Shaun[3]

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Direct cell programming via overexpression of transcription factors (TFs) aims to control cell fate with the degree of precision needed for clinical applications. However, the regulatory steps involved in successful terminal cell fate programming remain obscure. We have investigated the underlying mechanisms by looking at gene expression, chromatin states, and TF binding during the uniquely efficient Ngn2, Isl1, and Lhx3 motor neuron programming pathway. Our analysis reveals a highly dynamic process in which Ngn2 and the Isl1/Lhx3 pair initially engage distinct regulatory regions. Subsequently, Isl1/Lhx3 binding shifts from one set of targets to another, controlling regulatory region activity and gene expression as cell differentiation progresses. Binding of Isl1/Lhx3 to later motor neuron enhancers depends on the Ebf and Onecut TFs, which are induced by Ngn2 during the programming process. Thus, motor neuron programming is the product of two initially independent transcriptional modules that converge with a feedforward transcriptional logic.

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16:45 – 17:00

PIGGYBAC TRANSPOSON-MEDIATED DIRECT TRANSCRIPTIONAL REPROGRAMMING TO NEPHRON PROGENITORS

Vanslambrouck, Jessica M.[1], Woodard, Lauren[2], Suhaimi, Norseha[3], Howden, Sara[4], Wilson, Matthew[2] and Little, Melissa[4]

[1]Murdoch Childrens Research Institute, Melbourne, Australia, [2]Department of Veterans Affairs and Department of Medicine, Division of Nephrology and Hypertension, Vanderbilt University School of Medicine, Nashville, TN, U.S., [3]School of Biomedical Sciences, The University of Queensland, Brisbane, Queensland, Australia, [4]Murdoch Childrens Research Institute, The Royal Children's Hospital, Melbourne, Victoria, Australia

Cellular reprogramming holds great promise for the development of desperately needed novel treatment options for chronic kidney disease (CKD). The functional units of the kidney, known as nephrons, arise from a population of embryonic nephron progenitors (NPs). However, this population is depleted near birth in a final wave of nephron formation (nephrogenesis) that renders the mature kidney unable to form new nephrons regardless of damage or disease in later life. Recreation of NPs may allow regeneration of entire nephrons, making the NP population an ideal target cell for cellular reprogramming approaches to generate alternate CKD treatment options. Using a lentivirus-mediated screening approach, we previously identified 6 transcription factors (SIX1, SIX2, HOXA11, OSR1, EYA1 and SNAI2) sufficient to re-impose a NP-like state when co-expressed in adult human kidney epithelial (HK2) cells. To improve this reprogramming and allow transferability to in vivo models of kidney disease, we have now developed a multicistronic transposon construct. The reprogramming transposon was generated by engineering all 6 reprogramming genes into a piggyBac construct with intervening 2A sequences, a tetracycline response element for doxycycline inducibility and a reporter (mCherry) for cell enrichment. Adult human kidney cells co-transfected with the reprogramming transposon, a tetracycline activator transposon and a piggyBac transposase construct display doxycycline-inducible gene expression as well as phenotypic and functional characteristics of endogenous NP cells. These results not only demonstrate the feasibility of transposon-based direct reprogramming, but also bring us closer to realizing patient-specific reprogramming to NPs for cellular therapies, bioengineering applications and nephrotoxicity screening.

17:00 – 17:15

MOLECULAR MECHANISMS UNDERLYING HUMAN PLURIPOTENT STEM CELL FORWARD PROGRAMMING TO MEGAKARYOYCTES: FROM BIOLOGY TO TRANSFUSION MEDICINE

Moreau, Thomas, Dalby, Amanda, Evans, Amanda, Mueller, Annett, Baye, James, Tijssen, Marloes and Ghevaert, Cedri

Haematology, University of Cambridge, U.K.

We have published a novel method for the large scale generation of in vitro megakaryocytes (MKs), the blood platelet precursors, by applying a transcription factor (TF) driven forward programming strategy to human pluripotent stem cells (hPSCs). We have demonstrated that the concurrent expression of GATA1, FLI1 and TAL1 in hPSCs and chemically defined culture conditions with minimal supportive cytokines produce highly pure MK cultures with long-term growth and release of functional platelets. With application to transfusion medicine in mind, MK forward programming is currently tested on 18 clinical-grade hPSC lines leading to the identification of candidates endowed with the highest MK and platelet potential. In addition, further study of the biology of MK forward programming has brought new insights and potential improvements of our protocol. We have developed bespoke tools to interrogate the molecular

mechanisms underlying MK programming, focusing especially on the generation and characterisation of the progenitor instrumental for sustained culture and large scale MK output. Using a genetically engineered hPSC line enabling chemically-controlled MK programming, we first observed that transgene expression was only required for the first 8 days defining the time window of key programming events. Moreover, we have created rainbow lentiviral vectors quantitatively coupling the individual expression of each programming factor to reporter gene fluorescence. We were therefore able to follow the dynamic of expression of the three TFs along the progression of MK forward programming and aimed to identify the optimal transgene dose for the generation of MK progenitors at single-cell resolution. For this we used flow cytometry index sorting of rainbow programmed cells to link clonogenic colony assay output with transcriptome profiles from single cell RNA-sequencing to uncover the molecular events leading to productive MK programming and reveal the identity of the progenitor cell. This deeper biological characterisation is guiding refinements of the early forward programming steps to increase progenitor generation and improve culture conditions for their long-term maintenance to ultimately benefit further MK outcome and in vitro platelet yield.

17:15 – 17:30

QUALITATIVE DYNAMICAL MODELLING OF THE REGULATORY NETWORK CONTROLLING BLOOD CELL SPECIFICATION AND REPROGRAMMING

Collombet, Samuel[1], Sardina Ortega, Jose Luis[2], van Oevelen, Chris[2], Abou-jaoudé, Wassim[1], di Stefano, Bruno[2], Thomas-Chollier, Morgane[1], Graf, Thomas[2] and Thieffry, Denis[1]

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Blood cells arise from a common set of hematopoietic stem cells that differentiate into more specific progenitors, ultimately leading to different functional lineages. This process relies on the activation and repression of different genes modules, controlled by transcription factors (TFs). Novel high-throughput technologies allow the identification of cell-specific regulatory elements by characterising chromatin states and TFs binding sites, in conjunction with gene expression profiling. Proper integration and analysis of these data enable the delineation of novel regulatory interactions, which can be modelled and analysed using formal methods, thereby fostering our understanding of the mechanisms controlling cell fate at a system level, and enabling the prediction of the effects of molecular perturbations in silico. Combining public and novel data from molecular genetic experiments (qPCR, western blot, EMSA) or genome-wide assays (RNA-seq, ChIP-seq), we have assembled a comprehensive regulatory network encompassing the main transcription factors and signalling components involved in myeloid and lymphoid lineage development. Using a multilevel logical framework, we built a dynamical model allowing us to simulate cells differentiation, commitment and reprogramming in silico. To improve the accuracy of our model, we performed a meta-analysis of available TF ChIP-seq datasets for myeloid and lymphoid cells, confirming previously known regulations or confirming new ones (26 confirmed and 66 predicted regulations). We then iteratively included some predicted regulations in our model, performed static or dynamical analysis (stables states analysis or differentiation/reprogramming simulations), and compared the results with gene expression data and phenotypes. This approach enabled us to predict several important, previously unknown regulations, which were further confirmed experimentally. Finally we used our model to delineate novel trans-differentiation protocols that can be tested experimentally.

Funding Source: French Ministry of Superior Education and Research ; EU-FP7 BLUEPRINT (282510), Fundacio la Marato TV3 and AGAUR SGR 1136; Spanish Ministry of Economy and Competitiveness, 'Centro de Excelencia Severo Ochoa 2013-2017.'

17:30 – 17:55

INDUCTION OF PLURIPOTENCY WITHOUT OCT4

Schöler, Hans, Velychko, Sergiy, Wu, Guangming, MacCarthy, Caitlin and Adachi, Kenjiro

Max Planck Institute for Molecular Biomedicine, Muenster, Germany

Since the breakthrough discovery of transcription factor-driven reprogramming by Kazutoshi Takahashi and Shinya Yamanaka, multiple studies have addressed the function of each component of the reprogramming cocktail. Subsequent work from Yamanaka's laboratory showed that of the four transcription factors in the cocktail—octamer-binding protein 4 (Oct4), SRY-box containing gene 2 (Sox2), Krüppel-like factor 4 (Klf4), and c-Myelocytomatosis oncogene (c-Myc) (OSKM)—only c-Myc could be removed and the cocktail was still able to successfully mediate reprogramming. Moreover, while Sox2, Kfl4, and c-Myc could be replaced by other members of their transcription factor families, Oct4 could not be substituted by either Oct1 or Oct6. Since then, numerous attempts have been made to replace the components of the reprogramming factor mix. Thus Oct4 has be touted as the only factor from the original cocktail that is not interchangeable with other proteins from the same family, making it an essential factor for reprogramming to pluripotency. However, this point is at odds with our recent study demonstrating that Oct4 is not required for initiation of pluripotency in the early mouse embryo or for reprogramming through somatic cell nuclear transfer. In the current study, we found that Sox2, Klf4, and c-Myc can induce pluripotency in mouse somatic cells in the absence of Oct4. Cells reprogrammed without Oct4 also went through an MET, but followed an alternative pathway to mature pluripotency.

THURSDAY, 15 JUNE, 16:00 – 18:00

CONCURRENT IIC: STEM CELLS AND EARLY EMBRYOGENESIS

Level 2, Room 253ABC

16:05 – 16:30

MECHANISMS AND FUNCTION OF

MITOCHONDRIAL INHERITANCE IN GERM LINE STEM CELLS

Lehmann, Ruth, Hurd, Thomas, Lieber, Toby, Sanny, Justina, Herrmann, Beate and Sauerwald, Julia

HHMI and Skirball Institute, NYU School of Medicine, New York, NY, U.S.

Mutations in mitochondrial DNA (mtDNA) are a major cause of maternally inherited human disease. Mothers often contain a mixture, heteroplasmy, of mutant and wild-type mtDNA and transmit varying amounts of each to their progeny. We use Drosophila to study how mitochondria segregate into the primordial germ cells (PGCs) and how mitochondrial function is regulated during the germ line life cycle. We have identified the cellular mechanism that anchors mitochondria to the oocyte posterior. Asymmetric mitochondrial segregation into PGCs ensures maintenance mtDNA diversity from generation to generation.

16:30 – 16:45

BIOENGINEERED IN VITRO MODEL FOR POST-IMPLANTATION HUMAN EMBRYOGENESIS

Shao, Yue[1], Taniguchi, Kenichiro[1], Gurdziel, Katherine[2], Townshend, Ryan[1], Xue, Xufeng[1], Aw Yong, Koh Meng[1], Sang, Jianming[1], Spence, Jason[1], Miki, Toshio[3], Gumucio, Deborah[1] and Fu, Jianping[1]

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Implantation is a critical developmental milestone for early human embryogenesis and successful pregnancy. During implantation, the pluripotent epiblast gives rise to the squamous amnion and the columnar embryonic disc, which together enclose the amniotic cavity to form an asymmetric cystic structure termed the amniotic sac. The development of the amniotic sac is the keystone for post-implantation human embryogenesis, as the columnar epiblast and the squamous amnion eventually develop into the embryo proper and the enveloping amniotic membrane, respectively, which together constitute the core of a human embryo. Despite its fundamental and clinical significance, the development of the amnion and the amniotic sac in humans is poorly understood due to the technical and ethical challenges of harvesting and/or culturing early embryo specimens for study. Here, we report the first in vitro model for multiple post-implantation human embryogenic events centered around the amniotic sac development, by culturing human pluripotent stem cells (hPSCs) in a bioengineered niche that mimics the mechanical softness and the physical dimensionality of the implantation microenvironment. Specifically, we find that hPSCs can self-organize to form three-dimensional asymmetric cystic structure - herein termed the amniotic sac embryoid (ASE) - that recapitulates the differentiation of amnion, and further, the asymmetric morphogenesis and bipolar amnion-epiblast patterning seen in human amniotic sac development in vivo. Intriguingly, our findings show that biomimetic physical niche cues are both necessary and sufficient for the amniotic induction that is indispensable for the development of the ASE. In addition to the bipolar amnion-epiblast patterning, upon further development, the ASE initiates a process that resembles posterior primitive streak development at early gastrulation. We also unveil an endogenous activation and self-patterning of BMP-SMAD signaling during the ASE development in vitro. Together, Our findings reveal an unexplored developmental potential of hPSCs and highlight the self-organizing nature of post-implantation human embryogenesis. This study provides a novel and promising hPSC-based in vitro platform for advancing our fundamental understanding of early human development.

Funding Source: National Institutes of Health (R21 EB017078, R01EB019436, R01 DK089933); National Science Foundation (CMMI 1129611, CBET 1149401); American Heart Association (12SDG12180025); Rackham Predoctoral Fellowship

16:45 – 17:00

THE PLURIPOTENCY FACTOR ZFP281 COORDINATES TRANSCRIPTIONAL AND EPIGENETIC CONTROL OF EPIBLAST MATURATION

Huang, Xin[1], Balmer, Sophie[2], Yang, Fan[3], Fidalgo, Miguel[3], Li, Dan[3], Guallar, Diana[3], Hadjantonakis, Anna-Katerina[2] and Wang, Jianlong[3]

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Pluripotency is defined by a cell's potential to differentiate into any somatic cell type. How pluripotency factors regulate lineage specification events resulting in the establishment of the basic body plan is poorly understood. Here we report how the transcription factor Zfp281 functions in the naive-to-primed pluripotency transition occurring during pre- to post-implantation embryonic development. By characterizing mouse mutants and identifying gene targets and protein partners of Zfp281 during the transition from a naive-to-primed state of pluripotency, we establish critical roles for Zfp281 in activating Nodal signaling components and DNA methylation modifying enzymes within pluripotent epiblast cells. Zfp281 mutant embryos reach the blastocyst stage with indistinguishable gross morphology, but exhibit defects in epiblast maturation resulting in a failure to establish an anterior-posterior (A-P) axis at

post-implantation stage. Transcriptomic profiling of E6.5 embryos reveals a failure in activating Nodal signaling in the Zfp281 mutant embryos. Whole mount mRNA in situ hybridization (WISH) and immunofluorescence analysis confirm the impairment of Nodal signaling in Zfp281 mutant embryos dramatically reduces expressions of A-P specification markers Cer1, Hex, Lefty1, Hesx1, and Dkk1, leading to defects in distal and anterior visceral endoderm (DVE/AVE) specification and migration. Global chromatin-binding study of Zfp281 in naive mouse embryonic stem cells (ESCs) and primed epiblast stem cells (EpiSCs) reveals dynamic binding pattern and rearrangement of Zfp281 at target loci in transition between these two pluripotent states. Mechanistically, we demonstrate that Zfp281 is required for coordinating transcription factors (Oct4, Otx2) and epigenetic regulators, including histone acetyltransferases Tip60-Ep400 complex and p300, and polycomb repressive complex PRC2 to modulate expressions of lineage-specific genes (Otx2, T, Fgf5, and Fgf8), Nodal signaling components (Nodal, Lefty2) and DNA methyltransferases (Dnmt3a/3b/3l) during development. Our results provide mechanistic insights into the functions of a pluripotency factor in activating lineage-specific genes and reprogramming DNA methylation for transcriptional and epigenetic control of epiblast maturation.

Funding Source: This research was funded by grants from NIH to J.W. (R01-GM095942 and R21-HD087722) and to A.-K. H. (R01-DK084391 and P30-CA008748), and grants from NYSTEM to J.W. (C028103 and C028121) and to A.-K. H. (C029568).

17:00 – 17:15

LINEAGE SEGREGATION OF POST-IMPLANTATION MOUSE EMBRYO REVEALED BY SPATIAL AND SINGLE CELL TRANSCRIPTOME

Peng, Guangdun[1], Suo, Shengbao[2], Cui, Guizhong[3], Yu, Fang[1], Chen, Guoyu[2], Liu, Zhiwen[1], Sun, Na[2], Tam, Patrick[3], Han, Jingdong[2] and Jing, Naihe[1]

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The paradigm and blueprint of lineage segregation of early mouse embryo is established during gastrulation in which progenitors of various cell fates are regionalized and patterned in different embryo positions. The dynamic transcriptome landscape underpinning the cell fates determination is unknown. Here, we performed a spatial transcriptome study encompassing the whole gastrulation process. Combined with single-cell gene profiling at different time-points, we are able to reveal the lineage differentiating trajectories and molecular determinants that drive the pluripotent epiblast cell commitment. Our study also established the spatial zip codes which can be used as a reference positioning system for stem cells differentiation and reprogramming.

Funding Source: This work was supported in part by the "Strategic Priority Research Program" of the Chinese Academy of Sciences (XDA01010201), National Key Basic Research and Development Program of China (2014CB964804, 2015CB964500).

17:15 – 17:30

DISTINCT ROLES OF FGFR1 AND FGFR2 IN FATE ESTABLISHMENT WITHIN THE INNER CELL MASS OF THE MOUSE BLASTOCYST

Garg, Vidur[1], Kang, Minjung[2] and Hadjantonakis, Anna-Katerina[3]

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FGF4 is the signal regulating specification of primitive endoderm (PrE) versus pluripotent epiblast (EPI) within the inner cell mass (ICM) of the mouse blastocyst. To gain insight into how FGF receptors (FGFRs) mediate a response to FGF4 within individual ICM cells, we combined single-cell-resolution quantitative imaging with single-cell gene expression profiling. Our data reveal that despite the PrE-specific expression of Fgfr2, it is Fgfr1, a related receptor expressed by all ICM cells, that is critical for the establishment of a PrE identity. Signaling through FGFR1 is required to constrain levels of the pluripotency-associated factor NANOG. However, stable ICM lineage commitment requires the activity of both receptors. Gene expression profiling of 534 cells isolated from wild-type and mutant embryos identified distinct downstream targets associated with each receptor. These data lead us to propose a model whereby the distinct and additive roles of two FGF receptors coordinate lineage divergence within the ICM.

17:30 – 17:55

MODELING HUMAN CARDIOVASCULAR DEVELOPMENT WITH PLURIPOTENT STEM CELLS

Keller, Gordon M.

McEwen Centre for Regenerative Medicine, University Health Network, Toronto, ON, Canada

Human pluripotent stem cells (hPSCs) represent a novel cell source for modeling human cardiovascular development and disease in vitro and for developing new therapies to replace or regenerate heart tissue damaged by age or disease. To study and treat diseases that affect specific regions of the heart, it is essential to be able to generate different cardiomyocyte subtypes from hPSCs. Most protocols established to date support the development of mixed cell populations, the majority of which have characteristics of ventricular cardiomyocytes. In this study, we used a developmental biology based approach to identify the key signaling pathways that promote the efficient differentiation of each of the major cardiomyocyte subtypes

including ventricular, atrial and sinoatrial node cells. We found that the generation of populations highly enriched in NKX2-5+CTNT+MLC2V+ ventricular-like cardiomyocytes was dependent on the efficient induction of KDR+PDGFRa+ mesoderm by BMP and ACTIVIN A signaling between days 1 and 3 of differentiation. Activation of retinoic acid (RA) signaling in this mesoderm between days 3 and 5 promoted the development of NKX2-5+CTNT+MLC2V-COUPTFII+ atrial-like cardiomyocytes at the expense of the ventricular cells. The timing of RA signaling was critical to induce this lineage switch, as addition of the ligand beyond the day 5 time point had no effect on the type of cardiomyocyte generated. Continued BMP signaling together with inhibition of the FGF pathway in this day 3-5 window resulted in the generation of NKX2-5-CTNT+MLC2V- cardiomyocytes that displayed properties of sinoatrial node pacemaker-like cells, including the ability to pace host cardiac tissue. Taken together, these studies demonstrate that it is possible to generate the major cardiac subtypes from hPSCs through the stage specific manipulation of developmentally relevant signaling pathways.

THURSDAY, 15 JUNE, 16:00 – 18:00

CONCURRENT IID: GENE MODIFICATION AND GENE EDITING IN STEM CELLS

Level 2, Room 258AB

16:05 – 16:30

THE FUNCTIONAL ROLES AND PERCEPTION HISTORIES OF INTERCELLULAR SIGNALING SYSTEMS

Elowitz, Michael

California Institute of Technology, Pasadena, CA, U.S.

In developmental and disease, a handful of intercellular communication pathways, such as Notch and BMP, play an outside role in controlling cell fate decisions. While we have much information about the specific molecules and interactions that comprise these pathways, we often understand little about how they process signals, and what distinct capabilities each pathway provides. To address these issues, we have been developing a 'build-to-understand' approach, reconstructing or re-wiring these pathways using synthetic biology approaches, and analyzing their dynamic behaviors at the level of individual cells. Here I will focus on a particular architectural feature in which a pathway uses multiple distinct ligand and receptor variants that interact promiscuously with one another. New results suggest how this apparent redundancy can in fact provide critical capabilities in controlling signaling specificity. I will also discuss new synthetic approaches that can enable the analysis of signaling over longer timescales, by allowing cells to record signaling information in their own genome.

16:30 – 16:45

RAPID, ONE-STEP GENERATION OF BIALLELIC CONDITIONAL AND REVERSIBLE GENE KNOCKOUTS

Andersson Rolf, Amanda, Koo, Bon-Kyoung and Skarnes, William

WT-MRC Cambridge Stem Cell Institute, Cambridge, U.K.

Analysing gene function is a crucial step in our understanding of normal physiology and disease pathogenesis. While simple constitutive knockouts are useful and informative, it is desirable to engineer conditional loss-of-function models, particularly for genes essential for cell viability or embryonic development. Recently, the CRISPR/Cas9 gene editing technology has become the tool of choice for gene knockout studies due to its simplicity and robustness. However, conditional gene inactivation in diploid cells is still difficult to achieve and existing methods were not designed for the generation of conditional loss-of-function models in a single step, particularly where the target gene is essential for cell growth or viability. To overcome these limitations, our strategy combines an invertible intronic cassette (FLIP) with high efficiency Cas9-assisted gene editing. Critically, the non-mutagenic orientation of the FLIP cassette expresses a puromycin resistance gene allowing selection of correct nuclease-assisted targeting into the exon of one allele and simultaneous enrichment of cells that inactivate the second allele by nuclease-mediated NHEJ. Upon exposure to Cre recombinase the FLIP cassette is inverted to a mutagenic configuration resulting in the complete loss of gene function. Here, we present CRISPR-FLIP, a strategy that provides an efficient, rapid, and scalable method for conditional and reversible gene knockouts in diploid or aneuploid cells such as pluripotent stem cells, 3D organoids and cell lines by co-delivery of CRISPR/Cas9 and a universal conditional intronic cassette. In press in Nature Methods

Funding Source: A.A-R. is supported by the Medical Research Council. B-K.K. is supported by a Sir Henry Dale Fellowship from Wellcome Trust (WT) and the Royal Society [101241/Z/13/Z]. W.C.S received core grant support from WT to the WT Sanger Institute.

16:45 – 17:00

GENETIC DISSECTION OF THE EXIT FROM PLURIPOTENCY IN MOUSE EMBRYONIC STEM CELLS BY CRISPR SCREENING

Li, Meng and Yusa, Kosuke

Wellcome Trust Sanger Institute, Hinxton, U.K.

The ground state 'naïve' pluripotency is established in the epiblast of the blastocyst and can be captured by culturing mouse embryonic stem cells (mESCs) with MEK and GSK3 inhibitors (2i). The transcription network that maintains pluripotency has been well studied with the indispensable core factors being Oct4, Sox2 and Nanog, together with other ancillary factors reinforcing the network. However, how this network is dissolved at the onset of differentia-

tion is still not fully understood. To identify genes required for differentiation in an unbiased fashion, we conducted a genome-wide CRISPR screen in Rex1GFPd2 ESCs. This cell line expresses GFP specifically in the naïve state and rapidly downregulate upon differentiation. We differentiated mutagenized cells for three days and sorted mutants that kept higher GFP expression. gRNA representation was subsequently analysed by sequencing. We identified 563 and 8 genes whose mutant showed delayed and accelerated differentiation, respectively, at a false discovery rate (FDR) cut-off of 10%. The majority of the previously known genes were identified in our screen, suggesting faithful representation of genes regulating differentiation. Amongst the genes identified are 15 mTORC1 regulators and components of the mTORC2 complex. Deficiency in the TSC and GATOR1 complexes resulted in mTORC1 upregulation in consistent with previous studies; however, they showed opposite phenotype during ESC differentiation. We found that the pattern of GSK3b phosphorylation is highly correlated with differentiation phenotype. We conclude that mTORC1 is involved in pluripotency maintenance and differentiation through cross-talk with the Wnt signalling pathway. Our screen has provided further insights in biological pathways involved in regulating differentiation. It would be interesting to explore the remaining unstudied genes for better understanding of ESC differentiation.

17:00 – 17:15

MESENCHYMAL STEM CELL FATE FOLLOWING NANOPARTICLE-BASED GENE TRANSFECTION STRONGLY DEPENDS ON THE CHOICE OF DELIVERY VECTOR

Gonzalez Fernandez, Tomas[1], Sathy, Binulal[2], Hobbs, Christopher[3], Cunniffe, Grainne[2], McCarthy, Helen[4], Dunne, Nicholas[5], O'Brien, Fergal[6] and Kelly, Daniel[2]

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Controlling the phenotype of mesenchymal stem cells (MSCs) through the delivery of regulatory genes is a promising strategy in tissue engineering (TE). Essential to effective gene delivery is the choice of gene carrier. Non-viral delivery vectors have been extensively used in TE, however their intrinsic effects on MSC differentiation remain poorly understood. The objective of this study was to investigate the influence of three different classes of nanoparticle-based non-viral gene delivery vectors: (1) cationic polymers (polyethylenimine, PEI), (2) inorganic nanoparticles (nanohydroxyapatite, nHA) and (3) amphipathic peptides (RALA peptide) on modulating stem cell fate after reporter and therapeutic gene delivery. Despite facilitating similar reporter gene transfection efficiencies, these nanoparticle-based vectors had dramatically different effects on MSC viability, cytoskeletal morphology and differentiation. After reporter gene delivery (pGFP or pLUC), the nHA and RALA vectors supported an elongated MSC morphology, actin stress fibre formation and the development of mature focal adhesions, while cells appeared rounded and less tense following PEI transfection. These changes in MSC morphology correlated with enhanced osteogenesis following nHA and RALA transfection and adipogenesis following PEI transfection. When therapeutic genes encoding for transforming growth factor beta 3 (TGF-ß3) and/or bone morphogenic protein 2 (BMP2) were delivered to MSCs, nHA promoted osteogenesis in 2D culture and the development of an endochondral phenotype in 3D culture, while RALA was less osteogenic and appeared to promote a more stable hyaline cartilage-like phenotype. In contrast, PEI failed to induce robust osteogenesis or chondrogenesis of MSCs, despite effective therapeutic protein production. Taken together, these results demonstrate that the differentiation of MSCs through the application of non-viral gene delivery strategies depends not only on the gene delivered, but also on the gene carrier itself.

Funding Source: Funding from Science Foundation Ireland through the Advanced Materials and Bioengineering Research (AMBER) center and an Investigator Programme grant, as well as through the European Research Council.

17:15 – 17:30

OLIGOGENIC INHERITANCE OF FAMILIAL CARDIAC DISEASE INVOLVING MKL2 AND NKX2-5 VARIANTS REVEALED BY DISEASE MODELING

Gifford, Casey, Samarakoon, Ryan, Huang, Yu, Salunga, Hazel, Wyman, Staci, Metzler, Kim, Ivey, Kathy and Srivastava, Deepak

Gladstone Institutes, San Francisco, CA, U.S.

The ability to parse the genetic causes of oligogenic disorders has been challenging. Recent advances in genome sequencing and editing provide an opportunity to experimentally determine and test contributions of multiple genetic variants in human disease. Here, we report a case of familial left ventricular noncompaction (LVNC), a congenital heart defect characterized by an immature myocardium, with an inherited oligogenic cause. Exome sequencing of family members identified a novel heterozygous missense mutation in the transcription factor MKL2 (MRTF-B) that segregated with the disease and exhibited reduced transcriptional activity in vitro. Mice homozygous for this mutation exhibited abnormalities in the endocardium and ventricular myocardial wall, however heterozyosity was not lethal or sufficient to cause a LVNC-like phenotype in mice. Further exome analysis revealed a rare heterozygous missense mutation in NKX2-5 among subjects with early onset disease that was inherited from a healthy family member and had reduced DNA-binding activity. Mice homozygous for the Nkx2-5 variant were embryonic lethal, while heterozygous mice were normal. Compound heterozygous mice (Mkl2+/–Nkx-2-5+/–) were born at the expected Mendelian frequency, however they exhibited enlarged papillary mus-

cles, hypertrabeculated ventricular walls, and right ventricular expansion, mimicking the genotype and phenotype correlation observed in the familial case of LVNC. RNA sequencing from murine hearts identified genes associated with cellular adhesion and proliferation that were dysregulated in compound heterozygous hearts. Myocardial differentiation of patient-specific human induced pluripotent stem cells from subjects with and without CRISPR/Cas9 correction of alleles revealed transcriptional dysregulation of genes involved in heart development and cellular adhesion contributed by the NKX2-5 and MKL2 variants. These results integrating human genetics, mouse genetics, gene editing and human induced pluripotent stem cell-based disease modeling provide experimental evidence for complex inheritance of human disease and reveal novel mechanisms underlying cardiac disease.

17:30 – 17:55

ADVANCED GENETIC ENGINEERING OF HEMATOPOIESIS FOR TREATING INHERITED DISEASES

Naldini, Luigi

San Raffaele Telethon Institute for Gene Therapy-TIGET, Milan, Italy

Long-term follow-up of patients treated by lentiviral HSC gene therapy shows stable and extensive genetic engineering of hematopoiesis with polyclonal reconstitution by gene modified HSC with substantial therapeutic benefit. These results prove the feasibility to manipulate HSC ex vivo without hampering their long term repopulation potential and open the way to design improved gene therapy strategies. More precise genetic engineering can be achieved by correcting disease-causing mutations in situ, thus restoring both the function of the gene and its physiological expression control. Targeted gene editing, however, is constrained in HSC by quiescence and low expression of the DNA repair machinery. We could overcome these barriers by culture conditions that induce proliferation while preserving long-term engraftment capacity and provide evidence of correction of SCID-X1 causing mutations in the IL2RG gene. We have validated this approach in an ad hoc humanized SCID-X1 mouse model to support the scientific rationale and safety of the proposed treatment, and identify the conditioning regimen and degree of chimerism with edited cells required to correct the disease.

THURSDAY, 15 JUNE, 16:00 – 18:00

CONCURRENT IIE: CARDIAC REGENERATION

Level 2, Room 258C

16:05 – 16:30

IMMUNE CONTROL OF REGENERATION

Rosenthal, Nadia A.

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

The adult mammalian body does not retain the robust repair capacity of the embryo into adulthood and gradually loses its regenerative potential, generally attributed to the loss of adequate cell replacement and persistent inflammation with increased ageing or disease. Regeneration in both neonate and adult is orchestrated by immune regulatory networks that remove damaged cells and provide a cohort of growth factors and signaling molecules, promoting new vessel growth, and mediating scarring by regulating inflammation and fibroblast activation. Age-related variations in immune response play an important role in determining the potential for functional repair. The regenerative capacity of tissues and organs is also variable from an evolutionary perspective. The dramatic variability in regenerative capacity across species, as well as between recombinant inbred mouse strains, is correlated with distinct differences in immune composition and response. Using combination of genetic manipulation and pharmacological blockades we have modified the profile of immune cell infiltration, which can facilitate or prevent limb and cardiac regeneration in mouse and axolotl, an efficiently regenerating member of the urodele amphibian family. These studies collectively show that transition from wound healing to regeneration and restoration of tissue function relies on complex interactions between local progenitor cells, tissue environments and immune cell subsets to confer regrowth potential. They also uncover immune tolerance as a critical component of the regeneration process, suggesting new cell targets for clinical intervention.

16:30 – 16:45

FREQUENCY OF MONONUCLEAR DIPLOID CARDIOMYOCYTES UNDERLIES NATURAL VARIATION IN ADULT HEART REGENERATION

Patterson, Michaela[1], Barske, Lindsey[1], van Handel, Ben[2], Rau, Christoph[3], Guo, Peiheng[1], Sharma, Avneesh[1], Parikh, Shan[4], Denholtz, Matthew[3], Huang, Ying[5], Yamaguchi, Yuki[1], Shen, Hua[1], Allayee, Hooman[1], Crump, Gage[1], Force, Thomas[4], Lien, Ching-Ling[5], Makita, Takako[5], Lusis, Aldons[3], Kumar, S. Ram[1] and Sucov, Henry[1]

[1]University of Southern California (USC), Los Angeles, CA, U.S., [2]Carthronix, Los Angeles, CA, U.S., [3]University of California, Los Angeles, CA, U.S., [4]Vanderbilt University, Nashville, TN, U.S., [5]Childrens Hospital Los Angeles, CA, U.S.

Strong evidence from the literature supports the model that mononuclear, diploid cardiomyocytes (MNDCMs), a relatively rare population in the adult mammalian heart, are a regeneration-competent population, but this has not previously been subjected to experimental analysis. This project explores the hypothesis that the frequency of MNDCMs in the adult mammalian heart and regenerative potential are two interlinked, variable traits determined by multiple genetic parameters. If so, different individuals will have varying capacity to undergo heart regeneration following injury based on their unique genetic backgrounds. By surveying 120 inbred mouse strains, we found that the percentage of mononuclear cardiomyocytes in the adult mouse heart is a polygenic trait that is surprisingly variable (2.3%-17.0%). We confirmed experimentally that the degree of functional recovery and cardiomyocyte proliferation after permanent coronary artery ligation correlates with MNDCM content. Using genome-wide association, we identify Tnni3k as one gene with natural alleles that influence variation in this composition, and show in an isogenic strain background that Tnni3k knockout results in elevated MNDCM content and elevated cardiomyocyte proliferation after injury. Reciprocal to mammals, zebrafish are known to retain an almost pure MNDCM population through adulthood and are able to efficiently regenerate after adult heart injury. Here, we show that overexpression of Tnni3k in zebrafish promotes cardiomyocyte polyploidization and compromises heart regeneration, indicating a commonality in the regenerative process between the two species. Our results provide support for the requirement of the resident mononuclear diploid subpopulation of cardiomyocytes in heart regeneration. Moreover, our results imply that intrinsic heart regeneration is not uniform and limited in all individuals, but rather is a variable trait subject to the influence of multiple genes.

16:45 – 17:00

CRISPR/CAS9 GENOME-WIDE SCREEN IDENTIFYING DMAP1 AS A NEGATIVE REGULATOR OF CARDIAC PROGENITOR REPROGRAMMING FROM MOUSE FIBROBLASTS

Yu, Jason Shu Lim[1], Lim, CIndy[2], Drowley, Lauren[2], Plowright, Alleyn[2], Bohlooly-Y, Mohammad[2], Wang, Qing-Dong[2] and Yusa, Kosuke[1]

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Cardiac regeneration via in vivo reprogramming of resident cardiac fibroblasts (CF) is a highly attractive and prospective therapeutic intervention in ameliorating myogenic deterioration. Although a wealth of studies has established transcription factor-based reprogramming as an effective method by which this reprogramming is achieved, such an approach carries an inherent risk of tumorigenesis and is therefore ill-suited for therapeutic use. However, recent efforts have established chemical reprogramming as legitimate method by which to generate functional, lineage specific cell types including those of the cardiac lineage. We have developed a robust, transgene-independent chemical reprogramming protocol by which to generate cardiac progenitors (CP); a unique progenitor population that can give rise to endothelial, smooth muscle and cardiomyocyte subtypes. Taking advantage of this scalable protocol, we performed a genome-wide recessive screen with a CRISPR-gRNA library targeting 18,424 genes to identify novel mediators that regulate the reprogramming process. Validation of the top hits revealed the involvement of DMAP1, a DNA methyltransferase-associated protein that acts as a transcriptional co-repressor in mammalian cells. gRNA-mediated introduction of indels via CRISPR/Cas9 at the Dmap1 locus increases the propensity of CFs to convert to CPs via the upregulation of progenitor-specific genes such as Nkx2.5, Gata4, Tbx5, PDGFRa and KDR. Our results therefore establish DMAP1 as a critical modulator of CP induction and regenerative properties, providing a molecular basis through which to interrogate the use of these cells in a drug discovery and therapeutic context.

17:00 – 17:15

CHARACTERIZING GENETIC VARIATION ASSOCIATED WITH CARDIAC-SPECIFIC TRAITS IN HUMAN IPSC-DERIVED CARDIOMYOCYTES

D'antonio-Chronowska, Agnieszka[1], Farnam, KathyJean[1], Cook, Megan[1], Garcia, Melvin[1], D'Antonio, Matteo[2] and Frazer, Kelly[3]

[1]University of California, San Diego, La Jolla, CA, U.S., [2]Cancer Center, University of California, San Diego, La Jolla, CA, U.S., [3]Pediatrics, University of California, San Diego, La Jolla, CA, U.S.

Elucidating the functions of genetic variants is challenging because they often impact cell-specific phenotypes and therefore must be studied in relevant cell types. We

present the iPSCORE (iPSC Collection for Omic Research) study within which we generated iPSCs and derived cardiomyocytes (iPSC-CMs) from 137 different individuals, all of who were whole-genome sequenced. 82 individuals belong to 26 families (including 6 trios and 6 monozygotic twin pairs) and 55 are unrelated. To examine how genetic variation influences molecular phenotypes in iPSC and iPSC-CM lines derived from the same as well as different individuals, we analyzed the transcriptome and epigenome (RNA-seq, ATAC-seq, ChIP-seq for H3K27ac) of a subset of 24 iPSCORE lines derived from 6 monozygotic twin pairs and a mother-daughter set. We observed cell type-specific transcriptomic and epigenomic profiles that recapitulate those of embryonic stem cells (iPSCs) and fetal heart (iPSC-CMs). We also show that differences in the molecular phenotypes between cell lines carrying different genetic backgrounds are associated with the presence of nearby regulatory variants. These findings demonstrate the utility of iPSC-derived CMs as a model system for large-scale genetic associations studies. To derive the iPSCORE iPSC-CM lines we have developed a highly standardized, large-scale protocol, which yields up to 5.72x108 iPSC-CM from 450 cm2 cultures with average purity 87.5% and up to 99.5% of cTnT-positive cells measured by flow cytometry. We are successfully able to freeze and thaw the iPSC-CMs and have established their suitability for high-throughput multi-electrode array analysis. Thus, our protocol affords sufficient amounts of high-quality derived cardiomyocytes to examine how genetic variation is associated with molecular phenotypes in the naïve state, with electrophysiological traits, transcriptional and epigenetic changes in response to stress-triggered drug effects.

Funding Source: California Institute for Regenerative Medicine (CIRM) grant GC1R-06673 and NIH grants HG008118-01 and HL107442-05

17:15 – 17:30

H3K27ME3 DEPOSITION OVER SARCOMERIC AND ACTINOMYOSIN PROMOTERS IS REQUIRED FOR CARDIOMYOCYTE CYTOKINESIS AND WOUND INVASION DURING ZEBRAFISH HEART REGENERATION

Burns, Caroline E.[1], Ben-Yair, Raz[1], Butty, Vincent[2], Busby, Michele[3], Boyer, Laurie[2], Goren, Alon[4] and Burns, C. Geoffrey[5]

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Unlike humans, zebrafish readily regenerate their hearts following injury by stimulating proliferation of homeostatic cardiomyocytes. However, the genetic and epigenetic mechanisms controlling this transition remain poorly understood. Here, we investigated the global transcriptional changes that occur between homeostatic and proliferative cardiomyocytes in the zebrafish heart and uncovered an essential role for H3K27me3 deposition in facilitating successful myocardial regeneration. Specifically, we learned that cardiomyocyte proliferation is accompanied by repression of sarcomeric and actinomyosin cytoskeletal gene transcription. Using ChIPseq, we demonstrated that this transcriptional repression is associated with deposition of new H3K27me3 repressive modifications over the associated promoters, a finding consistent with our observation that the H3K27me3 histone methylase, ezh2, is upregulated following injury. Using new genetic zebrafish lines that allow for inducible and cardiomyocyte-specific expression of a mutant form of histone 3 that is unable to be tri-methylated on lysine 27 (H3.3K27M), we discovered that addition of H3K27me3 marks is essential for cardiac regeneration in vivo as 30 day post-amputation (dpa) hearts scar following ventricular resection. Earlier in the regenerative window, we found that H3.3K27M–expressing wound edge cardiomyocytes aberrantly maintain homeostatic levels of sarcomeric and actinomyosin gene expression and show significant retention of sarcomeric structure. While DNA replication occurs normally in these H3.3K27M cardiomyocytes, we observed significant increases in cardiomyocyte nucleation, a phenotype indicative of cytokinesis failures. In addition, nuclear density at the wound edge increases as new cardiomyocytes fail to colonize the injured area. Together, our study reveals that production of new cardiomyocytes and their infiltration into the injured region relies on H3K27me3-mediated sarcomeric and actinomyosin cytoskeletal gene repression.

Funding Source: This work was supported by an R01 (HL127067) from the National Institutes of Health.

17:30 – 17:55

NEW WINDOWS INTO MAMMALIAN CARDIAC REPAIR

Harvey, Richard P., Asli, Naisana, Xaymardan, Munira, Janbandhu, Vaibhao, Forte, Elvira, Farbehi, Nona, Waardenberg, Ashley, Cornwell, James, Abeygunawardena, Dhanushi and Nordon, Robert

Victor Chang Cardiac Research Institute, Sydney, Australia

The identification of multi-potent stem cells in the adult mammalian heart has opened up the possibility of stem cell regenerative therapies for myocardial infarction (MI) and heart failure, which are among the most significant causes of mortality and morbidity in Western societies. However, the extent of the contribution of endogenous stem cells to the generation of cardiomyocytes and vascular cell lineages in homeostasis and after injury, and how this could be augmented, is still unclear. In MI, endogenous stem cells may be lost or compromised by the hostile ischaemic and inflammatory environment, limiting the extent of natural repair processes. In addition to serving as linage progenitors, the cardiac stem and stromal cell compartment has complex roles as sentinels, and in the initiation and resolution of the inflammatory response during injury.

Imbalance of the pro-inflammatory and pro-resolving forces in the heart leads to worsening pathology. We are analysing the endogenous cardiac colony-forming and stromal elements of the murine heart as a stem/progenitor cell model using molecular and genetic tools. Cardiac MSC-like cells (defined as cardiac colony forming units, fibroblast – cCFU-F) are a multipotent adult stem cell population with their origins in the pro-epicardium of the developing heart. We have shown that platelet derived growth factors (PDGFs) are key injury factors encouraging quiescent stem and stromal cells to emerge from quiescence into higher metabolic states, allowing them to respond to proliferative and differentiation signals provided by the injury environment. Short-term PDGF delivery during MI leads to striking changes in cardiac lineage and inflammatory cell profiles, including florid myofibroblast differentiation and migration into the scar area, yet a quantum improvement in cardiac repair. Genetic lineage tracing and single cell transcriptomics are now allowing a unique vision of these events at unprecedented resolution.

THURSDAY, 15 JUNE, 16:00 – 18:00

CONCURRENT IIF: ENDODERMAL DERIVATIVES

Level 2, Room 205A

16:05 – 16:30

DIFFERENTIATING ES CELLS TO MATURE PANCREATIC BETA CELLS IN INCUBATORS

Rezania, Alireza

ViaCyte, Inc., San Diego, CA, U.S.

A number of recent studies claim in vitro generation of mature "functional" beta cells either through directed differentiation from pluripotent stem cells or through reprogramming of adult cells to treat diabetes. We also reported on the differentiation of pluripotent human stem cells into single hormonal insulin+ cells (stage 7 cells) that demonstrated some similarities with adult pancreatic beta cells. However, clear functional deficiencies were noted highlighting that additional milestones remain to be reached. Stage 7 cells did not possess some of the hallmarks of adult beta cells including brisk insulin release kinetics in response to various secretagogues, dynamic calcium flux in response to a glucose challenge, and appropriate mitochondrial respiration. RNA Seq analysis of S7 cells in comparison to adult beta cells revealed significant differences in genes/pathways essential for mitochondrial respiration and insulin secretion. Refinement of our previous protocol through identification of dysregulated pathways along with empirical testing of various media compositions/reagents resulted in production of insulin+ cells from human embryonic stem cell lines (hESCs, H1 and Cyt49) with insulin secretion kinetics and mitochondrial respiration similar to adult human islets. Newly generated insulin+ cells acquired some of the features attributed to mature beta cells, such as expression of UCN3, MAFA and GLUT1. Notably, these insulin+ cells survived within macroencapsulation devices following transplant in the subcutaneous space of immune compromised mice and yielded significant glucose responsiveness as early as four weeks post-implant and rapid reduction of insulin secretion following an insulin tolerance test. These results show the feasibility of generating insulin-producing cells from hESCs in vitro with characteristics of mature human beta cells.

16:30 – 16:45

SINGLE CELL MRNA SEQUENCING REVEALS THAT PANCREATIC ENDOCRINE DIFFERENTIATION IS SPATIALLY AND TEMPORALLY REGULATED WITHIN A PENINSULAR NICHE

Sharon, Nadav[1], Chawla, Raghav[2], Mueller, Jonas[3], Shvartsman, Dmitry[1], Vanderhooft, Jordan[1], Kixmoeller, Kathryn[1], Trapnell, Cole[2] and Melton, Douglas[1]

[1]Harvard, Cambridge, MA, U.S., [2]University of Washington, Seattle, WA, U.S., [3]Massachusetts Institute of Technology (MIT), Cambridge, MA, U.S.

The islets of Langerhans comprise the endocrine component of the pancreas, and are the major organ which regulates glucose homeostasis systemically. This burden lies first and foremost on ß cells which, by secreting Insulin, induce glucose uptake from the bloodstream. This function is countered by the second major cell population in the islets – the Glucagon secreting a cells. Elimination of ß cells causes type 1 diabetes, and their malfunction is related with type 2 diabetes. Hope for curing these diseases comes from recent advances in directing the differentiation of human embryonic stem cells (hESCs) into ß like cells, but limited understanding of islet development precludes the generation of these cells in the quality required for clinical use. To gain better understanding of islet development, we performed single cell mRNA sequencing of pancreatic endocrine progenitors as they differentiate into hormonal cells. Based on this, we created a detailed map of the sequential changes in gene expression that occur as endocrine progenitors differentiate into either ß or a cells. Furthermore, the detailed temporal analysis shed new light on the morphological basis of islet generation. Contrary to the prevailing notion that islets form through aggregation of dispersed endocrine cells, we show that endocrine progenitors migrate while constantly maintaining a cohesive structure. Thus, islets form through the formation of a bud like niche which we term peninsula. Moreover, we found that these endocrine peninsulae organize the differentiating endocrine cells in a manner which confers spatiotemporal co linearity to the forming organ. a cells, which emerge first, comprise the peninsular periphery, whereas the later forming ß cells are in its core. This way, early endocrine differentiation already lays the ground for the architecture of the mature islet. Finally, by generating peninsular equivalents from hESCs in vitro, we were able to establish an in vitro model for the study of pancreatic endocrine differentiation. This led us to uncover a role for

WNT inhibition in endocrine differentiation both in vitro and in vivo. This work provides a comprehensive database for the study of ß cell development, and a unique glance into the elusive interaction between cellular differentiation and organ morphogenesis.

16:45 – 17:00

GLYCOCAPTURE PROTEOMICS IDENTIFIES A NOVEL CELL SURFACE MARKER OF HUMAN PANCREATIC PROGENITOR CELLS

Nostro, M. Cristina[1], Cogger, Kathryn[2], Sinha, Ankit[3], Saunder, Diane[4], McGaugh, Emily[3], Sarangi, Farida[2], Aghazadeh, Yasaman[2], Dorrell, Craig[5], Mejia-Guerrero, Salvador[2], Grompe, Markus[5], Streeter, Philip[5], Powers, Alvin[4], Brissova, Marcela[4] and Kislinger, Thomas[2]

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PDX1+/NKX6-1+ pancreatic progenitors (PPs) can be successfully differentiated from human Pluripotent Stem Cells (hPSCs). These PPs hold the potential to generate an unlimited supply of ß-cells for diabetes treatment. However, the percentage of PPs produced in vitro is cell-line dependent, which has a critical impact on reproducibility and validation of in vitro and in vivo studies, and consequently, translation to the clinic. As glycosylated proteins are enriched on cellular membranes, we set out to identify novel cell surface markers by performing mass spectrometry analysis on enriched N-glycosylated proteins. To identify markers specific to the PPs, we compared this population to undifferentiated hESCs and polyhormonal cells (PH), the latter being pancreatic cells that are NKX6.1- and unable to generate functional ß-cells in vivo. Unsupervised clustering analysis clearly distinguished the different populations and identified peptides specifically enriched in each of the three cell populations. We positively identified known markers of undifferentiated hESCs such as CD90, KDR and PTPRZ1, as well as novel markers of the PP and PH populations. Here we present validation of these markers by qPCR, flow cytometry and immunocytochemistry. Remarkably, we uncovered a cell membrane protein, which specifically marks the NKX6-1+ population. To verify its expression pattern, we performed immunofluorescence labelling in human postnatal pancreas and confirmed its co-expression with NKX6-1 and PTF1A, consistent with it marking the multipotent pancreatic progenitors in vivo. We used antibodies against this marker to successfully enrich for H1 and H9-derived PPs by fluorescence-activated cell sorting and magnetic activated cell sorting. Notably, the enriched PPs generate a higher percentage of ß-like cells (C-peptide+/NKX6-1+) in vitro, compared to negative and unsorted populations, indicating that it could be used to isolate cells for therapeutic applications. These findings provide a pioneering method for isolation and quantification of PPs from hESC cultures and establish a more solid technology for studying lineage commitment in vivo and in vitro, as well as the ability to generate a safer population for therapeutic applications.

Funding Source: Funding sources: Toronto General and Western Hospital Foundation, McEwen Centre for Regenerative Medicine, Banting and Best Diabetes Centre.

17:00 – 17:15

DIGIT IS A LNCRNA THAT REGULATES DIFFERENTIATION OF EMBRYONIC STEM CELLS INTO DEFINITIVE ENDODERM

Daneshvar, Kaveh[1], Pondick, Joshua[2], Kim, Byeong-Moo[2], Zhou, Chan[2], York, Samuel[2], Macklin, Jillian[2], Abualteen, Ameed[2], Sigova, Alla[3], Marcho, Chelsea[4], Tremblay, Kimberly[4], Mager, Jesse[4], Choi, Michael[2] and Mullen, Alan[2]

[1]Harvard Medical School, MGH, Boston, MA, U.S., [2]Gastrointestinal Unit, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston, MA, U.S., [3]Whitehead Institute for Biomedical Research, Cambridge, MA, U.S., [4]Department of Veterinary and Animal Sciences, University of Massachusetts at Amherst, MA, U.S.

Activin/TGF-beta signaling initiates endoderm differentiation of embryonic stem cells (ESCs). We identified an lncRNA conserved between humans and mice that is divergently transcribed from Goosecoid (GSC) and induced in response to Activin signaling during endoderm differentiation. We show that CRISPR-mediated deletion of the SMAD3 enhancer proximal to lncRNA DIGIT (Divergent to GSC, Induced by TGF-beta family signaling) results in loss of DIGIT and GSC expression and inhibits endoderm differentiation. Disruption of DIGIT transcription by insertion of a GFP-polyA cassette downstream of its transcription start site, or depletion of DIGIT transcripts by RNA interference are sufficient to abolish GSC expression and inhibit endoderm differentiation. Moreover, this defect in endoderm differentiation is rescued with ectopic expression of DIGIT. In addition, the mouse ortholog of DIGIT is required for endoderm differentiation of mouse ESCs. We find that DIGIT promotes endoderm differentiation of human ESCs by regulating GSC expression and demonstrate that induction of endogenous GSC expression is sufficient to rescue endoderm differentiation in DIGIT-deficient hESCs. To identify the proteins that directly interact with the DIGIT transcript to regulate endoderm differentiation, we fused DIGIT with an aptamer that has a high affinity for streptavidin and inserted the DIGIT-aptamer expression cassette into the AAVS1 locus in human ESCs. We performed UV cross-linking followed by precipitation with streptavidin-coated beads to identify the proteins that directly interact with DIGIT. Our study defines DIGIT as a direct target of Activin/TGF-beta signaling and a key developmental regulator that is functionally conserved between humans and mice. We also identify proteins that interact with DIGIT in live cells and explore how these proteins function in endoderm differentiation.

17:15 – 17:30

DISSECT HUMAN ENDODERM DEVELOPMENT THROUGH A GENOME-WIDE CRISPR SCREEN IN EMBRYONIC STEM CELLS

Li, Qing[1], Dixon, Gary[1], Verma, Nipun[1], Rosen, Bess[1], Wang, Qiong[1], Soh, ChewLi[1], Xiang, Qing[1], Evans, Todd[2], Massague, Joan[1], Garippa, Ralph[1] and Huangfu, Danwei[1]

[1]Memorial Sloan Kettering Cancer Center, New York, NY, U.S., [2]Weill Cornell Medical College, New York, NY, U.S.

Genetic screens have been instrumental for understanding lineage decisions during embryonic development. However the forward genetic screening approach used in model organisms cannot be directly extended to humans. An additional challenge lies in the difficulty of increasing the throughput of phenotyping for screens conducted in vertebrates especially in mice. Combining human embryonic stem cells (hESCs) differentiation with the CRISPR/Cas technology, we conducted a genome-wide knockout screen for genes that cell-autonomously regulate the formation of human definitive endoderm, which gives rise to most cells in respiratory and gastrointestinal organs including the lung, pancreas and liver. Our screen identified previously known as well as unknown regulators of endoderm differentiation. We demonstrate that the dosage requirement of Nodal signaling is essential for DE differentiation and hESCs need a collection of transcription factors, epigenetic regulators, and signaling transduction molecules to enable proper differentiation to occur. Genes identified from our screen are potential great resources for understanding human embryonic development and congenital birth disorder.

17:30 – 17:55

FROM HUMAN PLURIPOTENT STEM CELL DERIVED CHOLANGIOCYTES TO BILIARY ORGANOIDS

Vallier, Ludovic, Sampaziotis, Fotis, Saeb-Persy, Kourosh, Justin, Alexander and Markaki, Athina

Cambridge Stem Cell Institute and Wellcome Trust Sanger Institute, Cambridge, U.K.

Cholangiopathies represent a diverse group of diseases affecting cholangiocytes which are the main cell type of the biliary tract. These disorders range from inherited (Cystic Fibrosis) and developmental (Alagille Syndrome, Biliary Atresia) to autoimmune (Primary Biliary Cirrhosis), idiopathic (Primary Sclerosing Cholangitis) and drug or toxin induced diseases. Cholangiopathies carry high morbidity and mortality, accounting for up to a third of chronic liver disorders. The absence of physiologically relevant in vitro systems to model and to study cholangiopathies prevents the development of new therapeutics while cell based therapy approach have been unexplored. Here, we used human pluripotent stem cells (hPSCs) to address these challenges. We have developed a protocol to differentiate hPSCs into biliary cell following a natural path of development. The resulting cholangiocyte like cells display key characteristics of their in vivo counterpart. In addition, we demonstrated the clinical interest of cholangiocyte like cells to model inherited disorders especially Cystic Fibrosis. We have then developed a 3D culture system to expend the cholangiocyte like cells as organoids. We expanded these culture systems to generate and to characterise for the first time a renewable source of primary cholangiocytes organoids from human biliary tissue. We are currently exploring the potential for in vitro generated cholangiocytes to be used in regenerative medicine applications including cell based therapy. Considered collectively, our results describe the development of a novel platform for the study of basic mechanisms controlling biliary development, disease modelling and drug screening in the context of cholangiopathies.

THURSDAY, 15 JUNE, 16:00 – 18:00

CONCURRENT IIG: MODELING NEURODEGENERATIVE DISEASE

Level 3, Ballroom East

16:05 – 16:30

USING STEM CELLS TO REVEAL THE SECRETS OF ALZHEIMERS DISEASE

Goldstein, Lawrence S.B.

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

I will discuss our recent work using IPS derived neurons to probe mechanisms of defects in Alzheimers Disease. Recent work with familial Alzheimers Disease mutations made using TALENs and CRISPRs in IPS cells derived from J Craig Venter are in an isogenic background so may be compared directly. We have discovered that FAD mutations have an early defect in the transcytosis of the amyloid precursor protein and lipoproteins from the somatodendritic to the axonal domain. We have also used drug screening and analysis of mutations to reveal that cholesterol levels control tau protein phosphorylation by control of proteolysis and the production of amyloid peptides by modification of gamma-secretase activity..

16:30 – 16:45

AGE-EQUIVALENT AND REJUVENATED INDUCED NEURONS FROM ALZHEIMER PATIENTS TO STUDY AGE-DEPENDENT DISEASE MECHANISMS

Mertens, Jerome and Gage, Fred

The Salk Institute for Biological Studies, San Diego, CA, U.S.

The inevitable process of aging represents a huge health threat for our aging societies as old age is the preeminent risk factor for several human diseases such as Alzheimer's disease (AD). With the rare exception of aggressive inherited versions of familial AD, this disease exclusively affects

old humans, while young and middle-aged humans never get affected. Biological aging can thus be regarded as a necessity for the development of AD in humans. However, our current understanding of the cell biological manifestation of old age, and how it makes our brain cells more vulnerable to disease is largely incomplete. Current iPSC differentiation paradigms allow us to study AD directly in human neurons that can be generated directly from patients' biopsy samples. However, the involved iPSC reprogramming process results in rejuvenation of the old patient material and thus yields cells that appear to resemble 'baby' neurons rather than age-equivalent, or 'old' neurons. Here, we have established that the direct conversion of patient fibroblasts into induced neurons (iNs) allows circumventing the rejuvenating reprogramming process and results in cultures of age-equivalent neurons that show aging signatures at the transcriptional, nuclear pore and other levels. To study the involvement of cellular aging in AD pathogenesis, we took advantage of combing both technologies to generate both, 'old' iNs as well as 'baby' iPSC-iNs from a large set AD patients and healthy control donors. Using whole transcriptome RNA-Seq analysis of purified neurons, we identify transcriptional signatures that are specific for AD in patient-specific neurons, and test which of those are exclusively visible in 'old' iN cells, and which ones are also present in rejuvenated iPSC-iNs. This strategy allows to study age-dependent mechanisms in AD, with the goal to identify pathways that can be targeted to prevent pathogenesis.

16:45 – 17:00

SMALL MOLECULE SCREEN FOR MODULATORS OF SURVIVAL OF MOTOR NEURON PROTEIN IN HUMAN MOTOR NEURONS

Makhortova, Nina R.[1], Lynes, Maureen[1], Hetie, Phylis[1], Mull, Jesse[2], Whye, Dosh[1], Davidow, Lance[1], Kiselyov, Alex[3] and Rubin, Lee[1]

[1]Harvard University, Stem Cell and Regenerative Biology, Cambridge, MA, U.S., [2]Neuroscience, Novartis Institutes for Biomedical Research, Cambridge, MA, U.S., [3]Genea Biocells US, Inc, La Jolla, CA, U.S.

Spinal muscular atrophy (SMA) is a childhood disease characterized by motor neuron degeneration, systemic organ defects, and subsequent mortality. This phenotype is caused by a mutation in the Survival of Motor Neuron (SMN1) gene. The SMN1 gene product is well known as a core protein of the gemin-containing splicing machinery. Understanding the biological pathways that govern the degeneration of human motor neurons has been hindered because these cells are inaccessible in vivo. We have developed a system for 3D large-scale production of motor neurons differentiated from SMA patient-derived iPS cells. We conducted a chemical screen on these cells using a quantitative single cell imaging method that measures SMN protein levels. Among the hits that increased SMN were structurally diverse HDAC6 inhibitors, known for their ability to stabilize microtubules. Altering microtubule stability using taxol and nocodazole effectively modulated SMN level in motor neurons as well. Furthermore, cell-free biochemical experiments confirmed that SMN can bind to microtubules directly and may also function as a microtubule-stabilizing protein. Further characterization of SMN microtubule binding domains is underway.

Funding Source: The work was supported by Grants from the SMA Foundation, NINDS (NS066888), Families of SMA, Takeda Pharmaceuticals International Inc. and the Harvard Stem Cell Institute.

17:00 – 17:15

DISCORDANT TWINS FOR CONGENITAL ZIKA SYNDROME SHOW DIFFERENTIAL ZIKA VIRAL INFECTION IN (HIPSC)-NPCS

Caires, Luiz Carlos[1], Goulart, Ernesto[1], Melo, Uirá[1], Araújo, Bruno[2], Alvizi, Lucas[1], Schanoski, Alessandra[3], Griesi-Oliveira, Karina[4], Kobayashi, Gerson[1], Astray, Renato[3], Suárez-Patiño, Sandra[3], Yamamoto, Guilherme[1], Ezquina, Suzana[1], Naslavsky, Michel[1], Van der Linden, Vanessa[5], Kalil, Jorge[3], Cunha-Neto, Edécio[1], Nakaya, Helder[1], Lee Ho, Paulo[3], Passos-Bueno, Maria Rita[1] and Zatz, Mayana[1]

[1]University of Sao Paulo, Brazil, [2]Federal University of Sao Paulo, Brazil, [3]Butantan Institute, Sao Paulo, Brazil, [4]Albert Eistein Hospital, Sao Paulo, Brazil, [5]AACD, Recife, Brazil

Congenital Zika Syndrome (CZS), caused by Zika virus (ZIKV) infection, has been associated to impairments during early brain development, particularly related to Neural Progenitor Cells (NPC) survival and growth. Reports on discordant dizygotic (DZ) twins suggest a host genetic susceptibility for the development of CZS. To address this question we have investigated NPC response to ZIKV infection in a pair of discordant DZ twins (an affected girl and normal twin brother, currently 14 months old) born from a mother infected by ZIKV during pregnancy. Human induced pluripotent stem cells (hiPSC)-derived NPC (monolayer and neurospheres culture) from both twins were infected with ZIKVBR in a MOI 0.01 and 0.1 during 96 hours. In the affected twin viral replication was highly increased (~15.5 fold higher than in the normal twin) and plaque-forming units / PFU after 96 hours post-infection were ~22 fold higher in the affected as compared to the normal twin. Confocal analysis showed a ~2.6-fold increased fluorescence intensity in ZIKV staining. Furthermore, a significant decrease in the cell number and cell covered plate area as well as an increased activity of mTOR signaling inhibitors (such as PTEN, TSC2 and GSK3ß) despite increased activity of effectors such as EIF4e were observed in the affected twin. Differences in cell growth using a 3D culture system was also confirmed with a significantly diameter decrease in the affected twin neurospheres after 48 hpi. We are currently repeating these experiments in two additional pairs of dizygotic twins which will be presented during the meeting. Discordant twins represent the best case-control model. If these results are confirmed and since NPCs drive brain development, they would indicate intrinsic host neuropro-

genitor cells viral response that could have an important role in the development of CZS.

Funding Source: FAPESP, CNPq and Ministerio da Saude

17:15 – 17:30

FUNCTIONAL AND BIOENERGETIC DEFECTS IN IPSC-DERIVED DOPAMINERGIC NEURONS FROM PATIENTS WITH LEIGH SYNDROME HARBORING SURF1 MUTATIONS

Inak, Gizem[1], Juettner, Rene[1], Mlody, Barbara[1], Swamy, Narashima[1], Lorenz, Carmen[1], Diecke, Sebastian[1], Wanker, Erich[1], Rathjen, Fritz[1], Schuelke, Markus[2] and Prigone, Alessandro[1]

[1]Department of Neuroproteomics, Max-Delbrueck Center for Molecular Medicine (MDC), Berlin, Germany, [2]Charité Universitätsmedizin Berlin, Germany

Leigh syndrome (LS) is one of the most common, often fatal, mitochondrial disorders in childhood. It is characterized by progressive neurodegeneration with symmetric necrotic lesions in basal ganglia and brainstem. There is no effective therapy against LS available and in vivo models to study the disease are lacking. One of the most severe forms of LS is associated with defects of the cytochrome C oxidase (COX) due to SURF1 gene mutations. SURF1 is a mitochondrial matrix protein involved in the biogenesis and assembly of the COX complex (complex IV), which is the terminal enzyme of electron transport chain. Even though the SURF1 gene is evolutionarily conserved, mouse models carrying SURF1 mutations fail to exhibit any abnormalities of brain morphology or overt clinical neurologic symptoms. In this project, we aim to develop a novel iPSC-based model of LS to investigate the molecular and pathophysiological mechanisms underlying the disease-specific neuronal cell death. Using Sendai viruses, we generated iPSCs from fibroblasts of two patients with different SURF1 mutations. We focused our differentiation protocol on midbrain dopaminergic neurons (mDANs) that are part of the basal ganglia motor loop. Importantly, patient-derived mDANs exhibited significant bioenergetic defects and elevated lactate levels. The latter is an important finding, given that lactic acidosis is a common feature observed in LS patients. Additionally, electrophysiological recordings showed that patient-derived mDANs failed to mature over time. We next employed the transcription activator-like effector nuclease (TALEN) system to generate isogenic lines for one of the patient iPSC line. This approach allowed us to determine which dysfunctions of the patient mDANs would be caused by the SURF1 mutation. Finally, we will use the cellular read-outs for high throughput compound screening. This approach was recently successful to identify counteractive substances using iPSC-derived neural progenitors from patients with LS due to mtDNA mutations. We plan to use the identified compounds to investigate whether nuclear genetic defects causing LS could be pharmacologically rescued as well. This may enable the development of novel treatment strategies against a debilitating and so far untreatable condition.

17:30 – 17:55

CORTICAL CULTURES OF EXCITATORY PROJECTION NEURONS AND INHIBITORY INTERNEURONS TO STUDY CORTICAL FUNCTION AND INJURY

Dawson, Valina L.

Johns Hopkins University School of Medicine, Baltimore, MD, U.S.

The human cerebral cortex is a complex structure with tightly interconnected excitatory and inhibitory neuronal networks that function in an interconnected manner in both physiologic and pathophysiologic actions. To permit the study of cortical function, neurotoxicity and neuroprotection and clinically relevant therapies, we developed a human cortical neuron culture system that expresses both excitatory and inhibitory neuronal networks resembling the composition of the human cortex. This differentiation of neuronal populations representative of the six cortical layers is functional and homeostatically stable. In human cortical neuron cultures, excitotoxicity or ischemia due to oxygen and glucose deprivation led to cell death that was dependent on N-methyl-D-aspartate (NMDA) receptors, nitric oxide (NO), and the poly (ADP-ribose) polymerase (PARP)-dependent cell death, a cell death pathway designated parthanatos. Neuronal cell death was attenuated by PARP inhibitors that are currently in clinical trials for cancer treatment. These cultures also undergo preconditioning induced neuroprotection. This culture system provides a new platform for the study of human cortical neurotoxicity and a platform to define and understand neuroprotective strategies in the human brain. These data also suggest that PARP inhibitors may be useful for ameliorating excitotoxic and ischemic cell death in human neurons.

FRIDAY, 16 JUNE, 9:00 – 11:20

PLENARY IV: CHROMATIN AND RNA BIOLOGY IN STEM CELLS

9:00 – 9:25

THE DEVELOPMENTAL DYNAMICS OF X-CHROMOSOME INACTIVATION

Heard, Edith

Institut Curie, Paris, France

X-chromosome inactivation during early female development is an essential epigenetic process that is required to achieve appropriate dosage for X-linked gene products. We are interested in understanding how the differential treatment of the two X chromosomes in the same nucleus is set up during development and how this differential expression is then maintained, or reversed in certain circumstances such as the inner cell mass of the mouse embryo or in the germ line. The establishment of X inactivation involves the non-coding Xist RNA that triggers chromosome-wide chromatin reorganisation and gene silencing. Recent insights have been made into the nature of these chromosome-wide changes but little is known about their functions or their stability. Our recent studies investigating the degree to which X-chromosome dosage compensation is essential during development and the mechanisms involved in silencing and reactivating the inactive X chromosome will be presented.

9:25 – 9:50

THE DIVERSITY AND FUNCTION OF LONG NONCODING RNAS

Chen, Ling-Ling

Shanghai Institute of Biochemistry and Cell Biology (SIBS), Chinese Academy of Sciences, Shanghai, China

Long noncoding RNAs (lncRNAs) comprise different types of RNA polymerase II-derived noncoding transcripts with sizes that are greater than 200 nt in length. While a large proportion of lncRNAs just look like mRNAs, a number of lncRNAs form their ends by unusual ways. We have recently uncovered different types of broadly expressed circular RNAs and linear RNAs with unexpected formats (ie. snoRNA-ended lncRNAs). Some such RNAs are highly expressed in human embryonic stem cells (hESCs) and are implicated in human diseases, including Prader-Willi syndrome (PWS), a neuro-developmental genetic disorder with undefined molecular basis. I will update our current understanding of snoRNA-ended lncRNAs with a focus on the recently characterized SPA and SLERT.

9:50 – 10:15

RNA TAILING IN THE REGULATION OF MATERNAL TRANSCRIPTOME

Kim, V. Narry, Yeo, Jin Ah and Chang, Hyeshik

Seoul National University, Seoul, Korea

In early embryos, maternal transcriptome is translationally activated through cytoplasmic polyadenylation, and subsequently degraded and replaced by zygotic transcriptome in a highly coordinated manner. However, it remains largely unknown how mRNA stability and translatability is temporally and specifically regulated during early development in vertebrates. Through genome-wide profiling of RNA abundance and 3' terminal sequences, we found that mRNA uridylation precedes the onset of maternal mRNA degradation. Such induction of uridylation is consistently observed in mouse, frog, and fish embryos, suggesting the conserved role of uridylation in vertebrate mRNA decay pathway. When TUT4 (Zcchc11) and TUT7 (Zcchc6), previously identified as mRNA uridylation enzymes in human cells, are knocked down, maternal mRNA clearance is significantly delayed, leading to impaired zygotic transcription and developmental defects during gastrulation in both zebrafish and frog. Maternal mRNAs with short poly(A) are preferentially targeted by TUT4 and TUT7, whereas maternal transcripts with long poly(A) are less affected by uridylation activity. Our study demonstrates that mRNA tailing such as cytoplasmic polyadenylation and uridylation is essential for timely regulation of maternal transcripts, thereby directing the progression of early development.

10:15 – 10:40

CHROMOSOME NEIGHBORHOODS AND GENE CONTROL IN HEALTH AND DISEASE

Young, Richard, Hnisz, Denes, Weintraub, Abraham, Li, Charlie, Zamudio, Alicia, Day, Daniel, Abraham, Brian and Jaenisch, Rudolf

Whitehead Institute for Biomedical Research, Cambridge, MA, U.S.

The control of cell identity is orchestrated by transcriptional and chromatin regulators in the context of specific chromosome structures. Genes and their regulatory elements typically occur together within specific DNA loop structures called insulated neighborhoods, which have emerged as structural and functional units of gene control. Insulated neighborhoods are chromatin loops that contain genes and their regulatory elements and are formed by the interaction of CTCF proteins bound to two distal DNA sites called loop anchors. I will discuss key features of insulated neighborhood structure and function and the roles these features play in health and disease.

10:40-10:50

POSTER TEASERS

F-1091

AGE- AND REGION-DEPENDENT ARCHITECTURAL REMODELING OF NICHE CONSTITUENTS IN THE HEMATOPOIETIC MICROENVIRONMENT CONTRIBUTES TO HEMATOPOIETIC STEM CELL AGING

Hoffman, Corey M.
University of Rochester Medical Center, NY, U.S.

F-1158

CLONAL ANALYSIS DEFINES THE HIERARCHICAL MODE OF MEDULLOBLASTOMA GROWTH AND A REQUIREMENT FOR COMBINATION THERAPY IN A PRE-CLINICAL MOUSE MODEL

Selvadurai, Hayden
The Hospital for Sick Children, ON, Canada

F-1088

OPTOGENETIC INVESTIGATION OF EFFECTS OF BETA-CATENIN SIGNALING DYNAMICS ON ADULT NEURAL STEM CELL DIFFERENTIATION

Rosenbloom, Alyssa
University of California, Berkeley, CA, U.S.

F-2001

GENOME TRANSFER PREVENTS FRAGMENTATION AND RESTORES DEVELOPMENTAL POTENTIAL OF DEVELOPMENTALLY COMPROMISED POSTOVULATORY AGED MOUSE OOCYTE

Yamada, Mitsutoshi
Keio University School of Medicine, Japan

F-1183

BOTTOM-UP ISLET ENGINEERING

Peterson, Quinn P.
Harvard University, MA, U.S.

10:55 – 11:20

ISSCR TOBIAS AWARD LECTURE: NORMAL AND LEUKEMIC HUMAN HEMATOPOIETIC STEM CELLS: CLONAL ASSAYS MATTER

Dick, John E.

Princess Margaret Cancer Centre, University Health Network and Department of Molecular Genetics, University of Toronto, ON, Canada

For decades, the hematopoiesis was described as a cellular hierarchy maintained by self-renewing hematopoietic stem cells (HSCs) that proceed through a series of multipotent, oligopotent and unipotent progenitors to make blood. Oligopotent intermediates are crucial to the model since they define the path from multipotent cells to unipotent cells. Although the standard model is still used extensively as an operational paradigm, further cell purification and functional clonal assays have led to key revisions of the model. For example, the earliest precursor with concomitant lymphoid (T, B, NK) potential also has myelomonocytic potential. Through novel cell-sorting and more sensitive single cells assays to assess multilineage My, Er, and Mk fate potential contemporaneously we find that oligopotent progenitors are a negligible component of the hierarchy of adult BM suggesting that multipotent cells differentiate into unipotent cells directly. These data support the concept of a 'two-tier' human blood hierarchy: a top-tier containing multipotent cells (HSCs and MPPs) and a bottom-tier composed of committed unipotent progenitors. To gain a deeper understanding of the molecular basis for the two tier hierarchy, transcriptional, proteomic, miRNA and ATAC-seq analysis has been undertaken in these highly sorted fractions. We have undertaken gain of function and loss of function approaches to determine the function of key regulators that have come from this integrated analysis. Our studies of AML have uncovered a hierarchical structure with many similarities to normal hematopoiesis: LSCs at the apex can self-renew and produce the bulk tumour cells. Moreover, like HSCs, LSCs are defined by their ability to initiate xenografts and are quiescent, making them insensitive to anti-proliferative chemotherapy. By combining xenograft assays with genetic tracking, we find that LSCs are genetically diverse and drive subclones related by complex branched evolutionary pathways; each subclone is organized as a functional hierarchy pointing to the influence of epigenetic determinants. By profiling the genetic diversity of LSC subclones in paired diagnosis-relapse samples, we have now uncovered two distinct classes of relapse-originating (RO) cells; in both cases they arose from rare stem cell-like populations.

FRIDAY, 16 JUNE, 13:15 – 15:15

CONCURRENT IIIA: EMBRYONIC STEM CELLS

Level 2, Room 258AB

13:20 – 13:45

MECHANISM OF SOMATIC CELL REPROGRAMMING

Guo, Shangqin, Hu, Xiao, Liu, Zongzhi, Chen, Xinyue, Hartman, Amaleah, Baccei, Anna, Cheng, Jijun, Zhong, Mei, Lu, Jun, Krause, Diane and Carroll, Christopher

Yale University, New Haven, CT, U.S.

Induction of pluripotency from somatic cells by Yamanaka factors is a slow and inefficient process. Since the cells destined to become pluripotent during Yamanaka reprogramming represent a minute fraction in most reprogramming systems, their identity has remained elusive. Is there a set of definable molecular and cellular characteristics that can help distinguish these rare cells from the majority of the other genetically identical cells which fail to reprogram? Recognizing these molecular and cellular features would greatly help the mechanistic understanding of somatic cell reprogramming, and of cell fate control in general. Following direct visualization of the reprogramming process and FACS sorting to prospectively enrich for the ultrafast cycling privileged cells, we recognize that the cells of increased reprogramming efficiency are of distinct cell size and morphology. This cell biological feature led us to define an important facet of cellular heterogeneity, which is under the control of a universally expressed somatic transcription factor whose activity needs to be sufficiently weakened to allow activation of the endogenous pluripotency.

13:45 – 14:00

THE 3D GENOME AND TRANSCRIPTIONAL CONTROL

Weintraub, Abraham and Young, Richard

Whitehead Institute, Cambridge, MA, U.S.

Chromosome structure plays an important role in the transcriptional control of gene expression. Transcription is driven by the formation of a DNA loop between enhancer-bound transcription factors and the transcription apparatus at gene promoters. These enhancer-promoter loops occur within larger DNA loops, formed by the structural regulator proteins cohesin and CTCF. However, we have a limited understanding of the proteins that contribute to structuring enhancer-promoter loops. Here we show that the dimerization of transcription factors is a key mechanism by which enhancer-promoter loops are structured. Perturbation of transcription factor binding with genetic and epigenetic editing results in decreased enhancer-promoter interactions. Thus we propose that transcription factors can act as structural regulators of enhancer-promoter loops.

14:00 – 14:15

DEFINING THE ESSENTIALOME OF HUMAN PLURIPOTENT STEM CELLS USING CRISPR/CAS9 SCREENING IN HAPLOID CELLS

Yilmaz, Atilgan[1], Peretz, Mordecai[2], Aharony, Aviram[2], Sagi, Ido[2] and Benvenisty, Nissim[3]

[1]The Azrieli Center for Stem Cells and Genetic Research, Department of Genetics, The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem, Israel, [2]The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University of Jerusalem, Israel, [3]The Hebrew University of Jerusalem, Israel

The maintenance of pluripotency requires a set of essential genes to be expressed. A thorough identification of these essential genes is vital for gaining a better understanding of the pluripotency state, as well as of the differences between this unique cellular state and differentiated states. Recently, we have isolated and characterized haploid human pluripotent stem cells (hPSCs) from parthenogenetic embryos, which allow high-throughput genetic screening for characterization of pluripotency-essential genes. To this end, we have generated a genome-wide loss-of-function library in haploid hPSCs using the CRISPR/Cas9 technology targeting more than 18000 coding genes, with 10 sgRNA constructs for each gene. Our data suggest that gene essentiality increases as the expression of the genes becomes more enriched in hPSCs. hPSC-essential genes consist of three main gene classes: transcription factors, mitosis-related proteins and metabolic enzymes. Furthermore, our screen revealed that half of the nuclear factors that have an enriched expression in the hPSCs are essential, highlighting the importance of the nuclear proteome in the maintenance of pluripotency. In addition to the pluripotency-essential genes, we also sought to identify mutations that provide growth advantage to pluripotent stem cells using our genome-wide loss-of-function library. This analysis led to the observation that mutations in multiple tumor suppressor genes and their pathways give growth advantage to hPSCs. Detailed analysis of one such pathway helped us identify a growth factor that increases hPSC growth rate by decreasing the rate of apoptosis, while having no significant effect on pluripotency and cell cycle progression. Overall, we have constructed an atlas of essential and growth regulating genes in hPSCs and present it as a reference tool for future studies on human pluripotency.

14:15 – 14:30

NEXT GENERATION SEQUENCING OF OVER 100 HUMAN EMBRYONIC STEM CELLS REVEALS DISEASE-CAUSING MUTATIONS IN MULTIPLE GENES, INCLUDING THE TUMOR SUPPRESSOR P53

Merkle, Florian[1], Ghosh, Sulagna[2], Kamitaki, Nolan[3], Mitchell, Jana[2], Mello, Curtis[3], Kashin, Seva[3], Mekhoubad, Shila[2], Ilic, Dusko[4], Charlton, Maura[2], Saphier, Genevieve[2], Handsaker, Robert[3], Genovese, Giulio[3], McCarroll, Steven[3] and Eggan, Kevin[2]

[1]Metabolic Research Laboratories and Medical Research Council Metabolic Diseases Unit, Wellcome Trust-Medical Research Council Institute of Metabolic Science, and Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute, University of Cambridge, U.K., [2]Harvard University, Cambridge, MA, U.S., [3]Harvard Medical School, Cambridge, MA, U.S., [4]King's College London, U.K.

Human embryonic stem cells (hESCs) provide a platform for studying development, modeling disease, and producing cell replacement therapies. However, the genetic make-up of hESCs has not been systematically studied at a genome-wide level with single nucleotide resolution. We

therefore collected and sequenced the whole exomes and whole genomes of 140 hESCs. This analysis confirmed previously described findings such as the recurrence of copy number variants at Chr20q11.21 and revealed revealed a number of surprising findings, including that approximately 5% of analysed cell lines carry dominant-negative mutations in the tumor suppressor P53 that confer growth selection in culture and are maintained during differentiation. We also found that some cell lines carry rare mutations known to cause autosomal dominant disease in vivo and that as a group, hESCs carry a significantly increased burden of infertility-associated variants, apparently inherited from the embryo donors. These findings suggest that the genomes of hESCs and their differentiated derivatives should be carefully studied prior to their clinical use. We provide an online resource to facilitate the exploration of these data and to enable the rational selection of hESC lines for applications ranging from disease modelling to transplantation medicine.

Funding Source: This work was supported by the HHMI, the Stanley Center for Psychiatric Research (Broad Institute), the NIH (HL109525, 5P01GM099117, 5K99NS08371), the Miller consortium of the HSCI, the Wellcome Trust, and the MRCI (MR/P501967/1).

14:30 – 14:45

COMPREHENSIVE CELL-SURFACE PROTEIN PROFILING IDENTIFIES NOVEL MARKERS OF HUMAN NAÏVE AND PRIMED PLURIPOTENT STATES

Panula, Sarita P.[1], Collier, Amanda[2], Rugg-Gunn, Peter[2] and Lanner, Fredrik[3]

[1]Karolinska Institutet, Huddinge, Sweden, [2]Babraham Institute, Cambridge, U.K., [3]Karolinska Institutet, Stockholm, Sweden

Human pluripotent stem cells (PSCs) exist in naïve and primed states, and provide important models to investigate the earliest stages of human development. Naïve cells can be obtained through primed-to-naïve resetting, however, there are no reliable methods to prospectively isolate unmodified naïve cells during this process. Here, we report the comprehensive profiling of cell-surface proteins by flow cytometry in naïve and primed PSCs, screening over 400 antibodies. We validated a cohort of antibodies in multiple naïve and primed PSC lines and culture conditions, and also found that several naïve-specific, but not primed-specific, proteins were expressed in the pluripotent cells of the human preimplantation embryo. We developed an antibody panel targeting multiple cell-surface proteins, and demonstrated that the panel could distinguish between naïve and primed PSCs, track the dynamics of naïve – primed interconversion, and isolate emerging naïve PSCs from a heterogeneous cell population. Molecular characterization showed that the transcriptome of the emerging naïve cells was more similar to naïve cells than to primed cells, but was not identical to established naïve PSCs. Furthermore, our analysis revealed that X-chromosome reactivation occurred primarily during the late-stage maturation of naïve cells. Thus, identification of state-specific proteins provides a robust set of molecular markers to unambiguously define human PSC state, and allows new insights into the molecular events leading to naïve cell resetting.

14:45 – 15:10

DERIVATION OF PLURIPOTENT STEM CELLS WITH IN VIVO EMBRYONIC AND EXTRAEMBRYONIC POTENCY

Deng, Hongkui

Peking University, Beijing, China

Among all known cultured stem cell types, pluripotent stem cells (PSCs) sit atop the landscape of developmental potency and are characterized by their ability to generate all cell types of an adult organism. However, PSCs show limited contribution to the extraembryonic placental tissues in vivo. Recently, we demonstrated that a chemical cocktail enables the derivation of stem cells with unique functional and molecular features from mice and humans, designated as extended pluripotent stem (EPS) cells, which are capable of chimerizing both embryonic and extraembryonic tissues. Notably, a single mouse EPS cell shows widespread chimeric contribution to both embryonic and extraembryonic lineages in vivo, and permits generating single EPS-derived mice by tetraploid complementation. Furthermore, human EPS cells exhibit interspecies chimeric competency in mouse conceptuses. Our findings constitute a first step towards capturing pluripotent stem cells with extraembryonic developmental potentials in culture, and open new avenues for basic and translational research

FRIDAY, 16 JUNE, 13:15 – 15:15

CONCURRENT IIIB: TISSUE REGENERATION AND HOMEOSTASIS

Level 3, Ballroom West

13:20 – 13:45

REGULATION OF ADULT NEURAL STEM CELL DYNAMICS

Doetsch, Fiona

University of Basel, Biozentrum, Switzerland

Adult stem cells reside in many organs and underlie tissue homeostasis and repair after injury. Specialized niches support the life-long maintenance of adult stem cells. Stem cells exist in both quiescent and actively dividing states in vivo. However the lineage dynamics of quiescent and activated stem cells, as well as the niche signals that regulate their behaviour are poorly understood. In the adult brain, neural stem cells generate new neurons that functionally integrate into restricted brain areas. The largest germinal niche in the adult mouse brain is the ventricular-subventricular zone (V-SVZ) adjacent to the lateral ventricles. Neural stem cells in the adult V-SVZ generate olfactory

bulb interneurons and small numbers of glia. Recent work has highlighted multiple dimensions of V-SVZ stem cell heterogeneity, including proliferation state and regional identity. I will present our findings about the functional and molecular properties of quiescent and activated adult neural stem cells as well as unique features of the specialized niche that regulate adult neurogenesis. Together these provide insight into novel regulators of adult neural stem cell dynamics and heterogeneity.

13:45 – 14:00

IDENTIFY VASCULAR ENDOTHELIAL STEM CELLS (VESC) BY THE EXPRESSION OF PROTEIN C RECEPTOR

Yu, Qing Cissy, Song, Wenqian, Wang, Waisong, Jiang, Weimin and Zeng, Yi Arial

Shanghai Institute of Biochemistry and Cell Biology, China

Vascular growth and remodeling are dependent on the generation of new endothelial cells (ECs) and involvement of perivascular cells to achieve functional integrity. It remains unclear how the ECs pool is replenished during homeostasis, i.e. whether it is from the proliferation of mature ECs, or the contribution of vascular stem/progenitor cell activities. The existence and cellular identity of vascular endothelial stem cells (VESCs) also remain controversial. Perivascular pericytes in adult tissues are thought to arise from the recruitment of mesenchymal progenitors. In this study, we identified Protein C receptor-expressing (Procr+) ECs as VESCs in multiple tissues. Procr+ VESCs actively contribute to postnatal angiogenesis in mammary, skin and retina vasculatures, ensuring organ development and homeostasis maintenance. Procr+ VESCs exhibit robust clonogenicity in culture, high vessel reconstitution efficiency in transplantation, long-term clonal expansion in lineage tracing, active participation in injury repair, and EndMT characteristics. Moreover, Procr+ VESCs are bipotent, giving rise to de novo formation of ECs and pericytes. This represents a novel origin of pericytes in adult angiogenesis, which argues against the current paradigm of a linear endothelial lineage, adding a subset of pericytes under the endothelial stem cell hierarchy, reshaping our understanding of blood vessel development and homeostatic process. Apart from being a novel VESC marker, we found Procr is also imperative for preserving VESC identity. Loss of Procr function leads to defective angiogenesis and disrupts vascular remodeling. Our study identifies Procr+ endothelial cells as bipotent VESCs in multiple vascular systems, which may provide more precise therapeutic targets to inhibit pathological angiogenesis and tumor growth.

14:00 – 14:15

LIVE IMAGING OF AXOLOTL DIGIT REGENERATION REVEALS SPATIOTEMPORAL CHOREOGRAPHY OF DIVERSE CONNECTIVE TISSUE PROGENITOR POOLS

Currie, Joshua D.[1], Kawaguchi, Akane[1], Moreno Traspas, Ricardo[1], Schuez, Maritta[1], Chara, Osvaldo[2] and Tanaka, Elly[3]

[1]Center for Regenerative Therapies Dresden, Germany, [2]Center for Information Services and High Performance Computing (ZIH), Technische Universität Dresden, Systems Biology Group (SysBio), Instituto de Física de Líquidos y Sistemas Biológicos (IFLySIB), CONICET, Universidad Nacional de La Plata (UNLP), Dresden, Germany, [3]The Research Institute of Molecular Pathology (IMP), Vienna, Austria

Connective tissues—skeleton, dermis, pericytes, fascia—are a key cell source for regenerating the patterned skeleton during axolotl appendage regeneration. This complexity has made it difficult to identify the cells that regenerate skeletal tissue. Inability to identify these cells has impeded a mechanistic understanding of blastema formation. By tracing cells during digit tip regeneration using brainbow transgenic axolotls, we show that cells from each connective tissue compartment have distinct spatial and temporal profiles of proliferation, migration, and differentiation. Chondrocytes proliferate but do not migrate into the regenerate. In contrast, pericytes proliferate, then migrate into the blastema and give rise solely to pericytes. Periskeletal cells and fibroblasts contribute the bulk of digit blastema cells and acquire diverse fates according to successive waves of migration that choreograph their proximal-distal and tissue contributions. We further show that platelet-derived growth factor signaling is a potent inducer of fibroblast migration, which is required to form the blastema.

14:15 – 14:30

CASPASE-3 REGULATES YAP-DEPENDENT ORGAN SIZE AND SKIN REGENERATION

Fuchs, Yaron[1], Yosefzon, Yahav[2], Soteriou, Despina[2], Kostic, Lana[2], Sedov, Egor[2], Koren, Elle[2] and Glaser, Fabian[2]

[1]Biology, Technion-Israel Institute of Technology, Haifa, Israel, [2]Technion, Haifa, Israel

Apoptosis culminates in the activation of caspase-3, which is responsible for implementing the cell death program. Here, we report a non-apoptotic role of caspase-3 as a key regulator of organ size and skin regeneration. Caspase-3 is specifically activated in the proliferating cells of the epidermis, but does not instruct cellular elimination. In mice, deletion or chemical inhibition of caspase-3 diminishes cellular proliferation, decreases cell number, reduces sebaceous gland size and impairs wound repair and hair follicle regeneration. In caspase-3 deficient mice, YAP, a vital transcriptional co-activator of the Hippo pathway, is retained in an inactivated state. We show that a-Catenin, known to

sequester YAP, is cleaved by caspase-3, thus facilitating the liberation and nuclear translocation of YAP. Accordingly, in vivo activation of caspase-3 leads to enhanced SG size and improved healing dynamics. Our data unravels a novel mechanism where caspase-3 plays a central role in regulating YAP-dependent organ size and skin regeneration.

14:30 – 14:45

IMPROVED VASCULAR DIFFERENTIATION OF HUMAN DIABETIC IPSC FOLLOWING STABLE REVERSION TO A NAÏVE PLURIPOTENT STATE

Park, Tea Soon[1], Zimmerlin, Ludovic[1], Ruzgar, Nensi[2], Evans, Rebecca[1] and Zambidis, Elias[1]

[1]Department of Pediatric Oncology and Institute for Cell Engineering, Johns Hopkins School of Medicine, Baltimore, MD, U.S., [2]Department of Biochemistry and Biomedical Sciences, Faculty of Health Sciences, McMaster University, Toronto, Canada

Cell-based therapies of diabetic vascular complications require efficient generation of angiogenic progenitors that can sustain long-term functional recovery in a clinical setting. Human induced pluripotent stem cell (hiPSC) technology may offer unlimited amounts of embryonic vascular progenitors (VP) to repair ischemic diabetic tissue. However, translation of hiPSC-derived VP to the clinic requires safe and efficient methods for reprogramming and differentiation of hPSC. We recently reported a novel small molecule LIF-3i (GSK3ß, ERK and tankyrase inhibitions) reversion method that stably reverted conventional human pluripotent stem cells (hPSC) to a naïve-like pluripotent state. LIF-3i naïve-reverted hPSC acquired transcriptomic, epigenetic, and signaling signatures of mouse and human pre-implantation epiblast with improved multi-lineage functional pluripotency and an associated decrease in non-specific lineage priming. To test the functionality and therapeutic potential of VP generated from improved naïve patient-specific hiPSC, we derived diabetic iPSC (D-iPSC) from skin fibroblasts of type-I diabetic patients via a non-integrative episomal 7-factor (SOX2, OCT4, KLF4, MYC, NANOG, Lin28, and SV40-t antigen) system. Short exposure to a GSK3ß inhibitor and ascorbic acid dramatically facilitated the reprogramming kinetics. We successfully applied the LIF-3i reversion method to D-iPSC and stably expanded naïve hiPSC lines for at least 15 passages. Naïve D-iPSC expressed high levels of phosphorylated STAT3, comparable to naïve non-diabetic hPSC. Both endothelial (CD31+CD146+) and perivascular (CD44+CD140b+) progenitors were efficiently generated from naïve-D-iPSC and -normal hPSC, at significantly higher levels than isogenic primed conventional hPSC cultures. Functional capacities of naïve D-iPSC-endothelial and -perivascular cells were compared to normal hPSC-derived progenitors using cell cycle, acetylated-Dil-LDL uptake, Matrigel tube and plug assays. Differentiated D-iPSC and control cells were also compared for diabetes-related and inflammatory gene expressions. Our results suggest that LIF-3i naïve reversion dramatically improves the differentiation efficiency and therapeutic production of functional vascular progenitor cells from conventional hiPSC.

Funding Source: TEDCO 2013-MSCRF-III-114936 (LZ), TEDCO 2014-MSCRFE-118153 (TSP), U01HL099775, NIH/NEI R01EY023962, NIH/NICHD R01HD082098, TEDCO 2013-MSCRFII-0032-00, Stein Innovation Award, and Novo Nordisk Diabetes Award (all ETZ)

14:45 – 15:10

DYNAMICS OF MOUSE MAMMARY STEM CELLS DURING BRANCHING MORPHOGENESIS

Simons, Benjamin D.

University of Cambridge, U.K.

During puberty, the mouse mammary gland develops into a highly branched epithelial network. Due to the absence of exclusive stem cell markers, the location, multiplicity and fate behavior of mammary stem cells, which drive branching morphogenesis, are unknown. Based on large-scale organ reconstructions, genetic lineage tracing and quantitative analysis, we show that mammary morphogenesis follows from the collective activity of equipotent stem cell pools localized at ductal tips that drive a time-invariant process of ductal elongation and stochastic tip bifurcation. By correlating cell cycle exit with proximity to maturing ducts, this dynamics results in the specification of a complex network of defined density and statistical organization. Further evidence, based on lineage tracing and whole organ reconstruction, show that the development of mouse kidney and pancreas conform to the same basic paradigm. Together, these results suggest that branched epithelial structures in mammalian tissues develop as a self-organized process, reliant upon a strikingly simple, but generic, set of local rules, without recourse to a rigid and deterministic sequence of genetically programmed events.

FRIDAY, 16 JUNE, 13:15 – 15:15

CONCURRENT IIIC: STEM CELL NICHES

Level 2, Room 205A

13:20 – 13:45

PROTEIN C RECEPTOR IN REGULATING MAMMARY STEM CELLS AND BREAST CANCER

Zeng, Yi Arial and Wang, Daisong

Shanghai Institute of Biochemistry and Cell Biology (SIBS), Chinese Academy of Sciences, China

The mammary gland is composed of multiple types of epithelial cells that are generated by mammary stem cells (MaSCs) residing at the top of the hierarchy. The identity of MaSCs was unclear. Our study demonstrates that Procr (Protein C receptor), a novel Wnt-target in the mammary gland, marks a population of multipotent MaSC. Procr-expressing cells display high regenerative capacity in transplantation assays and differentiate into all lineages of

the mammary epithelium by lineage tracing. These results define a novel multipotent mammary stem cell population that could be important in the initiation of breast cancer. Triple-negative breast cancer (TNBC) is a highly aggressive malignancy with no targeted treatment option. We found that PROCR is highly expressed in TNBC patient samples, and associated with poor prognosis. Remarkably, targeting PROCR by a neutralizing antibody inhibits TNBC tumor growth. PROCR represents a surface therapeutic target for human TNBC.

13:45 – 14:00

ANATOMICALLY AND FUNCTIONALLY DISTINCT LUNG MESENCHYMAL POPULATIONS MARKED BY LGR5 AND LGR6

Lee, Joo-Hyeon[1], Tammela, Tuomas[2], Hofree, Matan[3], Marjanovic, Nemanja[2], Canner, David[2], Jacks, Tyler[2], Regev, Aviv[3] and Kim, Carla[4]

[1]University of Cambridge, U.K., [2]David H. Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, U.S., [3]Broad Institute of MIT and Harvard, Cambridge, MA, U.S., [4]Boston Children's Hospital/ Harvard Stem Cell Institute, MA, U.S.

Numerous epithelial stem/progenitor cells have been identified and shown to play a role in lung homeostasis and lung injury repair, yet the diversity of lung mesenchymal cell types that influence epithelial regeneration is poorly defined. We used a combination of genetic lineage tracing, single cell RNA-seq and three-dimensional organoid co-culture approaches to show that Lgr5 and Lgr6, well known markers of stem cells in epithelial tissues, are markers of several types of mesenchymal cells in the adult lung. Lgr6-expressing cells were found surrounding bronchiolar epithelia and in the alveolar space in Lgr6-EGFP-CreERT2 mice, whereas lineage-labeled Lgr5+ cells were largely alveolar in Lgr5-CreERT2;R26-Tom mice. Single cell RNA-seq of individual cells isolated from these mice suggested that cellular populations with distinct transcriptional programs express Lgr5 and Lgr6; five robust clusters of cell populations were identified. Using marker genes known to be expressed in various mesenchymal cells, we distinguished Lgr5- and Lgr6-expressing cell types that are regionally distributed. Furthermore, lineage tracing studies demonstrate the proliferative potential of Lgr6 lineage-labeled cells in homeostasis and injury repair. Importantly, genetic ablation of cells expressing Lgr6 induces proliferation of airway epithelial cells prior to expansion of adjacent Lgr6-labeled cells. In addition, ablation of these cells prevents airway injury repair with impaired proliferative expansion of Lgr6+ cells. Ex vivo organoid co-culture of Scgb1a1 lineage-labeled cells with cells expressing Lgr6 showed that the Lgr6 lineage directs airway lineage differentiation of Scgb1a1+ cells. In contrast, Lgr5 mesenchymal cells promoted alveolar differentiation; co-cultures with Lgr6+ cells yielded 7.2-fold increased bronchiolar and 3.2-fold diminished alveolar colony per well compared to co-cultures with Lgr5+ cells ($p < 0.01$). These results indicate that in the adult lung, crosstalk between epithelial cells and their neighboring mesenchymal partners is region- and lineage-specific. The identification of these specific cellular partnerships provides new understanding of the complexity of how different cell types are maintained in the healthy lung.

Funding Source: This work was supported by the Wellcome Trust and the Royal Society (107633/Z/15/Z), European Research Council Starting Grant (679411), and the Cambridge Stem Cell Institute.

14:00 – 14:15

BONE MARROW ECOLOGICAL COLLAPSE IN ACUTE MYELOID LEUKEMIA IS MEDIATED BY REMODELING OF ENDOSTEAL VESSELS

Lo Celso, Cristina[1], Duarte, Delfim[1], Hawkins, Edwin[2], Akinduro, Olufolake[1], Ang, Heather[1], de Filippo, Katia[1], Haltalli, Myriam[1], Ruivo, Nicola[1], Weber, Tom[2], Khorshed, Reema[1], Pirillo, Chiara[1], Purton, Louise[3], Duffy, Ken[4] and Carlin, Leo[5]

[1]Imperial College London, U.K., [2]WEHI, Melbourne, Australia, [3]Melbourne University, Australia, [4]Mynooth University, Dublin, Ireland, [5]Beatson Institute, Glasgow, U.K.

Bone marrow vascular niches have been proposed to support acute myeloid leukemia (AML) propagation. However, anti-angiogenic therapies do not improve patient outcome suggesting a complex relationship between AML cells and the microenvironment influences the disease process. Using a murine model of AML we performed intravital microscopy to investigate leukemia behavior in the bone marrow. We show AML is an invasive species causing highly localized disruption of endosteal stroma, until eventually the whole marrow space is colonized. Particularly affected are endosteal microenvironments containing osteoblastic and type H endothelial cells, normally associated with hematopoietic stem cells. In contrast, splenic type H vessels increase, suggesting de novo niches in the spleen could potentially support extramedullary hematopoiesis in leukemia. Intravital microscopy also revealed that the endothelium in AML is more adhesive and permissive to transendothelial migration of hematopoietic cells. Together, these data suggest that AML-induced vascular damage contributes to cell egress from the bone marrow and that new therapeutic approaches aiming to normalize bone marrow vasculature may support normal hematopoiesis and increase drug delivery to endosteal areas.

14:15 – 14:30

EPCR AND TM GUIDE HEMATOPOIETIC STEM CELL HOMING TO THE BONE MARROW INDEPENDENT OF NICHE CLEARANCE

Gur-Cohen, Shiri[1], Avemaria, Francesca[2], Kollet, Orit[2], Avci, Seymen[2], Itkin, Tomer[2], Ramasamy, Saravana K.[3], Kusumbe, Anjali P.[3], Golan, Karin[2], Khatib-Massalha, Eman[2], Kumari, Anju[2], Carolina, Mayela M.[4], Yu, Qing-Cissy[5], Wu, Hua-Lin[6], Zeng, Yi Arial[5], Adams, Ralf H.[3], Edward, Conway M.[7], Shpall, Elizabeth J.[4], Erez, Ayelet[2], Sagi, Irit[2], Esmon, Charles T.[8], Ruf, Wolfram[9] and Lapidot, Tsvee[2]

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Bone marrow (BM) recognition, homing and lodgment of long term repopulating hematopoietic stem cells (LT HSCs) are essential first steps for durable blood cell production during embryonic development and in clinical stem cell transplantation. Rare, BM retained LT HSCs endowed with the highest repopulation potential highly express EPCR (endothelial protein c receptor) and PAR1, which control LT HSC retention and chemotherapy resistance by limiting nitric oxide levels. Whether EPCR signaling is essential to navigate transplanted LT HSC back to the BM remains unknown. We report that transplanted EPCR+ LT HSCs preferentially home to the BM, in contrast to immature progenitors. Homed EPCR+ LT HSCs were retained adjacent to BM thrombomodulin+ (TM)-expressing arterioles. Interestingly, LT HSC also express TM and its lectin domain, mediating recognition between LT HSC and BM arterial endothelial glycocalyx. LT HSC pretreated in vitro with the EPCR major ligand, activated protein c (aPC), displayed a striking advantage in competitive BM homing and repopulation. Homing enhancement by aPC treatment reached a plateau, demonstrating limited available BM niches for transplanted LT HSC. EPCR+ LT HSCs homed with higher efficiency to the BM of non-conditioned hosts, while pretreating irradiated mice with the thrombin inhibitor hirudin, to reduce irradiation-mediated thrombin production and mobilization, significantly enhanced LT HSC homing. Intriguingly, EPCR+ LT HSCs can engraft the BM of non-irradiated recipients, while remaining quiescent, without giving rise to differentiated progeny. Strikingly, the quiescent homed EPCR+ LT HSCs were awakened by treating engrafted hosts with nitric oxide donor or with low dose chemotherapy, revealing that preconditioning and clearance of occupied HSC niches are not required. Herein we define EPCR and TM as guidance molecules, navigating LT HSC specifically to the BM, independently of niche clearance. The BM harbors limited numbers of available niches, and EPCR engagement with aPC dramatically augments LT HSC BM homing and repopulation. Our study provides mechanistic insights concerning LT HSC homing, which may lead to improved BM transplantation protocols and be applied to prevent chemotherapy resistance of EPCR-expressing cancer stem cell.

14:30 – 14:45

COLLAGEN V MAINTAINS MOUSE MUSCLE STEM CELLS BY CELL-AUTONOMOUS ACTIVATION OF THE CALCITONIN RECEPTOR

Mourikis, Philippos[1], Baghdadi, Meryem[2], Tajbakhsh, Shahragim[2] and Relaix, Frederic[3]

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Adult skeletal muscle stem cells (MuSCs) are actively maintained in a quiescent state by interactions with the surrounding microenvironment. Although certain signalling pathways that regulate quiescence have been identified, the composition and source of the niche molecules remain largely unknown. By ChIP-sequencing we identified Notch/Rbpj-bound regulatory elements adjacent to specific collagen genes. Using genetically modified mice, we show that expression of these collagens is controlled by Notch activity in vivo. Notably, we find that the MuSC-produced collagen V (COLV) is a critical component of the quiescent niche, as conditional deletion of Col5a1 leads to anomalous cell cycle entry and differentiation of MuSCs. Strikingly, COLV, but not collagen I and VI, interacts with and activates the G-protein coupled Calcitonin receptor (CALCR), thereby acting as a surrogate ligand to retain MuSCs in their niche. This study unveils a Notch/COLV/CALCR signaling cascade that cell-autonomously maintains the MuSC quiescent state and raises the possibility of a similar mechanism acting in diverse stem cell populations.

14:45 – 15:10

METABOLIC REGULATION AND CHEMOTHERAPY RESISTANCE OF BONE MARROW RETAINED HEMATOPOIETIC STEM CELLS: THE ROLE OF REACTIVE OXYGEN SPECIES, MITOCHONDRIA TRANSFER AND NITRIC OXIDE

Lapidot, Tsvee

Weizmann Institute, Rehovot, Israel

Long term repopulating hematopoietic stem cells (LT-HSC) are mostly bone marrow (BM) retained, in a quiescent non motile mode via adhesion interactions. Only BM retained LT-HSC are protected from DNA damaging agents including chemotherapy, which prevents mortality from hematology failure. However, stem cell chemotherapy resistance, which requires metabolic regulation by BM endothelial cells and adhesion to stromal cells is not fully understood. In addition, hematopoietic stem cell BM rec-

ognition, homing and lodgment are essential first steps for their engraftment, repopulation and durable mature blood and immune cell production during development and following clinical bone marrow transplantation. Nevertheless, mechanisms and key players regulating LT-HSC BM recognition and homing are not fully understood. Of interest, hematopoietic stem cell homing, quiescent BM retention and chemotherapy resistance are all regulated by the same factors which have overlapping roles. These factors include the chemokine CXCL12, its major receptor CXCR4 and connexin 43 gap junctions. In addition, the endothelial and coagulation receptors protease activated receptor one (PAR1) and endothelial protein C receptor (EPCR), which are both functionally expressed by BM retained LT-HSC, as well as the major EPCR ligand aPC are also required. PAR1 is also functionally expressed by immature and mature leukocytes, bone forming progenitor cells, osteoblasts and endothelial cells. PAR1 is activated by aPC/EPCR which targets LT-HSC BM homing and retention by limiting nitric oxide generation. PAR1 activation by thrombin upregulates nitric oxide generation leading to CXCL12 secretion and stem cell mobilization. Reactive oxygen species and nitric oxide regulation control both LT-HSC migration and development and are also essential for their chemotherapy resistance. Preliminary results reveal mitochondria transfer between hematopoietic stem cells and stromal cells (in both directions). These results suggest that there is energy sharing in the BM to coordinately synchronize new bone formation and new mature blood production. Mitochondria transfer from BM retained LT-HSC to stromal cells is essential for their chemotherapy resistance and is connexin 43 gap junction dependent. These topics will be discussed.

FRIDAY, 16 JUNE, 13:15 – 15:15

CONCURRENT IIID: EPIGENETICS AND STEM CELLS

Level 3, Ballroom East

13:20 – 13:45

MECHANISMS OF EPIGENETIC REGULATION IN STEM CELLS AND DEVELOPMENT

Meissner, Alexander

Harvard University, Cambridge, MA, U.S.

Abstract not available at time of printing.

13:45 – 14:00

RNA-DEPENDENT CHROMATIN TARGETING OF TET2 FOR ENDOGENOUS RETROVIRUS CONTROL IN MAMMALIAN CELLS

Wang, Jianlong[1], Guallar, Diana[1], Bi, Xianju[2], Huang, Xin[1], Saenz-Ausejo, Carmen[1], Ding, Junjun[1], Faiola, Francesco[1], Li, Dan[1], Sanchez-Priego, Carlos[1], Saunders, Arven[1], Pan, Feng[3], Xu, Mingjiang[3], Fidalgo, Miguel[1] and Shen, Xiaohua[2]

[1]Icahn School of Medicine at Mount Sinai, New York, NY, U.S., [2]Tsinghua University, Beijing, China, [3]University of Miami, FL, U.S.

Ten-eleven translocation (TET) proteins play fundamental roles in regulating chromatin architecture and transcriptional events that define mammalian cell identity, but the molecular underpinnings that contribute to stable TET occupancy at the chromatin remain poorly understood. Here we show that Tet2 is recruited to chromatin by the RNA binding protein Paraspeckle component 1 (Pspc1) through transcriptionally active endogenous retroviruses (ERVs). ERVs are remnants of ancestral viral infections that have been co-opted by mammalian genomes as stage- and tissue-specific transcription regulatory modules. We find that Pspc1 and Tet2 contribute to ERV and ERV-associated gene regulation by both transcriptional repression via histone deacetylases and post-transcriptional destabilization of ERV RNAs through 5hmC modification. Our findings reveal a critical role for RNA in effecting Tet2 function at the chromatin level, and provide evidence for a functional role of transcriptionally active ERVs as specific docking sites for RNA epigenetic modulation and gene regulation.

Funding Source: This research was funded by grants from the National Institutes of Health (NIH) to J.W. (1R01-GM095942), the Empire State Stem Cell Fund through New York State Department of Health (NYSTEM) to J.W. (C028103, C028121).

14:00 – 14:15

RNA-BINDING PROTEIN DDX5 INHIBITS REPROGRAMMING TO PLURIPOTENCY BY MIRNA-BASED REPRESSION OF RYBP AND ITS PRC1-DEPENDENT AND -INDEPENDENT FUNCTIONS

Yao, Hongjie[1], Li, Huanhuan[1], Lai, Ping[1], Jia, Jinping[2], Song, Yawei[1], Xia, Qing[1], Huang, Kaimeng[1], He, Na[3], Ping, Wangfang[1], Chen, Jiayu[4], Hou, Chunhui[3], Gao, Shaorong[4], Pei, Duanqing[1] and Hutchins, Andrew[3]

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RNA binding proteins (RBPs), in addition to their functions in cellular homeostasis, play important roles in lineage specification and maintaining cellular identity. Despite their diverse and essential functions that touch on nearly all aspects of RNA metabolism, the roles of RBPs in somatic cell reprogramming are poorly understood. Here, we show that the DEAD-box RBP DDX5 inhibits reprogramming by repressing the expression and function of the non-canonical polycomb complex 1 (PRC1) subunit RYBP. Disrupting Ddx5 expression improves efficiency of iPSC generation and impedes processing of miR-125b, leading to Rybp upregulation and suppression of lineage-specific genes via RYBP-dependent ubiquitination of H2AK119. Furthermore, RYBP is required for PRC1-independent recruitment of OCT4 to the promoter of Kdm2b, a histone demethylase gene that promotes reprogramming by reactivating endogenous pluripotency genes. Together, these results reveal important functions of DDX5 in regulating reprogramming and highlight the importance of a Ddx5-miR125b-Rybp axis in controlling cell fate.

14:15 – 14:30

GENOMIC IMPRINTING ABERRATIONS IN HUMAN PLURIPOTENT STEM CELLS ARE DRIVEN BY CELL TYPE AND PARENTAL ORIGIN

Bar, Shiran, Schechter, Maya and Benvenisty, Nissim

The Hebrew University of Jerusalem, Israel

The parent-specific monoallelic expression of imprinted genes is controlled by epigenetic marks that are established differentially in the germline. Perturbation of these differentially methylated regions (DMRs) leads to loss-of-imprinting (LOI), which is associated with developmental disorders and malignancy, and may also obstruct various applications of human pluripotent stem cells (hPSCs). Previous studies of LOI in hPSCs were performed on relatively small number of cell lines, often leading to conflicting conclusions regarding their epigenetic stability. Here, we developed a new method to directly calculate the allelic usage of imprinted genes from existing RNA-Seq data, and utilize it to chart the landscape of LOI in over 270 hPSC samples. We show that reprogrammed hPSCs (induced PSCs and nuclear transfer derived PSCs) acquire significantly higher levels of LOI compared with embryonic stem cells. Additionally we demonstrate that LOI can pre-exist in a sub-population of the somatic cell-of-origin. We further show that LOI results in over-expression of some imprinted genes and is associated with aberrant patterns of DNA methylation. The biallelic expression also persists during differentiation to both neural lineage and beta cells. Furthermore, our analysis outlines that different imprinted genes vary with respect to LOI incidence, surprisingly revealing that those controlled by a paternal germline DMR being significantly more prone to disruption. Given the association of LOI with disease and developmental disorders, our findings are of direct clinical significance, emphasizing the importance of inspecting the epigenetic status of hPSCs.

14:30 – 14:45

ENHANCER SWITCHING SUBSETS GENE NETWORKS DURING THE TRANSITION FROM NAIVE TO PRIMED PLURIPOTENCY

Chen, Amy F., Liu, Arthur, Krishnakumar, Raga and Blelloch, Robert

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

During early mammalian development, pluripotent cells of the epiblast undergo extensive epigenetic remodeling. Interestingly, many genes undergo a switch in enhancer usage with little change in gene expression. The mechanisms and reasons behind this enhancer switch are largely unknown. Here, we identify a transcription factor, GRHL2, which is both necessary and sufficient to activate enhancers during the transition from naïve embryonic stem cells (ESC) to primed epiblast cells (EpiC). GRHL2 expression is activated during the ESC to EpiC transition and regulates expression of its target genes in EpiCs. However, many of these genes are expressed at equivalent levels in ESCs. Evaluation of alternative enhancers in ESCs uncovered the ESC-specific KLF transcription factors as likely drivers of GRHL2 targets in the naïve state. These alternative enhancers lose active enhancer marks in EpiCs, indicating that the target genes are undergoing an enhancer switch. GRHL2 assumes control of a specific subset of KLF targets required for maintaining an epithelial program, and GRHL2 loss results in an epithelial-mesenchymal transition in the primed state. Given that many KLF targets remain expressed in EpiCs at similar levels, additional TFs must assume regulation of these other subsets. These data suggest a model where the large network of KLF-regulated genes in the naïve state becomes partitioned into smaller networks regulated by distinct EpiC-specific transcription factors like GRHL2 in the primed state. We speculate that uncoupling regulation of the KLF network primes cells for lineage specification by allowing independent regulation of each subnetwork during gastrulation.

14:45 – 15:10

TRANSCRIPTIONAL PROGRAMMING AND REPROGRAMMING OF CARDIOMYOCYTE PROLIFERATION

Boyer, Laurie A., Rizki, Gizem, Butty, Vincent, Jimenez, Marta, Reiling, Stephan and Auld, Douglas

Massachusetts Institute of Technology, Cambridge, MA, U.S.

The heart loses up to a billion cardiac muscle cells in response to ischemic injury and cells are progressively lost during ageing leading to compromised function and heart failure. Unlike lower organisms such as zebrafish and neonatal rodents, the adult myocardium has low mitotic potential limiting its ability to repair itself. We have developed integrative computational and experimental approaches to investigate the molecular circuitry of heart development. We are now leveraging these approaches toward understanding how modulation of gene programs can be manipulated to stimulate adult cardiomyocyte proliferation in response

to injury. Our work recently showed that that the injury response is characterized by a transcriptional reversion of cardiac maturation, suggesting that adult cardiac regeneration may be achieved through resetting the developmental clock. To identify key pathways that stimulate cardiac proliferation, we performed a small molecule screen using known mechanism of action compounds targeting 1,600 distinct proteins in explant cultures of murine P2 cardiomyocytes. We validated ~25 compounds targeting multiple signaling pathways that showed robust and reproducible stimulation of CM proliferation and cytokinesis compared to fibroblasts. We combine phenotype screening with integrated transcriptional profiling to identify key regulatory nodes. To this end, we delineated compound class-specific changes in gene expression revealing dramatic changes in expression of transcription factors and chromatin regulators. We are now developing tools that enable us to reprogram this logic in response to cardiac injury to facilitate development of new strategies for cardiac repair in vivo.

FRIDAY, 16 JUNE, 13:15 – 15:15

CONCURRENT IIIE: EPITHELIAL STEM CELLS

Level 2, Room 258C

13:20 – 13:45

USING CLONAL DYNAMICS TO PROBE INTESTINAL STEM CELL PLASTICITY AND SELF RENEWAL

Winton, Doug J.

University of Cambridge, U.K.

The stem cells of the intestinal epithelium that are located at the base of glandular crypts are extensively studied due to their role in tissue maintenance and development of pathologies such as cancer. Phenotypic markers associating with stem cell function identify a multiplicity of stem cells in each crypt the precise number and identity of which can vary depending on the marker employed. An alternative approach to investigating stem cell organisation is to use clone dynamics that exploit the fact that stem cells produce clonal progeny and to observe how clone sizes and frequencies change over time. The rationale is that such changes relate directly to stem cell replacement events and that optimal solutions for the cellular rate of such events can be sought using different inference or computational methods. Application of such approaches in recent years has resulted in an understanding of the nature of the stem cell renewal process in the intestine that can be described in quantitative terms. A small subset of phenotypic stem cells are actively clonogenic. Within each crypt these compete with stochastic replacement and displacement until a single clonal victor populates the gland which is said to have undergone monoclonal conversion. Although the stochastic nature of the process makes predicting the fate of any individual stem cell impossible the dynamics of the overall process is extremely predictable and very robust. The presentation will describe how clone dynamics can be used as an investigative tool in both fundamental biology, to dissect the role of different progenitor populations in contributing to self renewal, and in application to studies of human stem cell organisation.

13:45 – 14:00

A POPULATION OF ORAL EPITHELIAL LABEL-RETAINING CELLS RESIDES IN A DISCRETE NICHE IN PALATAL RUGAE RIDGES

Williams, Scott E.[1], Byrd, Kevin[2] and Patel, Jeet[3]

[1]University of North Carolina at Chapel Hill, NC, U.S., [2]Oral Biology, University of North Carolina at Chapel Hill, NC, U.S., [3]Biology, University of North Carolina at Chapel Hill, NC, U.S.

The oral epithelia are a collection of diverse stratified epithelia that exhibit both rapid turnover and a remarkable capacity for regeneration without scarring. Yet compared to other continuously self-renewing stratified and simple epithelia such as the skin and intestine, little is known about their development, maintenance and renewal, and oral stem cells remain poorly characterized. The "neutral drift" model has provided evidence that the epidermis, and by implication, other stratified epithelia, consist of a single pool of progenitors with equivalent self-renewal potential, which stochastically undergo both symmetric and asymmetric divisions. Yet in other tissues such as the intestine, both "active" and slow-cycling "reserve" stem cell pools exist which play roles in maintenance and repair during homeostasis and wounding, respectively. Here, we adopt an unbiased genetic label retention approach to identify slow-cycling, label-retaining cells (LRCs) in the oral cavity. We have used two distinct promoters (Krt14 and Krt5) to drive expression of a doxycycline-regulatable histone H2B-GFP, which is diluted as cells divide during a variable chase period. Most oral epithelia, including the buccogingiva and dorsal tongue, rapidly dilute GFP label by 14 days of chase, consistent with a neutral drift model. However, we identified discrete pockets of GFPhi LRCs in regions of the oral cavity, including the oropharynx, salivary glands and palate. Notably, palatal LRCs retain GFP expression for 4 weeks or more, and are associated with rugae ridges. We isolated GFPhi LRCs by FACS and compared their gene expression profiles to GFPlo non-LRCs. Palatal LRCs are enriched for the transcription factor Sox9, as well as the TA isoform of p63, while the ΔN p63 isoform is enriched in the GFPlo population. Lineage tracing studies using K14-CreERT2 and Sox9-CreERT2 have revealed clonal populations with distinct sizes and morphologies reminiscent of stem and transit-amplifying cells. Finally, we have shown that GFPhi and GFPlo populations show different patterns of division orientation, with the former characterized by a greater number of planar/symmetric divisions. Collectively, these data suggest that palatal epithelium rugae may har-

bor stem cell niches that maintain reserve stem cell populations.

Funding Source: This work has been supported by the Sidney Kimmel Foundation (SKF-165 to S.E.W.), NIH/NIDCR (K08DE026537 to K.B.), and a CGIBD Pilot/Feasibility grant (supported by P30 DK034987 to S.E.W.)

14:00 – 14:15

AUTONOMOUS MOTILITY ENFORCES AN ORDERED SPATIAL DISTRIBUTION OF DROSOPHILA INTESTINAL STEM CELLS

O'Brien, Lucy Erin[1], Du, XinXin[2], Martin, Judy[2], Balachandra, Shruthi[2] and Riedel-Kruse, Ingmar[3]

[1]Stanford School of Medicine, CA, U.S., [2]Molecular and Cellular Physiology, Stanford School of Medicine, CA, U.S., [3]Bioengineering, Stanford School of Medicine, Stanford, U.S.

Many self-renewing, solid organs contain stem cell populations that are dispersed throughout the organ's spatial expanse. Spatial dispersal ensures that each tissue field contains stem cells. However, the mechanisms that give rise to proper stem cell spacing are unknown. Here we combine quantitative spatial analyses with long-term live imaging to investigate the basis of stem cell spacing in the intestinal epithelium of adult Drosophila. Comprehensive statistical maps of inter-stem cell distances reveal that stem cells exhibit an ordered spatial distribution during steady-state turnover, but not during organ growth. Overnight imaging of the intestine within living animals, together with tissue-wide cell tracking and spatio-temporal analysis of single cell displacements, show that stem cells are autonomously motile. Individual stem cells, propelled by actin-rich protrusions, flatten and slither beneath the basal epithelium. When motility is genetically inhibited, stem cell spacing becomes disordered, and animal viability is reduced. Our findings identify motility-dependent spatial dispersal as a hallmark of steady-state stem cell populations and imply that an ordered stem cell distribution is essential for optimal tissue function.

14:15 – 14:30

SPATIOTEMPORAL ANTAGONISM IN MESENCHYMAL-EPITHELIAL SIGNALING IN SWEAT VERSUS HAIR FATE DECISION

Lu, Catherine P., Polak, Lisa, Keyes, Brice and Fuchs, Elaine

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

The gain of eccrine sweat glands in hairy body skin has empowered humans to run marathons and tolerate temperature extremes. Epithelial-mesenchymal cross-talk is integral to the diverse patterning of skin appendages, but the molecular events underlying their specification remain largely unknown. Using genome-wide analyses and functional studies, we show that sweat glands are specified by mesenchymal-derived bone morphogenetic proteins (BMPs) and fibroblast growth factors that signal to epithelial buds and suppress epithelial-derived sonic hedgehog (SHH) production. Conversely, hair follicles are specified when mesenchymal BMP signaling is blocked, permitting SHH production. Fate determination is confined to a critical developmental window and is regionally specified in mice. In contrast, a shift from hair to gland fates is achieved in humans when a spike in BMP silences SHH during the final embryonic wave(s) of bud morphogenesis

Funding Source: NIH NIAMS grant K01-AR066073; NIH grant R01-AR050452; Howard Hughes Medical Institute; Robertson Therapeutic Development Fund

14:30 – 14:45

AIRWAY STEM CELLS GOVERN GLOBAL TISSUE RESPONSE TO INJURY

Pardo-Saganta, Ana[1], Saez, Borja[2], Roche, Marly[3], Villoria, Jorge[4], Causton, Benjamin[3], Tata, Purushotama[5], Petri, Eva[2], Zulueta, Javier[6], Prosper, Felipe[7], Medoff, Benjamin[3] and Rajagopal, Jayaraj[4]

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Novel functions have been attributed to stem cells beyond maintaining tissue homeostasis and contributing to repair after injury. Among those, we have showed that airway stem cells are essential to maintain their own daughter cells, behaving as niches for their progeny. Now, we demonstrate that basal stem cells also regulate the response of epithelial and mesenchymal cells to injury. Using a mouse model of allergic asthma and transgenic mice to deplete airway stem cells, we observed that in the absence of stem cells, the development of an allergen-induced adaptive immune response was impaired. Upon allergen induction we detected a decrease in the amount of dendritic cells as well as their activation and migration to the lymph nodes, antigen presentation, and T cell activation in animals in which the stem cell pool was previously depleted. Other immune cell populations such as macrophages and innate lymphoid cells type 2 were also reduced. As a consequence, mucous cell metaplasia was not observed in allergen-induced basal stem cell depleted airways. Mechanistically, we identified the Notch ligand Dll1 to modulate this injury-induced response. Disruption of basal stem cell-derived Dll1 mimics stem cell ablation leading to a decrease in the pool of immune cells and a lack of mucous cell metaplasia. In particular, we report that airway stem cells respond to injury by sending a Notch signal to Club cells instructing their differentiation to mucous cells. In the absence of this signal, mucous cell differentiation is abrogated. Hence, our results

reveal a dual role of basal stem cells regulating the initiation of the immune response in the mesenchyme as well as the differentiation of Club cells in the epithelial compartment under injury conditions. In summary, we demonstrate for the first time that tissue resident stem cells govern injury response modulating epithelium-mesenchyme interactions, which may have critical implications in cancer and fibrosis.

14:45 – 15:10

REVERSIBLE TRANSITIONS BETWEEN THE STEM AND DIFFERENTIATED CELL COMPARTMENTS IN MAMMALIAN EPIDERMIS

Watt, Fiona M.

King's College London, U.K.

Our current knowledge of tissue-resident stem cells is based largely on end-point analysis of cell populations. However, to understand tissue dynamics it is essential to analyse changes in the state of individual cells that occur within minutes or hours. In my presentation I will describe two newly identified mammalian epidermal cell state transitions and the mechanisms that control them. The first is commitment, when cells leave the stem cell compartment to undergo terminal differentiation, and the second is injury-induced dedifferentiation. Insights into the nature of these transitions provide new information about epidermal inflammation and cancer.

FRIDAY, 16 JUNE, 13:15 – 15:15

CONCURRENT IIIF: NEW TOOLS FOR STEM CELL RESEARCH

Level 2, Room 205BC

13:20 – 13:45

INTRAVITAL IMAGING REVEALS THE DYNAMIC BEHAVIOUR OF INTESTINAL AND MAMMARY STEM CELLS

van Rheenen, Jacco[1], Scheele, Colinda[2], Hannezo, Edouard[2], Ritsma, Laila[2], Ellenbroek, Saskia[2] and Simons, Benjamin D.[2]

[1]Hubrecht Institute, Utrecht, Netherlands, [2]University of Cambridge, U.K.

Over the years, we have developed intravital imaging techniques to study the dynamics of intestinal and mammary stem cells in living mice. During my talk, I will highlight two studies where we show that the behaviour and even the identity of stem cells cannot be linked directly to specific markers, but must be defined functionally. Lgr5-positive stem cells located at the base of intestinal crypts support the homeostasis of intestinal epithelium. In addition to the Lgr5 marker, intestinal stem cells have been associated with other markers that are expressed heterogeneously within the crypt base region. By intravital imaging of Lgr5/Confetti mice, we show that Lgr5-positive cells also have a heterogeneous short-term behaviour. After the division of proximate cells, stem cells located at the upper part of the niche can be passively displaced into the transit-amplifying domain, implying that the determination of stem-cell fate can be uncoupled from division. Therefore, stem cells at the crypt base experience a survival advantage over border stem cells. Importantly, since we found that the position of stem cells is constantly rearranged as result of cell division, every Lgr5-positive cell in the niche is endowed with long-term self-renewal potential. Interestingly, many of these findings also seem to hold true for mammary stem cells (MaSCs) that drive pubertal branching morphogenesis where the mouse mammary gland develops into a highly branched epithelial network. Owing to the absence of exclusive stem cell markers, the location, multiplicity, dynamics and fate of these MaSCs remained unknown. Using an unbiased lineage tracing approach, we show that the majority of terminal end bud cells function as highly proliferative, lineage-committed MaSCs that are heterogeneous in their expression profile and short-term contribution to ductal extension. Yet, through cell rearrangements during terminal end bud bifurcation, each MaSC is able to actively contribute to long-term growth. Combined our studies show that the behaviour of stem cells is not directly linked to a single expression profile. Instead, homeostasis and morphogenesis rely on heterogeneous stem cell populations that function as single equipotent pools in the long term.

13:45 – 14:00

A NOVEL HUMANIZED MOUSE MODEL INCORPORATING NON-FETAL TISSUE FOR INVESTIGATION OF INDUCED PLURIPOTENT STEM CELL IMMUNOGENICITY

Brown, Matthew E.[1], Zhou, Ying[2], McIntosh, Brian[3], Sackett, Sara[2], Norman, Ian[2], Lou, Hannah[2], Biermann, Mitch[2], Tremmel, Daniel[2], Swanson, Scott[4], Sullivan, Jeremy[2], Odorico, Jon[2], Kamp, Timothy[2], Thomson, James[5] and Burlingham, William[2]

[1]University of Wisconsin-Madison/Morgridge Institute for Research, Madison, WI, U.S., [2]University of Wisconsin-Madison, Madison, WI, U.S., [3]Covance Laboratories, Madison, WI, U.S., [4]Morgridge Institute for Research, Madison, WI, U.S., [5]University of Wisconsin-Madison/Morgridge Institute for Research/UC-Santa Barbara, Madison, WI, U.S.

We have developed a novel BLT-type humanized mouse model incorporating non-fetal tissue sources, called the NeoThy. BLT-type humanized mouse models, reconstituted with human hematopoietic stem cells and fetal thymus fragments, are particularly useful for induced pluripotent stem cell (iPSC) immunogenicity studies. The human T cells in these models develop in the presence of donor-specific major histocompatibility complexes and self-antigens and are well-suited for studies of allogeneic and syngeneic T cell-mediated immune responses. However, the research use of human fetal tissue-based BLT-type models is com-

plicated by ethical and logistical constraints, as well as the developmental immaturity of fetal tissues, which may negatively impact downstream applications. The NeoThy incorporates neonatal thymus and cord blood tissues, which are much more abundant than fetal sources, allowing for humanization of large numbers of animals per donor. This, in turn, allows for in-depth characterization and increased experimental consistency. The work presented here uses RNA sequencing, cell surface marker expression analysis, and in vitro functional assays to demonstrate phenotypic and functional similarity of the human immune reconstitution in the NeoThy and conventional fetal tissue model controls. Additionally, we reprogrammed and characterized multiple iPSC lines from various neonatal donors and created matched NeoThy mice to demonstrate allorejection of iPSC-derived cells and to investigate the immune response to patient-specific iPSC-derived cell transplants. The NeoThy humanized mouse enables robust and reproducible experimental validation of allogeneic and syngeneic iPSC therapies, in a manner which was not previously possible using conventional models.

Funding Source: M.E.B. is supported by NIH/NIAID training grant 1T32AI125231-01.

14:00 – 14:15

BIALLELIC GENOME EDITING OF A REFERENCE HUMAN STEM CELL LINE

Skarnes, William C.

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

Human pluripotent stem cells are an ideal model system to study basic cellular and developmental processes in a normal diploid cell. The advent of site-specific nucleases and improved conditions for human iPSC culture now permits efficient engineering of human stem cells. CRISPR-Cas9 technology, in particular, provides a facile tool for the generation of biallelic mutations, thus empowering functional studies of human genes in a model cell. Our aim is to generate and distribute arrays of human iPS cell knockouts that will be coupled to focused phenotyping screens in cultured cells. As a reference cell line for genome editing, we identified several low passage, karyotypically normal iPS cell lines form the HipSci resource (www.hipsci.org) and isolated a feeder-independent subclone, KOLF2-C1, that is highly amenable to genetic manipulation. Importantly, the cells have the proper consent for public release of whole genome sequence, allowing us to display cell line-specific variants in our public, genome browser-based, CRISPR design tool. Further detailed characterization of KOLF-C1 cells is ongoing, including single cell transcriptomics and epigenetic profiling of differentiating cultures. With this platform, we are beginning to scale the production drug-inducible conditional alleles. Similar to the yeast KO collection, a genome-wide resource of human KO cells will greatly accelerate the functional annotation of the human genome.

14:15 – 14:30

IMAGE-GUIDED EXTRACTION OF SINGLE CELLS FROM THE BONE MARROW OF LIVE MICE FOR SPATIALLY-RESOLVED TRANSCRIPTOMIC ANALYSIS

Haase, Christa[1], Oki, Toshihiko[2], Schajnovitz, Amir[2], Scadden, David[3] and Lin, Charles[1]

[1]Massachusetts General Hospital, Boston, MA, U.S., [2]Harvard Stem Cell Institute, Boston, MA, U.S., [3]Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Cambridge, MA, U.S.

Single-cell RNA-sequencing of hematopoietic stem cells (HSCs) and their niche can provide significant insight into the interaction of cells with their micro-environment and help to elucidate mechanisms regulating stem cell quiescence and proliferation. We present a method for image-guided cell extraction from the mouse calvarium bone marrow (BM) in vivo. It relies on precise femtosecond laser etching of bone to create a microchannel, through which a micropipette can be inserted to access the BM for cell aspiration. The procedure is carried out under image guidance, using video-rate intravital multi-photon microscopy to identify and extract specific target cells. The extraction protocol has been optimized for subsequent single-cell RNA sequencing and represents a new technique for performing spatially-resolved single-cell transcriptomics. To establish our experimental approach, we performed single cell extraction from murine BM seeded with AML cells that express a FRET-based sensor for caspase3 activation to ensure cell viability throughout the experimental procedure. We present the first successful cell extraction results from irradiated C57 Bl/6 recipients that were transplanted with HSCs from an actin-DsRed donor.

14:30 – 14:45

A CONDITIONAL HAPLOID ES CELL BIOBANK FOR FUNCTIONAL GENOMICS

Elling, Ulrich[1], Wimmer, Reiner[1], Marquis, Julien[2], Leibbrandt, Andreas[1], Burkard, Thomas[1], Michlits, Georg[1], Leopoldi, Alexandra[1], Micheler, Thomas[3], Zhuk, Sergei[1], Lefebvre, Gregory[2], Hubmann, Maria[1], Kinzer, Manuela[1], Schuller, Nicole[1], Wetzel, Ellen[1], Van De Loo, Nina[1], Ivics, Zoltan[4], Blaas, Dieter[5], Agu, Chukwuma[1], Hoepfner, Dominic[6], Descombes, Patrick[2], Stark, Alexander[7] and Penninger, Josef[1]

[1]Institute of Molecular Biotechnology (IMBA), Vienna, Austria, [2]Nestlé Institute of Health Sciences, Lausanne, Switzerland, [3]VBCF, Vienna, Austria, [4]PEI, Langen, Germany, [5]MFPL, Vienna, Austria, [6]NIBR, Basel, Switzerland, [7]IMP, Vienna, Austria

The ability to directly address the contributions of candidate genes to a given phenotype are key themes for cell biology experiments and tissue engineering. However, cell populations, including ES and iPS cells, exhibit large clonal variance, leading to unexpected findings when trying to reproduce results. Using genome saturated mutagen-

esis in haploid ES cells, here we report the creation of a biobank with over 100,000 individual murine ES cell lines with uniquely targeted, homozygous, genetically barcoded, and conditional mutations, targeting 16,950 genes, that we termed Haplobank. This is the largest available collection of mutant ES cell lines. It is generated as academic non-profit resource and will be shared with all researchers. Reversible mutagenesis permits robust functional annotation of the genome directly in comparison to sister cells, as we exemplify by temporal resolution of essential stem cell genes and, combined with a 3D differentiation protocol into endothelium, for the identification of multiple novel genes that control sprouting angiogenesis and blood vessel lineage specification. Furthermore, using haploid genetics as screening platform, we identify Pla2g16 as a druggable host factor for cytotoxicity by rhinoviruses and confirm it using Haplobank clones, providing a rationale therapy for the common cold, the most frequent human disease. Taken together, we developed a conditional, homozygous ES cell resource to empower controlled genetic studies in murine ES cells and derived cell lines and organoids, enabling genome wide reversible genetic approaches in ES cells.

14:45 – 15:10

CRE RECOMBINASE-DRIVEN ENDOGENOUS BARCODING TOWARDS DECONVOLUTION OF HEMATOPOIESIS

Rodewald, Hans-Reimer, Pei, Weike, Feyerabend, Thorsten, Roessler, Jens, Wang, Xi, Quedenau, Claudia, Postrach, Daniel, Busch, Katrin, Rode, Imnanuel, Klapproth, Kay and Hoefer, Thomas

German Cancer Research Center (DKFZ), Heidelberg, Germany

Morphological and functional analyses of organs and tissue development often depend on invasive methods such as histology, cell isolation, tissue grafting, and others. Non-invasive vivo cellular lineage tracing can be achieved by fate mapping. However, currently available numbers of fluorescent markers are limited and, depending on the tissue complexity (and other factors such as cell migration), insufficient to dissect developmental relationships of cellular lineage at high resolution. We have developed a genetic barcoding system, termed Polylox, that allows induction of stable barcodes in cells in vivo via Cre recombinase-dependent shuffling of DNA segments in an engineered Rosa26-Polylox locus. The system is capable of generating several hundred thousand barcodes, allowing in vivo tagging of single cells. Towards the practical usage of endogenous barcoding in vivo, we have induced barcodes in mice, examined barcode structures and diversity, and calculated barcode generation probabilities. We recognize that a key element in the development and use of in vivo barcoding systems lies in the identification of sufficiently rare and hence informative barcodes. We have applied endogenous barcoding to the blood and immune system and will present data on fates and pathways emerging from hematopoietic stem cells under unperturbed conditions in vivo.

FRIDAY, 16 JUNE, 13:15 – 15:15

CONCURRENT IIIG: ROAD TO THE CLINIC I

Level 2, Room 253ABC

13:20 – 13:45

HEALIOS CORPORATE STRATEGY TO ADVANCE REGENERATIVE MEDICINE GLOBALLY

Kagimoto, Hardy TS

HEALIOS K.K., Minato-ku, Japan

Healios will expand the possibilities for curing diseases to increase and further enrich quality of life through the development and supply of iPSC regenerative medicine products as part of the rapid progress of regenerative medicine. By making use of the latest iPSC therapies from Riken, we will heal and bring hope to those worldwide who are suffering. We will create a global infrastructure to develop, manufacture and promote our therapies from within the Healios family of businesses. We will build a biotechnology company founded on solid principles and technologies in which every individual can trust. Healios has pipelines which leverage the Japanese approval system and advancement of global stem cell therapy. The speaker will introduce Healios's core strategy and 3 major pipelines. Firstly, the world's first iPS based cell therapy using retinal pigment epithelial cells to treat wet and dry AMD (clinical research in Japan). Secondly, bone marrow derived somatic stem cells to treat acute brain stroke with immune modulation effect (clinical trials; P2/3 study in Japan). And finally, our platform Organ Bud technology, to create various types of smaller functional organs with the aim of initiating clinical research in Japan in 2019 for patients suffering from congenital liver enzyme deficiency.

13:45 – 14:00

HUMAN IPSC-DERIVED NEURAL PROGENITORS ARE AN EFFECTIVE DRUG DISCOVERY MODEL FOR NEUROLOGICAL MTDNA DISORDERS

Prigione, Alessandro[1], Lorenz, Carmen[1], Lesimple, Pierre[2], Zink, Annika[1], Mlody, Barbara[1], Inak, Gizem[1], Singh, Manvendra[1], Semtner, Marcus[1], Mielke, Thorsten[4], Meierhofer, David[3], Izsvák, Zsuzsanna[1], Meier, Jochen[4], Adjaye, James[5], Wanker, Erich[1], Schuelke, Markus[6] and Lombès, Anne[2]

[1]Max Delbrueck Center for Molecular Medicine (MDC), Berlin, Germany, [2]INSERM, Paris, France, [3]MPI MolGen, Berlin, Germany, [4]Braunschweig University, Braunschweig, Germany, [5]University of Duesseldorf, Germany, [6]Charite University Medicine, Berlin, Germany

Mitochondrial DNA (mtDNA) mutations frequently cause neurological diseases. Modeling of these defects has been difficult because of the challenges associated with engineering mtDNA. We show here that neural progenitor cells (NPCs) derived from human induced pluripotent stem cells

(iPSCs) retain the parental mtDNA profile and exhibit a neuronal-like metabolism depending on mitochondrial respiration. NPCs derived in this way from patients carrying a deleterious homoplasmic mutation in the mitochondrial gene MT-ATP6 (m.9185T>C) showed defective ATP production and abnormally high mitochondrial membrane potential (MMP), plus altered calcium homeostasis, which represents a potential cause of neural impairment. Post-mitotic neurons differentiated from patient NPCs exhibited the same cellular alterations, unlike patient fibroblasts or cybrids carrying the MT-ATP6 mutation. High-content screening of FDA-approved drugs carried out in patient NPCs using the MMP phenotype highlighted the PDE5 inhibitor avanafil, which we found was able to partially rescue the calcium defect in patient NPCs and differentiated neurons. iPSC-derived NPCs generated from patients carrying other MT-ATP6 mutations (m.8993T>C and m.8993T>G) were used to confirm the disease phenotypes and the beneficial effect of avanafil. Overall, our results show that iPSC-derived NPCs provide an effective model for drug screening to target mtDNA disorders that affect the nervous system.

Funding Source: e:Bio Young Investigator Grant AZ.031A318, Federal Ministry of Education and Research (BMBF)

14:00 – 14:15

THE K219T MUTATION IN LMNA GENE PERTURBS CARDIAC FUNCTION THROUGH EPIGENETIC MODULATION OF SCN5A GENE EXPRESSION IN A HUMAN IPSC-BASED CARDIAC MODEL OF LAMINOPATHY

Di Pasquale, Elisa[1], Crasto, Silvia[2], Salvarani, Nicolo[3], Miragoli, Michele[4], Paulis, Marianna[3], Kunderfranco, Paolo[2], Carullo, Pierluigi[3], Forni, Alberto[5], Faggian, Giuseppe[6] and Condorelli, Gianluig7

[1]Institute of Genetic and Biomedical Research (IRGB), UOS of Milan, National Research Council of Italy, Rozzano (Milan), Italy, [2]Humanitas Research Hospital, Rozzano (Milan), Italy, [3]Institute of Genetic and Biomedical Research, National Research Council of Italy, Milan, Italy, [4]Department of Clinical and Experimental Medicine, University of Parma, Italy, [5]Division of Cardiac Surgery, , University of Verona, Italy, [6]Division of Cardiac Surgery, University of Verona, Italy, [7]Humanitas University, Rozzano (Milan), Italy

Mutations in LMNA gene, encoding the nuclear lamina proteins Lamin A/C, lead to a heterogeneous group of diseases called laminopathies that, at the heart level, manifests with dilated cardiomyopathy typically anticipated by various conduction system defects. LaminA/C regulates a variety of biological processes, that range from maintenance of nuclear structure to mechano-sensing, regulation of transcription and chromatin organisation. However, studies so far have mainly focused on fibroblasts, while the pathophysiological mechanisms underlying defective Lamin A/C in cardiomyocytes (CMs) and their consequences in myocardial diseases remain undefined. To this aim we generated CMs from induced pluripotent stem cells (iPSCs) of patients carrying the K219T mutation, which gives rise to dilated cardiomyopathy. Using this cellular model, we performed a comprehensive analysis of the functional properties by electrophysiological techniques both, at the single cells levels and in a multi-cellular setting. Results from patch-clamp highlighted as major functional phenotypes significant changes in maximal upstroke velocity (dV/dt-max), action potential amplitude (APA) and overshoot (OV) in LMNA-CMs compared to CNTR, accompanied by a reduction of the peak sodium currents and a diminished conduction velocity, measured in strand of electrically-coupled CMs. Molecular studies targeting the main sodium channel protein Nav1.5 and its encoding gene, SCN5A, indicated a significant reduction of both transcript and protein in LMNA-CMs; this event was associated with an increased binding to SCN5A gene promoter of Lamin A/C, together with the Polycomb repressive complex 2 (PRC2) proteins and the H3K27me3 repressive mark. Consistently, 3D immuno-FISH experiments showed a preferential localization of SCN5A genomic loci at the nuclear periphery in LMNA-CMs. In conclusion, our findings support a model in which mutated Lamin A/C decreases SCN5A gene expression by favoring PRC2 binding and H3K27me3 methylation at its promoter, and leads to decreased sodium current densities and, as a consequence, slower conduction velocity which potentially justify for the conduction defects almost always observed in primary cardiomyopathies induced by Lamin A/C mutations.

Funding Source: Italian Ministry of Health, project GR-2011-02347743 to EDP; National Research Council (CNR) of Italy, project Interomics to EDP

14:15 – 14:30

TOWARDS THE STANDARDIZATION OF IPSC TECHNOLOGY FOR DRUG DEVELOPMENT IN NEUROSCIENCE: CHALLENGING DATA REPRODUCIBILITY USING IPSC-DERIVED TAU-MUTANT NEURONS

Cabrera Socorro, Alfredo[1], Garcia Leon, Juan[2], Pestana, Francisco[3], Kreir, Mohamed[3], Shih, Pei-Yu[3], Eggermont, Kristel[2], Stummann, Tina[4], Terryn, Joke[2], Geraerts, Martine[5], Craig, Peter[6], Nuthall, Hugh[6], Verheyen, An[3], Royaux, Ines[3], Fazal, Raheem[2], Quiles, Ana[2], Ordovas, Laura[2], Bruce, Kevin[7], Foerch, Patrik[5], Pita Almenar, Juan[3], Ebneth, Andreas[3] and Verfaillie, Catherine[2]

[1]Janssen Research Development, Beerse, Belgium, [2]Katholieke Universiteit Leuven, Belgium, [3]Janssen Pharmaceutical (J and J), Beerse, Belgium, [4]Lundbeck, Copenhagen, Denmark, [5]UCB Pharma, Braine l'Alleud, Belgium, [6]Eli Lilly and Company Limited, Surrey, U.K., [7]Roslin Cells Sciences, Midlothian, U.K.

The induced pluripotent stem cells (iPSCs) technology is not yet a fully consolidated pre-clinical model within pharmaceutical drug discovery programs. Duration of the differentiation process and the challenge to generate fully mature neurons has delayed application for drug develop-

ment. The translational value of iPSC technology can be demonstrated by developing models which reproducibility is demonstrated across laboratories. Here we present a joint effort between academic and industry partners across Europe aiming to establish two independent iPSC-models of neurodegeneration using tau mutations as entry point. At least 30 mutations in the tau gene (MAPT) have been associated with familial forms of frontotemporal dementia (FTD). Many of these mutations have been shown to increase tau aggregation and are thought to drive the synaptic failure observed during disease progression. Alternative splicing of exon 10 gives rise to tau isoforms with either three (3R) or four (4R) microtubule-binding domains. Both 3R and 4R-tau are expressed in the adult brain but iPSC-derived neurons essentially express only 3R-tau. We used Zinc-finger nucleases technology to generate a biallelic double mutant (2M) cell line carrying two pathogenic mutations linked to FTD. In parallel, we generated a monoallelic triple mutant (3M) line using CRISPR RNA-guided FokI nucleases to introduce three FTD mutations. By combining intronic and exonic mutations we increased inclusion of exon 10 and promoted endogenous expression of mutant 4R-tau. We then designed a multi-centric experiment to fully characterize 2M and 3M-derived neurons across sites by performing genetic, biochemical and functional analysis. We demonstrate that 2M and 3M neurons display endogenous 4R-tau aggregation without seeding, and are electrophysiologically more active than their respective isogenic controls. More importantly, we show that tau aggregation phenotype is fully reproduced when neurons are generated in independent laboratories, while functional readouts are partially replicated. Using different lines with tau-related mutations and replicating data across sites, we demonstrate that phenotype reproducibility can be achieved using the iPSCs technology, and validate a robust model to progress the identification of new therapies to treat AD.

Funding Source: Innovative Medicines Initiative Grant Agreements 115582 EBiSC and 115439 stemBANCC, with financial contribution from the European Union's Seventh Framework Programme (FP7/2007-2013) and in kind EFPIA companies contribution.

14:30 – 14:45

MODELING THE GENETIC COMPLEXITY OF HUMAN HEMATOLOGIC MALIGNANCIES USING CRISPR GENOME ENGINEERING

Tothova, Zuzana[1], Krill-Burger, John[2], Popova, Katerina[3], Landers, Catherine[2], Sievers, Quinlan[4], Yudovich, David[3], Belizaire, Roger[3], Aster, Jon[3], Morgan, Elizabeth[3], Tsherniak, Aviad[2] and Ebert, Benjamin[3]

[1]Dana Farber Cancer Institute, Cambridge, MA, U.S., [2]Broad Institute, Cambridge, MA, U.S., [3]Brigham and Women's Hospital, Boston, MA, U.S., [4]Harvard Medical School, Boston, MA, U.S.,

Hematologic malignancies are driven by combinations of genetic lesions that have been difficult to model in human cells. We used CRISPR/Cas9 genome engineering of primary human hematopoietic stem and progenitor cells (HSPCs), the cells of origin for myeloid malignancies, followed by transplantation into immunodeficient mice, to generate genetic models of clonal hematopoiesis and malignancy. We targeted nine recurrently mutated genes in MDS/AML with predicted loss-of-function (LOF) mutations: TET2, ASXL1, DNMT3A, RUNX1, TP53, NF1, EZH2, STAG2 and SMC3, in both umbilical cord and adult CD34+ cells and demonstrated feasibility and efficiency of multiplex targeting at a single cell level in vitro. In vivo, we first modeled clonal hematopoiesis of indeterminate potential (CHIP) and noted clonal expansion of TET2 and DNMT3A LOF clones over the course of 5 months. Since overt myeloid malignancies are generally associated with the acquisition of somatic mutations in multiple driver genes in a single clone, we performed multiplex genome editing in vivo using a combination of CRISPR/Cas9 and overexpression of gain of function oncogenes, such as FLT3-ITD and NPM1. Human cells bearing mutations in combinations of genes observed in myeloid malignancies, including cohesin genes, generated neoplastic clones capable of long-term, multi-lineage reconstitution and serial transplantation. In addition, multiplex targeting also allowed us to monitor in vivo clonal dynamics of human cells over time and model selective dominance of an individual genetic clone. Employing these models to investigate therapeutic efficacy, we found that TET2 and cohesin-mutated hematopoietic cells were sensitive to treatment with the hypomethylating agent azacitidine. Our approach of generating genetic models of human hematopoietic malignancies using multiplex CRISPR/Cas9 engineering provides a highly customizable approach to generate models that recapitulate the genetics, clonal evolution and dynamics, and therapeutic sensitivities observed in patients. With the ongoing improvements of efficiency of CRISPR/Cas9 genomic engineering technologies, these models may prove valuable in future studies of biology and therapeutic vulnerabilities of specific genetic lesions found in patients with hematologic malignancies.

14:45 – 15:10

THE ROLE OF RNA PROCESSING DEREGULATION IN BENIGN AND MALIGNANT PROGENITOR AGING

Jamieson, Catriona H.M.

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

Cancer stem cells (CSCs) are cells within tumors that exploit stem cell properties thereby enabling them to become dormant, survive and regenerate in protective microenvironments, albeit in a deregulated manner. In contrast to the majority of cells within a tumor, CSCs have the capacity to form self-renewing cells and differentiated cells that comprise the bulk tumor population. The prevalence of CSCs varies among tumor types and between individual patients. Recent data suggest that the capacity of CSCs to respond rapidly to environmental changes is predicated, at least in part, on changes in RNA processing. The mechanisms governing human transcriptome diversity involve different regulatory steps in RNA processing such as capping, cleavage and polyadenylation, RNA methylation,

editing and splicing. Nascent transcripts are susceptible to RNA editases, such as adenosine deaminases acting on double-stranded RNA (dsRNA) (ADARs). The activity of ADAR1 contributes to the oncogenic transformation of pre-malignant progenitors into leukemia stem cells (LSCs) that harbor clonal self-renewal and survival capacity. As another key mechanism in RNA processing regulation, pre-mRNA splicing activity dramatically influences RNA and protein diversity. Alternative splicing occurs in up to 95% of human multi-exon genes during development and aging. Aberrant RNA splicing has also been linked to LSC generation and can be distinguished by RNA sequencing from benign stem and progenitor cell aging. Lastly, emerging evidence suggests that N6-methyladenosine (m6A) modification of RNA also plays a central role in stem cell fate determination and cancer development. Understanding cell type and context-specific differences in RNA-processing is therefore key to distinguishing benign from malignant stem and progenitor cell aging that leads to the generation of CSCs capable of driving therapeutic resistance and cancer progression.

FRIDAY, 16 JUNE, 16:00 – 18:00

PLENARY V: STEM CELLS - STRESS, SENESCENCE AND AGING

Exhibit Level , Exhibition Hall B1

16:15 – 16:40

EPIGENETIC MECHANISMS OF STEM CELL AGING AND REJUVENATION

Rando, Thomas

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

There is an age-dependent decline in stem cell functionality in many tissues. Many molecular, biochemical, and functional features of stem cells have been characterized, and these changes have been assumed to be largely irreversible and inevitable accompaniments of aging. Supported by data from studies of heterochronic parabiotic pairings of mice, it is clear that the aged phenotype can be modified when aged cells are exposed to a youthful systemic milieu. These findings raise the question as to what extent, the aged phenotype is epigenetically determined. We have found changes in patterns of chromatin modification that occur during the aging of quiescent stem cells. In particular, there is a marked increase in the enrichment of the repressive mark, H3K27me3, at transcription sites along the genome, a change that we also observed as quiescent stem cells activate and enter the cell cycle. We have sought to correlate these epigenetic changes with both transcriptional changes and higher order chromatin structure to better define cellular age at a molecular level. Elucidating the underlying epigenetic features of aged stem cells will provide a framework for understand the fundamental molecular mechanisms of aging and the mechanisms by which environmental influences can reverse the aged phenotype.

16:40 – 17:05

STEM CELLS ORCHESTRATES HAIR FOLLICLE AGING PROGRAM

Nishimura, Emi

Tokyo Medical and Dental University, Tokyo, Japan

Tissues and organs undergo structural and functional declines due to aging, yet the exact aging processes and the underlying mechanism(s) involved have been poorly understood. The hair follicle is a mini-organ of the skin that is specialized to grow hair. Hair follicle stem cells (HFSCs) and melanocyte stem cells (McSCs) reside in mammalian hair follicles to sustain the cyclic growth of pigmented hair during each hair cycle. To understand the mechanisms of tissue aging, we have studied the physiological aging-associated changes in murine and human hair follicles and their underlying mechanisms. In vivo fate analysis of stem cells in naturally aging hair follicles revealed that those stem cells undergo specific fate changes through the proteolysis of hemidesmosomal transmembrane collagen (COL17A1), thereby causing aberrant differentiation and depletion of those stem cells and the resultant typical hair aging phenotypes in a stepwise manner. Furthermore, we found that the expression of those aging phenotypes can be prevented by the forced expression of COL17A1 in HFSCs. These results demonstrate the existence of a stem cell-centric aging program as the core to orchestrate tissue aging. In this symposium, I will introduce the concept of the "stemness checkpoint", which determines the fate of somatic stem cells under different kinds of genomic stress, and will discuss the role of that checkpoint in tissue aging and in developing cancer.

17:05 – 17:30

AGE-RELATED CHANGES TO STEM CELLS AND THE STEM CELL NICHE

Jones, Leanne

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

Adult stem cells support tissue homeostasis and repair throughout the life of an individual. Numerous changes occur with age that result in altered stem cell behavior and reduced tissue maintenance and regeneration. Changes can be cell autonomous including changes in cell cycle progression, decreased bioenergetic efficiency, increased DNA damage, and epigenetic alterations. In addition, poorly understood changes to the local and systemic environments occur that result in decreased stem cell activity or alterations in commitment or differentiation potential. We have developed Drosophila melanogaster as a model to uncover conserved mechanisms regulating stem cell aging and to explore how cellular and tissue aging impact longevity. Specifically, we compare and contrast age-related changes to germline and intestinal stem cells and present strategies to counter age-related changes in both tissues. In addition, we are extending our findings in flies to more

complex stem cell systems, such as the human intestine. Understanding the mechanistic basis for intrinsic and extrinsic age-related changes will facilitate stem cell based therapies to treat age-onset and degenerative diseases in older individuals.

17:30 – 17:55

SIRTUINS, NAD+ AND STEM CELLS

Guarente, Leonard P.

Department of Biology and Koch Institute, Massachusetts Institute of Technology, Cambridge, MA, U.S.

SIR2 and related genes (sirtuins) are NAD-dependent deacylases that link metabolism, epigenetics and aging in a variety of species. Sirtuins are also involved in the longevity conferred by dietary or calorie restriction (CR). The mammalian sirtuins SIRT1-7 also protect against many diseases of aging, including the major neurodegenerative diseases. New data underscore the importance of NAD+ metabolism in aging, and demonstrate that declining NAD+ limits health span and life span because it results in sirtuin inactivation. I will discuss the role of SIRT1 in intestinal stem cells (ISCs) in their response to dietary signals sent by the niche cells, Paneth cells. SIRT1 and mTORC1 are activated in ISCs by calorie restriction to drive an increase in cell number. I will also show that ISC number and function decline in old mice. The reactivation of the SIRT1/mTORC1 axis by NAD+ precursors can prevent the decline of ISCs during aging. Finally, I will present data demonstrating the critical role of SIRT1 in embryonic stem cells in maintenance of the most pluripotent state. Our finds indicate a central role of SIRT1 in stem cell biology.

SATURDAY, 17 JUNE, 9:00 – 11:05

PLENARY VI: TISSUE REGENERATION AND HOMEOSTASIS

Exhibit Level , Exhibition Hall B1

9:00 – 09:25

THE ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE: TISSUE LOGIC IN THE AIRWAY EPITHELIUM: NICHES, NOTCHES, CIRCUITS, HETER0GENEITY, AND PLASTICITY

Rajagopal, Jayaraj

Massachusetts General Hospital, Center for Regenerative Medicine, HHMI, Boston, MA, U.S.

Our laboratory seeks to understand how cells, within a given tissue, act in concert. The airway epithelium is comprised of a very simple lineage of 3 distinct cell types that represent each of the major functional subtypes of cells that participate in regeneration: a stem cell, a progenitor cell, and a post-mitotic differentiated cell. Thus, the model captures the simplest degree of cellular complexity necessary for the general study of dynamic intercellular processes during homeostasis and regeneration after injury. In parallel, we are attempting to use novel model systems to define aberrations in the ensemble behavior of cells in human disease tissues. The talk will reference our findings concerning plasticity, the definition of a niche, heterogeneity, and novel functions of stem cells.

9:25 – 09:50

THE CELLULAR AND MOLECULAR BASIS FOR REGENERATION IN PLANARIANS

Reddien, Peter W.

Whitehead Institute MIT, Cambridge, MA, U.S.

Planarians are flatworms and a classic model system for studies of regeneration. The regenerative abilities of planarians are dramatic: they can regenerate new heads, tails, sides, or entire organisms from small fragments of the body. Planarians have a complex anatomy including brain, eyes, musculature, intestine, kidney-like protonephridia, and epidermis, all arranged in complex patterns. Because small fragments of the body can regenerate an entire planarian, there must exist mechanisms in the adult for the production of all of these tissues and proper tissue patterns. The regenerative ability of planarians involves a population of dividing cells called neoblasts, which include pluripotent stem cells. Neoblasts can be specialized by expression of specific transcription factors to become progenitors for different regenerative lineages. For example, expression of ovo and other transcription factor-encoding genes specifies neoblasts to become eye progenitors. We used the eye to study the mechanistic basis for regeneration specificity: the capacity of the animal to respond to unpredictable injury by regenerating the correct specific tissue that is missing and at the appropriate scale. Surprisingly, we found that eye presence or absence did not regulate neoblast production of eye progenitors. Instead eye regeneration following specific injury is explained as an emergent property of a constant low rate of eye progenitor production. Amputated planarian fragments far from the head display de novo eye progenitor production during head regeneration. We propose this de novo induction of eye progenitors is explained by the existence of a positional information system harbored in planarian muscle. Following injury, this positional information system rapidly regenerates its pattern, resulting in remaining neoblasts being placed into a head signaling environment that results in eye progenitor production. Together these findings suggest a mechanistic model for regeneration specificity, in which progenitor production is "blind" to the presence or absence of their target tissue.

9:50 – 10:15

TISSUE CORRECTION OF ABERRANT GROWTH PRESERVES HOMEOSTASIS

Greco, Valentina

Yale Stem Cell Center, Yale Medical School, New Haven, CT, U.S.

Cells in healthy tissues acquire mutations with surprising frequency. Many of these mutations are associated with abnormal cellular behaviors such as differentiation defects and hyperproliferation, yet fail to produce aberrant phenotypes in structurally and functionally normal tissue 1-3. It is currently unclear how the tissue remains phenotypically normal, despite the presence of these mutant cells. Here we utilize intravital imaging to track the fate of the skin epithelium burdened with varying amounts of activated Wnt/ß-catenin stem cells. We show that all resulting growths that deform the skin tissue architecture regress, irrespective of their size. Wild-type cells actively eliminate the mutant cells from the tissue, while employing both endogenous and ectopic cellular behaviors to dismantle the aberrant structures. Following regression, the remaining structures are either completely eliminated or converted into functional skin appendages in a niche-dependent manner. Furthermore, tissue aberrancies generated from oncogenic Hras, and even mutation-independent deformations to the tissue can also be corrected, indicating that this tolerance phenomenon reflects a conserved principle in the skin. This study reveals an unanticipated plasticity of the adult skin epithelium when faced with mutational and non-mutational insult, and elucidates the dynamic cellular behaviors employed for its return to a homeostatic state.

10:15 – 10:40

DETERMINATION OF CELL FATE IN THE VERTEBRATE RETINA

Cepko, Constance, Wang, Sui, Sengel, Cem, Hafler, Brian, Suzenko, Natalia, Rompani, Santiago, Lapan, Sylvain and Rabe, Brian

Harvard Medical School, Boston, MA, U.S.

The complexity of the cellular composition of the central nervous system (CNS) presents a fascinating problem for developmental biologists. One approach to unraveling the mechanisms that generate such complexity is to determine the progenitor-progeny, or lineage, relationships. Such studies have been conducted in various areas of the CNS, with some of the initial studies using retroviral vectors to mark clones in the retina. These studies established that retinal progenitor cells (RPCs) are multipotent, capable of giving rise to more than one cell type. They also showed that the number and type of cells that derived from individual RPCs were highly variable. This raised the question of whether the variability was due to intrinsic differences among RPCs or to extrinsic and/or stochastic effects on equivalent RPCs or their progeny. Newer lineage studies have demonstrated some intrinsic aspects, in that terminally dividing RPCs can make specific pairs of daughter cells, with the specificity extending to very specific subtypes of retinal neurons. These terminally dividing cells are distinct from each other, as indicated by the expression of specific genes, which was revealed by single cell RNA profiling of individual RPCs. Notch 1 is required to create asymmetry in the fates of two daughter cells made by a terminally dividing RPC. Interestingly, transcription and translation of Notch1 in the newly postmitotic cells was required, not just inheritance of Notch signal from the RPC. In addition to these lineage studies, the talk will cover the recent elucidation of a gene regulatory network that governs a binary fate decision in the retina. If time permits, the development of GFP as a scaffold to allow the manipulation of gene expression only in GFP+ cells also will be described.

10:40 – 11:05

MCEWEN AWARD FOR INNOVATION LECTURE: FOUR DECADES OF RESEARCH ON SKIN STEM CELLS

Fuchs, Elaine

HHMI, The Rockefeller University, New York, NY, U.S.

Adult tissues require stem cells to replenish cells during normal turnover (homeostasis) and in response to injury. How stem cells balance self-renewal and differentiation is of fundamental importance to our understanding of normal tissue maintenance and wound repair. Moreover, increasing evidence suggests that the regulatory circuitry governing this balancing act is at the roots of aging as well as some types of cancers. The skin is an excellent model system to understand how stem cells function in normal tissue generation, why they reduce their activity in aging and how they accelerate it uncontrollably in cancer. Using skin as our paradigm, we've identified a niche of stem cells located within the hair follicle. In normal homeostasis, these stem cells become activated to fuel cyclical bouts of hair growth. Upon injury, these cells become activated to migrate upward and repair the skin epidermis. Upon acquiring oncogenic mutations, these cells give rise to squamous cell carcinomas (SCCs), which affect many epithelial tissues, making them among the most common and life-threatening cancers world-wide. We've been dissecting how extrinsic signaling to stem cells triggers a cascade of changes in chromatin and transcriptional re-modeling that governs the activation, polarization and migration of stem cells during tissue development, homeostasis, hair cycling and wound repair. We've also been exploring what instructs activated stem cells to return to quiescence and stop making tissue when wounds are repaired, why aging skin slows the process of tissue regeneration and how cancer stem cells avoid these brakes on tissue growth. Our findings have provided us with new insights into our understanding of stem cell dynamics, and in so doing have begun to unveil new avenues for therapeutics in skin regeneration, aging and cancer.

SATURDAY, 17 JUNE, 13:15 – 15:15

CONCURRENT IVA: PLURIPOTENCY AND IPS CELL REPROGRAMMING II

Level 3, Ballroom East

13:20 – 13:45

ALTERNATIVE PATH TO PLURIPOTENCY

Pei, Duanqing

Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

Oct4, Sox2, Klf4 and Myc can reprogram MEFs into iPSCs efficiently. It is not clear if there are alternatives to this classic combination of factors. Here we report a 7-factor (7F) combination that can convert MEFs to iPSCs (7F-PSCs) efficiently. The 7F colonies are dome-shaped in situ and can be isolated readily for cell line development. The 7F PSC lines resemble mouse embryonic stem cells (mESC) and can give rise to chimera and all PSC mice through 4n complementation. Mechanistically, we show that 7F reprogram MEFs through a distinct process that activates the pluripotent network directly. Indeed, 7F colonies isolated at Day 6 are chimera and germ line competent without further culturing. Our results suggest that there is alternative way to reprogram MEFs to iPSCs efficiently.

13:45 – 14:00

SINGLE-CELL CHROMATIN ACCESSIBILITY LANDSCAPES IN CELL FATE REPROGRAMMING

Loh, Yuin Han, Xing, Qiao Rui and El Farran, Chadi A.

Institute of Molecular and Cell Biology, Singapore

Somatic cells are converted to pluripotent stem cells by inducing the expression of specific transcription factors. However, derivation of bona-fide induced pluripotent stem cells is limited by low efficiency of the process and often heterogeneously reprogrammed cell populations. Here, we developed a live-cell fluorescent probe which specifically stains and sort for cells undergoing early reprogramming. We applied scATAC-seq to analyze these intermediate reprogramming cells to decipher the underlying mechanism governing epigenetic changes during the process. Our study revealed that cells undergoing reprogramming can exhibit bi-lineage chromatin profiles. This is confirmed by the co-detection of myoblast and fibroblasts genes or myoblast and pluripotent gene within a single cell. Additionally we identified novel functional enhancer nodes that regulate reprogramming. When coupled with high-resolution 4C-seq, we were able to capture the distant target genes controlled by the enhancer nodes. Analyzing single-cell chromatin profile of cells undergoing reprogramming, demonstrated the dynamic switching of enhancers' activity resulting in rewiring of cell fates.

14:00 – 14:15

A CONTINUOUS MOLECULAR ATLAS OF REPROGRAMMING TO IPSCS BY HIGH-THROUGHPUT SINGLE CELL RNA-SEQ

Shu, Jian[1], Tabaka, Marcin[1], Subramanian, Vidya[1], Brumbaugh, Justin[2], Hochedlinger, Konrad[3], Regev, Aviv[1], Jaenisch, Rudolf[4] and Lander, Eric[1]

[1]Broad Institute of MIT and Harvard, Cambridge, MA, U.S., [2]Massachusetts General Hospital, Boston, MA, U.S., [3]Massachusetts General Hospital Cancer Center and Center for Regenerative Medicine, Boston, MA, U.S., [4]Whitehead Institute, Cambridge, MA, U.S.

Reprogramming somatic cells to iPSCs is a low efficiency process, with only a small fraction of cells capable of reaching pluripotency. Single cell RNA-seq can study the heterogeneity during reprogramming, however previous single cell RNA-seq analyses were based on gene expression profiles from limited genes or cells. Here we report a continuous high-resolution molecular reprogramming roadmap to iPSCs by analyzing approx. 70,000 single cells, with a computational analysis method developed to analyze this large scale dataset. Through progression analysis of each time points, it was discovered that early stage reprogramming is homogenous and that bifurcation begins after withdrawal of exogenous transcription factors. Cells that failed to become iPSCs expressed activation of certain lineage specification genes. Our data provides a high-resolution roadmap of reprogramming and the methods developed here can be used for future analysis of complex cellular programming and other reprogramming processes.

14:15 – 14:30

SIGNALLING AND TRANSCRIPTIONAL NETWORK INTERPLAY ESTABLISHES THE NAIVE PLURIPOTENT IDENTITY VIA MULTIPLE MECHANISTICALLY DISTINCT ROUTES WITH KEY CONSERVED FEATURES

Stuart, Hannah T., Lim, Chee, Lohoff, Tim, Radzisheuskaya, Aliaksandra, Alves, Mariana, Nestorowa, Sonia, Nichols, Jennifer, Göttgens, Bertie and Silva, José

Stem Cell Institute, University of Cambridge, U.K.

Reprogramming of differentiated cells back to a naive pluripotent cellular identity is a process offering great promise as a tool for biological research and therapeutic applications. Furthermore, it provides an excellent model system for the study of how a small set of transcription factors can coordinate the global changes required to instruct and remember a new identity, since the destination cell type is extremely well defined in terms of molecular signature and indisputable functional assays such as chimeric contribution. In order to decipher how the naive pluripotent cellular identity is instructed by combinatorial control between transcriptional networks and extracellular signals, we have developed defined reprogramming systems in which genetic and environmental parameters can be independently varied and the transitioning cells isolated from the popu-

lation average. We discovered that establishment of naive pluripotency occurs via multiple routes, which are mechanistically distinct in terms of their sequence and kinetics of network rewiring and their signal requirements. Amongst these different routes there is a core of key conserved features that is essential for identity transition. Furthermore, scRNAseq analysis led us to identify transiently upregulated autocrine/paracrine signalling that is required for the majority of reprogramming routes and, strikingly, also for in vivo establishment of embryonic naive pluripotency, despite being dispensable for maintenance of the destination ESC/iPSC identity.

14:30 – 14:45

STRONG CONTRACTILE ACTIN FENCE AND CORNERSTONE ADHESIONS DIRECT HUMAN PLURIPOTENT COLONY MORPHOLOGY

Narva, Elisa[1], Stubb, Aki[1], Guzmán, Camilo[1], Blomqvist, Matias[1], Lerche, Martina[1], Saari, Markku[1], Otonkoski, Timo[2] and Ivaska, Johanna[1]

[1]Turku Center for Biotechnology, Turku University, Finland, [2]Helsinki University, Finland

Cell-type specific functions and identity are tightly regulated by cytoskeleton and the extracellular matrix (ECM) interactions. Focal adhesions (FAs) are multifaceted organelles that link the extracellular matrix (ECM) to the cell's contractile actin cytoskeleton to determine adhesion strength and mechanosensing potential to regulate cell polarity, morphology, survival and mitosis. Human pluripotent stem cells (hPSCs) have ultimate differentiation capacity and exceptionally low adhesion strength to ECM. In addition, recent studies have demonstrated the importance of Rho-ROCK-myosin signaling cascade in hPSC maintenance highlighting the crucial role of the contractile actin cytoskeleton in stem cell biology. However, the organization and the significance of the mechanotransducing units, FAs, and their connection to actin have remained unstudied in hPSC colonies. In the present study, we set out to characterize in detail the structure and distribution of FAs and their connection to the actin cytoskeleton with total internal reflection fluorescence microscopy in hiPSC colonies. Furthermore, we studied how the cytoskeletal network mediates traction stress and influences adhesion and colony morphology in pluripotency and differentiation. Imaging of hPSCs at the cell-ECM interface revealed that the colony edge-located adhesions were exceptionally large and connected by thick ventral stress fibers (VSF). The resulting actin fence around the colonies exerted extensive Rho-ROCK-myosin-dependent cytoskeletal mechanical stress and defined mitotic spindle orientation and colony morphology. Remarkably, differentiation altered adhesion organization and signaling characterized by a switch from ventral to dorsal stress fibers, reduced mechanical stress and increased integrin activity and cell adhesion strength to the ECM. Thus, pluripotency appears to be linked to unique colony organization and adhesion structure.

14:45 – 15:10

EARLY HUMAN REPROGRAMMED CELLS ARE MARKED WITH ESRG AND SHOW PROLIFERATION PAUSE REGULATED BY LIN41/P21/RB AXIS

Takahashi, Kazutoshi

Center for iPS Cell Research and Application, Kyoto University, Japan and Gladstone Institute of Cardiovascular Disease, San Francisco, CA, U.S.

Human induced pluripotent stem cells (iPSCs) can be generated from somatic cells by enforced-expression of OCT3/4, SOX2, KLF4 and c-MYC (OSKM) via an intermediate state marked with a surface antigen TRA-1-60. However, reprogramming processes prior to the emergence of TRA-1-60(+) cells remain elusive. In this study, we analyzed reprogramming processes from five types of human somatic cells and identified ESRG as a common marker earlier than TRA-1-60. ESRG (+) reprogrammed cells emerged three days after OSKM induction and showed proliferation pause, but yet to proceeded TRA-1-60 (+) state independently of cell division. Overcoming this proliferation pause in early reprogrammed cells is crucial for maturation toward iPSCs. This proliferation pause is dependent on retinoblastoma protein (RB) pathway. We also found that an RNA-binding protein LIN41 promoted RB inactivation and facilitated reprogramming efficiency in the early stage via post-transcriptional suppression of cyclin-dependent kinase inhibitor p21. The LIN41/p21/RB-regulated proliferation pause does not operate in immortalized fibroblasts, resulting in high reprogramming efficiency even in the absence of LIN41. These data demonstrated that RB-mediated proliferation pause is a critical blockade in the early phase of reprogramming and LIN41 promotes reprogramming by overcoming this blockade.

SATURDAY, 17 JUNE, 13:15 – 15:15

CONCURRENT IVB: STEM CELLS AND CANCER

Level 2, Room 253ABC

13:20 – 13:45

GLIOMA STEM CELLLS: ORIGIN AND MOLECULAR FEATURES

Parada, Luis F.

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

Through the study of fully penetrant genetically engineered mouse models of GBM, we have identified the stem/early progenitor cell pools in the adult brain as the most facile to transform and hence the most likely common source of these tumors. We have identified at least to distinct stem cell sources for tumor initiation. The development of additional transgenic tools have allowed the demonstration

that these GBMs grow in a hierarchical pattern with relatively quiescent cells at the apex. These relatively quiescent "cancer stem cells" are resistance to chemotherapy and mediate post therapy tumor regrowth. Primary culture experiments document rapid differentiation of these CSCs in culture over time. Yet these cells exhibit enhanced tumor sphere formation compared to other tumor cells. In intracranial transplantation assays, these CSCs are capable of successive generational engraftment, a property that other tumor cells fail to achieve. The use of deep sequencing and single cell sequencing affords a new enhanced ability to study in detail the molecular features of these unique GBM tumor cells.

13:45 – 14:00

FUNCTIONAL PROFILING OF MURINE LEUKEMIC STEM CELL FITNESS IN VIVO USING COMBINED CRISPR SCREENING AND MODELING OF CLONAL COMPETITION

Mercier, Francois[1], Shi, Jiantao[2], Sykes, David[3], Oki, Toshihiko[1], Kugadas, Abirami[4], Miller, Elizabeth[5], Zhu, Alex[5], Vasic, Radovan[5], Kfoury, Youmna[3], Doench, John[6], Hide, Wiston[7], Gadjeva, Mihaela[4], Michor, Franziska[2] and Scadden, David[8]

[1]Massachusetts General Hospital, Boston, MA, U.S., [2]Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, U.S., [3]Center for Regenerative Medicine, Massachusetts General Hospital, Boston, MA, U.S., [4]Brigham and Women's Hospital, Boston, MA, U.S., [5]Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, U.S., [6]Broad Institute, Cambridge, MA, U.S., [7]University of Sheffield, U.K., [8]Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Cambridge, MA, U.S.

A better understanding of how leukemic stem cells (LSC) adapt in vivo to outcompete normal hematopoiesis is crucial for the development of novel therapies. We report the development of an in vivo, genome-wide, dropout CRISPR screen in murine models of acute myeloid leukemia (AML) highly enriched in LSC. Screen results were combined with functional profiling of hits during leukemic clonal evolution to identify novel drivers of leukemic growth. We created murine models of AML amenable to genetic manipulation by overexpressing the human AML oncogenes HOXA9 and MEIS1, or the fusion protein MLL/MLLT3, in murine myeloid progenitors constitutively expressing Cas9. Cells were transduced ex vivo with genome-wide sgRNA libraries containing 130,209 sequences and transplanted in cohorts of recipients. The depletion in vivo of sgRNAs was compared to non-targeting library controls in the reconstituted leukemia. We then validated the effect of the top 1034 genes on leukemic cells and normal hematopoietic progenitors to identify lead candidates. In parallel, we established an experimental model of leukemic clonal evolution, where "dominant" and "losing" clones were tracked in vivo using distinguishable fluorescent proteins, and LSC-enriched fractions were profiled using RNA and whole-exome sequencing. This approach allowed for the correlation between the development of a clonal and aggressive phenotype and gene expression. In the pooled CRISPR screen, we identified 393 genes specific to leukemic growth in vivo. Gene set enrichment analysis showed that several pathways are associated with leukemic fitness in vivo, including oxidative phosphorylation, interferon signaling and Wnt signaling. We saw significant overlap between results of the CRISPR screen and the model of clonal evolution. Genetic or pharmacological perturbation of two novel candidates, MIF and UROD, showed anti-leukemic effects in murine experimental models of AML and human cell lines. In conclusion, a genome-wide in vivo CRISPR screen in parallel with experimental modeling of clonal evolution allows the identification of novel drivers of leukemic fitness in vivo. Both approaches provide a functional understanding of the leukemic genome that completes conventional mutational profiling.

Funding Source: This research was funded by a SCOR grant from the Leukemia and Lymphoma Society, a PS-OC grant from the National Cancer Institute, and a Clinician-Scientist Training Award from the Canadian Institutes of Health Research.

14:00 – 14:15

HIGH-FAT DIET DAMPENS IMMUNE SURVEILLANCE OF PREMALIGNANT INTESTINAL STEM CELLS

Beyaz, Semir[1], Bauer_Rowe, Khristian[2], Xifaras, Michael[2], Biton, Moshe[3], Regev, Aviv[3], Orkin, Stuart[1] and Yilmaz, Omer[2]

[1]Harvard Medical School, Boston, MA, U.S., [2]MIT, Cambridge, MA, U.S., [3]Broad Institute, Cambridge, MA, U.S..

A pro-obesity high fat diet (HFD) augments intestinal tumorigenesis in part by elevating the numbers and function of intestinal stem cell (ISC), which are the cells-of-origin for many intestinal tumors. Although interactions between tumor cells and the immune system play a significant role in tumor maintenance, little is known about how a HFD regulates intrinsic and extrinsic immune mechanisms of ISCs during the initial steps of intestinal tumorigenesis. Here, we find that ISCs express high levels of MHC-II on their membrane implicating a role for CD4+ T cell cross-talk in ISC fate determination and immune surveillance. Interestingly, a HFD leads to significant downregulation of genes involved in the MHC-II pathway in ISCs and decreased immune cell infiltration of the crypt independent of obesity—establishing a reduced inflammatory microenvironment for ISCs in HFD mice compared to controls. Mechanistically, we find that pharmacologic inhibition of the JAK/STAT pathway in ISCs mimics many of the intrinsic and extrinsic immune changes induced by a HFD. Notably, premalignant adenomas that arise in a HFD have less MHC-II expression, and in HFD mice MHC-II low expressing premalignant ISCs possess more tumor-initiating capacity in an orthotopic, syngeneic transplantation assay when compared to their MHC-II high expressing counterparts. These findings high-

light how a pro-obesity HFD alters the immune recognition properties of ISCs and how such changes contribute to the early steps of intestinal tumor formation.

14:15 – 14:30

IDENTIFYING AND TARGETING METASTATIC-INITIATING CELLS: A LINK BETWEEN WHAT WE EAT AND METASTASIS

Aznar-Benitah, Salvador

ICREA Researcher, Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain

Metastasis is the leading cause of cancer-related deaths. However, the identity of the cells that promote metastasis is unknown, hampering our ability to develop therapies to prevent or inhibit the spread of tumour cells to distant sites. We have identified the cells uniquely responsible for the formation of metastasis in different types of human tumors. These cells have intriguing characteristics: i) they form primary lesions as efficiently as their tumor-initiating counterparts, but are exclusive in their ability to generate metastases; ii) they express the fatty acid translocase CD36, and are characterized by a unique lipid metabolic signature; iii) they are exquisitely sensitive to the levels of fat in circulation, and consequently, they relate the predisposition of metastasis directly to the content of dietary fat; iv) they are highly sensitive to CD36 inhibition, which almost completely abolishes their metastatic potential in immunocompetent and immunodeficient preclinical models. I will discuss our latest results on the mechanisms utilized by CD36+ metastatic-initiating, and the influence of dietary fatty acids in metastasis.

Funding Source: Worldwide Cancer Research Foundation; European Research Council (ERC); Foundation Botin; Foundation La Marató-TV3

14:30 – 14:45

LKB1 INACTIVATION DRIVES EPIGENETIC LUNG CANCER LINEAGE SWITCHING FROM DISTINCT CELLS-OF-ORIGIN

Fillmore Brainson, Christine[1], Zhang, Haikuo[2], Kim, Carla[3] and Wong, Kwok-Kin[2]

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The epigenetic states and cells-of-origin of the two major subtypes of non-small cell lung cancer, namely adenocarcinoma and squamous cell carcinoma, remain unknown. The existence of adenosquamous lung tumors, clinically defined by the presence of both glandular adenocarcinoma lesions and fully stratified squamous lesions within the same tumor, suggest lung cancer lineage plasticity. LKB1 (encoded by STK11) is frequently mutated in adenosquamous tumors, as are KRAS and EGFR. To determine if adenosquamous lung cancer can be a result of lineage switching, we used a stepwise mouse model of tumorigenesis to delete Lkb1 in established KRAS-driven adenocarcinomas. Deletion of Lkb1 led to conversion of some KRAS-driven adenocarcinomas to squamous cell carcinomas in autochthonous and transplantation models. We explored the chromatin landscape of these tumors, and observed loss of the repressive mark histone H3 lysine 27 trimethylation (H3K27me3) at squamous lineage genes, included Sox2, deltaNp63 and Ngfr. Human squamous tumors likewise showed a decrease in H3K27me3 mark when compared with adenocarcinomas. Given that some, but not all, of the adenocarcinomas in the model transition to squamous fate after Lkb1 deletion, we reasoned that cell-of-origin may influence the cell fate switch. To test the fitness of varied lung stem and progenitor cells to serve as KRAS+/Lkb1-null tumor cells-of-origin, we isolated basal cells, club cells, bronchioalveolar stem cells (BASCs) and alveolar type 2 (AT2) and transduced the cells in organotypic cultures to express KRAS and delete Lkb1. These FACS-enriched lung cell populations had differential abilities to give rise to organoids and propagate lung tumors after KRAS activation and Lkb1 deletion; neither basal cells nor AT2 cells tolerated these oncogenic changes, whereas club cells and BASCs were able to produce mutated organoids in culture and lung tumors in vivo. Both adenocarcinoma and squamous cell carcinoma could be derived from both club cells and BASCs. We are next examining how cellular metabolism and the myeloid cell microenvironment influence lung cancer lineage and epigenetic identity. We hope to identify key pathways that control tumor initiation and lineage fate using this system, with a future focus on subtype-specific therapies.

Funding Source: Funded in part by K22 CA201036 to CFB

14:45 – 15:10

THE STROMAL CELL NICHE FOR EPITHELIAL STEM CELLS: A TEMPLATE FOR ORGAN REGENERATION AND A BRAKE ON MALIGNANCY

Beachy, Philip A.

Stanford University, CA, U.S.

One avenue to accelerate progress in the development of stem cell-based therapies is to elucidate signals from the stem cell niche, which profoundly influence stem cell physiology and might be used to therapeutically manipulate stem cell behavior. The Hedgehog pathway provides a particularly useful perspective for understanding niche signals and their role in normal as well as pathological stem cell activities, as Hedgehog signaling plays a central role in regulating niche signaling programs. In endodermal organs such as the urinary bladder, epithelial injury triggers augmented expression of the Hedgehog signal in epithelial cells, which then elicits a response from underlying stromal niche cells. This stromal response includes expression of signals that in turn trigger epithelial cell proliferation and differentiation. In this manner, the stromal niche serves as a template for the maintenance and repair of epithelia during ordinary homeostasis or in response to injury. Similar elicitation of

stromal niche signals by epithelial Hedgehog occurs in other organs of endodermal derivation. In addition, we have found recently that the hormone-sensitive niche signaling program for breast epithelial cells during puberty also depends on stromal activity of the major Hedgehog pathway transcriptional effector, Gli2. The hormone sensitivity results from Gli2-mediated expression of receptors for the mammatrophic hormones, estrogen and growth hormone. Stromally-expressed signals that promote epithelial differentiation, often BMPs, also play a role in restraining the progression of malignancies. We have found this to occur in mouse models of pancreatic, colon, and bladder cancers, where stromal restraint of cancer progression depends on stromal response to epithelial Hedgehog signals.

SATURDAY, 17 JUNE, 13:15 – 15:15

CONCURRENT IVC: GERM CELL DEVELOPMENT

Level 2, Room 258C

13:20 – 13:45

SELF-ORGANIZATION IN SYNTHETIC HUMAN EMBRYOS

Brivanlou, Ali H.

The Rockefeller University, New York, NY, U.S.

Cells have an intrinsic ability to self-assemble and self-organize into complex and functional tissues and organs. By taking advantage of this ability, embryoids, organoids and gastruloids have recently been generated in vitro, providing a unique opportunity to explore complex embryological events in a detailed and highly quantitative manner. Here, I examine how such approaches are being used to answer fundamental questions in embryology, such as how cells self-organize and assemble, how the embryo breaks symmetry, and what controls timing and size in development. I will also highlight how further improvements to these exciting technologies, based on the development of quantitative platforms to precisely follow and measure subcellular and molecular events, are paving the way for a more complete understanding of the complex events that help build the human embryo. In the adult, continued egg production relies on the balanced regulation of germ line stem cell (GSC) self-renewal and differentiation. In a transcriptome-wide in vivo RNAi screen, we uncovered a critical role for the mitochondrial ATP synthase complex in GSC differentiation. ATP synthase promotes the developmentally regulated maturation of the inner mitochondrial membrane into elaborate cristae during cyst differentiation independent of oxidative phosphorylation.

13:45 – 14:00

HUMAN PGCLC COMPETENCY DEPENDS ON TFAP2C AND INDUCTION OF CELLS WITH A PRIMITIVE STREAK/MESENDODERM IDENTITY

Chen, Di, Liu, Wanlu, Pastor, William, Lukianchikov, Anastasia, Kim, Rachel, Golic, Zoran, Ho, Jamie, Gell, Joanna, Jacobsen, Steven and Clark, Amander

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

In humans, competency for germ cell fate and the specification of primordial germ cells (PGCs) occurs in a restricted developmental window in early embryogenesis. This pioneering event is critical for fertility decades later given that a lack of germ cells at birth can lead to incurable infertility as adults. Despite the important of PGCs for human reproduction, the molecular mechanisms governing PGC specification remain largely unknown. To address this we used the differentiation of human PGC-like cells (PGCLCs) from pluripotent stem cells (PSCs). Using CRISPR/Cas9, we identified TFAP2C as essential for the induction of human PGCLCs. Surprisingly, we found that TFAP2C functions prior to BLIMP1 to regulate the expression of primitive streak/mesendoderm genes, most notably BRACHYURY in the immediate PGCLC progenitor. To further explore the importance of mesendoderm identity, we chemically blocked mesendoderm differentiation using SB431542 and DKK1 and also used CRISPR/Cas9 to delete BRACHYURY. Both strategies effectively blocked PGCLC formation from pluripotent stem cells. Finally, we induced PGCLC differentiation from eighteen hESC lines, and discovered that PGCLC induction efficiency similarly correlates with expression of BRACHYURY and primitive streak/mesendoderm genes in the immediate progenitor. Taken together, human PGC induction requires TFAP2C and the initiation of mesendoderm-like differentiation. Continuing immediate progenitor differentiation into definitive mesoderm severely diminishes PGCLC potential.

Funding Source: BSCRC fellowship

14:00 – 14:15

BRD4 IS A CONSERVED EPIGENETIC READER THAT PLAYS A KEY ROLE IN MOUSE AND HUMAN PRIMORDIAL GERM CELL SPECIFICATION AND MAINTENANCE

Itskovich, Elena[1], Gruhn, Wolfram[2], Irie, Naoko[2], Surani, Azim[2] and Hoeland, Katharina[2]

[1]University of Cambridge, U.K., [2]Gurdon Institute, Cambridge, U.K.

BRD4, a member of bromo and extra terminal (BET) domain protein family is an epigenetic reader, involved in regulating transcriptional elongation. Recently, it was demonstrated to control pluripotency, supporting, among others, transcription of Prdm14. Prdm14 is a key regulator of primordial germ cells (PGCs) that give rise to the sperm and egg of the embryo. PGCs are specified following BMP signaling that results in induction of Prdm1 and Prdm14 in mouse and SOX17 and PRDM1, and potentially

PRDM14, in primate PGCs. Here we show that repression of BRD4 prevents mouse PGC specification in vitro and in vivo. In mouse PGC-like cells, BRD4 binds to the putative enhancers of Prdm1 and Prdm14, likely facilitating RNA polymerase 2 (POL2) pause-release. BRD4 inhibition also abrogated human PGC-like cell fate, and dismantled the established PGC transcriptional network of a human germline TCam-2 seminoma. We further show that BRD4 has a conserved role in regulating the expression of PRDM1 in TCam-2, but not of SOX17, a specific regulator of human, but not mouse, PGCs. This study reveals a potential therapeutic target of human germ cell tumours, and elucidates a generally applicable role of BRD4 in cell fate decisions.

Funding Source: Wellcome Trust

14:15 – 14:30

THE GERM CELL FATE OF CYNOMOLGUS MONKEYS IS SPECIFIED IN THE NASCENT AMNION

Sasaki, Kotaro and Saitou, Mitinori

Kyoto University, Japan

The germ cell lineage is the most fundamental component of the life cycle of the multicellular organisms ensuring propagation of the genetic and epigenetic information across the generations and creation of new organisms. However, the mechanism underlying germ cell specification in primates, including humans has been unknown. In primates, upon implantation, the pluripotent epiblast segregates the amnion, an extra-embryonic membrane ensheathing an embryo, and thereafter initiates gastrulation to generate three germ layers. Here, we show that in cynomolgus monkeys, the SOX17/TFAP2C/BLIMP1-positive primordial germ cells (cyPGCs) arise from the dorsal amnion at embryonic day (E) 11. cyPGCs appear to migrate down the amnion and through proliferation and recruitment from the posterior amnion, expand in number around the posterior yolk sac by E17. Remarkably, the amnion itself expresses BMP4, a cytokine potentially critical for cyPGC specification, and responds primarily to them. Furthermore, human PGC-like cells in vitro exhibit a transcriptome similar to cyPGCs just after specification. Our study identifies the origin of PGCs and suggests a unique morphogenetic function of the amnion in primates.

14:30 – 14:45

BMP8 SUSTAINS SPERMATOGENESIS BY PROMOTING PROLIFERATION AND DIFFERENTIATION OF MOUSE SPERMATOGONIA THROUGH DIFFERENT SMAD PATHWAYS

Wu, Fang-Ju[1], Sung, Li-Ying[2] and Luo, Ching-Wei[3]

[1]National Yang-Ming University, Taipei, Taiwan, [2]Institute of Biotechnology, National Taiwan University, Tapei, Taiwan, [3]Department of Life Sciences and Institute of Genome Sciences, National Yang-Ming University, Taipei, Taiwan

Spermatogenesis is a complex developmental process in which many molecules participate in the balance between renewal and specification of spermatogonial stem cells (SSCs). By analyzing the public data of human testicular biopsy samples from patients with spermatogenic impairments and normozoospermia, we found that low expression of BMP8 was associated with spermatogenic failures. Consistently, previous studies also indicate that Bmp8-null mice exhibit a male infertility phenotype by showing severe degeneration of germ cells before puberty, supporting that BMP8 is involved in spermatogenesis. However, how BMP8 signaling affects spermatogonia or even SSCs remains unknown. In our study, we first demonstrated that BMP8 is localized at spermatogonia of neonatal mice. By culturing SSC-enriched spermatogonia isolated from neonatal mice, we found that BMP8 induced the division of spermatogonia through SMAD2/3 pathway as reflected by increases in cell numbers and the Ccnd1 and Ccne1 transcripts, whereas BMP8 promoted the differentiation of spermatogonia through the SMAD1/5/8 pathway as reflected by increases in Kit and Sohlh2 expression. Co-treatment with BMP8 impaired the GDNF effect on the maintenance of SSC stemness as reflected by suppression in the expression of GDNF-induced self-renewal genes. In the cultured testis explants, BMP8 treatment not only up-regulated the expression of meiotic and post-meiotic markers but also increased the production of meiotic germ cells. Round spermatid injection (ROSI) in combination with embryo transplantation demonstrated the spermatids derived from BMP8 treatment were functionally competent for fertilization and subsequent development into a pup. Thus, we concluded that BMP8 participates in the maintenance of spermatogenesis by promoting spermatogonia proliferation and subsequent differentiation through different SMAD pathways. Addition of BMP8 can sustain spermatogenesis in vitro and this may have clinical perspectives in assisted reproduction techniques.

Funding Source: This work was supported by Ministry of Science and Technology in Taiwan, under Grant MOST103-2314-B-010-006-MY3

14:45 – 15:10

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

Saitou, Mitinori

Kyoto University, Japan

The germ cell lineage ensures the creation of new individuals, perpetuating/diversifying the genetic and epigenetic information across the generations. We have been investigating the mechanism for germ cell development, and have shown that mouse embryonic stem cells (ESCs)/induced pluripotent stem cells (iPSCs) are induced into epiblast-like cells (EpiLCs), which are in turn induced into PGC-like cells (PGCLCs) with characteristics of migrating PGCs. Importantly, PGCLCs bear a robust capacity both for spermatogenesis and oogenesis, upon transplantation or aggregation with gonadal somatic cells followed by appropriate

culture. Based on this system, we have shown that human induced pluripotent stem cells (hiPSCs) with a primed pluripotency differentiate into incipient mesoderm-like cells (iMeLCs), which robustly generates human primordial germ cell-like cells (hPGCLCs) with a transcriptome similar to those in human PGCs. Furthermore, we have investigated the mechanism for the pre- and post-implantation development of a non-human primate, cynomolgus monkeys, and have defined a developmental coordinate of the spectrum of pluripotency among mice, monkeys, and humans. We have made an unexpected finding that the germ cell lineage in primates is specified in the nascent amnion segregated from early post-implantation epiblast, providing a critical insight into the biological relevance of the hPGCLC induction pathway. I would here like to discuss our ongoing efforts towards understanding the mechanism of and reconstituting in vitro of germ cell development in mice, monkeys, and humans.

SATURDAY, 17 JUNE, 13:15 – 15:15

CONCURRENT IVD: ETHICS AND REGULATORY CONSIDERATIONS

Level 2, Room 205A

13:20 – 13:45

HUMAN GENOME EDITING: ETHICS AND GOVERNANCE

Charo, Alta[1] and Hynes, Richard[2]

[1]University of Wisconsin, Madison, WI, U.S., [2]HHMI and Massachusetts Institute of Technology, Cambridge, MA, U.S.

On February 14, the National Academy of Sciences and National Academy of Medicine released a comprehensive study on human genome editing. Its main conclusions were that existing ethical norms and regulatory structures were sufficient to manage both laboratory research and somatic therapy; that uses of genome editing for so-called "enhancement" are unlikely at present to meet basic risk/benefit standards, but as risks will probably diminish over time, additional public consideration is needed for decisions about governance of these applications; and that germline editing should be moved from the category of "unthinkable" to the category of "maybe, but only if..." in the context of prevention of serious disease and disability. As co-chair of the study (with Richard Hynes of MIT/HHMI), this presentation will survey the highlights and discuss the evolution of thinking on the question of germline genetic modification.

13:45 – 14:00

ASSESSING AND ANALYZING THE 14-DAY GUIDELINE ON HUMAN EMBRYO RESEARCH FROM ETHICAL AND POLITICAL AND SCIENTIFIC PERSPECTIVES

Matthews, Kirstin RW[1] and Tsao, Sharon[2]

[1]Rice University, Houston, TX, U.S., [2]Baker Institute for Public Policy, Rice University, Houston, TX, U.S.

A 14-day limit guides embryo research in the US, U.K. and many other national and funding policies. No human embryo or embryonic cell can be grown in vitro past the 14th day of development. This deadline restricts human embryo research in the lab to a stage prior to the formation of the primitive streak, an observable, early step towards the formation of neural tissue. It has been adopted in several national and organization guidelines without review—analogous to some physician 'standard-of-care' decisions that can be guided by tradition and lack scientific evidence to support them. Until recently, the deadline was more theoretical, as scientists were unable to grow embryos that long in vitro. This changed in 2016 when two labs cultured embryos to 12 days. Examining human embryos past day 14 could improve our understanding of human developmental biology. But before scientists engage in advocacy to eliminate or move the date, they should also consider the ethical and political consequences of their actions. This research will review different ethical and political perspectives regarding expansion of embryo research beyond the current 14-day limit and how it was developed. Questions to consider include: How should decisions regarding the appropriate limit for embryo research be made? What are the questions scientists, ethicists and policymakers should be asking when assessing the deadline? What is the potential scientific knowledge and what are the potential therapeutic gains that may be achieved with increasing embryo research from 14 days to alternative later stages of embryo development, which cannot be obtained from alternative models? Should science determine the boundaries of embryo research, or should other ethical concerns take precedence? What questions should society ask when determining limitations to human embryo research? Are embryo research and funding policies consistent with public concerns and objectives for advancing science, protecting human life and improving human health? And how are these different in differing national contexts? Our approach to these various questions as well as our answers can lead us to different policies and guidelines.

Funding Source: This research is funded by the Baker Institute's Endowment for International Stem Cell Policy from the State of Qatar.

14:00 – 14:15

ETHICAL DISCUSSION ON THE FIRST-IN-HUMAN STUDY OF IPSC-DERIVED RPE WITH AMD: AN ANALYSIS OF THE REVIEW COMMITTEE MEETING MINUTES

Takashima, Kayo[1], Inoue, Yusuke[1], Tashiro, Shimon[2] and Muto, Kaori[1]

[1]The Institute of Medical Science, The University of Tokyo, Japan, [2]National Cancer Center, Tokyo, Japan

This presentation aims to verify ethical issues for an ethics committee review on a first-in-human (FIH) clinical study using novel stem cells. We examined the case of an FIH study of induced pluripotent stem cell (iPSC)-derived retinal pigment epithelium (RPE) in a patient with age-related macular degeneration in 2014 (hereafter, iPSC-FIH study), as few researchers have analyzed the minutes of ethical discussions on the iPSC-FIH study. First, we identified the ethical issues of the iPSC-FIH study based on two preceding studies and on the committee meeting minutes of the iPSC-FIH study. Seven themes were extracted from two studies: consideration of the favorable risk-benefit ratio; validity of preclinical evidence; evaluation of the previous embryo stem cell-derived RPE transplantation; validity of the target population; issues of informed consent form and therapeutic misconception; evaluation of patients' understanding; and accommodating patients' opinions with a research endpoint. Second, we examined 14 meeting minutes from five review committees to determine how ethical issues pertaining to the iPSC-FIH study were discussed. We divided the transcripts into 471 segments so that one segment contained one question and answer. The ethical issues were then assessed based on preceding studies, and additional ethical issues were identified. As the result, we found that proportions of discussion categories were 59% for scientific validity, 32% for participant protection, and 8% for the research review system and organization. Safety issues, including tumorigenicity and genomic instability, in the category of scientific validity were particularly discussed, indicating that these committees were mainly focused on evaluating the safety of using iPSC. The seven ethical issues mentioned above were more or less discussed; however, there was no indication on whether an endpoint was discussed with patient groups. Moreover, as a result of the minute analysis, three new discussion points were identified: press briefings, compensation for research-related injuries, and psychological care for participants. Based on the above results, we suggest that reviewers evaluating FIH study using novel stem cells could include the previously mentioned seven ethical issues as well as the three new discussion points.

Funding Source: This research was partially supported by the Highway Program for Realization of Regenerative Medicine from Japan Agency for Medical Research and Development, AMED.

14:15 – 14:30

THE IMPACT OF CIVIL LAWSUITS ON DIRECT-TO-CONSUMER MARKETING OF STEM CELL INTERVENTIONS

Master, Zubin[1], Horner, Claire[1], Sipp, Douglas[2] and Tenenbaum, Evelyn[3]

[1]Alden March Bioethics Institute, Albany Medical College, NY, U.S., [2]RIKEN, Kobe, Japan, [3]Albany Law School, NY, U.S.

The direct-to-consumer marketing of unproven stem cell interventions (SCIs) was originally thought to be a symptom of lax regulations and enforcement in developing nations. Two papers published in 2016 challenge this concept showing a significant rise of clinics in economically developed countries including the U.S., Australia, Ireland and Germany. Although further active enforcement with stiffer penalties may be able to shut down such clinics, regulatory policies in many countries have shifted in the opposite direction. National efforts to develop pathways for conditional approval of regenerative medicine products after preliminary safety testing are a notable example of this deregulatory trend. Here, we review the cases filed against stem cell companies and analyze the potential effectiveness of lawsuits as a tool to combat stem cell tourism. Lawsuits may be effective in seeking compensation for patients, raising public and political awareness, and setting practice standards for clinics. Individual lawsuits may raise awareness and set legal precedent. During discovery, individual lawsuits may uncover previously undisclosed information triggering an FDA investigation. Class action lawsuits, on the other hand, are less likely to be successful in combatting stem cell tourism than individual cases because it will be difficult to certify a class of similarly-situated plaintiffs given the differences in plaintiffs' medical conditions, the variety of SCIs sought, and the numerous individual clinics that operate as small entities instead of larger aggregates. Moreover, class actions often result in settlement without a judgment on the merits. While the settlement may include an agreement by the clinic to change its practices going forward, its effect as a legal precedent upon other clinics is limited and it may not attract sufficient media attention. While such lawsuits may be limited in their effectiveness if they settle, successful judgments for patients in individual or class action lawsuits will increase publicity on the possible adverse consequences of SCIs, set legal standards, and potentially encourage politicians and federal authorities to strengthen regulations and enforcement in developed economies.

14:30 – 14:45

20 YEARS OF HUMAN PLURIPOTENT STEM CELL IMPACT: PATENTS, PUBLICATIONS, AND FUNDING

Ludwig, Tenneille and Drape, Robert

WiCell, Madison, WI, U.S.

The impact of the original derivation and subsequent worldwide distribution of human embryonic stem (ES)

cells unlocked an entire new field of regenerative medicine. The resulting explosion in research and advances in technology were unimaginable just a quarter century ago. In the last 20 years, the initial five cell lines (H1, H7, H9, H13 and H14) have been distributed more than 4500 times to over 2000 investigators at nearly 800 separate institutions in 43 countries. We interrogated numerous databases and search engines (including PubMed, NIH RePorter, Google Scholar, Cellosaurus, Resource Identification Initiative, ScienceDirect, USPTO, etc.) to amass information on the total number human pluripotent stem cell (PSC) publications since the initial ES cell derivations. We also report the extent of governmental funding for PSC academic research and small businesses. Overall, NIH funding for PSC research from 1997-2016 exceeded $7.65 billion spread across more than 22,000 projects representing 739 investigators and 155 companies in 49 states and Canada. SBIR-STTR funding of PSC research exceeded $100 million for 368 projects involving 155 companies in 33 states. Additional data collected includes the total number of patents issued internationally, and highlights the resulting commercial expansion in the field. Taken together, these data provide insight into the overall global impact of human PSC research.

14:45 – 15:10

EMERGING BIOMEDICAL TECHNOLOGY: A BRAVE NEW WORLD

Daley, George Q.

Boston Children's Hospital and Harvard Medical School, MA, U.S.

Recombinant DNA technology, dating from the 70s, ushered in a revolution in biomedicine and the editing of genes and genomes—of bacteria, plants, and model organisms. In parallel, techniques for assisted human reproduction emerged, starting in 1978 with a birth by in vitro fertilization. Genome editing has been practiced since the advent of recombinant DNA, and recently has translated into curative therapies for genetic disease by gene therapy. Until recently, the methodology of gene editing has been cumbersome, but CRISPR/Cas9 has changed the prospects for altering our environment and ourselves. I will discuss the implications of this new technology for beneficial applications in medicine, while also highlighting regulatory efforts by the international scientific community.

SATURDAY, 17 JUNE, 13:15 – 15:15

CONCURRENT IVE: DISEASE MODELING

Level 3, Ballroom West

13:20 – 13:45

PATHWAYS REGULATING STEM CELL INDUCTION, SELF-RENEWAL, AND ENGRAFTMENT

Zon, Leonard I.

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

Hematopoietic stem cell transplantation involves the homing of stem cells to the marrow, an active process of engraftment, and the self-renewal of the blood stem cells. We have been using the zebrafish as a model to study the molecular biology of this process. Blood stem cells are born in the dorsal aorta of the developing embryo. By imaging RUNX1 GFP+ cells arriving in the next site of hematopoiesis (the caudal hematopoietic territory), engraftment can be visualized. This process involves an attachment phase and then an extravasation to the abluminal side of the endothelial cells. The endothelial cells cuddle the hematopoietic stem cell and the stem cells are maintained in a quiescent fashion or to divide symmetrically or asymmetrically. Using chemical screens, we have found small molecules that can enhance engraftment or suppress engraftment. We have also been studying the role of macrophages in the stem cells in their niche. We have used a pluripotent cell culture to produce HSCs, and have found certain culture conditions and transcription factors that induce markers of self-renewing HSCs. Our studies have uncovered stages of stem cell engraftment that are altered by chemicals, which could have therapeutic value in marrow transplantation procedures.

13:45 – 14:00

MODELING ZIKA VIRUS EXPOSURE AND SCREENING THERAPEUTIC COMPOUNDS WITH HUMAN IPSC-DERIVED NEURAL CELLS

Wen, Zhexing[1], Hammack, Christy[2], Ogden, Sarah[2], Qian, Xuyu[3], Xu, Miao[4], Lee, Emily[2], Zhang, Feiran[2], TCW, Julia[5], Li, Yujing[2], Yao, Bing[2], Shin, Jaehoon[3], Huang, Wei-Kai[3], Christian, Kimberly[3], Brennand, Kristen[5], Xia, Menghang[4], Jin, Peng[2], Zhang, Wei[4], Tang, Hengli[2], Song, Hongjun[3] and Ming, Guo-li[3]

[1]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, U.S., [2]Florida State University, Tallahassee, FL, U.S., [3]Johns Hopkins University School of Medicine, Baltimore, MD, U.S., [4]National Institutes of Health, Bethesda, MD, U.S., [5]Icahn School of Medicine at Mount Sinai, New York, NY, U.S.

Zika virus (ZIKV), a mosquito-borne flavivirus, is currently reported to be circulating in approximately 60 countries

and territories globally. While ZIKV infection has been linked to microcephaly in newborns and other brain abnormalities such as Guillain-Barré syndrome, how ZIKV impairs brain development and function is unknown. Here we show that three stains of ZIKV, Puerto Rican ZIKVPR, Asian ZIKVC and African ZIKVM, directly infects human induced pluripotent stem cell (hiPSC)-derived cortical neural progenitor cells (hNPCs) with high efficiency. Infected hNPCs further secrete infectious ZIKV particles. Importantly, ZIKV infection increases cell death and dysregulates cell cycle progression, resulting in attenuated hNPC growth. Gene expression analyses of infected hNPCs reveal transcriptional dysregulation, notably of cell cycle-related pathways. In addition, we performed a drug repurposing screen of ~6,000 compounds and identified leading compounds that either inhibit ZIKV infection or suppress infection-induced caspase-3 activity in hiPSC-derived neural cells. Our results thus fill a major gap in our knowledge about ZIKV biology and serve as an entry point to establish a mechanistic link between ZIKV and microcephaly. Our study also provides a tractable experimental model system for investigating the impact and mechanism of ZIKV on human brain development. Of equal importance, our high-throughput screening platform with hiPSC-derived neural cells has led to the identification of therapeutic compounds that either suppress ZIKV infection or ameliorate its pathological effects during neural development, which may have an immediate effect on the development of anti-ZIKV therapeutics.

14:00 – 14:15

USING AN INDUCED PLURIPOTENT STEM CELL MODEL TO UNDERSTAND AND TREAT IDIOPATHIC PULMONARY FIBROSIS

Gomperts, Brigitte[1], Vijayaraj, Preethi[1], Durra, Abdo[2], Mehrabi, Mehrsa[3], Minasyan, Aspram[1], Karumbayaram, Saravanan[1], Damoiseaux, Robert[1] and Graeber, Thomas[1]

[1]University of California, Los Angeles, CA, U.S., [2]InSpira LLC, Los Angeles, CA, U.S., [3]University of California, Irvine, CA, U.S.

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive and invariably lethal interstitial lung disease of unknown etiology. IPF represents the most common cause of death from progressive lung disease with no effective therapy besides lung transplantation. This is in large part due to the fact that the pathogenesis of IPF remains unclear. It is thought to mostly be a complex disorder involving a genetic predisposition and an environmental trigger. There are currently no assay systems for drug discovery or animal models for efficacy studies that truly recapitulate IPF. To address these issues, we have generated and extensively characterized an induced pluripotent stem cell (iPSC) based in vitro disease model that closely phenocopies IPF in a dish. These cells spontaneously and progressively form fibrotic foci when cultured over several days. Live cell imaging, transcriptomic analysis, atomic force microscopy, immunostaining, apoptosis assays and cytokine arrays were used to characterize these scars and compare them to IPF tissue. We found that the progressive scarring is driven by signals that include damage associated molecular patterns that drive a robust pro-inflammatory response, leading to the observed phenotype. Using the model, we developed a primary phenotypic high throughput drug screening assay to identify compounds that would target one or more of the phenotypic characteristics of our model, such as increasing apoptosis of hyper-proliferative fibroblasts, targeting extracellular matrix interactions, or targeting the increased stiffness of the cells. We identified a small molecule that prevents the formation of fibrosis and resolves fibrosis that has already formed in the dish as well as in lung slice tissue cultures from IPF patients. This small molecule imparts its wound healing and anti-fibrotic effect by activating TNF, IL-1 and interferon regulated genes including pentraxins (NPTX1 and PTX3). Pentraxins are endogenous regulators of tissue repair, that initiate the phenotypic switch of pro-inflammatory macrophages to pro-resolutive macrophages which may account for the anti-fibrotic effect seen in our pre-clinical models of IPF.

Funding Source: R01GM114259-01

14:15 – 14:30

A NOVEL 3D IN VITRO APPROACH TO MODEL LIVER DISEASES USING HUMAN INDUCED PLURIPOTENT STEM CELLS

Morell, Carola Maria[1], Perrin, Marion[1], Tilson, Samantha[1], Gieseck, Richard[1], Geti, Imbisaat[1], Rimland, Casey[1], Sampaziotis, Fotios[1] and Vallier, Ludovic[2]

[1]Wellcome Trust - Medical Research Council Stem Cell Institute, Anne McLaren Laboratory, Department of Surgery, University of Cambridge, U.K., [2]Wellcome Trust - Medical Research Council Stem Cell Institute, Anne McLaren Laboratory, Department of Surgery, University of Cambridge; Wellcome Trust Sanger Institute, Cambridge, U.K.

Liver disorders are becoming one of the most common causes of death in developed countries and liver transplantation is the only available treatment for end stage disease. This procedure carries considerable risk and also implies immune suppression treatment associated with heavy side effects. Furthermore, the development of new therapeutics has been hampered by the difficulty to grow primary hepatic cells and the lack of a suitable tool to faithfully reproduce human liver injuries. Human hepatocyte-like cells (HLCs) generated from human Induced Pluripotent Stem Cells (hIPSCs) could provide an advantageous alternative since they can be produced in large quantity from a diversity of patients. However, culture systems currently available don't reproduce the complexity of liver architecture and its cellular diversity, both of which necessary to model complex liver disorders. Here, we have optimized a 3D cell culture platform to mimic hepatic microenvironment and to reproduce complex cell-cell interactions by co-culturing different hepatic cell types known to be involved in liver fibrosis. More precisely, hepatic cells generated from hIPSCs were cultured in the Real Architecture for 3D Tissue system (RAFT), taking advantage of fluorescent reporter cell lines to monitor cell survival and cell-cell interactions. When grown in the RAFT, HLCs retained the expression of

hepatocytes markers (such as Alb, HNF4a, TTR, a1aT, albumin production, CYP3A4 activity) while their functional maturation improved, as confirmed by lower AFP expression with time in culture. Cholangiocytes grown in the RAFT also preserved their biliary identity and when co-cultured, HLCs spontaneously rearranged around biliary cells, without losing their functionality. Adding hepatic stellate cells to the RAFT did not induce an activated myofibroblast-like phenotype unless stimulated with TGFß. Similarly, macrophage polarization was not influenced by the 3D environment. Considered together, these results demonstrate that hepatic cell types can be grown in vitro in a 3D environment without losing their characteristics. This model mimics the physiological cellular interactions of the liver thereby providing a new platform for drug screening and for studying liver organogenesis.

Funding Source: This work is supported by the NC3Rs Project grant (NC/N001540/1) and the ERC consolidator grant Relive-IMDs

14:30 – 14:45

DISSECTING THE CELLULAR ORIGIN OF DOWN SYNDROME TMD AND AMKL

Ditadi, Andrea[1], Lechman, Eric[2], Dick, John[2] and Keller, Gordon[2]

[1]San Raffaele Telethon Institute for Gene Therapy-TIGET, Milan, Italy, [2]University Health Network, Toronto, ON, Canada

Down syndrome (DS)/trisomy 21 children have a high risk of developing hematopoietic malignancies, including the characteristic perinatal transient myeloproliferative disorder (TMD) and acute megakaryoblastic leukemia (AMKL). Both TMD and AMKL are associated with somatic mutations in GATA1, which result in the production of a truncated protein termed GATA1s. To date, the cell of origin that acquires the GATA1s mutation in TMD and AMKL remains unidentified. Analysis of the microRNAs (miRNAs) signature of adult myeloid leukemia stem cells identified miR-99a, miR-125b, miR-155, all encoded by chromosome 21. When engrafted into NSG recipients, CD34+CD38- cord blood cells overexpressing these 3 miRNAs (OE) initiate a lethal disease with characteristics of DS-AMKL, including splenomegaly and liver infiltration, and generated a high proportion of CD41+ megakaryocytes. Proteomic analysis revealed an increase in the naturally occurring GATA1 short splice form, suggesting that OE induces a rapid change in the splicing pattern of GATA1 or enriches for a population of cells preferentially expressing GATA1s. The perinatal onset of TMD and AMKL suggests an early developmental origin of the progenitors responsible for the disease. Using human pluripotent stem cell (hPSC) differentiation to recapitulate embryonic development, we found that cells sharing characteristics of yolk sac (YS)-derived erythro-myeloid progenitors (EMP), but not YS-derived primitive progenitors, are sensitive to the 3 miRNAs expression. OE in the EMP-like population led to an in vitro expansion of megakaryocytic progenitors that failed to undergo terminal differentiation and endowed them with engraftment capacity, as CD41+CD61+CD42+ xenografts were detected in NSG recipients. Taken together, our studies provide unique and previously unrecognized insights into the progenitor target population and the mechanism responsible for DS-associated leukemogenesis.

14:45 – 15:10

REGULATION OF PROGENITOR CELLS IN THE ADULT LUNG AND IN LUNG CANCER

Kim, Carla[1], Lee, Joo-Hyeon[2] and Rowbotham, Samuel[1]

[1]Boston Children's Hospital, MA, U.S., [2]University of Cambridge, U.K.

Our laboratory has pioneered the use of stem cell biology approaches for the study of adult lung progenitor cells and lung cancer. Through a combination of mouse genetics and cell biology, we have developed tools to identify and characterize cells with progenitor cell activity in adult lung tissue. We have also applied our expertise to the study of lung cancer, which resulted in our definition of the cancer stem cell populations in the two most common types of lung cancer. We have examined the mechanisms that regulate lung progenitor cell self-renewal and differentiation in the normal lung and in the context of lung cancer. One major focus in our lab has been the creation of three-dimensional co-culture and co-transplantation organoid systems that have begun to define the cell-cell crosstalk between epithelial progenitors, endothelial cells and mesenchymal cells in the lung. I will discuss how we have recently used our organoid system to define lung mesenchymal cell types that specifically regulate airway or alveolar epithelial cells. I will also present new studies in which we have examined how epigenetic factors, particularly H3K9 methyltransferases and demethylases, affect lung injury repair, lung tumorigenesis and response to therapy in lung cancer.

SATURDAY, 17 JUNE, 13:15 – 15:15

CONCURRENT IVF: ROAD TO THE CLINIC II

Level 2, Room 258AB

13:20 – 13:45

EPIDERMAL STEM CELL-MEDIATED COMBINED CELL AND GENE THERAPY FOR EPIDERMOLYSIS BULLOSA

De Luca, Michele

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

Abstract not available at time of printing.

13:45 – 14:00

PHASE I/IIA CLINICAL TRANSPLANTATION TRIAL OF HUMAN EMBRYONIC STEM CELL-DERIVED RETINAL PIGMENT EPITHELIUM (OPREGEN®) IN DRY AGE-RELATED MACULAR DEGENERATION: INTERIM RESULTS

Reubinoff, Benjamin E.[1], Banin, Eyal[2], Hemo, Yitzchak[2], Tareq, Jaouni[2], Marks-Ohana, Devora[2], Stika, Shelly[2], Zheleznykov, Svetlana[2], Obolensky, Alexey[2], Gurevich, Maria[3], Netzer, Nir[3], Bohana-Kashtan, Osnat[3], Tannenbaum, Shelly[4], Gamburg, Orit[3], and Irving, Charles[3]

[1]Center for Human Embryonic Stem Cell Research, Goldyne Savad Institute; and the Department of Gynecology and Obstetrics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [2]Center for Retinal and Macular Degenerations, Department of Ophthalmology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel, [3]Cell Cure Neurosciences Ltd, Jerusalem, Israel, [4]Center for Human Embryonic Stem Cell Research and the Department of Gynecology and Obstetrics, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Transplantation studies using autologous retinal pigmented epithelium (RPE) cells in age-related macular degeneration (AMD) patients suggest that introducing healthy RPE cells may be of benefit. Over the last decade we developed the technology to derive RPE cells from hESCs using a directed differentiation, xeno-free protocol. Safety and tolerability of this cell product, OpRegen, is now being evaluated in a dose-escalating Phase I/IIa clinical study in patients with advanced dry AMD accompanied by geographic atrophy (NCT02286089). Here we report accumulated safety and imaging data from the 1st and 2nd cohorts of patients, who received a subretinal transplant of 50k or 200k OpRegen cells in suspension, with up to 1 year follow up. Transplantation was performed by subretinal injection following conventional vitrectomy under local anesthesia. Systemic immunosuppression is administered from 1 week prior to transplantation until 1 year after. Systemic and ocular safety is closely monitored. Retinal function and structure are assessed using various techniques including BCVA, and color, OCT and fundus autofluorescence (FAF) imaging. At date of writing, dosing of cohort 1 of 3 patients (ages 74-80 years) who received 50k cells has been completed with a follow-up of 1 year, 9 and 6 months, and 2 out of 3 patients from cohort 2 (ages 65 and 82) were dosed with 200k cells. Surgery was uneventful, with subretinal fluid absorbing within < 48 hours. OCT imaging showed healing of the retinal penetration site by 2 weeks post-op. Treatment has been well tolerated systemically and with regard to ocular findings. Imaging changes associated with OpRegen include subretinal pigmentation in area of transplant in 4 out of 5 patients, often accompanied by hypo- and hyper-fluorescent spots on FAF imaging and irregular reflectance above areas of atrophy and host RPE on OCT scans. These changes develop over the first 2-3 months and persist through the latest time point examined. Of note, epiretinal membranes that do not require surgical intervention were observed. In conclusion, subretinal transplantation of OpRegen in patients with advanced dry AMD appears well tolerated to date. Findings on imaging suggest presence of cells in the subretinal space. These results provide a framework for functional assessments in cohorts at higher doses.

Funding Source: Cell Cure Neurosciences Ltd, Jerusalem Israel

14:00 – 14:15

ELIMINATING RESIDUAL UNDIFFERENTIATED CELLS FROM HUMAN IPS-DERIVED PRODUCTS BY HEAT SHOCK PROTEIN 90 INHIBITORS

Masuda, Shigeo, Miyagawa, Shigeru, Khurram, Maaz Asher, Kawaguchi, Kohei, Ishikawa, Tsuyoshi, Saito, Atsuhiro and Sawa, Yoshiki

Department of Cardiovascular Surgery, Osaka University Graduate School of Medicine, Japan

Heat shock protein 90 (HSP90) is a molecular chaperone that regulates protein folding and stabilizes protein. Since it has been demonstrated that cancer cells exhibit higher expression of HSP90 and are highly addicted to HSP90 for their survival, HSP90 inhibitors are emerging as a promising molecular-targeted drug for cancer treatment. Here, we explore whether HSP90 inhibitors are able to remove undifferentiated cells in vitro from human iPS-derived cardiomyocytes (iPS-CMs) in order to pursue safer clinical application of human iPS cells. First, we examined HSP90 mRNA expressions both in human iPS cells and human CMs (i.e. iPS-CMs and primary CMs), and found that human "pure" iPS cells show higher expression of HSP90 than CMs. Next, to determine the effects of HSP90 inhibitors on proliferation of human iPS cells or iPS-CMs, we added potent HSP90 inhibitors (TAS-116 or PU-H71) to these cells in vitro, and observed preferential killing of human "pure" iPS cells. Furthermore, it was shown that human iPS-CMs after treatment with HSP90 inhibitors contained fewer undifferentiated cells (which are positive for Lin28) than those without treatment, suggesting that residual undifferentiated cells were efficiently eliminated by treatment with HSP90 inhibitors, while leaving iPS-CMs intact. Although most HSP90 inhibitors under current clinical trials cause problematic toxicities, TAS-116 developed by Taiho Pharmaceutical Co. has been demonstrated to be a highly selective inhibitor with less-toxicity, and is currently under phase I/II trials targeting solid cancers. Taken together, these results indicate that HSP90 inhibitors (TAS-116 and PU-H71) are potent in ex vivo purging of undifferentiated cells among human iPS-derived products.

14:15 – 14:30

IDENTIFYING PATHWAYS TO STEM CELL TREATMENTS AND OPPORTUNITIES TO BUILD ROADBLOCKS: AN ANALYSIS OF THE EXPERIENCES OF PEOPLE WITH SPINAL CORD INJURY

Munsie, Megan[1], Tanner, Claire[1], Phillips, Kate[2] and Nunn, Andrew[3]

[1]Anatomy and Neuroscience, University of Melbourne, Parkville, Australia, [2]Health and Disability Strategy Group, Transport Accident Commission and Worksafe, Geelong, Victoria, Australia, [3]Spinal Cord Service, Austin Health, Heidelberg, Victoria, Australia

Most people with spinal cord injury (SCI) undertake their own search for curative or restorative therapies following injury. Some invest their hope in unproven commercial stem cell therapies (SCTs) and choose to undertake costly and potentially hazardous travel to receive them. Drawing on qualitative interviews with Australians with a SCI who had accessed unproven SCTs, this presentation considers the factors influencing people's decision to undergo unproven commercial SCTs. We identify and discuss key factors in their decision to pursue such interventions including: media reports; hopelessness following injury and diagnosis; perceived lack of care and emphasis on compensatory rather than curative strategies in healthcare settings at home; communication with providers and anecdotal stories of people who had undergone SCTs, and; perceived judgment and lack of clear, consistent information from professionals when seeking advice. We argue that there are clear opportunities for intervention throughout people's healthcare journey, particularly during rehabilitation, where those affected by SCI could be better supported. Further, that there is a clear need to engage with healthcare professionals and peer support agencies to better equip them to manage the hope invested in stem cell interventions by those with SCI. Finally, we suggest that empirical research into the experiences and needs of health professionals is required to develop effective education and professional development strategies tailored for specific health professions, conditions and healthcare settings.

14:30 – 14:45

GENERATION AND FUNCTIONAL CHARACTERIZATION OF SODIUM IODIDE SYMPORTER TRANSGENIC RHESUS INDUCED PLURIPOTENT STEM CELLS

Yada, Ravi Chandra[1], Ostrominski, John[1], Sato, Noriko[1], Lin, Yongshun[1], Zou, Jizhong[1], Palisoc, Maryknoll[1], Pittaluga, Stefania[1], Peng, Kah-Whye[2], Hong, So Gun[1] and Dunbar, Cynthia[1]

[1]National Institutes of Health, Bethesda, MD, U.S., [2]Imanis Life Sciences, Rochester, MN, U.S.

Non-human primate induced pluripotent stem cells (iPSCs) offer the opportunity to investigate safety, immunogenicity and functional integration of iPSC-derived cells and tissues in clinically relevant models. However, there have been limited preclinical longitudinal studies incorporating in vivo molecular imaging for long-term assessment of localization and persistence of iPSC-derived cells. Here we develop the sodium iodide symporter (NIS), a non-immunogenic endogenous reporter gene, to enable non-invasive radionuclide tracking of transplanted iPSC-derived cells via positron emission tomography-computed tomography (PET/CT). Endogenous NIS is expressed mainly in the thyroid, salivary glands, and stomach, and can be ectopically expressed in other cell types, conferring the ability to uptake various radionuclide tracers appropriate for imaging. Using the CRISPR/Cas9 mediate platform, we have successfully generated rhesus macaque iPSC (RhiPSC) clones with rhesus NIS introduced at one or both alleles of the adeno-associated virus site 1 (AAVS1) safe harbor locus. RhiPSC-NIS clones showed robust expression of NIS from a constitutive CAG promoter, confirmed by immunostaining and demonstrated significant uptake of the radiotracer in vitro compared to parental RhiPSC clones. Moreover, the uptake activity was blocked by KClO4, a specific inhibitor of NIS, indicating the accumulation of the radiotracer within the cells was mediated by NIS. To validate the functionality of the targeted NIS transgene in vivo, 5 million RhiPSCs-NIS were injected into the hindlimb of immunodeficient mice. RhiPSCs-NIS-derived teratomas could be visualized by PET/CT as early as 2 weeks post-injection, prior to visible or palpable teratoma development. Quantitative analysis of the PET/CT data over time showed that total intensity from the injection site as well as mean intensity steadily increased between 2, 4, and 6 weeks in all mice. Both monoallelic and biallelic RhiPSCs-NIS could be equally well detected. In conclusion, our data suggests that NIS-mediated in vivo imaging is feasible via safe-harbor targeting of NIS transgene in RhiPSCs. Directed differentiation of these RhiPSCs-NIS to clinically relevant target cells such as cardiomyocytes are on-going and functional data will be presented.

Funding Source: This research was supported by the Intramural Research Program of the NIH, NHLBI, Hematology Branch.

14:45 – 15:10

TOTAL HUMAN EYE ALLOTRANSPLANTATION: FROM EXPERIMENTAL MODEL TO CLINICAL REALITY

Washington, Kia

Department of Plastic Surgery, University of Pittsburgh, PA, U.S.

Approximately 37 million people throughout the world suffer from blindness with up to 20% having only visual light perception or less. The permanent nature of blindness from macular degeneration, diabetic retinopathy, glaucoma, and trauma results in a significant decline in quality of life, ability to return to the workforce, and presents pressing challenges to the medical and military communities. Whole eye transplantation can potentially provide an intact visual system in the setting of irreversible eye injury and blind-

ness. Many obstacles remain to implementing whole eye transplantation, including donor retinal ganglion cell preservation and optic nerve regeneration. We will review our progress with establishing a vascularized orthotopic whole eye transplantation small animal model. We will also review our progress in examining the ethical considerations, and lastly surgical implementation of whole eye transplantation with human cadaver dissection.

SATURDAY, 17 JUNE, 13:15 – 15:15

CONCURRENT IVG: TISSUE ENGINEERING AND CLINICAL APPLICATIONS

Level 2, Room 205BC

13:20 – 13:45

EXOGENOUS STEM CELL TRANSPLANTATION AND ENDOGENOUS STEM CELL STIMULATION IN THE CENTRAL NERVOUS SYSTEM

Shoichet, Molly S., Mitrousis, Nick, Tuladhar, Anup, Payne, Samantha, Ballios, Brian G. and Cooke, Michael

University of Toronto, ON, Canada

Regenerative medicine strategies include both exogenous stem cell transplantation and endogenous stem cell stimulation. Overcoming devastating diseases of the central nervous system, such as stroke and blindness, is particularly challenging because the delivery strategies themselves are complicated by the blood-brain barrier. To overcome this limitation, we have designed strategies that circumvent the blood-brain barrier requiring direct stem cell transplantation in the tissue and/or direct delivery of biomolecules to the tissue. In diseases, such as blindness due to age-related macular degeneration and stroke, we are focused on delivery of stem cell progenitors. For blindness, photoreceptors and retinal pigment epithelial cells are promising cells for delivery. Using an innovative hydrogel matrix comprised of hyaluronan and methyl cellulose (HAMC), retinal stem cell distribution, survival and integration have been enhanced in mouse models of blindness. For stroke, neural stem cells and induced pluripotent stem cell-derived neuroepithelial stem cells are promising cells for delivery to the cortex in rodent models of stroke. For tissue repair after stroke, we investigated endogenous stem cell stimulation of the adult neural stem/progenitor cells of the subventricular zone that line the lateral ventricles. The sequential delivery of epidermal growth factor (EGF) and erythropoietin (EPO) from polymeric nanospheres, dispersed in HAMC and applied directly on the mouse brain cortex, showed tissue repair. Similarly, the co-delivery of cyclosporineA (CsA) and EPO from polymeric nanospheres from HAMC and applied directly to the rat brain cortex, promotes tissue and functional repair in an endothelin-1 model of stroke. In this way, the blood-brain barrier was circumvented and the invasive strategy associated with intraventricular delivery obviated. We continue to refine our bioengineering strategies with: co-delivery of cells and pro-survival and/or pro-integration factors; and innovative ways to control release, taking advantage of affinity and/or electrostatic interactions.

13:45 – 14:00

RESTORATION OF A NEUROEPITHELIAL NETWORK AND NEURON-DEPENDENT MOTILITY IN HUMAN INTESTINAL ORGANOID-DERIVED TISSUE-ENGINEERED SMALL INTESTINE

Schlieve, Christopher R.[1], Fowler, Kathryn[1], Hajjali, Ibrahim[1], Hou, Xiaogang[1], Huang, Sha[2], Thorton, Matthew[1], Grubbs, Brendan[1], Spence, Jason[2] and Grikscheit, Tracy[1]

[1]Children's Hospital Los Angeles, CA, U.S., [2]University of Michigan, Ann Arbor, MI, U.S.

Failed migration, acquired dysfunction, or death of enteric neural crest cells (ENCC) can lead to significant mechanical dysmotility of the enteric nervous system (ENS). Restoration of the ENS through cellular transplantation of human pluripotent stem cell (hPSC)-derived ENCC could provide an alternative approach for treating enteric neuropathies. We have previously generated hPSC-derived tissue-engineered small intestine (TESI) from human intestinal organoids (HIO). However, HIO-TESI is devoid of an ENS. In a previous report of combined HIO with hPSC-derived ENCC, a fetal-like ENS was established that lacked mature neurocircuitry and retention of specific neuronal subtypes observed in postnatal intestine. The purpose of our study is to establish a mature ENS derived exclusively from hPSC in HIO-TESI. ENCC supplementation of HIO-TESI generates ENCC-HIO-TESI with mature submucosal and myenteric ganglia that retain expression of several ENCC markers (PHOX2B, RET, TRKC and EDNRB) after 3 months in vivo. ENCC-HIO-TESI repopulates ChAT-positive excitatory neurons, nNOS-positive inhibitory neurons, and 5-HT-positive interneurons. In ENCC-HIO-TESI, Tuj1-positive neurons associate with CKIT-positive interstitial cells of Cajal (ICCs) within the smooth muscle and form synaptic connections with epithelial ChgA-positive enteroendocrine cell neuropods, restoring the neuroepithelial circuit observed in mature postnatal intestine. Light-sheet microscopy demonstrated robust Tuj1-positive axonal projections throughout ENCC-HIO-TESI. Methylene blue, an inhibitor of ICC pacemaker activity of the smooth muscle, ablated contractile movements in HIO-TESI. However, neuron-dependent contractility and relaxation was demonstrated in the presence of methylene blue treatment in ENCC-HIO-TESI and terminated with the addition of a potent neurotoxin, tetrodotoxin. Our findings support an innovative approach to restore ENS intraluminal sensory function and motility in ENCC-HIO-TESI and implicate hPSC-derived ENCC as a potential cellular therapy for enteric neuropathies.

14:00 – 14:15

TOWARDS VASCULAR REPAIR USING HUMAN INDUCED PLURIPOTENT STEM CELL-BASED TISSUE-ENGINEERED BLOOD VESSELS

Qyang, Yibing[1], Gui, Liqiong[1], Luo, Jiesi[1], Dash, Biraja[1],Levi, Karen[2], Qin, Lingfeng[1],Wu, Hongwei[1], Zhao, Liping[1], Yamamoto, Kota[1], Hashimoto, Takuya[1], Qiu, Caihong[1], Dardik, Alan[1],Tellides, George[1], Rolle, Marsha W. [2], and Niklason, Laura[1]

[1]Yale University, New Haven, CT, U.S., [2]Worcester Polytechnic Institute, MA, U.S.

Vascular disease due to arterial stenosis or narrowing is the largest cause of morbidity and mortality in the developed world. Tissue-engineered blood vessels (TEBVs) grown using vascular smooth muscle cells (VSMCs) isolated from primary tissue hold great potential as tools for surgical replacement of the affected vessels in patients with vascular diseases. However, the development of TEBVs for clinical application using VSMCs has been hampered by limited accessibility to patient VSMCs, rapid loss of VSMC differentiation in culture, and limited ability of primary VSMCs to expand. Human induced pluripotent stem cells (hiPSCs) offer unlimited supply of cells that can be differentiated into functional VSMCs for tissue engineering. We have developed a robust approach to derive a large quantity of highly enriched VSMCs from hiPSCs (hiPSC-VSMCs) expressing VSMC markers such as alpha-smooth muscle actin, calponin and myosin heavy chain. Based on a highly efficient, one-step self-assembly approach, 3D tissue rings were established using hiPSC-VSMCs. The tissue rings are mechanically robust and can be used for vascular tissue engineering, drug screening and disease modeling of supravalvular aortic stenosis syndrome. Moreover, hiPSC-VSMCs were seeded onto biodegradable polyglycolic acid (PGA) scaffold in bioreactors for vascular tissue growth. A biological blood vessel was constructed with abundant collagen matrix and sound mechanics, which contained cells largely positive for alpha-smooth muscle actin and myosin heavy chain. When TEBVs were implanted into nude rats as abdominal aorta interposition grafts, they remained mechanically intact and patent during a 2-week proof-of-principle study. Additionally, host cells were actively recruited to the adventitial side of the implanted TEBVs. These results indicate that hiPSC-derived TEBVs are implantable and support vascular remodeling. Furthermore, inclusion of pulsatile stretching during bioreactor culture significantly enhanced cellular growth, viability and matrix production of hiPSC-VSMCs, resulting in TEBVs with highly augmented mechanical properties. This is the first report of hiPSC-based implantable TEBVs, and sets the stage for developing autologous or allogeneic grafts for clinical intervention in patients with vascular diseases.

Funding Source: This work was supported by NIH 1K02HL101990-01, 1R01HL116705-01, and Connecticut's Regenerative Medicine Research Fund 12-SCB-YALE-06 (Y.Q.). Work was also supported by R01HL083895-08 (L.E.N.) and R01HL118245-03 (L.G.).

14:15 – 14:30

MESODERM PROGENITOR SELECTION OPTIMIZATION AND 3D MICRONICHE CULTURE ALLOW HIGHLY EFFICIENT ENDOTHELIAL DIFFERENTIATION AND ISCHEMIC TISSUE REPAIR FROM HUMAN PLURIPOTENT STEM CELLS

Na, Jie, Zhang, Fengzhi and Wang, Lin

Tsinghua University, Beijing, China

Generation of large quantities of endothelial cells is highly desirable for vascular research, for the treatment of ischemia diseases, and for tissue regeneration. To achieve this goal, we developed a simple, chemically defined culture system to efficiently and rapidly differentiate endothelial cells from human pluripotent stem cells by going through an MESP1 mesoderm progenitor stage. MESP1 is a key transcription factor that regulates the development of early cardiovascular tissue. Using an MESP1-mTomato knock-in reporter human embryonic stem cell line, we compared the gene expression profile of MESP1+ and MESP1- cells and identified new signaling pathways that may promote endothelial differentiation. We also used a 3D scaffold to mimic the in vivo microenvironment to further improve the efficiency of endothelial cell generation. Finally, we performed cell transplantation to a critical limb ischemia mouse model to test the repair potential of endothelial primed MESP1+ cells. MESP1+ mesoderm progenitors, but not MESP1- cells, have strong endothelial differentiation potential. Global gene expression analysis revealed that transcription factors, essential for early endothelial differentiation, were enriched in MESP1+ cells. MESP1 cells highly expressed Sphingosine-1-phosphate (S1P) receptor and the addition of S1P significantly increased the endothelial differentiation efficiency. Upon seeding in a novel three-dimensional (3D) microniche and priming with VEGF and FGF, MESP1+ cells markedly upregulated genes related to vessel development and regeneration. The 3D microniche also enabled long-term endothelial differentiation and proliferation from MESP1+ cells with minimal medium supplements. Finally we showed that transplanting a small number of endothelial primed MESP1+ cells in 3D microniches was sufficient to mediate rapid repair of critical limb ischemia in a mouse model. Our study demonstrates that combining MESP1+ mesoderm progenitor cells with tissue engineered 3D microniche and a chemically defined endothelial induction medium is a promising route to maximizing the production of endothelial cells in vitro and to augment their regenerative power in vivo.

Funding Source: National Natural Science Foundation of China grants 31171381 and by the National Basic Research Program of China, 973 program, 2012CB966701 to JN.

14:30 – 14:45

TRANSLATION OF TISSUE ENGINEERED HEART REPAIR

Zimmermann, Wolfram H. and Tiburcy, Malte

Institute of Pharmacology and Toxicology, Georg-August-University Goettingen, Germany,

Heart muscle engineering is evolving rapidly towards first-in-patient trials. Proof-of-concept for safety and efficacy according to the proposed mode of action, i.e., functional remuscularization, has been presented in pig and rodent models, respectively. Here we report on the development of a cGMP-compatible protocol for the construction of engineered human myocardium (EHM) for late preclinical trials. EHM are constructed under defined, serum-free conditions and are comprised of either embryonic or induced pluripotent stem cell-derived cardiomyocytes, skin fibroblasts, and collagen type I. Isometrically suspended EHM demonstrated increasing force of contraction with time in culture (6.230.8 mN/mm2 at 8 weeks of culture under 1.5 Hz electrical field stimulation; n=8). Morphologically, EHM are comprised of a functional syncytium composed of rod-shaped cardiomyocytes with classical ultrastructural sarcomere assembly including M-bands. Systolic twitch forces and responses to preload (Frank-Starling Mechanism) and electrical stimulation (Bowditch phenomenon) were similar as observed in bona fide postnatal myocardium. Transcriptome profiling by RNAseq confirmed advanced maturation in EHM vs. parallel 2D culture (n=3/group). We finally demonstrated scalability according to clinical demands (40 million cardiomyocytes in a 35x24 mm single unit tissue patch format) and developed a non-destructive potency assay for the analysis of EHM patch contractile performance. Taken together, we provide proof-of-concept for a cGMP-compatible EHM design with scalability according to clinical demands as well as evidence for morphological, molecular and functional properties of postnatal myocardium. The presented EHM design is presently under evaluation for clinical translation.

Funding Source: DZHK (German Center for Cardiovascular Research), BMBF FKZ 13GW0007A (CIRM-ET3), DFG ZI 708/7-1, 8-1, 10-1; SFB 937 TP18, SFB 1002 TPs C04, S1; IRTG 1618), the Foundation Leducq, NIH (U01 HL099997).

14:45 – 15:10

LENS REGENERATION USING ENDOGENOUS STEM CELLS WITH GAIN OF VISUAL FUNCTION

Zhang, Kang

Shiley Eye Center, University of California, San Diego, CA, U.S.

The repair and regeneration of tissues using endogenous stem cells represents an ultimate goal in regenerative medicine. Human lens regeneration has not yet been successfully demonstrated. Currently, the only treatment for cataracts, the leading cause of blindness worldwide, is to surgically extract the cataractous lens and implant an artificial intraocular lens. However, this procedure has limitations and poses significant risk of complications in infants with cataract. Therefore, the in situ regeneration of a functional lens would be appealing. Here we identify and isolate lens epithelial stem/progenitor cells (LECs) in mammals and show that Pax6 and Bmi-1 are required for LEC renewal and proliferation. We designed a surgical method for cataract removal that preserves the integrity of the lens capsule and its associated endogenous LECs. Using this method, we achieved functional lens regeneration in rabbits and macaques, as well as in human infants with cataract. Our approach conceptually differs from current practice, as it maximally preserves endogenous LECs and their natural environment, and regenerates lenses with visual function. Our findings demonstrate a novel treatment strategy for cataract and provide a new paradigm for tissue regeneration using endogenous stem cells.

SATURDAY, 17 JUNE, 16:00 – 18:30

PLENARY VII: FRONTIERS OF CELL THERAPY

Exhibit Level , Exhibition Hall B1

Sponsored by: Burroughs Wellcome Fund

16:05 – 16:40

KEYNOTE ADDRESS: TECHNOLOGIES FOR READING AND WRITING OMES

Church, George

Harvard Medical School, Boston, MA, U.S.

Beyond transgenics and nuclease-induced knockouts lies the vast possibilities offered by genome-scale reading, writing and testing (aka GP-Write). Applications: (a) humanization for xenotransplants, (b) resistance to viruses and (c) testing of millions of human "variants of unknown significance" (VUS) in vascularized organoids. A comprehensive human transcription-factor library (TF-ome) enables rapid differentiation (4 days) with high efficiency (98%) for many cell types (some previously limited to >60 day and <9% protocols). "In situ sequencing" (FISSeq) provides atlases of omni-omics -- up front to aid choice of TF combinations, and later, to determine/debug fidelity of syn-tissue and organoid function.

16:40 – 17:05

JOHN MCNEISH MEMORIAL LECTURE: EVOLVING GENE THERAPY FOR PRIMARY IMMUNODEFICIENCIES

Thrasher, Adrian

University College London Great Ormond Street Institute of Child Health, London, U.K.

At the start of the 1990s, the first clinical trials of gene therapy were attempted for an inherited severe combined immunodeficiency (SCID) caused by deficiency of the intracellular enzyme adenosine deaminase. In the absence of

definitive treatment, SCID of any molecular type is usually fatal within the first year of life, although patients with ADA deficiency can be supported by administration of exogenous enzyme replacement. Even so, this is often only partially effective, and is extremely expensive. The rationale for the development of gene therapy PID therefore derives from the severity of the illness, the inadequacy of conventional therapy, and the considerable morbidity and mortality associated with stem-cell transplantation, particularly from a mismatched donor. Although retroviruses are highly effective for gene transfer, their dependence on chromosomal integration brings a risk of inadvertent gene activation or inactivation. Reports of adverse events in several applications paved the way to the development of refined vector technologies. Clinical trials using next-generation self-inactivating gammaretroviral and lentiviral vectors have now been reported, and clearly demonstrate the huge potential of gene therapy for haematopoietic disorders including SCID-X1, Wiskott-Aldrich Syndrome, and ADA-SCID. At the same time, the safety profile appears to have been significantly enhanced, and efforts are being made to develop licensed products. New technologies including homologous recombination or gene repair to accurately correct genetic mutations may eventually supersede gene addition once limitations of efficiency and toxicity have been addressed.

17:05 – 17:30

REPLACING NEURONS BY TRANSPLANTATION IN THE DISEASED HUMAN BRAIN

Lindvall, Olle

University of Lund, Sweden

Thirty years have now passed since we performed the first transplantations in Parkinson's disease (PD) using human fetal mesencephalic tissue rich in dopaminergic neuroblasts. At that time, it was unknown (i) whether grafted neurons can survive and form connections in the diseased adult human brain; (ii) if grafted neurons can become functionally integrated into patient's brain's neural circuitry; and (iii) whether neuronal replacement by cell transplantation can lead to a measurable/clinically valuable functional improvement in humans. In my lecture, I will briefly describe the development in this field and that we and others have shown that grafted dopaminergic neurons can provide a local reinnervation of the striatum, restore striatal dopamine release and, in some cases, induce major, long-lasting improvement of motor function. There is evidence that the grafted neurons, despite being located at an ectopic site, become functionally integrated into host brain. I will also summarize what will be required for successful outcome of the planned transplantations using grafted ES cell- or iPS cell-derived dopaminergic neurons in PD patients. In contrast to PD, ongoing clinical trials with stem cells in stroke are not aiming for neuronal replacement but target mechanisms such as immunomodulation, trophic support, and stimulation of neural plasticity. In fact, the evidence for neuronal replacement and reconstruction of circuitry after cell transplantation in animal models of stroke is scarce and little is known about whether these mechanisms contribute to the observed functional recovery. New experimental tools to address these issues are now available. I will at the end of my lecture present evidence that synaptic inputs from stroke-injured brain to grafted human iPS cell-derived neurons, implanted into rat cerebral cortex, are activated by cutaneous stimulation of nose and paw. Thus, the stroke-affected host brain can regulate the activity of grafted human stem cell-derived neurons and these neurons can become incorporated into injured cortical circuitry. It remains to be demonstrated, though, that neuronal replacement contributes to the functional improvements after cell transplantation in stroke, which will be a necessary step in the clinical translation of this approach.

17:30 – 17:55

RETINAL CELL THERAPY USING IPS CELLS

Takahashi, Masayo

RIKEN Center for Developmental Biology, Kobe, Japan

The first in man application of iPS-derived cells started in September 2014, targeted age-related macular degeneration (AMD). AMD is caused by the senescence of retinal pigment epithelium (RPE), so that we aimed to replace damaged RPE with normal, young RPE made from iPS cells. In the first clinical study, we generated iPS cells from patient's skin fibroblast. RPE cells were differentiated from iPS cells. Picking up the brown cluster of cells, hiPS-RPE cells were purified. Cells were evaluated their purity, function, and various genetic examination. Grafted cell sheet went through various tests and tumorigenicity test using immunodeficient mice to check the safety. We also evaluated plasmid remnant and gene alteration using WGS, epigenetic characteristics and purity using single cell RT-PCR other than our original quality control (QC). We judged the outcome 1 year after the surgery. Primary endpoint was the safety, mainly the tumor formation and immune rejection. The grafted RPE cell sheet was not rejected nor made tumor after two years. The patient's visual acuity stabilized after the surgery whereas it deteriorated before surgery in spite of 13 times injection of anti-VEGF in the eye. Since autologous transplantation is time consuming and expensive, it is necessary to prepare allogeneic transplantation to establish a standard treatment. RPE cells are suitable for allogeneic transplantation because they suppress the activation of the T-cell. From in vitro and in vivo study, it is possible that the rejection is considerably suppressed by using the iPS cell with matched HLA. Our new protocol has accepted by ministry in Feb 2017. We are planning transplantation using allogeneic iPS-RPE cell suspension and sheet, and also autologous iPS-RPE. For the cell suspension transplantation we will not combine CNV removal and apply to milder cases than sheet transplantation. In Japan, pharmaceutical law has been changed and a new chapter for regenerative medicine was created for clinical trial. Also the separate law for safety of regenerative medicine for clinical research (study) was enforced in 2015. These laws made the suitable condition for the brand new field of regenerative medicine. We are making regenerative medicine in co-operation with ministry and academia.

17:55 – 18:20

MAKING PANCREATIC ISLET CELLS FOR DIABETICS AND DIABETES RESEARCH

Melton, Douglas

Harvard University, Cambridge, MA, U.S.

Research in the Melton laboratory focuses on finding a significant new treatment for Type 1 diabetes. Our laboratory analyzes the normal development of pancreas in order to understand how pancreatic beta cells are made and how they become the target of autoimmunity. The main focus of the lab is to use human stem cells to make pancreatic islet cells for transplantation into diabetics. Most recently we have reported on methods for large scale in vitro differentiation of human stem cells (ES and iPS) into functional pancreatic beta cells. A detailed analysis of the in vitro differentiation will be presented.

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