ISSCR 2016 ANNUAL MEETING PROGRAM GUIDE

SAN FRANCISCO, CALIFORNIA • 22-25 JUNE

ISSCR
INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

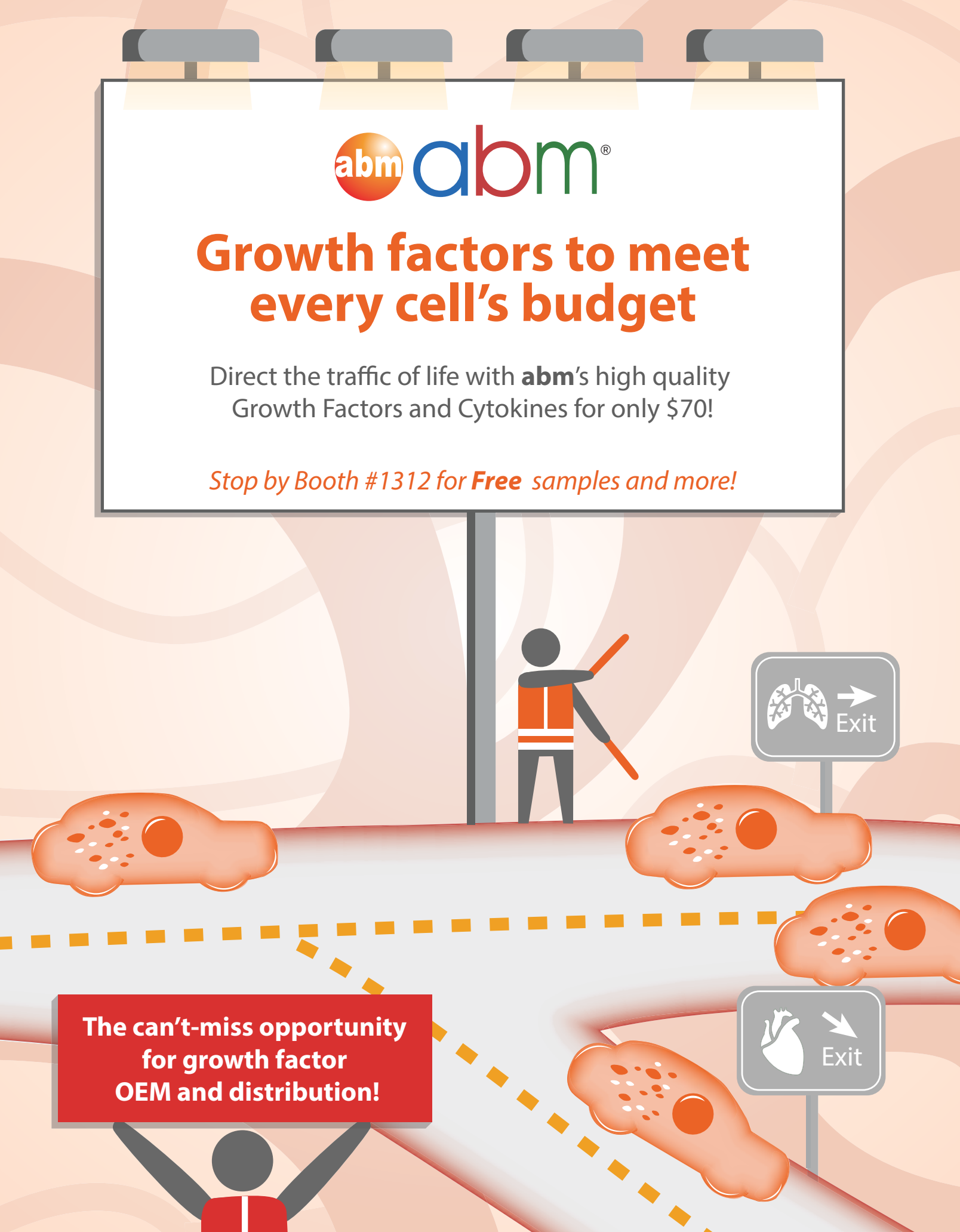
co-sponsored by: CIRM

ISSCR 2016
ANNUAL MEETING
SAN FRANCISCO
22-25 JUNE
CALIFORNIA • USA

THE GLOBAL STEM CELL EVENT

PROGRAM GUIDE

isscr2016.org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ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Dear Colleagues,

On behalf of the International Society for Stem Cell Research (ISSCR), we are pleased to welcome you to our 2016 annual meeting, the heart of the global stem cell community. This year we highlight the many ways in which the stem cell field can translate promise to progress by expanding scientific understanding to advance new therapies.

The San Francisco Bay Area has been at the forefront of stem cell research and regenerative medicine. Likewise, the enormous public support of stem cell research in California has played a significant role in the development of our field. The ISSCR is excited to be here in San Francisco to showcase stem cell research and application from around the world.

A key objective of this meeting is to offer you the best science and the opportunity to interact with a wide array of professionals. The ISSCR 2016 Program Committee has crafted an expanded scientific program to capture the latest findings in all areas of stem cell research and regenerative medicine. Please take advantage of the scientific sessions, posters, networking events, and the exhibition hall to share your work and to make connections. Trainees and early career researchers should check out the many events targeted for this group, especially the social night on Wednesday evening at Ruby Skye.

We hope you will come away from this meeting with excitement about the promise and progress of stem cell research. Thank you for your continued support of the ISSCR and the important work you do to advance the frontiers of human health.

Sincerely,

Deepak Srivastava
Program Chair

Sean Morrison
ISSCR President

Office of the Mayor
City & County of San Francisco

Edwin M. Lee

GREETINGS FROM THE MAYOR

On behalf of the City and County of San Francisco, I am pleased to welcome you to the International Society for Stem Cell Research (ISSCR) Annual Meeting being held June 22-25, 2016 at Moscone West.

Each year, ISSCR brings together professionals in the area of stem cell research to share and discuss the latest scientific breakthroughs. This event is at the heart of stem cell science, serving as a place where great science, collaboration, and research across the breadth of the field can come together to turn the promise of the stem cell field into scientific progress. The work done here is changing the face of human health for the better and will benefit many for generations to come. This meeting's collaborative atmosphere also bears witness to a strong scientific community that takes pride in promoting the importance of stem cell research as well as raising public awareness and understanding. San Francisco is not only a world-class city; it is a hub for innovation and technology, and I can think of no better place to host this one-of-a-kind event.

Thank you to everyone at ISSCR, the California Institute for Regenerative Medicine (CIRM), and the 2016 ISSCR Annual Meeting Program Committee for working to ensure the ISSCR Annual Meeting is a great success. Best wishes to you all for a productive and fruitful event.

With warmest regards,

Edwin M. Lee
Mayor

CIRM
CALIFORNIA'S STEM CELL AGENCY

California's Stem Cell Agency Can Partner with Teams Anywhere in the World

On behalf of the California Institute for Regenerative Medicine (CIRM) I would like to welcome you to San Francisco for what I know will be a terrific meeting: the ISSCR 2016 Annual Meeting. CIRM is delighted to co-sponsor this year's meeting and support the gathering of the best science from around the world in California. I would also like to debunk one of the great myths in the stem cell community, namely that only California-based institutions can apply to us for funding. In reality, anyone, anywhere can apply for CIRM funding—within defined limits.

The reason for this is simple; we want to attract the best science and the best scientists to help us fulfill our mission of accelerating stem cell treatments to patients with unmet medical needs.

For example, if you are conducting a multicenter clinical trial, it could make great sense to set up a clinical trial site in California and we could fund a significant portion of that effort. Or, you could contract to have the therapy manufactured here, for example. In the pre-clinical setting a team could choose to contract with a California entity to conduct the assay development, safety testing or other activities.

If more than half of your employees are in California you will get a better deal. But if you are based elsewhere, whether in Boston or Paris, it is worth considering a partnership with CIRM.

A year and a half ago we launched what we call CIRM 2.0, which greatly accelerates the entire award process. Applicants for clinical projects can get a decision in 90 days and funds in hand within 120 days.

One of our goals over the next five years is to fund 50 new clinical trials. It's ambitious, but we know that the field is advancing rapidly and we want to do everything we can to further accelerate that progress.

So ask us how you apply for funding. We have almost $1 billion left to invest in the best science. Why shouldn't that be you?

Sincerely,
Jonathan Thomas
Chair, CIRM Governing Board

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GENERAL INFORMATION

REGISTRATION AND BADGE PICKUP

Pick up your attendee name badge in the registration area (Moscone West, Level 1, 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 Exhibition & Poster Hall. Badges may be picked up during the following times:

TUESDAY, 21 JUNE	**14:00 – 18:00**
WEDNESDAY, 22 JUNE	**7:30 – 20:30**
THURSDAY, 23 JUNE	**8:15 – 18:30**
FRIDAY, 24 JUNE	**8:15 – 18:30**
SATURDAY, 25 JUNE	**8:15 – 18:30**

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

ATTENDEE ORIENTATION

Curious to find out how to best navigate through ISSCR 2016? Join us at the Moscone West, Level 3, Lobby for our Attendee Orientation where ISSCR staff along with engaged and experienced ISSCR members will explain the annual meeting's highlights and allow attendees to get to know one another before the meeting kicks off. There will be two scheduled Attendee Orientations:

TUESDAY, 21 JUNE	**15:00 – 16:30**
WEDNESDAY, 22 JUNE	**8:30 – 10:00**

THINGS YOU SHOULD KNOW

Recordings Prohibited

Still photography, video and/or audio taping of the sessions, presentations and posters at the ISSCR 2016 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.

Smoking

Smoking is prohibited in the Moscone West convention center.

Internet Access

Enjoy complimentary WI-FI throughout the Moscone West convention center thanks to our supporter STEMCELL Technologies.

To connect to the WI-FI:

1. Enable your wireless and search for open networks
2. Connect to the network called ISSCR2016
3. Open a web browser
4. Some mobile devices require you to "log in" when prompted. If you see this message pop up, please click "log in" to proceed.
5. You will then be redirected to the sponsored landing page.

Lost And Found

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

Coat Check

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

WEDNESDAY, 22 JUNE	**8:00 – 21:00**
THURSDAY, 23 JUNE	**8:00 – 20:30**
FRIDAY, 24 JUNE	**8:00 – 20:30**
SATURDAY, 25 JUNE	**8:00 – 19:30**

Mothers' Room

A private room is available in Moscone West, Level, 1 Lobby near the registration area. Please follow onsite signage accordingly. The Mothers' Room will be open WEDNESDAY, 22 JUNE THROUGH SATURDAY, 25 JUNE FROM 8:00 – 19:00. If you require access outside these hours, please visit the registration area.

GENERAL INFORMATION

Meeting Rooms

Sign up for first-come, first-served ISSCR ad hoc meetings in Moscone West, Level 2, Rooms 3018, 3020, 3022, 3024. 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 Exhibition & Poster Hall as well as the Learning Lab & Lounge in Level 2, Lobby.

Concession Stand

Attendees can purchase snacks and beverages in Moscone West's concession stand, Corner West, located on Level 1. Hours of operation are 8:30 – 17:00 WEDNESDAY, 22 JUNE THROUGH FRIDAY, 24 JUNE AND 8:30 – 16:00 ON SATURDAY, JUNE 25.

Parking

Parking is available for Moscone West at the Fifth and Mission Garage located at 833 Mission Street. Maximum daily rate is $22 USD. Please note attendees are responsible for paying their own parking garage fees.

San Francisco Travel Delegate Services

Visit the San Francisco Travel Delegate Services hospitality desk at the Moscone West, Level 1, Lobby by the main Fourth Street Entrance to plan your dining, activities, and tours.

WEDNESDAY, 22 JUNE	**9:00 – 17:00**
THURSDAY, 23 JUNE	**9:00 – 17:00**
FRIDAY, 24 JUNE	**9:00 – 17:00**

Speaker Ready Room

Speakers are welcome to review their uploaded presentations in the Speaker Ready Room (Moscone West, Level 2, Room 2006) during the following times:

WEDNESDAY, 22 JUNE	**8:00 – 19:00**
THURSDAY, 23 JUNE	**8:00 – 19:00**
FRIDAY, 24 JUNE	**8:00 – 19:00**
SATURDAY, 25 JUNE	**8:00 – 16:30**

Media Office

Credentialed members of the media may use work stations, wireless internet, and printer during posted hours in the Media Office (Moscone West, Level 2, Room 2010). Please visit the Media Office for media panel details.

WEDNESDAY, 22 JUNE	**8:00 – 16:00**
THURSDAY, 23 JUNE	**8:00 – 16:00**
FRIDAY, 24 JUNE	**7:45 – 16:00**
SATURDAY, 25 JUNE	**9:00 – 12:00**

Message Center

Post messages for friends and colleagues using the message board in ISSCR Central located in Moscone West, Level 1, Exhibition & 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 2016 mobile app. Read more on page 2.

Job Opportunities

Post resumes and employment opportunities on the designated board in ISSCR Central located in Moscone West, Level 1, Exhibition & Poster Hall. Better yet, participate in our brand new ISSCR Career Fair on THURSDAY, 23 JUNE AND FRIDAY, 24 JUNE. Find out more onpage 25.

Mobile App

Have the ISSCR 2016 schedule in the palm of your hand thanks to our supporter Bio-Techne.

Download the free ISSCR 2016 Mobile App from the Apple Store or Google Play to your smartphone and/or tablet device to have immediate access to many features in support of your annual meeting program experience:

- Browse or search for scientific content, presenters, exhibitors or events
- Reach out to fellow attendees onsite using the Friends networking feature
- Sync the app across all of your devices with Multi-Device Sync

- Check the locations of sessions and exhibitors under the maps icon
- Receive important real-time communications from ISSCR
- Build a personalized schedule
- Bookmark exhibitors
- Rate the sessions you attend and comment on them, too
- Stay in-the-know and join in on social media with #ISSCR2016 and #GlobalStemCellEvent

Downloading the mobile app is easy! Simply go to the App Store or Google Play and search for "ISSCR 2016." For all other web-enabled devices, including tablets, Blackberry and Windows phones enter m.core-apps.com/isscr_2016 into your browser to be automatically directed to the proper download version for your mobile device.

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JOIN US IN HONORING THE RECIPIENTS OF THE 2016 ISSCR AWARDS

MCEWEN AWARD FOR INNOVATION

PRESIDENTIAL SYMPOSIUM, WEDNESDAY, 22 JUNE

Award supported by the McEwen Centre for Regenerative Medicine

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 toward the understanding or treatment of human disease or affliction.

Austin Smith, PhD, FRS, FRSE, Wellcome Trust Centre for Stem Cell Research and Institute for Stem Cell Biology and Qi-Long Ying, PhD, University of Southern California, are the joint recipients of the 2016 McEwen Award for Innovation in recognition of their contributions to the fundamental understanding of pluripotency and how this knowledge can be leveraged to develop new tools that advance our understanding and treatment of human disease.

Austin Smith, FRS, FRSE, is the founding Director of the Cambridge Stem Cell Institute and a Medical Research Council Professor. His research interest is pluripotency and in particular embryonic stem cells. His ambition is to elucidate the molecular and developmental foundations of pluripotent stem cell states. He hopes to determine generic principles underlying pluripotent stem cell properties and apply this knowledge to control their derivation, expansion and differentiation.

Qi-Long Ying, PhD, is Associate Professor of Stem Cell Biology at the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, University of Southern California. He obtained his Ph.D in molecular biology in 1995 and completed his postdoctoral training in Austin Smith's group at the University of Edinburgh in 2006. His current research focuses on understanding the molecular basis of embryonic and tissue-specific stem cell self-renewal.

Join us for the 2016 award presentation which will take place during the Presidential Symposium on the afternoon of Wednesday, 22 June.

ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR

PLENARY II: TISSUE GROWTH AND MORPHOGENESIS, WEDNESDAY, 22 JUNE

Award supported by the Dr. Susan Lim Endowment for Education and Research Ltd.

The ISSCR Dr. Susan Lim Award for Outstanding Young Investigator recognizes the exceptional achievements of an investigator in the early part of his or her independent career in stem cell research.

Fernando Camargo, PhD, Professor, Stem Cell and Regenerative Biology, Harvard University and Principal Faculty, Stem Cell Program at Boston Children's Hospital, U.S., is the recipient of the eighth annual Outstanding Young Investigator Award. Dr. Camargo's innovative research on adult stem cells, regulation of organ size, and cancer, together with the development of a paradigm-shifting stem cell tracking technique, has greatly impacted our understanding of stem cell biology and disease, and opens new avenues in regenerative medicine.

Join us for the 2016 award presentation which will take place during Plenary Session II on the afternoon of Wednesday, 22 June.

ISSCR TOBIAS AWARD LECTURE

PLENARY II: TISSUE GROWTH AND MORPHOGENESIS, WEDNESDAY, 22 JUNE

Award supported by the Tobias Foundation

The ISSCR Tobias Award Lecture recognizes original and promising basic hematology research as well as direct translational or clinical research related to cell therapy in hematological disorders.

Leonard I. Zon, MD, Grousbeck Professor of Pediatric Medicine at Harvard Medical School, Investigator at Howard Hughes Medical Institute, and Director of the Stem Cell Program at Boston Children's Hospital, U.S., is the inaugural recipient of the ISSCR Tobias Award Lecture. Dr. Zon has demonstrated long-standing scientific leadership in the fields of hematology, stem cell biology, and zebrafish biology. His research using zebrafish as a model organism has contributed greatly to fundamental understanding of hematopoiesis and cancer biology and to the discovery and development of two new novel therapeutics now being evaluated in clinical trials for patients with leukemia and melanoma.

Join us for the 2016 award presentation which will take place during Plenary Session II on the afternoon of Wednesday, 22 June.

2016 TRAVEL AWARDS

CONGRATULATIONS TO THE 2016 TRAVEL AWARD RECIPIENTS

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

PROUDLY SUPPORTED BY THE ISSCR

Mohsen Afshar Bakooshli
Ryoji Amamoto
Miki Ando
Lay Teng Ang
Mariaceleste Aragona
Yishai Avior
Diego Balboa
Xiaoping Bao
Goezde Bekki
Anahi Binagui-Casas
Michael Bukys
Jessica C. Butts
Richard Carpenedo
Fang-pei Chang
Jennifer Chase
Amy Cochrane
Amanda Collier
Faranak Fattahi
Max Friesen
Laura Garcia-Prat
Imbisaat Geti
German Gornalusse
Carolina Guibentif
Rajesh Dattaram Gunage
Elliott Hagedorn
Tomer Halevy
Dong Han
Helen Baixia Hao
Jonathan Henninger
Theodore T Ho
Kazuyoshi Itoh
Johannes Jungverdorben
Nigel Kee
Yonghwan Kim
Eunhye Kim
Vladislav Krupalnik
Tjasa Lepko
Wenli Li
Anna Lilja
Wenqiang Liu
Kyle Loh
Agnes Maillet
Miyeko Mana
Victoria Mascetti
Patricia Camacho Mazzonetto
Louise Menendez
Masanori Miyanishi
Shingo Miyawaki
Miha Modic
Yuika Morita
Pniel Nham
Minna Oksanen
Pierre Osteil
Tomoki Otani
Guangdun Peng
Rebecca Playne
Sarah Pringle
Stephanie Protze
Julian Pulecio
Giorgia Quadrato
Nafees Rahman
Durrgah Ramachandra
Pia Rivetti di Val Cervo
Marta Roccio
Goncalo Rodrigues
Leonardo Romorini
Samuel Rowbotham
Ido Sagi
Hideya Sakaguchi
Max Salick
Khanit Sa-ngiamsuntorn
Rahul Sarate
Brett Shook
Maija Slaidina
Jihee Sohn
LouJin Song
Yonatan Stelzer
Hayami Sugiyama
Shih-Yu Sung
Minoru Takasato
Sara Tamagno
Kenichiro Taniguchi
Jamie Trott
Nguyen T.A. Truong
Alexander Tsankov
Noelia Urbán
Katie Vermillion
Evgenia Verovskaya
Dan Vershkov
Chiara Vezzali
Xusheng Wang
Curtis Warren
Ami Watanabe
Yanxing Wei
Wei Wen
Feng Xiao
Masaki Yagi
Xiaolei Yin
Rui Yue
Nadja Zeltner
Jin Zhang
Bo Zhao
Hanzhi Zhao
Dongxin Zhao

WEDNESDAY 22 JUNE, PLENARY I

JOHN DICK, *UNIVERSITY HEALTH NETWORK, CANADA*

John Dick, PhD, is a Senior Scientist at the Princess Margaret Cancer Centre and McEwen Centre for Regenerative Medicine, University Health Network, Professor of Molecular Genetics, University of Toronto and Director of the Cancer Stem Cell Program, Ontario Institute for Cancer Research. He is recognized for developing a system for transplanting normal and malignant human hematopoietic cells into immune-deficient mice and identifying and characterizing normal and leukemic human stem cells. His contributions have been recognized through election as a Fellow of the Royal Society of Canada (2004) and London (2014) and several awards including the Clowes Award (AACR 2008), Dameshek (2005) and Thomas (2009) Awards (ASH), and the Canadian Cancer Research Alliance Award for Outstanding Achievements in Cancer Research (2013).

IRVING WEISSMAN, *STANFORD UNIVERSITY, U.S.*

Irving L. Weissman, MD, is the Director of the Stanford Institute for Stem Cell Biology and Regenerative Medicine and Director of the Stanford Ludwig Center for Cancer Stem Cell Research. Dr. Weissman co-founded, was a Director, and chaired the Scientific Advisory Board at SyStemix 1988-1996, StemCells in 1996-present, and Cellerant in 2001-9.

His research encompasses the biology and evolution of stem cells and progenitor cells, mainly blood-forming and brain-forming. He is also engaged in isolating and characterizing the rare cancer and leukemia stem cells as the only dangerous cells in these malignancies, especially with human cancers. He has a long-term research interest in the phylogeny and developmental biology of the cells that make up the blood-forming and immune systems.

ELAINE FUCHS, *ROCKEFELLER UNIVERSITY, U.S.*

Elaine Fuchs, PhD, is the Rebecca Lancefield Professor in Mammalian Cell Biology and Development at The Rockefeller University, and a Howard Hughes Medical Institute Investigator. Using skin as a model, Fuchs studies how resident stem cells communicate and respond to their niche. Fuchs' team has made major contributions towards understanding how tissues repair injuries and how abnormalities in stem cell behavior can lead to cancers. Fuchs has devised and employed innovative and imaginative approaches to biomedical research for over three decades. Recently, her team developed technology to conduct genome-wide RNAi screens in mice for oncogenic regulators of growth, and they've identified a population of stem cells in cancers that are resistant to chemotherapy.

PIER PAOLO PANDOLFI, *HARVARD MEDICAL SCHOOL, U.S.*

Pier Paolo Pandolfi, MD, PhD presently holds the Reisman Endowed Chair of Medicine and is Professor of Medicine and Pathology at Harvard Medical School. He is also a member of the Department of Pathology at BIDMC. He was recently appointed to serve as the Cancer Center director and the director of the Cancer Research Institute at BIDMC and HMS. The research carried out in Dr. Pandolfi's laboratory has been seminal to elucidating the molecular mechanisms and the genetics underlying the pathogenesis of leukemias, lymphomas, and solid tumors as well as in modeling these cancers in the mouse. More recently, Dr. Pandolfi and colleagues have presented a new theory describing how mRNA, both coding and non-coding, exert their biological functions, with profound implications for human genetics, cell biology, and cancer biology.

FEATURED SPEAKERS

ANNE MCLAREN MEMORIAL LECTURE, FRIDAY 24 JUNE, PLENARY IV

KATHRYN V. ANDERSON, *SLOAN KETTERING INSTITUTE, U.S.*

Kathryn V. Anderson, PhD, is Chair of the Developmental Biology Program, Sloan Kettering Institute. The goal of the Anderson lab is to characterize the genetic pathways that control patterning and morphogenesis of the mouse embryo. Using forward genetic strategies, the lab has identified mutations in more than 100 genes and used these mutations to define the cellular basis of fundamental aspects of early mammalian development. The lab showed that a microtubule-based organelle, the primary cilium, is required for mammalian Hedgehog signal transduction, linked the core Hedgehog pathway to cilia structure through the KIF7/Cos2 protein, and identified genes and processes that control the formation of primary cilia in vivo. The lab also studies the cell biology of early development, including the collective migration that specifies the anterior-posterior body axis, epithelial morphogenesis and the gastrulation epithelial-to-mesenchymal transition.

JOHN MCNEISH MEMORIAL LECTURE, FRIDAY 24 JUNE, PLENARY V

Supported by the ISSCR Industry Committee

FYODOR URNOV, *SANGAMO BIOSCIENCES INC., U.S.*

Fyodor Urnov, PhD, is Project Leader and Senior Scientist at Sangamo BioSciences, Inc. where he co-developed human genome editing with engineered zinc finger nucleases (ZFNs). Dr. Urnov previously led the company's research and development efforts in deploying genome editing for crop trait engineering (in partnership with Dow Agrosciences) and in generation of engineered cell lines for manufacturing, improved generation of transgenic animals and as research reagents (in partnership with Sigma-Aldrich). In his current role as Project Leader for the Hemoglobinopathies, Dr Urnov heads Sangamo's partnership with Biogen to develop genome editing as a one time, lasting treatment for beta-thalassemia and sickle cell disease. Dr. Urnov is also an associate adjunct professor in the department of Molecular and Cell Biology at the University of California, Berkeley.

The John McNeish Memorial Lecture was established by the ISSCR Industry Committee in memory of John McNeish (1958-2015). The lecture honors his legacy within the Society and his contributions in stem cell research in industry towards diagnosis, drug discovery and clinical translation. Dr. McNeish spent that last four years of his career at GlaxoSmithKline and previously held senior positions at Pfizer. He was an active member of the ISSCR Industry Committee.

FEATURED SPEAKERS

ERNST MCCULLOCH MEMORIAL LECTURE, SATURDAY 25 JUNE, PLENARY VI

GUY SAUVAGEAU, *INSTITUTE FOR RESEARCH IN IMMUNOLOGY & CANCER, CANADA*

Guy Sauvageau, MD, FRCP, PhD, is professor at the Department of Medicine at University of Montreal. His laboratory is located at the Institute for Research in Immunology and Cancer (IRIC) at Université de Montréal where he served as Founding Scientific Director from 2003-2014 and CEO. He holds the Canada Research Chair in Molecular Genetics of Stem Cells. Dr. Sauvageau is an internationally recognized researcher and clinician-scientist, with a research focus on the molecular signals that regulate self-renewal activity of normal and leukemia stem cells. Chemo-genomics approaches are fully exploited to this endeavour. The laboratory also invests major efforts in translational research activities, mostly in cord blood transplantation and in diagnostics / therapeutics of acute myeloid leukemia.

CLOSING KEYNOTE ADDRESS, SATURDAY 25 JUNE, PLENARY VII

ROBERT TJIAN, *UNIVERSITY OF CALIFORNIA, BERKELEY, U.S.*

Robert Tjian, PhD, is President of HHMI and Professor of Molecular and Cell Biology at the University of California, Berkeley where he has been a faculty member since 1978. His research is in the biochemistry of gene regulation in humans and animals. In particular, the nature of the molecular machinery that controls the turning up and down of gene expression in human cells, and how disruption of this highly regulated process lead to various disease states.

SCHEDULE AT A GLANCE

REGISTRATION OPEN	
TUESDAY, 21 JUNE	14:00 – 18:00
WEDNESDAY, 22 JUNE	7:30 – 20:30
THURSDAY, 23 JUNE	8:15 – 18:30
FRIDAY, 24 JUNE	8:15 – 18:30
SATURDAY, 25 JUNE	8:15 – 18:30

EXHIBITION HALL OPEN	
WEDNESDAY, 22 JUNE	15:15 – 20:30
THURSDAY, 23 JUNE	11:00 – 20:00
FRIDAY, 24 JUNE	11:00 – 20:00
SATURDAY, 25 JUNE	11:00 – 16:00

EXHIBITION SETUP	
TUESDAY, 21 JUNE	9:00 – 16:00
WEDNESDAY, 22 JUNE	8:00 – 12:00

EXHIBITION DISMANTLE	
SATURDAY, 25 JUNE	16:00 – 19:00

CAREER FAIR	
THURSDAY, 23 JUNE	9:00-17:00
FRIDAY, 24 JUNE	9:00-17:00

TUESDAY, 21 JUNE	
9:00 - 17:00	ISSCR/ASGCT WORKSHOP ON CLINICAL TRANSLATION
15:00- 16:30	ATTENDEE ORIENTATION
18:00 - 19:30	PUBLIC SYMPOSIUM

SCHEDULE AT A GLANCE

WEDNESDAY, 22 JUNE	
8:30 - 10:00	ATTENDEE ORIENTATION
8:15 - 9:00	MORNING COFFEE
9:00 - 12:00	FOCUS SESSIONS
11:25 - 12:45	EARLY-CAREER GROUP LEADER LUNCHEON
13:00 - 15:15	PLENARY I PRESIDENTIAL SYMPOSIUM: STEM CELLS AND CANCER
15:15 - 16:00	REFRESHMENT BREAK
15:15 - 18:30	POSTER SET UP
16:00 – 18:00	PLENARY II: TISSUE GROWTH AND MORPHOGENESIS
18:00 - 20:30	OPENING RECEPTION
18:30 - 20:30	POSTER SESSION I
21:00 - 01:00	JUNIOR INVESTIGATOR NETWORKING SOCIAL NIGHT

THURSDAY, 23 JUNE	
8:00- 8:30	INNOVATION SHOWCASES
8:15 - 9:00	MORNING COFFEE
9:00 - 11:20	PLENARY III: CELLULAR PLASTICITY AND REPROGRAMMING
11:15 - 13:15	POSTER SET UP
11:30 - 12:30	INNOVATION SHOWCASES
11:30 - 13:15	LUNCH BREAK
11:30 - 13:00	NETWORKING WITH LEADERS LUNCHEON
12:15 - 13:00	MEET-UPS
13:15 - 15:15	CONCURRENT SESSIONS I
13:15 - 14:30	MEET-UPS
15:15 - 16:00	REFRESHMENT BREAK
15:15 - 16:00	MEET-UPS
16:00 - 18:00	CONCURRENT SESSIONS II
18:00 - 20:00	POSTER RECEPTION & POSTER SESSION II

SCHEDULE AT A GLANCE

FRIDAY, 24 JUNE	
8:00- 8:30	INNOVATION SHOWCASES
8:15 - 9:00	MORNING COFFEE
9:00 - 11:15	PLENARY IV: GENE NETWORKS AND EPIGENETICS
11:15 - 13:15	POSTER SET UP
11:30 - 12:30	INNOVATION SHOWCASES
11:30 - 13:15	LUNCH BREAK
11:30 - 13:00	NETWORKING WITH LEADERS LUNCHEON
12:15 - 13:00	MEET-UPS
13:15 - 15:15	CONCURRENT SESSIONS III
15:15 - 16:00	REFRESHMENT BREAK
15:15 - 16:00	MEET-UPS
16:00 - 18:00	PLENARY V: GENE THERAPY AND STEM CELLS
18:00 - 20:00	POSTER RECEPTION & POSTER SESSION III

SATURDAY, 25 JUNE	
8:15 - 9:00	MORNING COFFEE
9:00 - 11:15	PLENARY VI: DISEASE MODELING USING STEM CELLS
11:20 - 13:15	LUNCH BREAK
11:30 - 13:00	JUNIOR INVESTIGATOR CAREER PANEL LUNCHEON
13:15 - 15:15	CONCURRENT SESSIONS IV
15:15 - 16:00	REFRESHMENT BREAK
16:00 - 18:20	PLENARY VII: CELL THERAPY IN CLINICAL TRIALS
18:20 - 19:20	CLOSING RECEPTION

CONGRATULATIONS

Boston Children's Hospital
Stem Cell Program

Boston Children's Hospital congratulates you on receiving these prestigious awards!

Inaugural Recipient

ISSCR Tobias Award Lecture

Leonard I. Zon, MD

Recipient

ISSCR Dr. Susan Lim Award for Outstanding Young Investigator

Fernando Camargo, PhD

ISSCR
INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

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THE GLOBAL STEM CELL EVENT

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inspiring SCIENCE
STEM CELL
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Researchers around the world continue to advance the science of stem cells. The ISSCR Annual Meeting is where they come together, work together and find inspiration together. Plan now to experience inspiring stem cell science and technology delivered with the insight you need to meet your research goals.
Join us at ISSCR 2017 in Boston.

NETWORKING AT A GLANCE

ISSCR 2016 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 and offers various avenues to help scientists foster and strengthen their professional networks. Here is a quick glance at what ISSCR 2016 has to offer.

TUESDAY, 21 JUNE

15:00 – 16:30

Attendee Orientation

Moscone West, Level 3, 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 2016 experience and work with other attendees to solve a fun challenge. You may even walk away with a prize.

WEDNESDAY, 22 JUNE

8:30 – 10:00

Attendee Orientation

Moscone West, Level 3, 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 2016 experience and work with other attendees to solve a fun challenge. You may even walk away with a prize.

11:25 – 12:45

Early-Career Group Leader Luncheon

Moscone West, Level 3, Lobby

This is a ticketed event that requires pre-registration. To learn more, see page 26.

15:15 – 20:30

Exhibition Hall

Moscone West, Level 1, Exhibition & Poster Hall

Network with industry professionals with over 130 exhibiting companies. Explore the possibilities on page 26. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

18:30 – 20:30

Poster Session I and Opening Reception

Moscone West, Level 1, Exhibition & Poster Hall

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 – 01:00

Junior Investigator Networking Social Night

Ruby Skye, 420 Mason St, San Francisco, CA

This is a ticketed event that requires pre-registration. To learn more, see page 26.

THURSDAY, 23 JUNE

9:00 – 17:00

ISSCR 2016 Career Fair

Moscone West, Level 2, Lobby

Stop by in between program sessions to meet face-to-face with companies hiring positions within the stem cell community.

11:30 – 13:00

Networking with Leaders Luncheon

Moscone West, Level 3, Lobby

This is a ticketed event that requires pre-registration. To learn more, see page 26.

11:00 – 20:00

Exhibition Hall

Moscone West, Level 1, Exhibition & Poster Hall

Network with industry professionals with over 130 exhibiting companies. Explore the possibilities on page 26. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

12:15 – 13:00

Meet-Up: German Stem Cell Network (GSCN)

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about the GSCN Meet-Up, see page 24.

12:15 – 13:00

Meet-Up: How EBiSC Helps Researchers in Accessing High-Quality Research-Grade iPSC Lines

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about the EBiSC Meet-Up, see page 24.

13:15-14:30

Meet-Up: Solutions Exchange

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about endeavors of clinical translation, see page 24.

15:15 – 16:00

Meet-Up: Let's Talk Clinical Translation

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about endeavors of clinical translation, see page 24.

18:00 – 20:00

Poster Session II and Reception

Moscone West, Level 1, Exhibition & 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, 24 JUNE

9:00 – 17:00

ISSCR 2016 Career Fair

Moscone West, Level 2, Lobby

Stop by in between program sessions to meet face-to-face with companies hiring positions within the stem cell community.

11:30 – 13:00

Networking with Leaders Luncheon

Moscone West, Level 3, Lobby

This is a ticketed event that requires pre-registration. To learn more, see page 26.

11:00 – 20:00

Exhibition Hall

Moscone West, Level 1, Exhibition & Poster Hall

Network with industry professionals with over 130 exhibiting companies. Explore the possibilities on page 26. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

12:15 – 13:00

Meet-Up: Get an Inside Look at the CIRM iPSC Collection at Coriell

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about CIRM's iPSC collection, see page 25.

12:15 – 13:00

Meet-Up: How to Leverage the World's Largest iPSC Bank to Study Pathological Phenotypes

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about this iPSC bank, see page 25.

15:15 – 16:00

Meet-Up: Meet the Editors of Stem Cell Reports

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about Meet the Editors, see page 25.

15:15 – 16:00

Meet-Up: Meet the Coordinator of ISSCR Connect Webinars

Moscone West, Level 1, Exhibition & Poster Hall, Meet-Up Hubs

Meet-Ups are open to all attendees. To learn more about ISSCR Connect Webinars, see page 25 .

18:00 – 20:00

Poster Session III and Reception

Moscone West, Level 1, Exhibition & 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, 25 JUNE

11:00 – 16:00

Exhibition Hall

Moscone West, Level 1, Exhibition & Poster Hall

Network with industry professionals with over 130 exhibiting companies. Explore the possibilities on page 83. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Lounge.

11:30 – 13:00

Career Panel Luncheon – Strategies for Success: Choosing the Best Career Path for Your Bioscience PhD

Moscone West, Level 3, Lobby

This is a ticketed event that requires pre-registration. To learn more, see page 27.

18:20 – 19:20

Closing Reception

Moscone West, Level 3, Lobby

Join fellow scientists as ISSCR bids farewell to this year's attendees and thanks participants for another great annual meeting. Complimentary light snacks and wine/beer available.

Mobile App Guide

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Take the first step to a successful networking strategy by reaching out to researchers attending ISSCR 2016 via our free mobile app. To learn how to download the ISSCR 2016 mobile app, refer to page 2. 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 2016 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 Connect webinars
- ISSCR member benefits
- Meet with a Boston representative to learn more about the city for ISSCR 2017
- Stem Cell Report's commemorative issue
- The ISSCR Job Board and Message Center

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.

MEET-UP: SOLUTIONS EXCHANGE

THURSDAY, 23 JUNE 13:15-14:30

Students and postdoctoral fellows face a host of challenges in their scientific training including choosing a graduate advisor or postdoctoral mentor, developing presentation and writing skills and selecting a postdoctoral laboratory or a career, to name a few. We would like to hear the issues you are facing and to engage the community of students and postdocs to help provide solutions to help navigate these and other issues. Please join the ISSCR and select facilitators in this interactive, group problem-solving session.

GERMAN STEM CELL NETWORK

THURSDAY, 23 JUNE 12:15 - 13:00

Exhibition Hall - Meet-up Hub #1 *[Meet up Hub 1 is supported by Thermo Fisher Scientific]*

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

HOW EBISC HELPS RESEARCHERS IN ACCESSING HIGH-QUALITY RESEARCH-GRADE IPSC LINES

THURSDAY, 23 JUNE 12:15 – 13:00

Exhibition Hall - Meet-up Hub #2 *[Meet up Hub 1 is supported by Thermo Fisher Scientific]*

Meet with representatives of the European Bank for induced pluripotent Stem Cells (EBiSC)! Discover the EBiSC iPSC Catalogue (https://cells.ebisc.org) and discuss how to best engage with EBiSC if you are interested in:

- Ordering lines from the EBiSC catalogue
- Bio-sample procurement or depositing cell lines and
- Collaborating with EBiSC on future iPSC research projects.

Learn more about the project's approach to iPSC Cryopreservation, Automation, Quality Assurance, Banking, Data Management & the overall Supply Chain. Find out more about this large European public-private partnership at www.ebisc.eu.

LET'S TALK CLINICAL TRANSLATION

THURSDAY, 23 JUNE 15:15 – 16:00

Exhibition Hall - Meet-up Hub #1 *[Meet-up Hub 1 is supported by Thermo Fisher Scientific]*

Connect with your colleagues around the world to discuss your cell therapy clinical translational endeavors and share best practices and challenges. Let's talk about how to design a pre-clinical roadmap, common considerations and useful tips to help expedite your path to the clinic. This hub is organized by Thermo Fisher Scientific.

HOW TO LEVERAGE THE WORLD'S LARGEST IPSC BANK TO STUDY PATHOLOGICAL PHENOTYPES

FRIDAY, 24 JUNE **12:15 – 13:00**

Exhibition Hall - Meet-up Hub #2

Meet key researchers from academia and industry to explore best practices and pitfalls in modeling diseases in large iPSC cohorts. Talk to researchers who have designed studies, developed assays, and collected data aimed at extracting to get the most meaningful data from large iPSC banks.

GET AN INSIDE LOOK AT THE CIRM IPSC COLLECTION AT CORIELL

FRIDAY, 24 JUNE **12:15 – 13:00**

Exhibition Hall - Meet-up Hub #2

What does the world's largest iPSC bank look like? Get an inside look at the CIRM iPSC collection at Coriell. Meet key players from CIRM, Coriell, and CDI to learn how the quality and collaboration across this unmatched resource can drive your iPSC research.

MEET THE EDITORS OF STEM CELL REPORTS

FRIDAY, 24 JUNE **15:15 – 16:00**

Exhibition Hall - Meet-up Hub #1 *[Meet up Hub 1 is supported by Thermo Fisher Scientific]*

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 you are interested in around open-access, scientific publishing. Hear more about what the journal means for the ISSCR now and heading into its fourth year.

MEET THE COORDINATOR OF ISSCR CONNECT WEBINARS

FRIDAY, 24 JUNE **15:15 – 16:00**

Exhibition Hall - Meet-up Hub #2

Do you want to learn more about ISSCR *Connect* Webinars or have an idea for a program or series? Come and meet with Jack Mosher, ISSCR Scientific Affairs Manager and ISSCR *Connect* Webinars coordinator. ISSCR *Connect* Webinars provides members and the public access to the leading minds, latest ideas and emerging issues in stem cell research and its application.

ISSCR 2016 Career Fair

New this year, the two-day career fair allows you to meet face-to-face with companies hiring positions within the stem cell community. It is a must-attend for those seeking career advancement opportunities, professional development resources, and access to some of the industry's top employers. Stop by in between program sessions 9:00 – 17:00 ON THURSDAY, 23 JUNE AND FRIDAY, 24 JUNE in Moscone West, Level 2, Lobby.

Learning Lab & Lounge

ThermoFisher SCIENTIFIC

Stop by the Learning Lab & Lounge *supported by Thermo Fisher Scientific* for a chance to refresh your stem cell research skills. Discuss some of the most common questions researchers ask and learn how to optimize your cell culture system. Relax in between sessions or participate in one of Thermo Fisher's training demonstrations during scheduled times.

DEMONSTRATION TOPICS INCLUDE:

- Rise of the Machines - Breaking Down Common Myths of Counting Cells.
- Optimizing Protocols to Produce Stem Cell Images Worthy of Publication.

- Tips and Tricks for the Best Western Analysis.
- Techniques and Recommendations for Colony Selection During Reprogramming.
- Creating a Stem Cell Characterization Profile to be Proud of and Get Published.
- The Matrix Equation - Solving for the Best Cell Culture Goals.

DEMONSTRATIONS SCHEDULE

WEDNESDAY, 22 JUNE **15:15 – 16:00**

THURSDAY, 23 JUNE **8:15 – 9:00; 11:20 – 13:15 AND 15:15 – 16:00**

FRIDAY, 24 JUNE **8:15 – 9:00; 11:20 – 13:15 AND 15:15 – 16:00**

SATURDAY, 25 JUNE **8:15 – 9:00; 11:20 – 13:15 AND 15:15 – 16:00**

Early Career Group Leader Luncheon

BIASES IN OUR SCIENTIFIC CAREERS: UNDERSTANDING THEIR IMPACT

WEDNESDAY, 22 JUNE **11:25 – 12:45**

Moscone West, Level 3, Lobby

Supported by Ontario Institute for Regenerative Medicine

We all carry subconscious professional biases that impact our decision-making. We collect them through our education, training and personal experiences. While they are key to navigating some aspects of our professional life, they may also have the power to push us to make poor choices that impact our success and that of our colleagues. These biases may impact how we review grants and manuscripts, assess the fundability of projects, interpret data, form collaborations, negotiate salary and hire staff. Join leading senior scientists for a conversation about how to recognize and navigate these biases and discuss solutions that can help successfully move scientific discovery forward.

This is a ticketed event that requires pre-registration.

Junior Investigator Networking Social Night

WEDNESDAY, 22 JUNE **21:00 – 01:00**

Always a highlight of the meeting, the Junior Investigator Networking Social Night is where young investigators from around the world meet, mingle, dance and socialize. This fun-filled night of entertainment will take place at Ruby Skye nightclub, just 15 minutes walking-distance from the Moscone West convention center.

Venue: Ruby Skye Nightclub
Address: 420 Mason St, San Francisco, CA 94109

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 Investigator Committee
22:40 - 01:00	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.

Networking with Leaders Luncheons

THURSDAY, 23 JUNE AND FRIDAY, 24 JUNE
11:30 – 13:00

Moscone West, Level 3, Lobby

Supported by Stem Cell Program at Boston Children's Hospital, Harvard Stem Cell Institute, Massachusetts General Hospital Center for Regenerative Medicine

Meet with experts 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. This is a ticketed event that requires pre-registration.

Career Panel

STRATEGIES FOR SUCCESS: CHOOSING THE BEST CAREER PATH FOR YOUR BIOSCIENCE PHD

SATURDAY, 25 JUNE **11:30 - 13:00**

Moscone West, Level 3, Lobby

Organized by the ISSCR Junior Investigators Committee

This year's career panel, "Strategies for Success: Choosing the Best Career Path for your Bioscience PhD" will focus on PhD careers beyond the academic setting. A bioscience PhD opens the door to a multitude of rewarding and challenging career paths, yet many students and postdocs are unaware of their options. Our PhD panelists from various professional backgrounds will discuss how they found their own path to success. Come and hear tips and strategies in finding a rewarding job that leverages your skill set and, as always, come with your questions!

This is a ticketed event that requires pre-registration.

MODERATOR

Esteban O. Mazzoni, PhD
Assistant Professor of Biology, New York University, U.S.
Member, ISSCR Junior Investigators Committee

PANELISTS

SCIENTIFIC START-UP

Emily Leproust, PhD
Chief Executive Officer
Twist Bioscience, U.S.

ACADEMIC / PRINCIPAL INVESTIGATOR

Kim B. Jensen, PhD
Associate Professor
BRIC University of Copenhagen, Denmark

INDUSTRY SCIENTIST

Allen C. Eaves, MD, PhD, FRCPC
Founder, President and Chief Executive Officer
STEMCELL Technologies Inc., Canada

COMMERCIALIZATION / BUSINESS DEVELOPMENT

Michael May, PhD
Chief Executive Officer
Centre for Commercialization of Regenerative Medicine (CCRM), Canada

IP / GRANT OFFICE / PROGRAM MANAGEMENT

Ingrid W. Caras, PhD
Associate Director
California Institute for Regenerative Medicine (CIRM), U.S.

Focus Sessions

WEDNESDAY, 22 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.

FIGHTING CANCER WITH OFF-THE-SHELF IPSC IMMUNOTHERAPIES

Level 2, Rooms 2020/2022

Organized by Fate Therapeutics

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

- Generating genetically-engineered, naïve iPSCs for therapeutic applications
- Differentiation and industrial-scale expansion of iPSCs into cell types of the hematopoietic lineage
- 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 and related fields in capacities spanning basic research, translational medicine and commercialization.

AGENDA

9:00 – 9:10 Program Introduction: Fighting Cancer with Off-the-Shelf iPSC Immunotherapies
Daniel Shoemaker, *PhD, Chief Scientific Officer, Fate Therapeutics, Inc*

9:10 – 9:40 Better Cells for Better Therapies: Basic Biology & Genomic Engineering of Human iPSCs
Rudolf Jaenisch, MD, *Professor of Biology, MIT, Member, Whitehead Institute, Member, Institute of Medicine*

9:40 – 10:10 Harnessing Hematopoiesis: Creating the Ideal Platform for Large-Scale Expansion of iPSC-Derived, Engineered Hematopoietic Cells
Bob Valamehr, PhD, *Executive Director, Reprogramming Biology, Fate Therapeutics, Inc*

10:10 – 10:40 iPSC Derived NKs: Targeting Cancer with an Engineered, iPSC-Derived NK Cell
Dan Kaufman, MD, PhD, *Professor, Department of Medicine, Director of Cell Therapy Program, University of California-San Diego*

10:40 – 11:10 iPSC Derived CAR-Ts: Targeting Cancer with an Engineered, iPSC-Derived T Cell
Michel Sadelain, *MD, PhD, Director, Center for Cell Engineering & Gene Transfer and Gene Expression Laboratory, Stephen and Barbara Friedman Chair, Memorial Sloan Kettering Cancer Center*

11:10 – 11:40 Clinical & Commercial Translation of iPSC Therapies: Considerations for Advancing iPSC-Derived Therapeutics into the Clinic and onto the Market
Stewart Abbot, PhD, *Chief Development Officer, Fate Therapeutics, Inc*

11:40 – 11:50 Path Forward for Off-the-Shelf iPSC Cellular Immunotherapies
Daniel Shoemaker, PhD, *Chief Scientific Officer, Fate Therapeutics, Inc*

TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY

Level 2, Rooms 2009/2011

Organized by STEMCELL Technologies and Thermo Fisher Scientific

This session is organized by Stem Cell COREdinates (www.COREdinates.org), a consortium of human pluripotent stem cell-

focused shared facilities that have joined forces to share experiences, expertise with protocols and reagents, and to establish "best practices". This open line of communication has helped to disseminate critical information that make science more reproducible; such details are often left out of scientific publications. We share our experience with the field by making protocols available online at Stembook.org and COREdinates.org. Our focus session will be divided into two sessions:

1) Selected COREdinates consortium member lab presentations from core facilities highlighting bioengineering, disease modeling and cell therapies.

2) Panel discussion on pluripotent stem cell-based therapies. A conversation on the strategies, challenges and opportunities for pluripotent stem cell-based therapies. Panelists will include groups that are actively developing and manufacturing cell therapies.

This session is for pluripotent stem cell biologists interested in basic and applied applications.

AGENDA

1) Selected presentations from Stem Cell COREdinates member labs highlighting bioengineering, disease modeling and cell therapies.

Session Chair
Rich Gronostajski, *University of Buffalo, Director of Western New York Stem Cell Culture and Analysis Center (WNYSTEM)*

9:00 Overview of COREdinates

9:05 Implementing Human Naïve Pluripotent Stem Cell Generation in iPSC Core Facilities.
Laurent David

9:20 Standardized tools for iPS cell generation and characterization
Michael Riedel, *STEMCELL Technologies*

9:30 Genome edited iPSCs: creating tools for making blood.
Deborah French, *University of Pennsylvania*

9:45 Chris Kirton*, Sanger Institute, TBD.*

10:00 Materials-based and high content approaches to stem cell research.
Brigette Arduini, *Rensselaer Polytechnic Institute*

10:15 Differentiation as a means to developing physiologically relevant cells for disease modeling and toxicology
David Kuninger, *Associate Director R&D, Thermo Fisher Scientific*

10:25 Core facilities for cell manufacturing applications.
Isabelle Rivière*, Sloan Kettering Institute*

10:40 - 11:00 Break

2) Panel discussion on pluripotent stem cell-based therapies: Panel discussion on the strategies, challenges and opportunities for pluripotent stem cell-based therapies. The panelists are selected from groups that are actively developing and manufacturing pluripotent stem cell therapies.

Session Chair
Stefan Irion, *Sloan Kettering Institute, Program Manager of NYSTEM-funded Parkinson's disease project led by Lorenz Studer*

Katharine Spink, *Chief Operating Officer from Asterias*

Kevin D'Amour, *Vice President, Research and Chief Scientific Officer from Viacyte*

Joseph Gold, *Assistant Director, Translational Research from the Stanford Cardiovascular Institute*

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

HUMANITY IN A DISH

Level 2, Rooms 2014/2016/2018

Organized by WiCell Research Institute

The Next Generation Genetic Association Studies (Next Gen) program is a five-year, $80 million program to investigate functional genetic variation in humans by assessing cellular profiles that are surrogates for disease phenotypes. To achieve this, consortium researchers have derived iPS cell lines from more than 1,500 individuals

representing various conditions (left ventricular hypertrophy, cardiovascular disease, pulmonary hypertension, diabetes, sickle cell disease, etc.) as well as healthy controls (including some from the Framingham Heart Study), resulting in an extensive panel of cell lines with unprecedented diversity. Extensive characterization, including phenotyping, genome sequencing, gene expression, and –omics analysis (e.g., lipidomic, proteomic, methylomic) has resulted in a rich resource to perform advanced "Disease in a Dish" investigative research. In this session, Next Gen consortium members will present findings on their individual cohorts, as well as analyses performed across all 9 studies, highlighting the impact of genetic variation on disease pathology.

This session is for investigators interested in functional genomics and those studying disorders related to heart, lung, and blood - also, investigators interested in whole genome sequencing data, and obtaining materials for use in alternate studies that has extensive characterization data, including genomic data, associated*. Please note that this session will end at 12:30.*

Moderator: Cashell Jaquish *(NIH HHLBI, U.S.)*

Invited Speakers

9:00 - 9:20 Humanity In A Dish: Uncovering The Common Genetic Basis For Human Metabolic Disease With iPSCs.
Dr. Curtis Warren, *Cowan Laboratory, Harvard University, U.S.*

9:20 - 9:40 Modeling Lipid-Associated Hepatic Regulatory Variation In iPS-Hepatocytes
Dr. Evanthia Pashos*, Rader Laboratory, University of Pennsylvania, U.S.*

9:40 - 10:00 Human iPSC Transcriptional Variability And Complex Disease Modeling
Ivan Carcamo-Orive, *Quertermous Laboratory, Stanford University, U.S.*

10:00 - 10:20 Human iPSC Derivation And Genome Editing For Modeling Blood And Vascular Diseases
Dr. Linzhao Cheng, *Johns Hopkins University, U.S.*

10:20 - 10:40 IPSC-Based Modeling And Discovery In Blood-Borne Disease
Dr. George Murphy, *Boston University, U.S.*

10:40 - 10:50 Break

10:50 - 11:10 Unraveling Genetic Risk For Coronary Artery Disease Using Large Scale Genome Editing Of iPSCs.
Dr. Kristin Baldwin, *The Scripps Research Institute, U.S.*

11:10 - 11:30 IPSC Differentiated To Endothelial Cells Reveal New Modifiers Of Pulmonary Arterial Hypertension
Dr. Marlene Rabinovitch**,** *Stanford University, U.S.*

11:30 - 11:50 Functional Analysis Of iPSC-Derived Cardiomyoyctes To Understand Cardiac Disease Mechanisms
Dr. Ulrich Broeckel, *Medical College of Wisconsin, U.S.*

11:50 - 12:10 Genetic Determinants Of Gene Expression In A Collection Of 215 Human induced Pluripotent Stem Cells
Dr. Kelly Frazer, *University of California San Diego, U.S.*

12:10 - 12:30 Overview Of Genomic Integrity Of hiPSC Across Nine Independent Studies.
Dr. Rasika Mathias, *Johns Hopkins University, U.S.*

ETHICAL IMPLICATIONS OF GENOME EDITING TECHNOLOGIES

Level 2, Room 2004

Organized by the ISSCR Ethics Committee

Recent advances in mitochondrial replacement techniques as well as the exploitation of engineered recombinant nucleases have provided facile and reliable methods for genome editing. In particular, with the development of the CRISPR/Cas9 system and the discovery of various versions of Cas9 proteins and delivery carriers, it is now possible to introduce targeted mutations in the human germline, to correct disease-related mutations, and to activate or suppress genes of interest. In advancing toward

clinical application, there are, however, unknown risks to human health and well-being, and a fundamental socio-ethical debate regarding the moral acceptability of modifying the human germline is needed.

Join us for an open dialogue on the socio-ethical implications of human germline genome modification research, and consider the relevant guidelines and legislation in different countries. Speakers will present scientific, regulatory and ethical challenges followed by a moderated debate.

9:00 - 9:05 Introduction
Jonathan Kimmelman, PhD
Biomedical Ethics / Social Studies of Medicine
Department Human Genetics, McGill University, Canada
Chair, ISSCR Ethics Committee and Guidelines Update Task Force

9:05 - 9:25 Science Behind Mitochondrial Replacement Techniques
Robin Lovell-Badge, PhD, FMedSci, FRS
Group Leader, Laboratory of Stem Cell Biology and Developmental Genetics
The Francis Crick Institute, U.K.

9:25 - 9:45 Science Behind Genome Editing Techniques
Bruce R. Conklin, MD
Senior Investigator, Gladstone Institute of Cardiovascular Disease, Gladstone Institutes / Professor, UCSF School of Medicine, U.S.

9:45 - 10:00 Ethical Aspects of Genome Editing
Jeremy Sugarman, MD, MPH, MA
Harvey M. Meyerhoff Professor of Bioethics and Medicine
Johns Hopkins Berman Institute of Bioethics, U.S.
Member, ISSCR Ethics Committee, Guidelines Update Task Force and Public Policy Committee

10:05 - 10:25 Coffee Break

10:25 - 10:45 Germline Modification: The Regulatory Landscape
Timothy Caulfield, LLM, FRSC, FCAHS
Canada Research Chair in Health Law & Policy
Trudeau Fellow and Professor, Faculty of Law and School of Public Health
Research Director, Health Law Institute, University of Alberta, Canada
Member, ISSCR Ethics Committee and Guidelines Update Task Force

10:45 - 11:05 Hinxton Group Consensus Statement
Debra JH Mathews, PhD, MA
Assistant Director for Science Programs
Johns Hopkins Berman Institute of Bioethics
Associate Professor, Department of Pediatrics
Johns Hopkins University School of Medicine, U.S.

11:05 - 11:50 Discussion

11:50 - 12:00 Wrap Up
Jonathan Kimmelman, PhD

A PRACTICAL GUIDE TO STARTING A COMPANY AND A TASTE OF THE SHARK TANK*

Level 2, Room 2024

Organized by the ISSCR Industry Committee

Inspirational talks from people who have succeeded in building their companies can spark a fire for an entrepreneur, but equally important is the practical guidance on how to translate an idea from a concept to a company. This session will provide practical tools and advice to help scientists take the leap to start their own company and will cover a range of topics: evaluating an idea and creating a plan to move it forward, navigating licensing the product, building a winning team, pitching the idea to both investors and customers and developing the product. Bring your questions as the audience will be invited to pose questions to the panel of speakers. In the final portion of the session, our panelists will provide an insider perspective on developing a successful start-up business plan and avoiding major pitfalls. In this roundtable

discussion you will have the opportunity to pose questions, even briefly present your ideas and gain expert feedback.

9:00 - 9:05 Moderator Welcome
Jesper Ericsson, PhD
Sales Manager
BioLamina, Sweden

9:05 - 10:05 Early Startup
Michael H. May, PhD
President and Chief Executive Officer
Centre for Commercialization of Regenerative Medicine (CCRM), Canada
Member, ISSCR Industry Committee

Negotiation-Licensing
Stephen Chang, PhD
Vice President, Research & Development
The New York Stem Cell Foundation (NYSCF), U.S.

Creating a Culture
Kristian Tryggvason, PhD, MBA
Founder and Chief Executive Officer
BioLamina, Sweden
Member, ISSCR Industry Committee

Financing-Sales and Marketing
Allen C. Eaves, MD, PhD, FRCPC
President and Chief Executive Officer
STEMCELL Technologies Inc., Canada

10:05 - 10:20 Refreshment Break

10:20 - 10:50 Product Development/ Manufacturing
Benjamin Fryer, PhD
Team Leader, Processing/Manufacturing, Heart Regeneration Program
University of Washington School of Medicine, U.S.

Wrap Up - Bringing It All Together
Claudia Zylberberg, PhD
Founder and Chief Executive Officer
Akron Biotechnology, LLC, U.S.
Member, ISSCR Industry Committee

10:50 – 12:00 Panel Discussion

**Shark Tank is a U.S. reality television series based on the format of the Dragon's Den series, which originally aired in Japan. The concept has aspiring entrepreneur-contestants making business presentations to a panel of investors (sharks/dragons).*

HOW EBISC CAN HELP RESEARCHERS IN ACCESSING HIGH-QUALITY RESEARCH-GRADE IPSC LINES

Level 2, Room 2002

Organized by EBiSC (European Bank for induced pluripotent Stem Cells)

This session is organized by the EBiSC consortium, a 3-years research project aiming to set up the not-for-profit European Bank for induced pluripotent Stem Cells (EBiSC).

We share our experience on:

- the establishment of an iPS cell bank with core and mirror facilities,
- the set-up of a robust and reliable supply chain for iPS lines including the generation of disease specific, control, gene edited and isogenic cell lines,
- standardized work flows from tissue procurement to generation, characterisation, preservation and supply
- standardized quality control expansion and
- the set-up of the ethical and legal governance structure for stem cell banking and distribution (informed consents, patient engagement, EBiSC MDA/AUA).

The Focus Session, which will be supported by public funding, targets both academic and commercial scientists using iPSC in disease modeling and other forms of pre-clinical research. We also seek interactions with the attendees to discuss research needs and opportunities to engage with EBiSC. This session is for academic

and commercial scientists generating iPSC and/or using them in disease modelling and other forms of pre-clinical research.

AGENDA

9:00 – 10:30 The EBiSC Project

Introduction to EBiSC
Timothy Allsopp*, Stem Cell & Cell Therapy lead, Pfizer Ltd, U.K.*

Building a European iPSC collection meeting research demand
Julie Holder*, Roslin Cells Sciences, U.K.*

Demonstration of the EBISC Catalogue
Laura Clarke**,** *European Molecular Biology Laboratory, European Bioinformatics Institute, U.K.*

Setting quality control standards to enhance research
Glyn Stacey**,** *National Institute for Biological Standards & Control, U.K.*

Establishing a unique ethical and legal governance structure for international iPSC banking
Aidan Courtney, *Roslin Cells Sciences, U.K.*

10:30 – 11:00 Networking Break

11:00 – 12:00 Delivering A Robust iPSC Resource-Panel Session

Initial cell line catalogue users from academia and industry will share their EBiSC experiences with you. With the panelists in a Q&A session, understand more as to how EBiSC fits into the global iPS research landscape and explore how the EBiSC approach can meet your research needs now and facilitate future collaborations.

Timothy Allsopp, *Stem Cell & Cell Therapy lead, Pfizer Ltd, U.K.*
Aidan Courtney*, Roslin Cells Sciences, U.K.*

12:00 Closure

HOW RESEARCHERS ANYWHERE CAN USE CIRM FUNDS TO ADVANCE STEM CELL SCIENCE

Level 2, Rooms 2001/2003/2005/2007

Organized by The California Institute for Regenerative Medicine (CIRM)

Over the past year CIRM has completely overhauled its funding system. It is now speedier, taking just 120 days from application to funding in hand for clinical programs. CIRM has made it easier for companies and research teams outside of California to use CIRM funds for trial sites or other work done in California and have also created an incentive program offering $150,000 seed funding to basic research teams who pass along their projects to the next stage of translation. CIRM has also created an Accelerating Center and a Translation Center to help with pre-IND work, IND filing, trial design and execution. Clinical and translational researchers from all over the globe as well as basic researchers from California are invited to learn how you can partner with CIRM to advance your stem cell science, regardless of stage, toward the clinic.

This session is for clinical and translational researchers from all over the globe and basic researchers from California. *Please note that this session will end at 10:30.*

Speakers

C. Randal Mills, Ph.D., *President and CEO, CIRM*
Patricia Olson, Ph.D., *Executive Director, Discovery & Translation, CIRM*
Maria T. Millan, M.D., *Senior Director, Medical Affairs & Strategic Centers, CIRM*
Abla Creasey, Ph.D., *Associate Director for Therapeutics, CIRM*


Save
the Date
WHAT:
Cell Biology 2016
ASCB Annual Meeting
WHEN:
December 3–7, 2016
WHERE:
Moscone Center,
San Francisco, CA
Submit an abstract by Aug. 2 to speak at ASCB 2016
Minisymposium (15-min talk incl. Q&A)
Microsymposium (7-min talk incl. Q&A)
Cell Biology 2016 is offering more speaking opportunities than ever before, along with:
Workshops on CRISPR, cryo electron and super-resolution microscopy
Full-day symposium on the Cancer of Cell Biology
Career center offering one-on-one CV review and career counseling, career panels, and a science writing workshop
Find out more at ascb.org/2016meeting
ascb
an international forum for cell biology
cell biology 2016
ascb annual meeting

PROGRAM SCHEDULE

TUESDAY, 21 JUNE

9:00 - 17:00	**ISSCR/ASGCT WORKSHOP ON CLINICAL TRANSLATION**	Level 3, Rooms 3014/3016
14:00 - 18:00	**REGISTRATION OPEN**	Level 1, Lobby
15:00 - 16:30	**ATTENDEE ORIENTATION I**	Level 3, Lobby

WEDNESDAY, 22 JUNE

7:30 - 20:30	**REGISTRATION OPEN**	Level 1, Lobby
8:30 - 10:00	**ATTENDEE ORIENTATION II**	Level 3, Lobby
	FOCUS SESSIONS	
9:00 - 12:00	**FIGHTING CANCER WITH OFF-THE-SHELF IPSC IMMUNOTHERAPIES** *Presented by Fate Therapeutics*	Level 2, Rooms 2020/2022
9:00 - 12:00	**TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY** *Presented by STEMCELL Technologies and Thermo Fisher Scientific*	Level 2, Rooms 2009/2011
9:00 - 12:30	**HUMANITY IN A DISH** *Presented by WiCell Research Institute*	Level 2, Rooms 2014/2016/2018
9:00 - 12:00	**ETHICAL IMPLICATIONS OF GENOME EDITING TECHNOLOGIES** *Presented by The ISSCR Ethics Committee*	Level 2, Room 2024
9:00 - 12:30	**A PRACTICAL GUIDE TO STARTING A COMPANY AND A TASTE OF THE SHARK TANK** *Presented by The ISSCR Industry Committee*	Level 2, Room 2004
9:00 - 12:00	**HOW EBISC CAN HELP RESEARCHERS IN ACCESSING HIGH-QUALITY RESEARCH-GRADE IPSC LINES** *Presented by The European Bank for induced pluripotent Stem Cells (EBiSC)*	Level 2, Room 2002

WEDNESDAY, 22 JUNE *(continued)*

9:00 - 10:30	**HOW RESEARCHERS ANYWHERE CAN USE CIRM FUNDS TO ADVANCE STEM CELL SCIENCE** *Presented by The California Institute for Regenerative Medicine (CIRM)*	Level 2, Rooms 2001/2003/2005/2007
11:25 - 12:45	**EARLY-CAREER GROUP LEADER LUNCHEON** *(Advance registration required)* *Supported by The Ontario Institute for Regenerative Medicine (OIRM)*	Level 3, Lobby
13:00 - 15:15	**PLENARY I PRESIDENTIAL SYMPOSIUM: STEM CELLS AND CANCER** *Supported by Fate Therapeutics* **Chair: Sean J. Morrison** *Children's Research Institute at UT Southwestern, U.S.*	Level 3, Plenary Hall
13:00 - 13:10	**OPENING REMARKS**	
13:10 - 13:20	**ISSCR PRESIDENT'S ADDRESS: SEAN J. MORRISON**	
13:20 - 13:25	**THE MCEWEN AWARD FOR INNOVATION PRESENTATION TO AUSTIN SMITH AND QI-LONG YING**	
13:25 - 13:45	**Austin Smith** *Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute, U.K.* ESCAPE FROM THE GROUND STATE	
13:45 - 14:05	**John Dick** *Princess Margaret Cancer Centre, Canada* THE ROLE OF CANCER STEM CELLS IN THERAPY FAILURE AND DISEASE RECURRENCE	
14:05 - 14:25	**Irving L. Weissman** *Stanford University School of Medicine, U.S.* STEM CELL COMPETITION AND CANCER	
14:25 - 14:45	**Elaine Fuchs** *Rockefeller University, U.S.* SKIN STEM CELLS IN SILENCE, ACTION, AGING AND CANCER	

WEDNESDAY, 22 JUNE *(continued)*

14:45 - 15:05	**Pier Paolo Pandolfi** *Beth Israel Deaconess Medical Center, U.S.* THE NON-CODING RNA REVOLUTION IN BIOMEDICAL RESEARCH	
15:15 - 20:30	**ISSCR EXHIBITION HALL OPEN**	Level 1, Exhibition & Poster Hall
15:15 - 16:00	**REFRESHMENT BREAK**	Level 1, Exhibition & Poster Hall
16:00 - 18:00	**PLENARY II: TISSUE GROWTH AND MORPHOGENESIS** **Chair: Masayo Takahashi** *RIKEN, Center for Developmental Biology, Japan*	Level 3, Plenary Hall
16:00 - 16:05	**THE ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR PRESENTATION TO FERNANDO CAMARGO**	
16:05 - 16:30	**Fernando Camargo** *Boston Children's Hospital, U.S.* CLONAL ANALYSIS OF NATIVE HEMATOPOIESIS	
16:30 - 16:55	**Duojia Pan** *Johns Hopkins University School of Medicine, U.S.* HIPPO SIGNALING IN GROWTH CONTROL AND BEYOND	
16:55 - 17:20	**Jennifer Zallen** *Howard Hughes Medical Institute and Sloan Kettering Institute, U.S.* A POSITIONAL CODE AND POLARIZED FORCES CONTROL TISSUE REMODELING IN DROSOPHILA	
17:20 - 17:30	**POSTER TEASERS**	
17:30 - 17:35	**THE ISSCR TOBIAS AWARD PRESENTATION TO LEONARD I. ZON**	
17:35 - 18:00	**Leonard I. Zon** *Boston Children's Hospital, U.S.* PATHWAYS REGULATING BLOOD STEM CELL SELF-RENEWAL AND MIGRATION: TRANSLATING DEVELOPMENT INTO CLINICAL THERAPIES	

WEDNESDAY, 22 JUNE *(continued)*

18:00 - 20:30	**OPENING RECEPTION** *Supported by Takeda Pharmaceutical*	Level 1, Exhibition & Poster Hall
18:30 - 20:30	**POSTER SESSION I** ODD numbered posters present from 18:30-19:30 EVEN numbered posters present from 19:30-20:30	Level 1, Exhibition & Poster Hall
21:00 - 01:00	**JUNIOR INVESTIGATOR SOCIAL NETWORKING NIGHT** *(Junior Investigator event; advance registration required)*	Ruby Skye Nightclub, 420 Mason St.

THURSDAY, 23 JUNE

INNOVATION SHOWCASES

8:00 - 8:30	**UNION BIOMETRICA INC.** Automation for Analysis and Handling of Cells and Cell Clusters in Stem Cell Research **Rock Pulak** *Union Biometrica, Inc.*	Level 2, Room 2002
8:00 - 8:30	**STEMCELL TECHNOLOGIES INC.** BrainPhys™ Neuronal Medium Supports Neurophysiological Activities of Human Pluripotent Stem Cell-derived Neurons **Cedric Bardy** *Salk Institute for Biological Studies*	Level 2, Rooms 2009/2011
8:00 - 8:30	**THERMO FISHER SCIENTIFIC** Predict the Unpredictable: Using the In Vivo Niche to Assess Lineage Potential and Functionality of PSC-derived cells **Hideki Masaki** *Institute of Medical Science, University of Tokyo*	Level 2, Rooms 2020/2022
8:15 - 9:00	**MORNING COFFEE**	Level 3, Lobby
8:15 - 18:30	**REGISTRATION OPEN**	Level 1, Lobby

THURSDAY, 23 JUNE *(continued)*

9:00 - 17:00	**ISSCR CAREER FAIR**	Level 2, Lobby
9:00 - 11:20	**PLENARY III: CELLULAR PLASTICITY AND REPROGRAMMING** **Chair: Deepak Srivastava** *Gladstone Institutes, U.S.*	Level 3, Plenary Hall
9:00 - 9:25	**ISSCR BUSINESS MEETING**	
9:25 - 9:50	**Shinya Yamanaka** *Gladstone Institutes, U.S. and CiRA, Kyoto University, Japan* RECENT PROGRESS IN IPS CELL RESEARCH AND APPLICATION	
9:50 - 10:15	**Fiona Watt** *King's College London, U.K.* PLASTICITY OF EPIDERMAL STEM CELLS	
10:15 - 10:25	**POSTER TEASERS**	
10:25 - 10:50	**Marius Wernig** *Department of Pathology, Stanford University, U.S.* HOW TO MAKE A NEURON	
10:50 - 11:15	**Malin Parmar** *Lund University, Sweden* BRAIN REPAIR AND REPROGRAMMING	
11:00 - 20:00	**ISSCR EXHIBITION HALL OPEN**	Level 1, Exhibition & Poster Hall

THURSDAY, 23 JUNE *(continued)*

INNOVATION SHOWCASES

11:30 - 12:30 — **IRVINE SCIENTIFIC** — Level 2, Room 2002

Optimizing the Culture Medium that Maintains Mouse Hematopoietic Stem Cells

Hideyuki Oguro

Howard Hughes Medical Institute, Children's Medical Center Research Institute, and Department of Pediatrics, UT Southwestern Medical Center

Impacts of Undefined Components for Primary Cell Cultures

Jessie H.-T. Ni

R&D Department, Irvine Scientific

11:30 - 12:30 — **STEMGENT, A REPROCELL GROUP COMPANY** — Level 2, Room 2004

Novel RNA Reprogramming Platform to Generate iPSC Lines from Blood, Skin, Urine, and Translational Application to Retinal Phenotypes

Sarah Eminli-Meissner

Stemgent, a ReproCELL Group Company

Jason Meyer

Indiana University Purdue University Indianapolis

11:30 - 12:30 — **ESI BIO (ASCENDANCE BIOTECHNOLOGY)** — Level 2, Rooms 2001/2003/2005/2007

Clinically Relevant Stem Cells and Matrices - The ReadyStem™ mRNA Reprogramming Kit for iPSC; ESI hES Cells; HyStem® Hydrogels

Jens Durruthy-Durruthy

Institute for Stem Cell Biology and Regenerative Medicine, Stanford University

Tom Zarembinski

BioTime, Inc.

11:30 - 12:30 — **NIKON CORPORATION** — Level 2, Rooms 2009/2011

Developing a Live Cell System for Visualizing Neuronal Degeneration

Lee L. Rubin

Harvard Department of Stem Cell and Regenerative Biology

THURSDAY, 23 JUNE *(continued)*

11:30 - 12:30	**FLUIDIGM** Rediscover Stem Cell Biology at Single-cell Resolution **Alex Pollen** *University of California, San Francisco* **Jay Gibson** *University of Connecticut*	Level 2, Rooms 2014/2016/2018
11:30 - 12:30	**BD BIOSCIENCES** Biological Perspectives in Multicolor Flow Analysis: Moving to 50-color Flow Cytometry **Bob Balderas** *BD Biosciences*	Level 2, Rooms 2020/2022
11:30 - 12:30	**BIO-TECHNE** Get the Most Out of Your Cells: Tools to Optimize Pluripotent Stem Cell Cultures and Differentiation **Joy Aho** *Stem Cell Research & Development, Bio-Techne* **Scott Schachtele** *Bio-Techne*	Level 2, Room 2024
11:30 - 13:00	**NETWORKING WITH LEADERS LUNCHEON** *(Junior Investigator event; advance registration required)* *Supported by Stem Cell Program at Boston Children's Hospital, MGH Center for Regenerative Medicine, and The Harvard Stem Cell Institute (HSCI)*	Level 3, Lobby
11:30 - 13:15	**LUNCH BREAK**	
12:15 - 13:00	**MEET-UP: LEARN WHAT'S NEW IN THE GERMAN STEM CELL NETWORK** *Organized by The German Stem Cell Network (GSCN)*	Meet-up Hub #1 (Hub supported by Thermo Fisher Scientific)
12:15 - 13:00	**MEET-UP: HOW EBISC HELPS RESEARCHERS IN ACCESSING HIGH-QUALITY RESEARCH-GRADE IPSC LINES** *Organized by The European Bank for induced pluripotent Stem Cells (EBiSC)*	Meet-up Hub #2

THURSDAY, 23 JUNE *(continued)*

13:15 - 15:15 **CONCURRENT I: NEURAL STEM CELLS** Level 2, Rooms 2014/2016/2018
Supported by Innovative Cell Technologies Inc.
Chair: Arturo Alvarez-Buylla
University of California San Francisco, U.S.

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

13:20 - 13:45 **Saul Villeda**
University of California, San Francisco, U.S.
ROLE OF CLASSICAL IMMUNE MOLECULES IN REGULATING AGE-RELATED DECLINE IN ADULT NEUROGENESIS

13:45 - 14:00 **Steven Pollard**
University of Edinburgh, U.K.
EFFICIENT CRISPR/CAS9-BASED GENE TARGETING IN MAMMALIAN NEURAL STEM CELLS ENABLES COMPLEX AND DIVERSE GENETIC MANIPULATIONS

14:00 - 14:15 **Noelia Urbán**
The Francis Crick Institute, U.K.
HUWE1 PROMOTES THE QUIESCENCE OF ADULT NEURAL STEM CELLS VIA TARGETED ELIMINATION OF ASCL1

14:15 - 14:30 **Elizabeth Kirby**
Stanford University, U.S.
ADULT HIPPOCAMPAL NEURAL PROGENITORS REGULATE SEIZURE-INDUCED NEUROINFLAMMATION VIA SECRETED VEGF

14:30 - 14:45 **Anna Falk**
Karolinska Institutet, Sweden
AN IN VITRO MODEL OF LISSENCEPHALY: EXPANDING THE ROLE OF DCX DURING NEUROGENESIS

14:45 - 15:10 **Hongjun Song**
Johns Hopkins University, U.S.
IMPACT OF ZIKA VIRUS ON HUMAN CORTICAL NEUROGENESIS

THURSDAY, 23 JUNE *(continued)*

13:15 - 15:15 **CONCURRENT I: PARADIGMS FROM MODEL ORGANISMS** Level 2, Room 2024

Chair: Leonard I. Zon

Boston Children's Hospital, U.S.

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

13:20 - 13:45 **Yukiko Yamashita**

University of Michigan, U.S. and Howard Hughes Medical Institute, U.S.

THE NICHE LIGAND-RECEPTOR DIRECTLY ORIENTS THE SPINDLE IN DROSOPHILA MALE GERMLINE STEM CELLS

13:45 - 14:00 **Yonatan Stelzer**

Whitehead Institute for Biomedical Research, U.S.

PARENT-OF-ORIGIN DNA METHYLATION DYNAMICS DURING MOUSE DEVELOPMENT AT SINGLE-CELL RESOLUTION

14:00 - 14:15 **Amy Reilein**

Columbia University, U.S.

DROSOPHILA FOLLICLE STEM CELLS RESIDE IN LAYERS WITH POSITION-DEPENDENT SPECIFICATION OF DISTINCT DIRECT STEM CELL DERIVATIVES GUIDED BY A WNT SIGNALING GRADIENT

14:15 - 14:30 **Duc Dong**

Sanford Burnham Prebys Medical Discovery Institute, U.S.

INDUCED IN VIVO REPROGRAMMING OF ZEBRAFISH MUSCLE INTO ENDODERM BY DIRECT TRANSDIFFERENTIATION

14:30 - 14:45 **Jackson Liang**

Stanford University, U.S.

AN INTERCELLULAR E-CADHERIN-EGFR RELAY MAINTAINS ORGAN SIZE DURING RENEWAL BY COUPLING CELL DIVISION AND DEATH

14:45 - 15:10 **Alejandro Sanchez Alvarado**

Stowers Institute for Medical Research, U.S.

STEM CELL POPULATION DYNAMICS, TISSUE HOMEOSTASIS AND REGENERATION

THURSDAY, 23 JUNE *(continued)*

13:15 - 15:15 **CONCURRENT I: MECHANISMS OF PLURIPOTENCY** Level 2, Rooms 2001/2003/2005/2007
Chair: Kathrin Plath
UCLA School of Medicine, U.S.

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

13:20 - 13:45 **Qi Zhou**
Institute of Zoology ,Chinese Academy of Sciences, China
DECIPHERING THE PLURIPOTENCY OF RODENT AND NON-HUMAN PRIMATE STEM CELLS

13:45 - 14:00 **Thorold Theunissen**
Whitehead Institute for Biomedical Research, U.S.
NAIVE PLURIPOTENT STEM CELLS DISPLAY MOLECULAR SIGNATURES OF THE HUMAN PREIMPLANTATION EMBRYO

14:00 - 14:15 **Fredrik Lanner**
Karolinska Institutet, Sweden
SINGLE-CELL RNA-SEQ REVEALS LINEAGE FORMATION AND X-CHROMOSOME DOSAGE COMPENSATION IN HUMAN PREIMPLANTATION EMBRYOS

14:15 - 14:30 **Victoria Mascetti**
University of Cambridge, U.K.
HUMAN-MOUSE CHIMERISM VALIDATES HUMAN STEM CELL PLURIPOTENCY

14:30 - 14:45 **Alexander Tsankov**
Harvard University/Broad Institute, U.S.
SINGLE CELL RNA SEQUENCING UNCOVERS CELL CYCLING MARKERS OF LINEAGE SPECIFICATION DURING HUMAN EMBRYONIC STEM CELL DIFFERENTION

14:45 - 15:10 **Rudolf Jaenisch**
Whitehead Institute for Biomedical Research, U.S.
HUMAN IPS CELLS, PLURIPOTENCY AND DEVELOPMENTAL POTENTIAL

THURSDAY, 23 JUNE *(continued)*

13:15 - 15:15 **CONCURRENT I: DISEASE MODELING I** Level 2, Rooms 2020/2022
Chair: Hongkui Deng,
Peking University, China

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

13:20 - 13:45 **Guanghui Liu**
Institute of Biophysics, Chinese Academy of Sciences, China
USING STEM CELL AND GENE EDITING TECHNIQUES TO STUDY AND TREAT AGING-ASSOCIATED DISORDERS

13:45 - 14:00 **Wenli Li**
Medical College of Wisconsin, U.S.
AN EPIDEMIOLOGICAL APPROACH TO IDENTIFY BIOMARKERS OF LEFT VENTRICULAR HYPERTROPHY USING AN HIPSC-CM COHORT

14:00 - 14:15 **Justin Ichida**
Broad CIRM Center, Keck School of Medicine, University of Southern California, U.S.
IDENTIFICATION OF THERAPEUTIC TARGETS AND PATHOGENIC MECHANISMS FOR C9ORF72 ALS USING PHENOTYPIC CHEMICAL SCREENING

14:15 - 14:30 **Yishai Avior**
The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University of Jerusalem, Israel
DEVELOPMENTAL AND TUMORIGENIC ASPECTS OF TRILATERAL RETINOBLASTOMA MODELED IN HUMAN EMBRYONIC STEM CELLS

14:30 - 14:45 **Filip Roudnicky**
F. Hoffmann La Roche Ltd., Switzerland
MODELING OF SEVERE METABOLIC GENETIC DISEASES IN VITRO USING GENOME EDITING AND HUMAN PLURIPOTENT STEM CELL DIFFERENTIATION TO VASCULAR ENDOTHELIAL CELLS

14:45 - 15:10 **Christine Mummery**
Leiden University Medical Center, Netherlands
CHALLENGES OF IMMATURITY AND PROLIFERATION IN USING HPSC-DERIVED CARDIOMYOCYTES AS DISEASE MODELS

THURSDAY, 23 JUNE *(continued)*

13:15 - 15:15 **CONCURRENT I: STEM CELL PLASTICITY** Level 2, Room 2004
Chair: Martin Pera
University of Melbourne, Australia

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

13:20 - 13:45 **Erika Matunis**
Johns Hopkins University, U.S.
STEM CELLS AND PLASTICITY IN THE TESTIS

13:45 - 14:00 **Laralynne Przybyla**
University of California, San Francisco, U.S.
MATRIX TENSION DIRECTS WNT-DEPENDENT MESODERM DIFFERENTIATION OF HUMAN EMBRYONIC STEM CELLS

14:00 - 14:15 **Lijian Hui**
Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, China
ATM-P53 ACTIVATION BLOCKS HEPATIC CONVERSION BY SENSING CHROMATIN OPENING

14:15 - 14:30 **Jihee Sohn**
University of Pittsburgh, U.S.
INFLUENCE OF CHOLESTEROL/CAVEOLIN-1/CAVEOLAE HOMEOSTASIS ON HUMAN MESENCHYMAL STEM CELL MEMBRANE PROPERTIES AND ADHESIVE CHARACTERISTICS

14:30 - 14:45 **Kristopher Kilian**
University of Illinois at Urbana-Champaign, U.S.
MICROENVIRONMENT ENGINEERING TO AUGMENT MESENCHYMAL TO EPITHELIAL TRANSITIONS AND CELLULAR REPROGRAMMING

14:45 - 15:10 **Shaorong Gao**
Tongji University, China
ESTABLISHMENT OF HISTONE MODIFICATIONS IN PRE-IMPLANTATION MOUSE EMBRYOS

THURSDAY, 23 JUNE *(continued)*

13:15 - 15:15 **CONCURRENT I: MUSCLE STEM CELLS** Level 2, Room 2002
Chair: Amy Wagers
Harvard University, U.S.

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

13:20 - 13:45 **April Pyle**
University of California, Los Angeles Eli and Edythe Broad Stem Cell Research Center, U.S.
DEFINING THE DEVELOPMENTAL AND FUNCTIONAL POTENTIAL OF HUMAN PLURIPOTENT STEM CELL DERIVED SKELETAL MUSCLE PROGENITOR CELLS

13:45 - 14:00 **Helen Blau**
Stanford University School of Medicine, U.S.
NOVEL INDUCER OF QUIESCENCE THAT AUGMENTS MUSCLE STEM CELL ENGRAFTMENT AND REGENERATION REVEALED BY PROTEIN LIBRARY SCREEN

14:00 - 14:15 **Wenxuan Liu**
University of Rochester, U.S.
INDUCIBLE DEPLETION OF SATELLITE CELLS ACCELERATES AGE-RELATED MOUSE NEUROMUSCULAR JUNCTION DETERIORATION

14:15 - 14:30 **Joseph Rodgers**
Eli and Edythe Broad Center, Keck School of Medicine of University of Southern California, U.S.
SYSTEMIC REGULATION OF QUIESCENT STEM CELL FUNCTION AND REGENERATIVE POTENTIAL

14:30 - 14:45 **Alessandra Sacco**
Sanford Burnham Prebys Medical Discovery Institute, U.S.
DEVELOPMENTAL PROGRESSION OF SKELETAL MUSCLE STEM CELLS IS MEDIATED BY AUTONOMOUS EXTRACELLULAR MATRIX REMODELING

14:45 - 15:10 **Pura Muñoz-Cánoves**
Universitat Pompeu Fabra, ICREA and CNIC, Spain
MUSCLE STEM CELL REGENERATIVE DECLINE WITH AGING

THURSDAY, 23 JUNE *(continued)*

13:15 - 15:15	**CONCURRENT I: CARDIAC DEVELOPMENT AND REGENERATION** **Chair: Deepak Srivastava,** *Gladstone Institutes, U.S.*	Level 2, Rooms 2009/2011
13:15 - 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 - 13:45	**Chulan Kwon** *Johns Hopkins University, U.S.* MAKING ADULT CARDIOMYOCYTES FROM PLURIPOTENT STEM CELLS	
13:45 - 14:00	**Stephanie Protze** *McEwen Centre for Regenerative Medicine, Canada* TRANSGENE INDEPENDENT GENERATION AND ISOLATION OF FUNCTIONAL SINOATRIAL NODE PACEMAKER CELLS FROM HUMAN PLURIPOTENT STEM CELLS	
14:00 - 14:15	**Tamer Mohamed** *Gladstone Institutes, University California, San Francisco, U.S.* SMALL MOLECULE COCKTAIL ENHANCEMENT OF IN VITRO AND IN VIVO DIRECT CARDIAC REPROGRAMMING OF POSTNATAL CARDIAC FIBROBLASTS	
14:15 - 14:30	**Lei Yang** *University of Pittsburgh, U.S.* REGENERATE WHOLE HEART USING HUMAN IPS CELL-DERIVED CARDIOVASCULAR PROGENITOR CELLS	
14:30 - 14:45	**LouJin Song** *Columbia University Medical Center, U.S.* UNDERSTANDING THE REGULATION OF CARDIAC CALCIUM CHANNELS USING IPSC-DERIVED CARDIOMYOCYTES	
14:45 - 15:10	**Deborah Yelon** *University of California, San Diego, U.S.* REINFORCEMENT OF CELL FATE DECISIONS IS CRUCIAL FOR MAINTAINING CARDIAC CHAMBER INTEGRITY	

THURSDAY, 23 JUNE *(continued)*

13:15 - 14:30	**SOCIAL MEET-UP: SOLUTIONS EXCHANGE** *Organized by the International Society for Stem Cell Research (ISSCR)*	Meet-up Hubs #1 and #2 (Hub #1 supported by Thermo Fisher Scientific)
15:15 - 16:00	**REFRESHMENT BREAK**	Level 1, Exhibition & Poster Hall
15:15 - 16:00	**MEET-UP: LET'S TALK CLINICAL TRANSLATION** *Organized by Thermo Fisher Scientific*	Meet-up Hub #1 (Hub supported by Thermo Fisher Scientific)
16:00 - 18:00	**CONCURRENT II: NEURAL DISEASE** **Chair: Hideyuki Okano** *Keio University School of Medicine, Japan*	Level 2, Rooms 2001/2003/2005/2007
16:00 - 16:05	**TOPIC OVERVIEW BY CHAIR**	
16:05 - 16:30	**Vania Broccoli** *San Raffaele Scientific Institute, Italy* MYELINOGENIC AND NERVE REGENERATING INDUCED SCHWANN CELLS DERIVED BY TWO-FACTOR SKIN FIBROBLAST REPROGRAMMING	
16:30 - 16:45	**ChangHui Pak** *Stanford University, U.S.* HUMAN NEUROPSYCHIATRIC DISEASE MODELING USING CONDITIONAL DELETION REVEALS SYNAPTIC TRANSMISSION DEFECTS CAUSED BY HETEROZYGOUS MUTATIONS IN NRXN1	
16:45 - 17:00	**Max Salick** *Novartis Institute for Biomedical Research, U.S.* GENE-EDITED HUMAN STEM CELL MODELS OF TUBEROUS SCLEROSIS EXHIBIT TREATABLE DISEASE PHENOTYPES UPON 2D AND 3D NEURONAL DIFFERENTIATION	
17:00 - 17:15	**Mahmoud Pouladi** *Agency for Science, Technology and Research, Singapore and National University of Singapore, Singapore* SEAMLESS GENE CORRECTION IN HUNTINGTON DISEASE PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS USING CRISPR-CAS9 AND PIGGYBAC	

THURSDAY, 23 JUNE *(continued)*

17:15 - 17:30 **Anja Nitzsche**
Pfizer Ltd, Neuroscience & Pain Research Unit, U.K.
MODELLING THE PHARMACOLOGICAL AND CLINICAL RESPONSE IN PRIMARY ERYTHROMELALGIA USING INDUCED PLURIPOTENT STEM CELLS

17:30 - 17:55 **Mark Tuszynski**
University of California, San Diego, U.S. and Veterans Administration Medical Center, U.S.
NEURAL STEM CELL THERAPY IN SPINAL CORD INJURY: SPINAL CORD "REPLACEMENT" ENABLES HOST AXONAL REGENERATION

16:00 - 18:00 **CONCURRENT II: STEM CELLS IN ORGAN DEVELOPMENT AND MAINTENANCE** Level 2, Rooms 2020/2022
Chair: Elly Tanaka
DFG Research Center for Regenerative Therapies, Technische Universitaet Dresden, Germany

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

16:05 - 16:30 **Marc van de Wetering**
Hubrecht Institute, Netherlands
LGR5 STEM CELL-BASED ORGANOIDS IN HUMAN DISEASE

16:30 - 16:45 **Katie Vermillion**
Morgridge Institute for Research, U.S.
SINGLE-CELL RNA-SEQ ENABLES SPATIAL ALIGNMENT OF CHICK PRIMITIVE STREAK CELLS TO REVEAL NOVEL MARKERS OF ENDODERM AND MESODERM DIFFERENTIATION

16:45 - 17:00 **Frank Edenhofer**
University of Innsbruck, Austria
BREAKDOWN OF GAP JUNCTIONAL COMMUNICATION RESULTS IN BLOCK OF PRIMITIVE ENDODERM FORMATION

17:00 - 17:15 **Steffen Rulands**
University of Cambridge, U.K.
UNVEILING LINEAGE DECISIONS IN DEVELOPING TISSUES

THURSDAY, 23 JUNE *(continued)*

17:15 - 17:30 **Jamie Trott**
Institute of Medical Biology, Singapore
MODELING DIABETIC BETA CELL FAILURE USING HUMAN MULTIPOTENT PANCREATIC PROGENITORS

17:30 - 17:55 **Paola Arlotta**
Harvard University, U.S.
REPROGRAMMING NEURONAL DIVERSITY IN VIVO

16:00 - 18:00 **CONCURRENT II: MECHANISMS OF ASYMMETRIC CELLULAR DIVISION** Level 2, Room 2004
Chair: Yukiko Yamashita
University of Michigan, Ann Arbor, U.S.

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

16:05 - 16:30 **Xin Chen**
Johns Hopkins University, U.S.
BREAKING SYMMETRY- ASYMMETRIC EPIGENETIC INHERITANCE DURING DROSOPHILA GERMLINE STEM CELL ASYMMTERIC DIVISION

16:30 - 16:45 **Kirsten Obernier**
University of California, San Francisco, U.S.
PRIMARY NEURAL PROGENITOR CELLS IN THE ADULT MOUSE V-SVZ UNDERGO SYMMETRIC CONSUMING DIVISIONS AND LIMITED SELF-RENEWAL

16:45 - 17:00 **Mathieu Daynac**
University of California, San Francisco, U.S.
LETHAL GIANT LARVAE 1 (LGL1) REGULATES CELL FATE, POLARITY, PROLIFERATION AND MIGRATION OF CORPUS CALLOSUM PROGENITOR CELLS

17:00 - 17:15 **Tara TeSlaa**
University of California, Los Angeles, U.S.
ALPHA-KETOGLUTARATE ACCELERATES THE INITIAL DIFFERENTIATION OF PRIMED HUMAN PLURIPOTENT STEM CELLS

THURSDAY, 23 JUNE *(continued)*

17:15 - 17:30 **TISSUE ENGINEERING PREVIEW FROM LATE BREAKING ABSTRACTS**
Christopher Ross Schlieve
Children's Hospital Los Angeles, U.S.
GENERATION OF TISSUE-ENGINEERED SMALL INTESTINE WITH AN ENTERIC NERVOUS SYSTEM DERIVED EXCLUSIVELY FROM HUMAN PLURIPOTENT STEM CELLS

17:30 - 17:55 **Su Guo**
University of California, San Francisco, U.S.
BALANCING SELF-RENEWAL AND DIFFERENTIATION THROUGH REGULATING MODES OF DIVISION IN VERTEBRATE NEURAL STEM CELLS

16:00 - 18:00 **CONCURRENT II: NUTRITIONAL EFFECTS ON STEM CELLS** Level 2, Room 2024
Chair: Sean J. Morrison
Children's Research Institute at UT Southwestern, U.S.

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

16:05 - 16:30 **Matthew Rodeheffer**
Yale University, U.S.
UNDERSTANDING HOW WE GET FAT: DIETARY REGULATION OF ADIPOCYTE PRECURSORS

16:30 - 16:45 **Theodore T Ho**
University of California San Francisco, U.S.
AUTOPHAGY IS ACTIVATED DURING AGING TO MAINTAIN MOUSE HEMATOPOIETIC STEM CELL METABOLISM AND FUNCTIONAL CAPACITY

16:45 - 17:00 **Miyeko Mana**
Massachusetts Institute of Technology (MIT), U.S.
DIETARY CONTROL OF THE INTESTINAL STEM CELL NICHE IN CANCER INITIATION

17:00 - 17:15 **Max Friesen**
Harvard University, U.S.
INSULIN SIGNALING AND RESISTANCE IN HUMAN PLURIPOTENT STEM CELL-DERIVED MODELS OF METABOLIC DISEASE

THURSDAY, 23 JUNE *(continued)*

17:15 - 17:30 **ROAD TO THE CLINIC PREVIEW FROM LATE BREAKING ABSTRACTS**
Stephen Huhn
StemCells, Inc., U.S.
MOTOR AND FUNCTIONAL GAINS DEMONSTRATED IN A DOSE-ESCALATION ARM OF A PHASE II NEURAL STEM CELL TRANSPLANTATION STUDY IN CERVICAL SPINAL CORD INJURY

17:30 - 17:55 **Omer Yilmaz**
Massachusetts General Hospital, U.S. and Massachusetts Institute of Technology (MIT), U.S.
DIETARY CONTROL OF STEM CELLS IN PHYSIOLOGY AND DISEASE

16:00 - 18:00 **CONCURRENT II: STEM CELL NICHES** Level 2, Rooms 2009/2011
Chair: Austin G. Smith
Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute, U.K

16:00 - 16:05 TOPIC OVERVIEW BY CHAIR

16:05 - 16:30 **Isabel Fariñas**
University of Valencia, Spain
STEM CELL-NICHE INTERACTIONS IN THE ADULT MOUSE BRAIN: THE ROLE OF CYTOKINE TNF ALPHA

16:30 - 16:45 **Elliott Hagedorn**
Boston Children's Hospital, U.S.
GENOME-WIDE RNA TOMOGRAPHY OF THE HEMATOPOIETIC STEM CELL NICHE IN ZEBRAFISH REVEALS UNEXPECTED FUNCTIONAL MACROPHAGE-STEM CELL INTERACTIONS

16:45 - 17:00 **Bo Zhou**
Children's Research Institute at UT Southwestern, U.S.
THE CELLULAR COMPOSITION OF THE HEMATOPOIETIC STEM CELL NICHE CHANGES DURING REGENERATION AFTER IRRADIATION

THURSDAY, 23 JUNE *(continued)*

17:00 - 17:15 **Aurelie Herault**
University of California, San Francisco, U.S.
MYELOID PROGENITOR CLUSTER FORMATION DRIVES REGENERATIVE AND LEUKEMIC MYELOPOIESIS IN MICE

17:15 - 17:30 **Xiling Shen**
Duke University, U.S.
DYNAMIC REGULATION OF INTESTINAL STEM CELL NICHE RECOVERY IN REAL-TIME

17:30 - 17:55 **Takashi Nagasawa**
Graduate School of Frontier Biosciences and Graduate School of Medicine, Osaka University, Japan
THE MICROENVIRONMENTAL NICHES FOR HEMATOPOIETIC STEM CELLS IN THE BONE MARROW

16:00 - 18:00 **CONCURRENT II: STEM CELLS AND SOLID CANCERS** Level 2, Rooms 2014/2016/2018
Chair: Nissim Benvenisty
Hebrew University, Israel

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

16:05 - 16:30 **Hao Zhu**
Children's Research Institute, UT Southwestern Medical Center, U.S.
THE SWI/SNF COMPONENT ARID1A REGULATES REGENERATIVE CAPACITY AND CARCINOGENESIS IN A DOSE-DEPENDENT FASHION

16:30 - 16:45 **Maider Zabala**
Stanford University, U.S.
THE HIPPO PATHWAY REGULATES MAMMARY EPITHELIAL CELL PROLIFERATION THOUGH H4K20ME1

16:45 - 17:00 **Samuel Rowbotham**
Boston Children's Hospital, U.S. and Harvard Medical School, U.S.
H3K9 METHYLTRANSFERASES REGULATE LUNG TUMOR PROPAGATING CELLS AND LUNG STEM CELLS

THURSDAY, 23 JUNE *(continued)*

17:00 - 17:15 **Massimo Saini**
HI-STEM gGmbH, Germany
AN UNEXPECTED METASTASIS-INITIATING SUBSET OF HUMAN PRIMARY CARCINOMA CELLS DEFINED BY ROBUST EPITHELIAL DIFFERENTIATION AND STEM CELL PROPERTIES

17:15 - 17:30 **Shuyuan Zhang**
UT Southwestern Medical Center, U.S. and Oberlin College, U.S.
DEFINING THE ROLE OF POLYPLOIDY IN MOUSE LIVER

17:30 - 17:55 **Frederic de Sauvage**
Genentech, Inc, U.S.
TARGETING INTESTINAL STEM CELLS IN CANCER

16:00 - 18:00 **CONCURRENT II: DEVELOPMENT AND REGENERATION IN ENDODERMAL DERIVATIVES** Level 2, Room 2002
Chair: Janet Rossant
The Hospital for Sick Children Research Institute
Toronto, Canada

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

16:05 - 16:30 **Stuart Forbes**
University of Edinburgh, U.K.
THE INHIBITION OF HEPATOCYTE PROLIFERATION IN MOUSE TRIGGERS BILIARY CELLS TO BECOME FACULTATIVE STEM CELLS FOR HEPATOCYTES

16:30 - 16:45 **Carmen Unzu**
University of Geneva, Switzerland
INDUCTION OF HEPATIC PROGENITOR CELLS FOR THE HIGHLY EFFICIENT EX VIVO EXPANSION OF PRIMARY HUMAN HEPATOCYTES

16:45 - 17:00 **Michael Bukys**
Cleveland Clinic, U.S. and Trailhead Biosystems, U.S.
MODELING PANCREATIC FATE DECISIONS USING A DESIGN-OF-EXPERIMENT (DOE) METHOD FOR THE DIRECTED DIFFERENTIATION OF PLURIPOTENT CELLS

THURSDAY, 23 JUNE *(continued)*

17:00 - 17:15 **Lay Teng Ang**
Genome Institute of Singapore, Singapore
TOWARDS GENERATION OF PURE AND AUTHENTIC HUMAN LIVER CELLS FROM PLURIPOTENT STEM CELLS

17:15 - 17:30 **Hideki Masaki**
Division of Stem Cell Therapy, Institute for Medical Science, Japan
A UNIQUE SYSTEM TO ASSESS THE IN VIVO LINEAGE POTENTIALS OF DEVELOPMENTALLY-ADVANCED CELLS BY BLASTOCYST INJECTION

17:30 - 17:55 **Markus Grompe**
Oregon Health & Science University, U.S.
TISSUE REGENERATION IN LIVER: PLASTICITY OR STEM CELLS?

FRIDAY, 24 JUNE

INNOVATION SHOWCASES

8:00 - 8:30 **AXOL BIOSCIENCE** Level 2, Room 2002
Electrophysiological Maturation and Pharmacological Responses of Human Induced Pluripotent Stem Cell-derived Cortical Neuronal Networks in Long-term Culture
Ikuro Suzuki
Tohoku Institute of Technology

8:00 - 8:30 **MILL CREEK LIFE SCIENCES** Level 2, Room 2004
Characterization and Production of Platelet Lysate for In Vitro Expansion of Mesenchymal Stem Cells
Vanesa Alonso Camino
Mill Creek Life Sciences

8:00 - 8:30 **BIO-RAD LABORATORIES, INC.** Level 2, Rooms 2001/2003/2005/2007
Radioresistance of Canine Cancer Stem-like Cells Purified Based on Aldehyde Dehydrogenase (ALDH) Activity
Hiroeki Sahara and Atsushi Tanabe
Laboratory of Biology, Azabu University Graduate School of Veterinary Medicine

FRIDAY, 24 JUNE *(continued)*

8:00 - 8:30	**STEMCELL TECHNOLOGIES** STEMdiff™Kits for Robust and Efficient Differentiation of Human Pluripotent Stem Cells to Multiple Cell Types **Melanie Kardel** *STEMCELL Technologies Inc.*	Level 2, Rooms 2009/2011
8:00 - 8:30	**TAKARA BIO USA, INC.** Novel System for 2D and 3D Stem Cell Culture, Differentiation and Scale Up - From Research to Clinical **Catharina Ellerstrom** *Takara Bio Europe AB* **Liz Quinn** *Clontech Laboratories, Inc.*	Level 2, Rooms 2014/2016/2018
8:00 - 8:30	**MILLIPORESIGMA** From Research to GMP Manufacturing: Covering All the Bases **Julie Murrell** *MilliporeSigma* **Ethan Patterson** *MilliporeSigma*	Level 2, Rooms 2020/2022
8:00 - 8:30	**STEMBIOSYS INC.** StemBioSys BM-HPME®: A Novel 3-Dimensional Microenvironment to Enhance Mesenchymal Stem Cell Expansion **Sy Griffey** *StemBioSys* **Bob Hutchens** *StemBioSys*	Level 2, Room 2024
8:15 - 9:00	**MORNING COFFEE**	Level 3, Lobby
8:15 - 18:30	**REGISTRATION OPEN**	Level 1, Lobby
9:00 - 17:00	**ISSCR CAREER FAIR**	Level 2, Lobby

FRIDAY, 24 JUNE *(continued)*

9:00 - 11:15	**PLENARY IV: GENE NETWORKS AND EPIGENETICS** **Chair: Rudolf Jaenisch** *Whitehead Institute for Biomedical Research, U.S.*	Level 3, Plenary Hall
9:00 - 9:25	**Howard Y. Chang** *Stanford University School of Medicine, U.S.* PERSONAL REGULOME NAVIGATION	
9:25 - 9:50	**Kenneth Zaret** *University of Pennsylvania School of Medicine, U.S.* DISSECTING CHROMATIN TO ENHANCE CELL REPROGRAMMING	
9:50 - 10:15	**Karen Adelman** *NIEHS - NIH, U.S.* ESTABLISHING ENHANCER LANDSCAPES REQUIRES COLLABORATION BETWEEN TRANSCRIPTION FACTORS, CHROMATIN MODIFIERS AND PAUSED POL II	
10:15 - 10:40	**Benoit Bruneau** *Gladstone Institutes of Cardiovascular Disease, U.S.* TRANSCRIPTIONAL REGULATION OF CARDIAC DIFFERENTIATION AND CHROMATIN STRUCTURE	
10:40 - 10:50	POSTER TEASERS	
10:50 - 11:15	**Kathryn V. Anderson** *Sloan Kettering Institute, U.S.* ANNE MCCLAREN MEMORIAL LECTURE: THE DYNAMICS OF THE EPITHELIAL-TO-MESENCHYMAL TRANSITION DURING MOUSE GASTRULATION	
11:00 - 20:00	**ISSCR EXHIBITION HALL OPEN**	Level 1, Exhibition & Poster Halll

FRIDAY, 24 JUNE *(continued)*

INNOVATION SHOWCASES

11:30 - 12:30	**BIOLOGICAL INDUSTRIES** An Innovative Xeno-Free Culture Medium for the Expansion of Cell Therapy-Compliant Human Endothelial Cells **Sharon Daniliuc** *Biological Industries*	Level 2, Room 2002
11:30 - 12:30	**AJINOMOTO CO., INC.** The Generation and Expansion of High-quality Human Pluripotent Stem Cells and Their Derivatives for Applications in Medical Science **Peter Andrews** *The Center for Stem Cell Biology and Department of Biomedical Science, The University of Sheffield, UK* **Kiichiro Tomoda** *Gladstone Institute of Cardiovascular Disease*	Level 2, Room 2004
11:30 - 12:30	**MILTENYI BIOTEC GMBH** Generation of Purified Human iPSC Derived Cardiomyocytes using Clinically Relevant Workflows **Todd Herron** *Center for Arrhythmia Research, University of Michigan* Enabling GMP-compliant iPSC Expansion and Differentiation on the CliniMACS® Prodigy Platform **Sebastian Knöbel** *Miltenyi Biotec GmbH*	Level 2, Rooms 2001/2003/2005/2007

FRIDAY, 24 JUNE *(continued)*

11:30 - 12:30	**STEMCELL TECHNOLOGIES INC** 11:30-12:00 Expansion of Human Pluripotent Stem Cells as Aggregates in mTeSR™3D Suspension Cultures **Eric Jervis** *STEMCELL Technologies Inc.* 12:00-12:30 Robust and Consistent Conversion of Primed Human Pluripotent Stem Cells to Naïve-like Phenotypes **Arwen Hunter** *STEMCELL Technologies Inc.*	Level 2, Rooms 2009/2011
11:30 - 12:30	**CORNING LIFE SCIENCES** Stem Cell Culture, Differentiation and Scale-up – Novel Technologies Enabling Research and Cell Processing Applications **Paula Flaherty** *Corning Life Sciences*	Level 2, Rooms 2014/2016/2018
11:30 - 12:30	**THERMO FISHER SCIENTIFIC** 11:30-12:00 Standardized Generation and Characterization of Patient-specific iPSC Lines and Gene Editing of hESCs and iPSCs **Emily Titus** *Centre for Commercialization of Regenerative Medicine (CCRM)* 12:00-12:30 Neuronal Differentiation of Parkinson's Patient-derived iPSCs into Functional Dopaminergic Neurons **Birgitt Schuele** *Parkinson's Institute and Clinical Center*	Level 2, Rooms 2020/2022

FRIDAY, 24 JUNE *(continued)*

11:30 - 12:30	**MTI-GLOBALSTEM** New Tools for iPSC Reprogramming, Differentiation and CRISPR-Cas9 Gene-Editing **Jens Durruthy –Durruthy** *Stanford University, Institute for Stem Cell Biology and Regenerative Medicine* **James Kehler** *MTI-GlobalStem* **Phillip Beske** *United States Army Medical Research Institute of Chemical Defense (USAMRICD)*	Level 2, Room 2024
11:30 - 13:00	**NETWORKING WITH LEADERS LUNCHEON** *(Junior Investigator event; advance registration required)*	Level 3, Lobby
11:30 - 13:15	**LUNCH BREAK**	
12:15 - 13:00	**MEET-UP: HOW TO LEVERAGE THE WORLD'S LARGEST IPSC BANK TO STUDY PATHOLOGICAL PHENOTYPES** *Organized by The Coriell Institute for Medical Research*	Meet-up Hub #1 (Hub supported by Thermo Fisher Scientific)
12:15 - 13:00	**MEET-UP: THE CIRM IPSC COLLECTION AT CORIELL** *Organized by The Coriell Institute for Medical Research*	Meet-up Hub #2
13:15 - 15:15	**CONCURRENT III: NEURODEVELOPMENT AND REGENERATION** **Chair: Sally Temple** *Neural Stem Cell Institute, U.S.*	Level 2, Rooms 2001/2003/2005/2007
13:15 - 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 - 13:45	**Ana Martin-Villalba** *German Cancer Research Center (DKFZ), Germany* STEM CELL HETEROGENEITY IN THE ADULT NAIVE AND INJURED BRAIN: LESSONS FROM SINGLE CELL TRANSCRIPTOMICS	

FRIDAY, 24 JUNE *(continued)*

13:45 - 14:00 **Ernest Arenas**
Karolinska Institutet, Sweden
MOLECULAR ANATOMY OF MIDBRAIN AND DOPAMINE NEURON DEVELOPMENT IN MOUSE, HUMAN AND STEM CELLS

14:00 - 14:15 **Randolph Ashton**
Wisconsin Institutes for Discovery, University of Wisconsin-Madison, U.S.
HARNESSING WNT/BETA-CATENIN SIGNALING TO ENABLE HIGHLY EFFICIENT DERIVATION OF HUMAN MOTOR NEURONS FROM ANY SPINAL CORD REGION

14:15 - 14:30 **Mercedes Paredes**
University of California, San Francisco, U.S.
WIDESPREAD MIGRATION AND INTEGRATION OF NEURONS IN THE EARLY POSTNATAL HUMAN FRONTAL CORTEX

14:30 - 14:45 **Andrew Field**
University of California, Santa Cruz, U.S.
CHARACTERIZATION OF LONG NON-CODING RNAS EXPRESSED DURING CELL TYPE TRANSITIONS IN CORTICAL NEURON DIFFERENTIATION FROM HUMAN, CHIMPANZEE, ORANGUTAN, AND RHESUS MACAQUE PLURIPOTENT STEM CELLS

14:45 - 15:10 **Arturo Alvarez-Buylla**
University of California, San Francisco, U.S.
ORIGIN AND MAINTENANCE OF ADULT NEURAL STEM CELLS; NOT WHAT WE IMAGINED

13:15 - 15:15 **CONCURRENT III: GERMLINE STEM CELLS** Level 2, Rooms 2020/2022
Chair: Joanna Wysocka
Stanford University, U.S.

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

13:20 - 13:45 **Michael Buszczak**
UT Southwestern Medical Center, U.S.
USING CRISPR/CAS9 TO INTERROGATE GERM CELL FORMATION AND FUNCTION

FRIDAY, 24 JUNE *(continued)*

13:45 - 14:00 **Maija Slaidina**
New York University, School of Medicine, Skirball Institute, U.S.
GERM CELL SELECTION IN DROSOPHILA EMBRYO

14:00 - 14:15 **Ido Sagi**
The Hebrew University, Israel
DERIVATION AND DIFFERENTIATION OF HAPLOID HUMAN EMBRYONIC STEM CELLS

14:15 - 14:30 **Mayu Inaba**
UT Southwestern Medical Center, U.S. and University of Michigan, U.S.
A NOVEL NICHE–STEM-CELL SIGNALLING MACHINERY IN THE DROSOPHILA TESTIS

14:30 - 14:45 **Jianhong Zhu**
Fudan University Huanshan Hospital, China
CELLULAR ORGANELLE REPLACEMENT FOR PREVENTION OF INCURABLE MITOCHONDRIAL DISEASES

14:45 - 15:10 **Azim Surani**
Wellcome Trust/Cancer Research UK Gurdon Institute/ University of Cambridge, U.K.
DEVELOPMENT OF THE HUMAN GERMLINE

13:15 - 15:15 **CONCURRENT III: STEM CELL AGING** Level 2, Room 2004
Chair: Hans Schöler
Max Planck Institute for Molecular Biomedicine, Germany

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

13:20 - 13:45 **Derrick Rossi**
Department of Pediatrics, Harvard Medical School, U.S. and Harvard Medical School and Boston Children's Hospital, U.S.
DIMINISHED APOPTOTIC PRIMING UNDERLIES INCREASED SURVIVAL OF AGED HEMATOPOIETIC STEM CELLS IN RESPONSE TO DNA DAMAGE

FRIDAY, 24 JUNE *(continued)*

13:45 - 14:00 **Evgenia Verovskaya**
Department of Medicine, Division of Hematology/Oncology, The Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco, U.S.
REMODELING OF THE MULTIPOTENT PROGENITOR (MPP) POOL DIRECTLY CONTRIBUTES TO BLOOD AGING IN MICE

14:00 - 14:15 **Martin Resnik-Docampo**
University of California, Los Angeles, U.S.
MECHANISMS UNDERLYING LOSS OF INTESTINAL HOMEOSTASIS WITH AGE IN DROSOPHILA MELANOGASTER

14:15 - 14:30 **Krzysztof Szade**
Jagiellonian University, Faculty of Biochemistry, Biophysics and Biotechnology, Poland
HO-1 DEFICIENCY IN THE NICHE TRIGGERS PREMATURE EXHAUSTION OF MOUSE HEMATOPOIETIC STEM CELLS

14:30 - 14:45 **Bo Zhao**
Kunming Institute of Zoology, Chinese Academy of Sciences, China
ESC-SPECIFIC FILIA/FLOPED/BLM COMPLEX REGULATES REPLICATION STRESS RESPONSE AND SAFEGUARDS GENOMIC STABILITY

14:45 - 15:10 **Anne Brunet**
Stanford University, U.S.
EPIGENETIC REGULATION OF AGING NEURAL STEM CELLS

13:15 - 15:15 **CONCURRENT III: DIRECT CELLULAR REPROGRAMMING** Level 2, Rooms 2009/2011
Chair: Fred H. Gage
Salk Institute for Biological Studies, U.S.

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

13:20 - 13:45 **Sophie Jarriault**
IGBMC, France
THE MECHANISMS UNDERLYING CELLULAR PLASTICITY: LICENSERS AND DRIVERS OF A NATURAL REPROGRAMMING EVENT

FRIDAY, 24 JUNE *(continued)*

13:45 - 14:00 **Louise Menendez**
Broad CIRM Center, Keck School of Medicine, University of Southern California, U.S.
MODELING ACQUIRED AND GENETIC HEARING LOSS USING INDUCED SENSORY HAIR CELLS THROUGH DIRECT CELLULAR REPROGRAMMING OF HUMAN FIBROBLASTS

14:00 - 14:15 **Pia Rivetti di Val Cervo**
Karolinska Institutet, Sweden
DIRECT REPROGRAMMING OF HUMAN AND RODENT ASTROCYTES INTO FUNCTIONAL INDUCED DOPAMINERGIC NEURONS IN VITRO AND IN VIVO

14:15 - 14:30 **Moritz Mall**
Stanford University, U.S.
ACTIVE LINEAGE-SPECIFIC TRANSCRIPTIONAL REPRESSION IS REQUIRED FOR PROPER CELL FATE TRANSITIONS

14:30 - 14:45 **Nicole Stone**
Gladstone Institute of Cardiovascular Disease, U.S.
MOLECULAR MECHANISMS UNDERLYING DIRECT CARDIAC REPROGRAMMING OF NEONATAL MOUSE CARDIAC FIBROBLASTS

14:45 - 15:10 **Li Qian**
University of North Carolina at Chapel Hill, U.S.
EPIGENETIC BARRIERS TO DIRECT CARDIAC REPROGRAMMING

13:15 - 15:15 **CONCURRENT III: SKELETAL STEM CELLS** Level 2, Room 2024
Chair: David T. Scadden
MGH/Harvard Stem Cell Institute, U.S.

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

13:20 - 13:45 **Pamela Robey**
NIDCR/NIH/DHHS, U.S.
SKELETAL STEM CELLS: HISTORY, ORIGINS AND FUNCTIONS IN HEALTH AND DISEASE

FRIDAY, 24 JUNE *(continued)*

13:45 - 14:00 **Dongsu Park**
Baylor College of Medicine, U.S.
A PERIOSTEAL SUBSET OF SKELETAL STEM/PROGENITOR CELLS CONSTITUTES A MAJOR SOURCE OF NEW OSTEOBLASTS DURING FRACTURE REPAIR IN VIVO

14:00 - 14:15 **Rui Yue**
Children's Research Institute at UT Southwestern, U.S.
CLEC11A IS AN OSTEOGENIC FACTOR THAT IS NECESSARY AND SUFFICIENT FOR THE MAINTENANCE OF THE ADULT SKELETON

14:15 - 14:30 **Urmas Roostalu**
University of Manchester, U.K.
HETEROGENEITY AND PLASTICITY OF MOUSE PERICYTES REVEALED BY IN VIVO FATE MAPPING

14:30 - 14:45 **Denis Evseenko**
University of Southern California, U.S.
NOVEL SMALL MOLECULE AGONIST OF GP130 ACTIVATES PROGENITOR PROGRAM IN DIFFERENTIATED ARTICULAR CHONDROCYTES AND PROMOTES ARTICULAR CARTILAGE REPAIR IN RAT MODELS OF ARTHRITIS

14:45 - 15:10 **Michael Longaker**
Stanford University, U.S.
SKELETAL STEM CELLS

13:15 - 15:15 **CONCURRENT III: HEMATOPOIESIS** Level 2, Rooms 2014/2016/2018
Chair: Iannis Aifantis
New York University School of Medicine and Howard Hughes Medical Institute, U.S.

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

13:20 - 13:45 **Atsushi Iwama**
Chiba University Graduate School of Medicine, Japan
ROLE OF NON-CANONICAL POLYCOMB REPRESSIVE COMPLEX 1 IN FATE DECISION OF HEMATOPOIETIC STEM CELLS

FRIDAY, 24 JUNE *(continued)*

13:45 - 14:00 **Jonathan Henninger**
Boston Children's Hospital, U.S.
CLONAL FATE MAPPING QUANTIFIES THE NUMBER OF HEMATOPOIETIC STEM CELLS BORN IN THE DEVELOPING AORTA

14:00 - 14:15 **Masanori Miyanishi**
Stanford University, U.S.
REVEALING HETEROGENEITY IN MOUSE HEMATOPOIETIC STEM CELL COMPARTMENT

14:15 - 14:30 **Kristin Hope**
McMaster University, Canada
MUSASHI-2 POST-TRANSCRIPTIONALLY ATTENUATES ARYL HYDROCARBON RECEPTOR SIGNALING TO EXPAND HUMAN HEMATOPOIETIC STEM CELLS

14:30 - 14:45 **Bin Zhou**
Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, China
ENDOCARDIAL PROGENITOR CELLS CONTRIBUTE TO BLOOD VESSELS IN HEART AND LIVER

14:45 - 15:10 **Hans-Reimer Rodewald**
German Cancer Research Center (DKFZ), Germany
FATE MAPPING AND ENDOGENOUS BARCODING OF UNPERTURBED HEMATOPOIESIS

13:15 - 15:15 **CONCURRENT III: EPITHELIAL CELL DEVELOPMENT AND REGENERATION** Level 2, Room 2002
Chair: Melissa Little
Murdoch Children's Research Institute, Australia and Department of Pediatrics, University of Melbourne, Australia

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

FRIDAY, 24 JUNE *(continued)*

13:20 - 13:45	**Salvador Aznar Benitah** *ICREA, Institute for Research in Biomedicine (IRB Barcelona), Spain* ADULT STEM CELLS UNDERGO DIET-DEPENDENT CIRCADIAN REPROGRAMMING DURING AGEING	
13:45 - 14:00	**Mariaceleste Aragona** *Université Libre de Bruxelles, Belgium* BALANCING STEM CELL PROLIFERATION, DIFFERENTIATION AND MIGRATION DURING WOUND HEALING	
14:00 - 14:15	**Brett Shook** *Yale University, U.S.* MATURE ADIPOCYTES LOSE ADIPOCYTE-SPECIFIC CHARACTERISTICS AND CONTRIBUTE TO MULTIPLE ASPECTS OF EPITHELIAL TISSUE REGENERATION	
14:15 - 14:30	**Wan Jin Lu** *Stanford University, U.S.* HEDGEHOG SIGNALING IN TASTE CELL MAINTENANCE AND REGENERATION	
14:30 - 14:45	**Yuko Oda** *VA Medical Center/University of California, San Francisco, U.S.* MEDIATOR 1 DEFICIENCY ENHANCES EPIDERMAL CELL FATE AND ACCELERATES INJURY INDUCED EPIDERMAL REGENERATION IN MURINE SKIN	
14:45 - 15:10	**Michaela Frye** *University of Cambridge, U.K.* STEM CELL FUNCTION AND SENSITIVITY TO CYTOTOXIC STRESS ARE CONTROLLED BY PROTEIN TRANSLATION RATES	
15:15 - 16:00	**REFRESHMENT BREAK**	Level 1, Exhibition & Poster Hall
15:15 - 16:00	**MEET-UP: MEET THE EDITORS OF STEM CELL REPORTS** *Organized by the International Society for Stem Cell Research (ISSCR)*	Meet-up Hub #1 (Hub supported by Thermo Fisher Scientific)

FRIDAY, 24 JUNE *(continued)*

15:15 - 16:00	**MEET-UP: MEET THE COORDINATOR OF ISSCR CONNECT WEBINARS** *Organized by the International Society for Stem Cell Research (ISSCR)*	Meet-up Hub #2
16:00 - 18:00	**PLENARY V: GENE THERAPY AND STEM CELLS** **Chair: Sally Temple** *Neural Stem Cell Institute, U.S.*	Level 3, Plenary Hall
16:00 - 16:25	**Michel Sadelain** *Memorial Sloan-Kettering Cancer Center, U.S.* CAR THERAPY, BEYOND THE CD19 PARADIGM	
16:25 - 16:50	**Christine Brown** *Beckman Research Institute, City of Hope, U.S.* CHIMERIC ANTIGEN RECEPTOR T CELLS FOR THE TREATMENT OF CANCER: FROM BLOOD TO BRAIN	
16:50 - 16:55	**Adrienne Shapiro** *Patient Advocate* SCIENTISTS AND ADVOCATES WORKING TOGETHER NOW AND IN THE FUTURE	
16:55 - 17:20	**Alessandra Biffi** *Dana-Farber/Boston Children's Cancer and Blood Disorders Center, U.S.* HEMATOPOIETIC STEM CELL BASED GENE THERAPY FOR THE TREATMENT OF LYSOSOMAL STORAGE DISORDERS	
17:20 - 17:25	**JOHN MCNEISH IN MEMORIUM: TIMOTHY ALLSOPP**	
17:25 - 17:50	**Fyodor Urnov** *Sangamo BioSciences, Inc., U.S.* JOHN MCNEISH MEMORIAL LECTURE: PRECLINICAL AND CLINICAL DEVELOPMENT OF GENOME-EDITED 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	Level 1, Exhibition & Poster Hall

PROGRAM SCHEDULE

SATURDAY, 25 JUNE

8:15 - 9:00	**MORNING COFFEE**	Level 3, Lobby
8:15 - 18:30	**REGISTRATION OPEN**	Level 1, Lobby
9:00 - 11:15	**PLENARY VI: DISEASE MODELING USING STEM CELLS** **Chair: George Q. Daley** *Boston Children's Hospital, U.S.*	Level 3, Plenary Hall
9:00 - 9:25	**James Wells** *Cincinnati Children's Hospital, U.S.* HUMAN PLURIPOTENT STEM CELL-DERIVED TISSUES AS NEW MODELS TO STUDY DEVELOPMENT AND DISEASE OF THE DIGESTIVE TRACT	
9:25 - 9:50	**Kim Jensen** *BRIC - Biotech Research & Innovation Centre, Denmark* DEVELOPMENT OF AN IN VITRO PARADIGM MODELING TISSUE REPAIR IN INFLAMMATORY BOWEL DISEASE	
9:50 - 9:55	**Laura Steinfeldt** *Patient Advocate* FUTURE ADVANCEMENTS WILL SAVE MY LIFE	
9:55 - 10:20	**Steven Finkbeiner** *Gladstone Institutes, U.S.* APPLICATIONS OF PATIENT IPSCS TO UNDERSTANDING CAUSES AND FINDING TREATMENTS FOR NEURODEGENERATIVE DISEASE	
10:20 - 10:45	**R. Alta Charo** *University of Wisconsin, U.S.* GENE EDITING: LESSONS FROM STEM CELL TOURISM	
10:45 - 11:10	**Guy Sauvageau** *Institute for Research in Immunology & Cancer, Canada* ERNEST MCCULLOCH MEMORIAL LECTURE: CHEMO GENOMIC DISSECTION OF HSC SELF RENEWAL	
11:00 - 16:00	**ISSCR EXHIBITION HALL OPEN**	Level 1, Exhibition & Poster Hall

SATURDAY, 25 JUNE *(continued)*

11:20 - 13:15	**LUNCH BREAK**	
11:30 - 13:00	**JUNIOR INVESTIGATOR CAREER PANEL LUNCHEON** *(Junior Investigator event; advance registration required)*	Level 3, Lobby
13:15 - 15:15	**CONCURRENT IV: ROAD TO THE CLINIC** **Chair: Timothy Allsopp** *Pfizer Ltd, Neuroscience & Pain RU, U.K*	Level 2, Rooms 2001/2003/2005/2007
13:15 - 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 - 13:45	**Heather Young** *University of Melbourne, Australia* CELL THERAPY FOR GUT MOTILITY DISORDERS	
13:45 - 14:00	**Cory Nicholas** *Neurona Therapeutics, U.S.* TRANSPLANTATION OF HUMAN EMBRYONIC STEM CELL (HESC)-DERIVED GABAERGIC NEURONS AMELIORATES NEUROGENIC BLADDER DYSFUNCTION AND CENTRAL NEUROPATHIC PAIN	
14:00 - 14:15	**Stefan Irion** *Memorial Sloan Kettering Cancer Center, U.S.* A CELL THERAPY FOR PARKINSON'S DISEASE	
14:15 - 14:30	**German Gornalusse** *University of Washington, U.S.* GENERATION OF HLA CLASS I-ENGINEERED PLURIPOTENT STEM CELLS THAT ARE NOT RECOGNIZED AS ALLOGENEIC OR LYSED BY NK CELLS	
14:30 - 14:45	**Jane Lebkowski** *Asterias Biotherapeutics, U.S.* CLINICAL ASSESSMENT OF HESC-DERIVED OLIGODENDROCYTE PROGENITOR CELLS (AST-OPC1) IN PATIENTS WITH SENSORIMOTOR-COMPLETE THORACIC AND CERVICAL SPINAL CORD INJURIES.	

SATURDAY, 25 JUNE *(continued)*

14:45 - 15:10	**Donald Kohn** *University of California, Los Angeles, U.S.* HEMATOPOIETIC STEM CELL GENE THERAPY FOR ADENOSINE DEAMINASE-DEFICIENT SEVERE COMBINED IMMUNE DEFICIENCY (ADA-SCID)	
13:15 - 15:15	**CONCURRENT IV: TISSUE ENGINEERING** *Supported by The Society for Biomaterials* **Chair: Todd McDevitt** *Gladstone Institutes, U.S.*	Level 2, Rooms 2020/2022
13:15 - 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 - 13:45	**Milica Radisic** *University of Toronto, Canada* PLATFORM TECHNOLOGY FOR MATURATION OF HUMAN STEM CELL DERIVED CARDIOMYOCYTES AND DRUG DISCOVERY	
13:45 - 14:00	**Minoru Takasato** *Murdoch Children's Research Institute, Australia* REGULATING MESODERM REGIONALIZATION GENERATES KIDNEY ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS	
14:00 - 14:15	**Nafees Rahman** *University of Toronto, Canada* ENGINEERING THE HEMOGENIC NICHE TO ENHANCE DEFINITIVE BLOOD PROGENITOR CELL GENERATION FROM HUMAN PLURIPOTENT STEM CELLS	
14:15 - 14:30	**Takanori Takebe** *Cincinnati Children's Hospital, U.S. and Yokohama City University, Japan* DE NOVO GENERATION OF DIVERSE ORGAN BUDS FROM IPSCS TOWARDS THERAPY	
14:30 - 14:45	**Jessica C. Butts** *Gladstone Institute of Cardiovascular Disease, U.S. and Graduate Program in Bioengineering University of California – San Francisco and Berkeley, U.S.* DIFFERENTIATION OF V2A INTERNEURONS FROM HUMAN PLURIPOTENT STEM CELLS	

SATURDAY, 25 JUNE *(continued)*

14:45 - 15:10	**Shelly Sakiyama-Elbert** *Washington University, U.S.* USING TISSUE ENGINEERING APPROACHES TO BETTER UNDERSTAND NEURAL DEVELOPMENT AND INJURY
13:15 - 15:15	**CONCURRENT IV: STEM CELL METABOLISM** Level 2, Rooms 2009/2011 **Chair: George Q. Daley** *Boston Children's Hospital, U.S.*
13:15 - 13:20	**TOPIC OVERVIEW BY CHAIR**
13:20 - 13:45	**Daisuke Nakada** *Baylor College of Medicine, U.S.* AMPK MAINTAINS METABOLIC HOMEOSTASIS IN LEUKEMIA-INITIATING CELLS
13:45 - 14:00	**Nora Yucel** *Stanford University School of Medicine, U.S.* METABOLIC REGULATION OF MUSCLE STEM CELL EPIGENETIC STATE DURING REGENERATION
14:00 - 14:15	**Glenn Marsboom** *University of Illinois at Chicago, U.S.* GLUTAMINE METABOLISM REGULATES THE PLURIPOTENCY TRANSCRIPTION FACTOR OCT4 IN HUMAN EMBRYONIC STEM CELLS VIA A POST-TRANSLATIONAL REDOX-SENSITIVE MECHANISM
14:15 - 14:30	**Jin Zhang** *Harvard Medical School/ Boston Children's Hospital, U.S.* LIN28 REGULATES MOUSE NAIVE/PRIMED PLURIPOTENCY AND STEM CELL METABOLISM
14:30 - 14:45	**Kenichiro Taniguchi** *University of Michigan, U.S.* THE APICOSOME: A NOVEL CALCIUM-HARNESSING ORGANELLE THAT ENHANCES SURVIVAL OF DISSOCIATED HUMAN EMBRYONIC STEM CELLS

SATURDAY, 25 JUNE *(continued)*

14:45 - 15:10 **Andrew Dillin**
Howard Hughes Medical Institute, University of California, Berkeley, U.S. and California Institute for Regenerative Medicine, University of California, Berkeley, U.S.
THE ACTIVATION OF THE UPR^{ER} IS AN ESSENTIAL STEP IN THE ACQUISITION OF PLURIPOTENCY DURING REPROGRAMMING

13:15 - 15:15 **CONCURRENT IV: REGULATORY NETWORKS IN DIFFERENTIATION AND DISEASE** Level 2, Room 2002
Chair: Haifan Lin
Yale University School of Medicine, U.S.

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

13:20 - 13:45 **Jian Xu**
Children's Medical Center Research Institute at UTSW, Pediatrics, U.S.
NON-CODING REGULATORY GENOME IN BLOOD STEM CELL DEVELOPMENT AND MALIGNANCIES

13:45 - 14:00 **Kyle Loh**
Stanford University School of Medicine, U.S.
MAPPING THE REGULATORY LANDSCAPE OF HUMAN MESODERM DEVELOPMENT

14:00 - 14:15 **Miguel Foronda**
University of Edinburgh, U.K.
FUNCTIONAL CRISPR/CAS9 SCREENS IN MOUSE ESCS UNVEIL CRITICAL ENHANCERS FOR EXITING PLURIPOTENCY

14:15 - 14:30 **Dongxin Zhao**
University of California, San Diego, U.S.
DE NOVO MAPPING OF GENE REGULATORY NETWORKS AND THEIR DYNAMICS DURING PLURIPOTENT STEM CELL DIFFERENTIATION VIA COMBINATORIAL CRISPR-CAS9 SCREENS

14:30 - 14:45 **Eran Meshorer**
The Hebrew University of Jerusalem, Israel
SYSTEMATIC IDENTIFICATION OF GENE FAMILY REGULATORS IN MOUSE AND HUMAN EMBRYONIC STEM CELLS

SATURDAY, 25 JUNE *(continued)*

14:45 - 15:10 **Berthold Göttgens**
Cambridge University, U.K.
REGULATORY NETWORK CONTROL OF BLOOD CELL DEVELOPMENT

13:15 - 15:15 **CONCURRENT IV: DISEASE MODELING II** Level 2, Rooms 2014/2016/2018
Chair: Marius Wernig
Stanford University, U.S.

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

13:20 - 13:45 **Toshiro Sato**
Keio University, Japan
DISEASE MODELING OF COLORECTAL CANCER USING ORGANOIDS

13:45 - 14:00 **Nadja Zeltner**
Sloan-Kettering Institute for Cancer Research, U.S.
CAPTURING THE BIOLOGY OF MILD VERSUS SEVERE DISEASE IN A PLURIPOTENT STEM CELL-BASED MODEL OF FAMILIAL DYSAUTONOMIA

14:00 - 14:15 **Tomer Halevy**
Hebrew University, Israel
CHROMOSOMAL INSTABILITY AND MOLECULAR DEFECTS IN INDUCED PLURIPOTENT STEM CELLS WITH NIJMEGEN BREAKAGE SYNDROME

14:15 - 14:30 **Raymond Wong**
Centre for Eye Research Australia, Australia and Centre for Eye Research Australia, Australia
GENETIC CORRECTION OF A HIPSC MODEL FOR MITOCHONDRIAL DISEASE

14:30 - 14:45 **Tomonaga Ameku**
Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan
IDENTIFICATION OF A NOVEL RISK FACTOR FOR INTRACRANIAL ANEURYSMS IN ADPKD USING IPSC MODELS

14:45 - 15:10 **Melissa Little**
Murdoch Children's Research Institute, Australia and Department of Pediatrics, University of Melbourne, Australia
MODELLING GENETIC KIDNEY DISEASE USING PATIENT-DERIVED IPSC

SATURDAY, 25 JUNE *(continued)*

13:15 - 15:15 **CONCURRENT IV: LEUKEMIA AND STEM CELLS** Level 2, Room 2024
Chair: John Dick
University Health Network, Canada

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

13:20 - 13:45 **David Kent**
Cambridge Stem Cell Institute, U.K.
SINGLE CELL BIOLOGY IDENTIFIES STEM CELL FATE REGULATORS IN HEMATOLOGICAL MALIGNANCIES

13:45 - 14:00 **Pengxu Qian**
Stowers Institute for Medical Research, U.S.
THE CONSERVED METHYLATION-SENSITIVE ENHANCER DERARE MAINTAINS HEMATOPOIETIC STEM CELLS THROUGH REGULATION OF HOXB CLUSTER

14:00 - 14:15 **Yoon-A Kang**
Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, Department of Medicine, Division of Hematology/Oncology, University of California, San Francisco, U.S.
MYELOID-BIASED MULTIPOTENT PROGENITOR EXPANSION BY DEREGULATED NOTCH AND WNT SIGNALING DRIVES MYELOID MALIGNANCY

14:15 - 14:30 **Heather Himburg**
University of California, Los Angeles, U.S.
INHIBITION OF THE VASCULAR NICHE PROTEIN, PLEIOTROPHIN, ABROGATES CHRONIC MYELOID LEUKEMIA PATHOGENESIS

14:30 - 14:45 **Qingfei Jiang**
University of California, San Diego, U.S.
RNA EDITASE ADAR1 REGULATES CELL CYCLE OF HEMATOPOIETIC STEM CELL

14:45 - 15:10 **Iannis Aifantis**
New York University Langone Medical Center, U.S.
MED12 REGULATES HEMATOPOIETIC STEM CELL SUPER-ENHANCER DYNAMICS

SATURDAY, 25 JUNE *(continued)*

13:15 - 15:15	**CONCURRENT IV: TECHNOLOGY FRONTIERS** **Chair: Bruce Conklin** *Gladstone Institutes, U.S.*	Level 2, Room 2004
13:15 - 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 - 13:45	**Mark Labow** *Novartis Institutes for Biomedical Research, U.S.* APPLICATION OF REPROGAMMING AND IPSC APPROACHES TO DRUG DISCOVERY	
13:45 - 14:00	**Pier Federico Gherardini** *Stanford University, U.S.* HIGHLY MULTIPLEXED SIMULTANEOUS DETECTION OF PROTEINS AND RNA IN SINGLE CELLS	
14:00 - 14:15	**Ester Perales Clemente** *Mayo Clinic, U.S.* AMPLIFICATION OF OCCULT MTDNA MUTATIONS DURING NUCLEAR REPROGRAMMING CAUSES INTRA-PERSON HIPSCS VARIABILITY	
14:15 - 14:30	**Cristian Perez** *Coriell Institute for Medical Research, U.S.* CIRM'S HUMAN INDUCED PLURIPOTENT STEM CELL BANK AT THE CORIELL INSTITUTE: THE WORLD'S LARGEST PUBLIC COLLECTION OF PLURIPOTENT STEM CELLS FOR THE UNDERSTANDING AND TREATMENT OF COMPLEX GENETIC DISEASES	
14:30 - 14:45	**Yuichiro Miyaoka** *Tokyo Metropolitan Institute of Medical Science, Japan* IDENTIFICATION OF GENOME-EDITING CONDITIONS THAT FAVOR HDR IN HUMAN IPS CELLS BY SYSTEMATIC QUANTIFICATION OF HDR AND NHEJ	
14:45 - 15:10	**Hirohide Saito** *Kyoto University, Japan* MIRNA SWITCHES THAT IDENTIFY AND ISOLATE TARGET CELLS IN HIGH-RESOLUTION	
15:15 - 16:00	**REFRESHMENT BREAK**	Level 1, Exhibition & Poster Hall

SATURDAY, 25 JUNE *(continued)*

16:00 - 18:20	**PLENARY VII: CELL THERAPY IN CLINICAL TRIALS** *Supported by Burroughs Wellcome Fund* **Chair: Elly Tanaka** *DFG Research Center for Regenerative Therapies, Technische Universitaet Dresden, Germany*	Level 3, Plenary Hall
16:00 - 16:10	**PRESIDENT-ELECT ADDRESS: SALLY TEMPLE**	
16:10 - 16:35	**Roger Barker** *University of Cambridge, U.K.* WHERE ARE WE CLINICALLY WITH CELL BASED THERAPIES FOR PARKINSON'S DISEASE IN 2016?	
16:35 - 17:00	**Koji Eto** *Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan* HOW SHOULD WE GENERATE 300B PLATELETS FROM IPS CELLS?	
17:00 - 17:05	**Kristin MacDonald** *Patient Advocate* SECOND VISION	
17:05 - 17:30	**Edwin Stone** *University of Iowa Carver College of Medicine, U.S.* PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS FOR MODELING AND TREATMENT OF INHERITED RETINAL DISEASE	
17:30 - 18:05	**KEYNOTE ADDRESS** **Robert Tjian** *Howard Hughes Medical Institute and University of California, Berkeley, U.S.* PROBING TRANSCRIPTION REGULATION IN ES CELLS AND DISEASE MODELS BY SINGLE MOLECULE IMAGING	
18:05 - 18:15	**ISSCR 2016 CLOSING REMARKS**	
18:20 - 19:20	**CLOSING RECEPTION**	Level 3, Lobby

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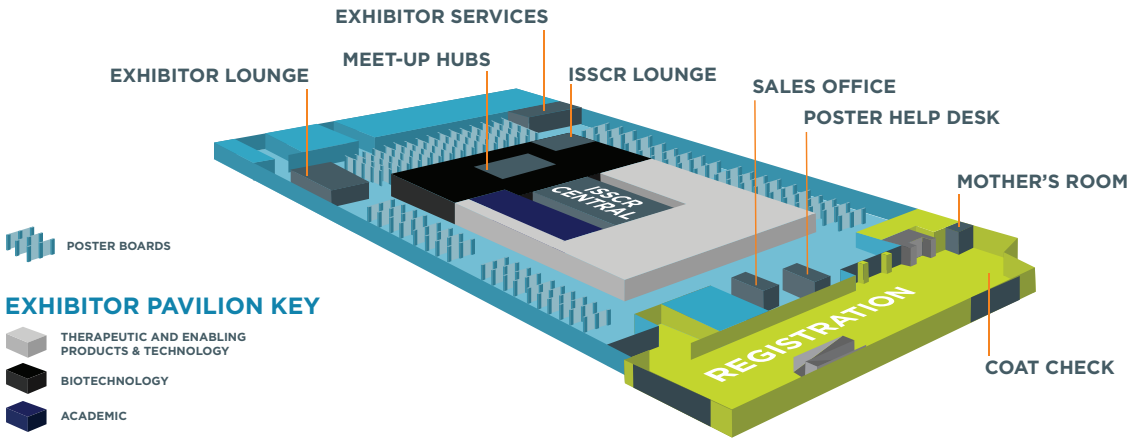
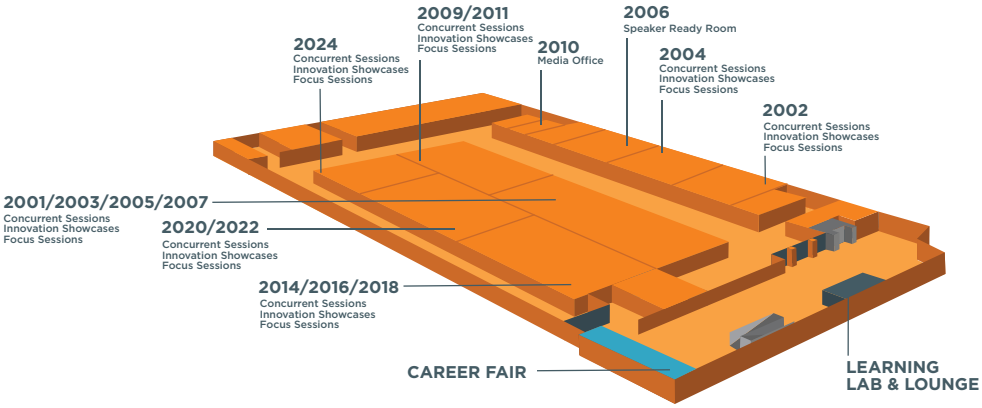


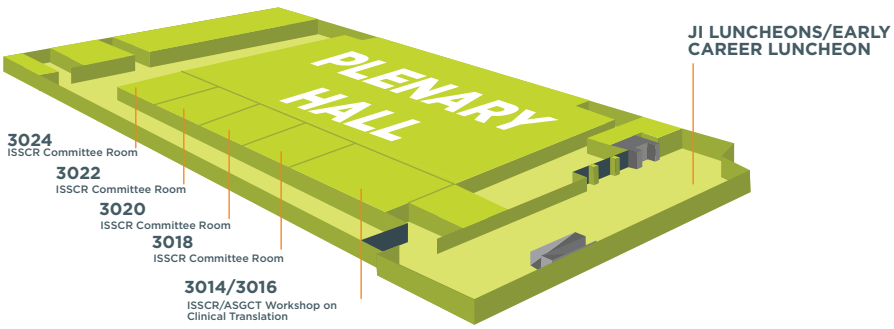
MOSCONE WEST, LEVEL 2

Session Rooms, Career Fair, Media Office



MOSCONE WEST, LEVEL 3

Plenary Hall, Committee Rooms, Luncheons



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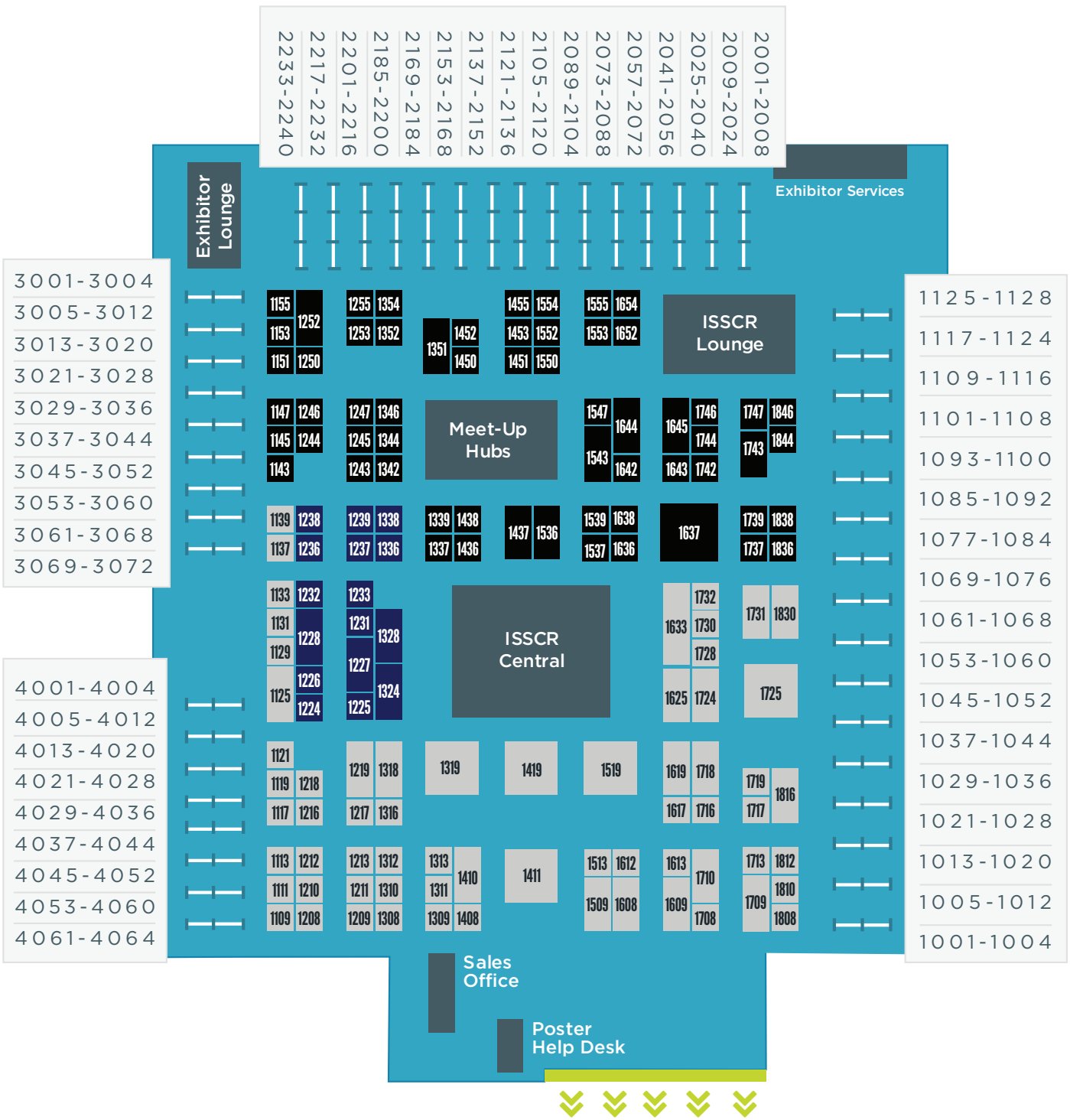

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www.appliedstemcell.com

Applied StemCell, Inc is currently focusing on three areas: (1) cell line generation for bio-production and bioassays (2) patient-relevant cell models for personalized medicine and (3) physiologically predictive animal models of human diseases.

APPLIKON BIOTECHNOLOGY, INC. - STAND 1553

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www.applikonbio.com

Applikon bioreactors and control systems are used worldwide for basic research, process development, and cGMP manufacturing. Our customers range from large pharmaceutical corporations, to contract organizations, young companies, and universities. For 30 years, our mission has been to offer reliable hardware and expertise for customers at every step along the way in their bioprocess development.

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Axion BioSystems is the leader in microelectrode array (MEA) data acquisition and analysis. With the Maestro MEA platform, analysis of neural or cardiomyocyte stem cell network activity is easily performed on the benchtop. Understanding of the functional activity of these cells can then be applied to stem cell development/validation and in vitro disease modeling.

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Axol specializes in human cell culture, producing highly validated, human cells and reagents such as media and growth supplements. Our expertise includes reprogramming cells to iPSCs and then differentiating to various cell types. We supply differentiated cells derived from healthy donors and patients of specific disease backgrounds. As a service, we also take customer cells (primary or iPSC) and then do the reprogramming and differentiation.

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BD Biosciences, a segment of Becton, Dickinson and Company, is one of the world's leading businesses focused on bringing innovative tools to life science researchers and clinicians. Its product lines include: flow cytometers, cell imaging systems, monoclonal antibodies, research reagents, diagnostic assays, and tools to help grow tissue and cells. For more information, please visit: bdbiosciences.com

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BioCision provides solutions for standardizing cell cryopreservation and thawing. The breakthrough ThawSTAR technology platform sets a new standard for thawing cells and cell-based materials. The ThawSTAR cell thawing system is an intuitive, error-free method for achieving reproducible thawing and recovery results. The intuitive design and compact footprint make it ideal for GMP processes performed in a laminar-flow hood that require stringent control and reproducible outcomes.

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BioLegend develops and manufactures world-class, cutting-edge antibodies and reagents at an outstanding value. The broad product portfolio includes flow cytometry, cell biology, and functional reagents for research in immunology, neuroscience, cancer, and stem cells. Custom services include assay development, sample testing, and conjugation. BioLegend is certified for ISO 9001:2008 and ISO 13485:2003.

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BioMedTech offers optimized cell culture surface coatings & matrices supporting: Spheroid formation, Maintenance of Stem Cell pluripotency, Propagation & Differentiation into specialized cell types, and development of 3-D organotypic structures. Our surfaces are offered on All formats, from T-25 flasks to 1536-well plates. Xeno-Free & Animal Protein Free options available. BioMedTech delivers high performance coated tissue culture-ware for your Research, High-Content and High-Throughput applications.

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The Burroughs Wellcome Fund is an independent private foundation dedicated to advancing the biomedical sciences by supporting research and other scientific and educational activities. Within this broad mission, BWF has two primary goals, to help scientists early in their careers develop as independent investigators and to advance fields in the basic biomedical sciences that are undervalued or in need of particular encouragement.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (CIRM) - STAND 1236

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www.cirm.ca.gov

The California Institute for Regenerative Medicine, the state stem cell agency, was created via a voter initiative that set aside $3 billion in bond proceeds to fund stem cell research. Our highly trained team partners with both academia and industry to fast track the most promising technologies. The agency currently has more than 280 active stem cell programs in its portfolio.

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The NHLBI Progenitor Cell Biology Consortium has characterized the phenotype, function, genotype and differentiative potential of >60 iPSC and hESC lines, deposited all the raw and analyzed data, and developed platforms and tools for analysis of the data on the Synapse web portal as a resource for researchers. This booth will provide hands-on training on accessing the data and tools for analysis for researchers.

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CCRM is a Canadian not-for-profit organization funded by the Government of Canada, the Province of Ontario, and leading academic and industry partners. It supports the development of regenerative medicines and associated enabling technologies, with a specific focus on cell and gene therapy. CCRM aims to accelerate the translation of scientific discovery into marketable products for patients. Visit us at www.ccrm.ca.

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HSCI, a unique scientific collaborative aimed at fulfilling the promise of stem cells, funds novel research and implements new collaborative academic and industrial models for advancing stem cell biology into the clinic.

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AlphaMed Press publishes internationally peer-reviewed journals in oncology, stem cell research, regenerative medicine, and translational medicine. STEM CELLS provides a forum for prompt publication of original investigative papers and concise reviews covering stem and progenitor cell biology. STEM CELLS TRANSLATIONAL MEDICINE is dedicated to significantly advancing the clinical utilization of stem cell molecular and cellular biology by bridging stem cell research and clinical trials.

STEMBIOSYS INC. - STAND 1513

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

StemBioSys, Inc. based in San Antonio, Texas, is a privately-held biomedical company focused on enhancing the isolation, growth and delivery of adult stem cells for research, therapeutic or drug discovery applications.

STEMCELL TECHNOLOGIES, INC. - STAND 1633

570 West 7th Avenue
Suite 400
Vancouver, BC
V5Z 1B3 Canada
+1 604-877-0713
www.stemcell.com

STEMCELL Technologies is a leading provider of reagents for hematopoietic, mesenchymal, neural, mammary, epithelial, and pluripotent stem cell research. From generation of iPS cells to maintenance, differentiation, characterization and cryopreservation of stem cells, we provide a full range of leading-edge products that support every step of your workflow.

STEMCELLS, INC.

7707 Gateway Boulevard
Suite 140
Newark, CA
94560 United States
+1 510-456-4000
www.stemcellsinc.com

StemCells, Inc. is currently engaged in clinical development of its proprietary HuCNS-SC® (purified human neural stem cells) platform technology to treat diseases of the human central nervous system (CNS).

STEMCULTURES - STAND 1117

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

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

STEMMERA INC. - STAND 1250

3475 Edison Way
Suite J-2
Menlo Park, CA
94025 United States
+1 650-262-5498
www.stemmera.com

Stemmera Inc. is a privately owned biotechnology company located in Bay Area, California that focus in developing innovative technology and application solution for stem cell research. Our products include kit, culture medium, reagents, antibodies, buffer and solution, cell lines that are convenient tools used in stem cell research.

SYNTHECON INC. - STAND 1109

8977 Interchange Drive
Houston, TX
77054 United States
+1 713-741-2582
www.synthecon.com

Synthecon, Incorporated is a biotechnology company that specializes in the design and manufacture of 3D cell culture systems, electrospun 3D materials and the spheroid forming material, Phenodrive. Synthecon's rotating bioreactors have applications in various fields of cell culture and tissue engineering, the latest of which is stem cell culture for regenerative medicine.

TAKARA BIO USA, INC. - STAND 1743

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94043 United States
+1 650-919-7300
www.clontech.com

Clontech Laboratories, Inc., a Takara Bio Company, is committed to developing high-quality innovative tools and services to accelerate discovery. Through its Cellartis® brand, Clontech offers a broad range of iPS cells, highly functional human ES and iPS cell-derived hepatocytes and cardiomyocytes, along with reagents for iPS cell culture and differentiation. We also provide customizable services ranging from sourcing to generation to differentiation.

TAKASAGO FLUIDIC SYSTEMS - STAND 1554

1900 West Park Drive
Suite 280
Westborough, MA
01581 United States
+1 508-983-1434
www.takasago-fluidics.com

Takasago Fluidic Systems is exhibiting a portable medium exchange system, a 3D perfusion system for a 6-well plate, a micro perfusion system for live cell imaging, micro pumps, disposable fluidic chips, etc. We manufacture fluidic devices to handle culture media, reagents and other liquids. Our mission is to assist your research by automating or prototyping your cell culture setups.

TAKEDA PHARMACEUTICAL COMPANY

Regenerative Medicine Unit
2-26-1, Muraoka-Higashi
Fujisawa, Kanagawa 251-8555
Japan
http://betterhealth.takeda.com/

Our mission is simple and compelling: we are committed to strive toward better health for people worldwide through leading innovation in medicine. Our commitment to improving health and supporting our employees, partners, and the larger community gives us the purpose to build on the tremendous success we enjoy as an emerging global leader in the pharmaceutical industry.

TERUMO BCT - STAND 1652

10811 W. Collins Avenue
Lakewood, CO
80215 United States
+1 303-232-6800
www.teruombct.com

Terumo BCT, a global leader in blood component, therapeutic apheresis and cellular technologies, is the only company with the unique combination of apheresis collections, manual and automated whole blood processing, and pathogen reduction. We believe in the potential of blood to do even more for patients than it does today. This belief inspires our innovation and strengthens our collaboration with customers.

THERMO FISHER SCIENTIFIC - STAND 1725

5791 Van Allen Way
Carlsbad, CA
92008 United States
+1 800-955-6288
www.thermofisher.com

Thermo Fisher Scientific supplies innovative solutions for the world's stem cell research. With applications that span basic research and commercial scale-up to disease modeling and downstream clinical research – we provide a broad range of products and services including high quality media, non-integrating reprogramming technologies, reagents and instruments for characterization and analysis, and cutting edge plastics.

THRIVE BIOSCIENCE, INC. - STAND 1812

500 Cummings Center
Suite 3150
Beverly, MA
01915 United States
+1 978-720-8044
www.thrivebio.com

Thrive Bioscience automates cell culture with a process management and image analysis instrument for research and GMP environments. Protocols include maintenance of established and primary cell lines, iPSC maintenance and expansion, and iPSC directed differentiation.

TRANSPOSAGEN - STAND 1844

535 West 2nd Street
Suite 10
Lexington, KY
40508 United States
+1 774-573-8989
www.transposagenbio.com

Transposagen is a worldwide leader in genome engineering technologies and services with applications in therapeutics, research & drug discovery, bioproduction, clinical genetic testing and agriculture. Our products and services include Footprint-Free™ Gene Editing, NextGEN™ CRISPR, XTN™ TALENs, custom cell lines, stem cells, and animal models. Our unique genome engineering capabilities allow for the creation of nearly any genetic modification in any genome.

UNION BIOMETRICA, INC. - STAND 1436

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

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

UPM-KYMMENE CORPORATION - STAND 1730

Biomedicum 2U
Tukholmankatu 8
Helsinki,
00290 Finland
+358 204-15-111
www.growdex.com

As the frontrunner of the new forest industry UPM leads the integration of bio and forest industries into a new, sustainable and innovation-driven future. We create value from renewable and recyclable materials. In 2014, UPM's sales exceeded € 9.9 billion. UPM is present in 45 countries. The company employs approximately 20,000 people worldwide. UPM shares are listed on the NASDAQ OMX Helsinki stock exchange.

WAFERGEN BIOSYSTEMS - STAND 1346

7400 Paseo Padre Parkway
Fremont, CA
94555 United States
+1 877-923-3746
www.wafergen.com

WaferGen Bio-systems, Inc. is a biotechnology company that offers innovative genomic technology solutions for single-cell analysis and clinical research. We offer a powerful set of tools for biological analysis at the molecular and single-cell level in the life sciences, pharmaceutical, and clinical laboratory industries.

WAISMAN BIOMANUFACTURING - STAND 1337

1500 Highland Avenue
Madison, WI
53705 United States
+1 608-262-9547
www.gmpbio.org

Waisman Biomanufacturing (WB) is a cGMP facility with comprehensive experience in providing contracting manufacturing services including the clinical production of cell therapeutics, as well as gene therapeutics, recombinant proteins, and vaccines for Phase I and Phase II clinical trials.

WAKO PURE CHEMICAL INDUSTRIES, LTD. - STAND 1147

4-1, Nihonbashi Honcho 2-Chome
Chuo-ku
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103-0023 Japan
+81 3-3270-8571
www.wako-chem.co.jp/english/labchem/index.htm

We are supporting your R&D endeavors by addressing needs in a wide range of fields including next generation technology, life science, organic synthesis and environmental measurement. We provide high quality products including the cell culture media s, rBC2LCN (novel undifferentiated probe of human ES/iPS cells) and the small molecule useful for maintenance of ES/iPS cells and induction of differentiation.

WICELL - STAND 1336

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

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

WILEY - STAND 1224

111 River Street
Hoboken, NJ
07030 United States
+1 201-748-6000
www.wiley.com

Wiley is a global provider of knowledge and knowledge-enabled services that improve outcomes in areas of research, professional practice, and education.

WORLD STEM CELL SUMMIT 2016 / REGENERATIVE MEDICINE FOUNDATION - STAND 1233

11924 Forest Hill Boulevard
Suite 10A-290
Wellington, FL
33414 United States
+1 650-847-1640
www.worldstemcellsummit.com

Produced by the Regenerative Medicine Foundation (RMF), The 2016 World Stem Cell Summit & RegMed Capital Conference will deliver over 225+ speakers, 7 tracks and 90+ hours of programming focused on advancing translational research outcomes. Save the dates, December 6-9, and plan join many from the community at the Palm Beach County Convention Center, West Palm Beach, Florida. Collect Opportunities, Expand Knowledge, Forge Collaborations. For more information visit www.worldstemcellsummit.com.

WORTHINGTON BIOCHEMICAL CORPORATION - STAND 1309

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Register to win an iPAD! New! Celase® GMP for Adipose Stem Cells, Animal Free Collagenases, DNases, RNases and STEMxyme® Collagenase/Neutral Protease Blends. Request our latest 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 online at Worthington-Biochem.com

THURSDAY, 23 JUNE

UNION BIOMETRICA INC

Level 2, Room 2002
8:00 - 8:30

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

Rock Pulak, *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 variability that can be introduced between researchers and by the same researcher from one day to the next.

STEMCELL TECHNOLOGIES INC.

Level 2, Rooms 2009/2011
08:00 - 08:30

BRAINPHYS™ NEURONAL MEDIUM SUPPORTS NEUROPHYSIOLOGICAL ACTIVITIES OF HUMAN PLURIPOTENT STEM CELL-DERIVED NEURONS

Cedric Bardy, *Salk Institute for Biological Studies*

Neurons derived from human pluripotent stem cells (hPSCs) are useful in vitro models for the study of neurological disease and development. To increase the relevance of these studies, it is important that neurons are cultured in a medium that closely resembles the normal physiological conditions of the brain. Traditional media, such as Neurobasal and DMEM/F-12, were designed for neuronal survival, but do not support neurophysiological activities. To resolve this problem, we have developed a new basal medium formulation, BrainPhys™. When supplemented with the appropriate growth factors, BrainPhys™ sustains cell survival and optimal activity of neurons in vitro. Furthermore, electrophysiological recordings and calcium imaging studies showed that the neuronal activities suppressed in Neurobasal and DMEM/F-12-based cultures could be rescued when the media were replaced with a BrainPhys™-based medium. Together, these data show that BrainPhys™ is a novel basal medium that efficiently supports the growth of neurons under conditions that are truly physiologically compatible to that of the central nervous system.

THERMO FISHER SCIENTIFIC

Level 2, Rooms 2020/2022
8:00 - 8:30

PREDICT THE UNPREDICTABLE: USING THE IN VIVO NICHE TO ASSESS LINEAGE POTENTIAL AND FUNCTIONALITY OF PSC-DERIVED CELLS

Hideki Masaki, *Institute of Medical Science, University of Tokyo*

The lack of consistency in the differentiation and functional maturation of PSC-derived cells limits the application of these cells in translational research and regenerative medicine. One way to circumvent such issue is the usage of in vivo niche that provides the proper microenvironment to regulate cell fate. Our previous research demonstrated derivation of hematopoietic stem cells from PSCs via teratoma. We also reported the generation of whole organ from donor PSCs in allogeneic / xenogeneic organ-deficient animals. These proof-of-concept studies elucidated principles of a potential strategy for the design of stem-cell research and therapeutics. Recently, we discovered that by preventing apoptosis in the pre-implantation stage embryos we were able to form chimera from primed PSCs and even endodermal progenitors. In this presentation, we will discuss the potential impact of such in vivo system and its utility in accurately assessing lineage potential of stem cells and progenitor cells.

IRVINE SCIENTIFIC

Level 2, Room 2002
11:30 - 12:30

OPTIMIZING THE CULTURE MEDIUM THAT MAINTAINS MOUSE HEMATOPOIETIC STEM CELLS

Hideyuki Oguro, *Howard Hughes Medical Institute, Children's Medical Center Research Institute, and Department of Pediatrics, University of Texas Southwestern Medical Center*

Hematopoietic stem cell expansion in culture is a critical yet challenging goal to achieve to facilitate gene therapy and increase the transplantation safety and efficacy. In this workshop, we will share the evaluation results of culturing 20 isolated, CD150+CD48-/lowCD34-/lowLineage-Sca-1+c-kit+ highly enriched HSCs from young-adult mouse bone marrow in prototypes media comparing to the commonly used SF-O3, supplemented with SCF and TPO. Data from colony assay and transplantation studies demonstrated a simplified, ready-to-use medium that could allow us to continue fine tuning the culture components to further improve HSC maintenance ex vivo.

IMPACTS OF UNDEFINED COMPONENTS FOR PRIMARY CELL CULTURES

Jessie H.-T. Ni, *R&D Department, Irvine Scientific*

Natures of stem/progenitor cells generated from ex vivo cultures are critically depend on qualities of supplemented serum or serum-replacement components, e.g. cytokines or lipids. We will demonstrate through historic data and case studies how these "undefined" components impact the culture performance of major adult stem cells and immune cells. Potential solutions will be recommended that could allow researchers to best achieve consistent and desired ex vivo expansions of targeted stem/primary cells under less-defined culture conditions.

STEMGENT, A REPROCELL GROUP COMPANY

Level 2, Room 2004
11:30 - 12:30

NOVEL RNA REPROGRAMMING PLATFORM TO GENERATE IPSC LINES FROM BLOOD, SKIN, URINE, AND TRANSLATIONAL APPLICATION TO RETINAL PHENOTYPES

Sarah Eminli-Meissner, *Stemgent, a ReproCELL Group Company*

Jason Meyer, *IUPUI (Indiana University Purdue University Indianapolis)*

mRNA-mediated cellular reprogramming is generally recognized as the fastest, most efficient method for the derivation of clinically relevant human iPS cell lines from patient fibroblasts. This presentation will highlight the next generation StemRNA™non-modified (NM) RNA reprogramming platform technology that enables highly reproducible iPS cell line establishment from patient-derived fibroblasts, as well as for more clinically accessible and minimally invasive patient samples such as blood and urine. Data presented will focus on the robustness and reproducibility of novel GMP-compatible reprogramming protocols for the three different cell types, as well as the in vitro pluripotentiality of derived RNA-iPS cell lines.

Additionally, recent publications have focused on the downstream translational application of RNA-iPS cell lines. Data presented will focus on the impact of RNA-iPS cell lines on the differentiation of neural cell types from both normal and diseased patient samples. RNA-iPS cell lines robustly and efficiently yielded retinal phenotypes upon directed differentiation. Specifically, when derived from patients with retinal degenerative diseases, these cells served as faithful and reliable in vitro models of neurodegeneration.

ESI BIO (ASCENDANCE BIOTECHNOLOGY)

Level 2, Rooms 2001/2003/2005/2007
11:30 - 12:30

CLINICALLY RELEVANT STEM CELLS AND MATRICES - THE READYSTEM™ MRNA REPROGRAMMING KIT FOR IPSC; ESI HES CELLS; HYSTEM® HYDROGELS

Jens Durruthy-Durruthy, *Stanford University, Institute for Stem Cell Biology and Regenerative Medicine*

Tom Zarembinski, *BioTime, Inc.*

ESI BIO, now Ascendance Biotechnology, presents data from leading stem cell researchers on its new ReadyStem™ mRNA reprogramming kit, the newest product in Ascendance's platform of clinically compliant pluripotent stem cells and hydrogel-based extracellular matrices.

Human induced Pluripotent Stem Cells (hiPSCs) and human Embryonic Stem Cells (hESC) hold great promise in clinical applications including drug screening, disease modeling and tissue regeneration. Optimization of clinical research requires hiPSCs/hESCs and cellular matrices meet clinical, regulatory and commercial standards to be utilized in regenerative medicine. Therefore, derivation of hiPSCs should eliminate risks of random insertion of exogenous DNA that can lead to insertional mutagenesis or add excess time and expense to remove such exogenous material. Protocols should be feeder-free, rapid, efficient, cost-effective and scalable. hESCs should meet internationally recognized ethical and safety standards and matrix materials should be clinically compliant. Learn how the ReadyStem™ mRNA reprogramming kit, ESI hESC and HyStem® Hydrogel products combine these features to advance translational research and to offer a clinically compliant platform for research and clinical product development.

NIKON CORPORATION

Level 2, Rooms 2009/2011
11:30 - 12:30

DEVELOPING A LIVE CELL SYSTEM FOR VISUALIZING NEURONAL DEGENERATION

Lee L. Rubin, *Harvard Department of Stem Cell and Regenerative Biology*

The advent of iPS stem cell technology and the ability to generate patient-derived neurons provides a new opportunity for drug screening in neurodegenerative diseases. Live cell imaging of these neurons is a rich source of information revealing morphological changes that occur when cells are exposed to stressful conditions causing them to malfunction and, ultimately, to die. Further, the use of cell type specific fluorescent reporters allows the study of specific kinds of neurons in heterogeneous cultures. The Rubin lab and Nikon Corporation have collaborated to develop a platform using the BioStation CT that permits single cell tracking over extended periods of time (up to weeks). This technique facilitates the identification of changes that provide early warning signs of impending death. Interestingly, neurons can be fully rescued at these early times, providing an opportunity to screen for therapeutics that can block neurodegeneration in a physiologically meaningful way. These studies are a step toward in vitro clinical assays, in which multiple patient-derived neurons can be analyzed for responses to potential therapeutics.

FLUIDIGM CORP

Level 2, Rooms 2014/2016/2018
11:30 - 12:30

REDISCOVER STEM CELL BIOLOGY AT SINGLE-CELL RESOLUTION

Alex Pollen, *University of California, San Francisco*

Jay Gibson, *University of Connecticut*

Using single-cell transcriptome analysis, stem cell biologists have uncovered novel cell types that revolutionized our understanding of cell states, fate decisions and response to stimuli. Now, the stem cell community is exploring the transcriptome, epigenome and proteome of individual cells to gain new insight into the biological mechanisms that drive self-renewal, pluripotency and differentiation as well as discover critical signatures of disease progression and cell lineage.

In this workshop, hear from leading stem cell researchers about their latest discoveries using our comprehensive suite of single-cell technologies, and learn how we can help make your next breakthrough. Learn more at fluidigm.com/isscr-2016

BD BIOSCIENCES

Level 2, Rooms 2020/2022
11:30 - 12:30

BIOLOGICAL PERSPECTIVES IN MULTICOLOR FLOW ANALYSIS: MOVING TO 50-COLOR FLOW CYTOMETRY

Bob Balderas, *BD Biosciences*

The advent of human genome sequencing and analysis have greatly enhanced our understanding of the underlying biochemistry of complex biological systems. More recently, significant advances in molecular and cellular analysis have continued to deepen our scientific insights in many different biological fields, including immune system function in normal and disease states. The development of the BD FACSymphony™ flow cytometer, with capabilities to analyze up to 50 parameters, now provides a powerful approach to unravel highly complex molecular structure and function relationships in genomics, proteomics, systems immunology, and biology. This research approach holds the promise of increasing our knowledge of cancer biology, accelerating vaccine development, and enhancing the drug discovery process.

As a result of the availability of new BD Horizon Brilliant™ polymer fluorochromes, a study of receptor density and expression, and the launch of the BD FACSymphony high parameter cell analyzer, this year we demonstrated practical 27-color flow cytometry. In this presentation, we will discuss a systematic strategy for successful panel design for high parameter multicolor assays.

BIO-TECHNE

Level 2, Room 2024
11:30 - 12:30

GET THE MOST OUT OF YOUR CELLS: TOOLS TO OPTIMIZE PLURIPOTENT STEM CELL CULTURES AND DIFFERENTIATION

Joy Aho, *Stem Cell Research & Development, Bio-Techne*

Scott Schachtele, *Bio-Techne*

Pluripotent stem cells are a powerful tool for developmental biology research, disease modeling, and drug discovery. Variability in the identification and differentiation of pluripotent stem cells can confound protocol development and undermine interpretation of downstream experiments. This showcase starts with a brief discussion of strategies for optimizing your pluripotent stem cell workflow, including new data highlighting products that simplify cell characterization and differentiation. The second segment of the showcase focuses on exciting and progressive tools that can be used to improve stem cell culture and differentiation protocols. First, we will demonstrate how our Tocriscreen™ small molecule screening libraries have been utilized to optimize stem cell differentiation, including data from a recent collaboration that revolved around identifying signaling pathways involved in muscle differentiation. In addition, Proteome Profiler™ Antibody Arrays and Luminex® Assays are powerful, yet under-utilized techniques in stem cell research. Using hepatocyte differentiation as an example, we demonstrate how these techniques enable researchers to profile cell changes during differentiation and help identify strategies to improve cell culture and differentiation.

FRIDAY, 24 JUNE

AXOL BIOSCIENCE

Level 2, Room 2002
8:00 - 8:30

ELECTROPHYSIOLOGICAL MATURATION AND PHARMACOLOGICAL RESPONSES OF HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED CORTICAL NEURONAL NETWORKS IN LONG-TERM CULTURE

Ikuro Suzuki, *Tohoku Institute of Technology, Japan*

The functional network of human induced pluripotent stem cell-derived neurons is a potentially powerful in vitro model for evaluating disease mechanisms and drug responses. We investigated the development of spontaneous electrophysiological activity and pharmacological responses for over 1 year in culture using multi-electrode arrays (MEAs). The complete maturation of spontaneous firing, evoked responses, and modulation of activity by glutamatergic and GABAergic receptor antagonists/agonists required 20–30 weeks. Neural networks also demonstrated epileptiform synchronized burst firing (SBF) in response to pro-convulsants and SBF suppression using clinical anti-epilepsy drugs. We also attempted the induction of long-term potentiation (LTP) and long-term potentiation depression (LTD) phenomena using MEA systems. High-frequency stimulation produced a potentiated and depressed transmission in a neuronal circuit for 1 hr in the evoked responses by test stimulus. The cross-correlation of responses revealed that spike patterns with specific timing were generated during LTP induction and disappeared during LTD induction. Our results reveal the feasibility of long-term MEA measurements from hiPSC-derived neuronal networks in vitro for mechanistic analyses and drug screening.

MILL CREEK LIFE SCIENCES

Level 2, Room 2004
8:00 - 8:30

CHARACTERIZATION AND PRODUCTION OF PLATELET LYSATE FOR IN VITRO EXPANSION OF MESENCHYMAL STEM CELLS

Vanesa Alonso Camino, *Mill Creek Life Sciences*

Mesenchymal stromal/stem cells have potential benefits in a variety of clinical conditions. Expansion of MSCs for therapeutic use must meet specific criteria to meet GMP requirements and maintain product performance. Choosing conditions for cell culture is a critical decision that influences product outcomes.

Traditionally, fetal bovine serum (FBS) has been used as a supplement for in vitro culture of MSCs. However, the use of xenogenic elements in cell growth media for clinical applications potentially increases patient risk. Platelet lysates provide an alternative to FBS.

Mill Creek Life Sciences' PLTMax® is the first human platelet lysate used for in vitro expansion of human cells in clinical applications. It has been shown to maintain genetic fidelity, expand cells at high rates of proliferation and generate a repair proteome.

Mill Creek uses a proprietary cell kinetic method to monitor performance of manufactured lots. This technology offers insight into active biological processes and provides important information about platelet lysate.

BIO-RAD LABORATORIES, INC.

Level 2, Rooms 2001/2003/2005/2007
8:00 - 8:30

RADIORESISTANCE OF CANINE CANCER STEM-LIKE CELLS PURIFIED BASED ON ALDEHYDE DEHYDROGENASE (ALDH) ACTIVITY

Hiroeki Sahara and Atsushi Tanabe, *Laboratory of Biology, Azabu University Graduate School of Veterinary Medicine*

Accumulating evidence indicates that cancer stem-like cells (CSCs) are responsible for the initiation, recurrence and metastasis of cancer. Moreover, CSCs possess an ability to resist radiation, which is considered a possible cause of the recurrence of cancer. Therefore, it is an important consideration that cancer radiotheraphy can be targeted to CSCs.

Numerous studies have been performed to characterize CSCs in human cancer, whereas little is known about the characteristics of canine cancer in the veterinary field. In this presentation, we will introduce an effective cell sorting protocol based on aldehyde dehydrogenase (ALDH) activity of canine CSCs.

STEMCELL TECHNOLOGIES INC.

Level 2, Rooms 2009/2011
8:00 - 8:30

STEMDIFF™KITS FOR ROBUST AND EFFICIENT DIFFERENTIATION OF HUMAN PLURIPOTENT STEM CELLS TO MULTIPLE CELL TYPES

Melanie Kardel, *STEMCELL Technologies Inc.*

Human pluripotent stem cells (hPSCs) have many applications in developmental biology studies, disease modeling, drug screening and regenerative medicine. Advancement in each of these areas requires robust and efficient differentiation methods to direct hPSCs to specific cell types of interest. STEMCELL Technologies' STEMdiff™ kits are standardized reagents that are rigorously optimized for robust differentiation to specific cell types derived from the three germ layers: ectoderm, mesoderm and endoderm. In this showcase presentation, we will highlight the development of our most recent STEMdiff™ products. These include the STEMdiff™ Trilineage Differentiation Kit, a simple culture assay for rapid assessment of pluripotency, as well as new kits for directed differentiation to several mesodermal lineages: STEMdiff™ Mesoderm Induction Medium, STEMdiff™ Hematopoietic Kit and STEMdiff™ Mesenchymal Progenitor Kit. Finally, we will discuss the expansion of our endodermal-related STEMdiff™ system to include the STEMdiff™ Pancreatic Progenitor Kit. In summary, this tutorial will highlight STEMCELL Technologies' expanding differentiation product portfolio for hPSC research.

TAKARA BIO USA, INC.

Level 2, Rooms 2014/2016/2018
8:00 - 8:30

NOVEL SYSTEM FOR 2D AND 3D STEM CELL CULTURE, DIFFERENTIATION AND SCALE UP -FROM RESEARCH TO CLINICAL

Catharina Ellerstrom, *Takara Bio Europe AB*

Liz Quinn, *Clontech Laboratories, Inc.*

Pluripotent stem cells hold great potential to advance our collective understanding of specific diseases and to illuminate new pathways towards improved therapeutic treatments. To advance the utilization of human induced pluripotent stem cells for research and clinical applications, we have developed a novel, non-colony, monolayer stem cell culture system. In contrast to colony culture, this innovative monolayer culture system maintains high levels of stemness and suppresses any unwanted differentiation in your stem cell culture, all in a robust, easy-to-use, reproducible system. Available in 2D, 3D, feeder-free, xeno-free, and GMP formats, this system enables you to select the combination of features that best suit your specific research needs. This new stem cell culture system provides the ideal pluripotent, homogeneous starting population of iPS cells necessary for the success of downstream applications, such as directed differentiation into various cell lineages, single cell cloning and selection, and 3D spheroid scale-up for research and large-scale clinical research.

MILLIPORESIGMA

Level 2, Rooms 2020/2022
8:00 - 8:30

FROM RESEARCH TO GMP MANUFACTURING: COVERING ALL THE BASES

Julie Murrell, *MilliporeSigma*

Ethan Patterson, *MilliporeSigma*

When making the translation from research to the clinic, demonstrating efficacy is only the first step to a successful product. Long-term commercial viability requires high quality materials that offer a safe and sustainable supply coupled with early process scalability. The Cell Design Studio specializes in genome engineering, enabling alterations in patient-derived iPSCs that introduce or correct disease-related mutations in order to make ideal isogenic cell models. Here we will provide examples for stem cell engineering, focusing on knockouts, targeted integration, and SNP introduction/correction along with the validation process and downstream differentiation options. This provides researchers with a useful tool for high content analysis, high throughput screening, target validation, and other cell-based assays. We will also present a model for translating small scale cell therapy processes to a robust manufacturing process including media, reagents, bioreactor expansion, and harvest. A well thought out strategy for GMP processing requirements from phase I trials to commercialization is essential in successfully translating a potential therapy to a commercial product.

STEMBIOSYS INC.

Level 2, Room 2024
8:00 - 8:30

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

Sy Griffey, *StemBioSys*

Bob Hutchens, *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 cell derived 3-dimensional microenvironment allows a variety of stem cells to replicate more rapidly, maintain a small cell size and express markers indicative of retained stem cell potency 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.

BIOLOGICAL INDUSTRIES

Level 2, Room 2002
11:30 - 12:30

AN INNOVATIVE XENO-FREE CULTURE MEDIUM FOR THE EXPANSION OF CELL THERAPY-COMPLIANT HUMAN ENDOTHELIAL CELLS

Sharon Daniliuc, *Biological Industries*

Human Endothelial cells (hEC) form a single cell layer which lines the interior surface of blood and lymphatic vessels, termed endothelium. Creating a functional vascular network in vitro is crucial for preventing ischaemia in engineered tissues. Consequently, EC have become a key element in tissue engineering and cell-based therapy to improve graft implantation.

Currently, there is no efficient xeno-free (XF) medium for the growth and expansion of hEC. A defined XF culture system optimized for hEC expansion would greatly facilitate development of a robust, clinically accepted culture process for quality-assured cells.

The present study evaluated a novel XF culture system comprising hEC medium (EndoGo™ XF) and auxiliary solutions for attachment, dissociation, and cryopreservation of hEC.

Results show that the hEC culture system efficiently supports long-term expansion of hEC from large vessels (arteries and veins, e.g. HUVEC) and small vessels (lymph and blood). Expanded cells maintain EC features: typical cobblestone-like cell morphology, phenotypic surface markers, gene expression profile, and capillary-like structure formation.

AJINOMOTO CO., INC.

Level 2, Room 2004
11:30 - 12:30

THE GENERATION AND EXPANSION OF HIGH -QUALITY HUMAN PLURIPOTENT STEM CELLS AND THEIR DERIVATIVES FOR APPLICATIONS IN MEDICAL SCIENCE

Peter Andrews, *The Center for Stem Cell Biology and Department of Biomedical Science, The University of Sheffield, UK*

Kiichiro Tomoda, *Gladstone Institute of Cardiovascular Disease*

Human pluripotent stem cells (PSC), whether embryonic stem cells derived from early embryos, or induced pluripotent stem cells derived by reprogramming somatic cells, offer an unprecedented opportunity for producing a wide range of specific differentiated cell types that could be used for replacing diseased or damaged tissues, or to explore the mechanisms by which particular diseases arise at the cellular level. In either case, the challenge is to understand the underlying biology of the PSC so that we can develop protocols to promote their conversion to a required somatic cell type with both genetic and phenotypic fidelity. In this workshop we will discuss how developmental mechanisms can be adapted to optimize culture conditions and control the differentiation of PSC, and how genetic variation that could comprise the use of those cells in regenerative medicine or disease studies can be monitored and minimized.

MILTENYI BIOTEC GMBH

Level 2, Rooms 2001/2003/2005/2007
11:30 - 12:30

GENERATION OF PURIFIED HUMAN IPSC DERIVED CARDIOMYOCYTES USING CLINICALLY RELEVANT WORKFLOWS

Todd Herron, *Center for Arrhythmia Research, University of Michigan*

We have developed workflows for standardized preparations of clinically useful hiPSC derived cardiomyocytes (hiPSC-CMs). hiPSCs have been generated via integration-free reprogramming of dermal fibroblasts and maintained in fully defined, xeno-free media (StemMACS™ iPS-Brew XF). Cardiac directed differentiation of hiPSCs is performed using small molecule modulators of the Wnt signaling pathway. hiPSC-CMs are subsequently enriched using SIRPA2a antibody with subsequent magnetic bead-based sorting. Purified hiPSC-CMs can be cryopreserved, thawed, and utilized for electrophysiological testing. hiPSC-CMs generated in this way represent a cell product that may be developed for future cellular therapies to treat cardiomyopathy.

ENABLING GMP-COMPLIANT IPSC EXPANSION AND DIFFERENTIATION ON THE CLINIMACS® PRODIGY PLATFORM

Sebastian Knöbel, *Miltenyi Biotec GmbH*

When translating research protocols into clinical applications, regulatory requirements call for rigorously characterized cell lines and highest quality reagents, such as GMP-grade media, cytokines, and antibodies. Therefore, we have improved mRNA reprogramming of dermal fibroblasts and renal epithelial cells to fit a 5-day transfection schedule when generating integration-free iPSC lines. We will introduce iPS-Brew GMP Medium, a GMP-compliant version of StemMACS™ iPS-Brew XF, for the expansion and maintenance of pluripotent stem cells along with StemMACS™ Cryo-Brew, a chemically defined cryo-preservation medium, and compelling assays for phenotypic and functional quality control.

Purification of cellular products through cell sorting and standardized, automated processing play central roles in the manufacturing of hPSC-derived cellular products. We present a closed system process for the expansion and differentiation of pluripotent stem cells.

STEMCELL TECHNOLOGIES INC.

Level 2, Rooms 2009/2011
11:30 - 12:00

EXPANSION OF HUMAN PLURIPOTENT STEM CELLS AS AGGREGATES IN MTESR™3D SUSPENSION CULTURES

Eric Jervis, *STEMCELL Technologies Inc.*

Carrier-free 3D suspension culture enables the convenient scale-up of human pluripotent stem cell (hPSC) production. STEMCELL Technologies has developed mTeSR™3D media optimized for fed-batch culture of hPSC aggregates in suspension. A daily fed-batch culture system is employed, which eliminates the need for daily medium exchanges. By day 4 post-seeding, hPSC aggregates grow to a mean diameter of 400 µm, with a 5-fold increase in viable cell number. Confocal imaging of optically-cleared hPSC aggregates revealed uniform staining of hPSC markers and high viability. hPSC aggregates can be serially passaged by dissociating into small clumps using enzyme or enzyme-free methods, and re-seeding into new flasks. Use of STEMCELL Technologies STEMdiff™ Trilineage Differentiation Kit confirmed that cultures maintained in mTeSR™3D media differentiated into all 3 germ layers with high efficiency. Volumetric productivities were 0.7 and 6.9 (x105) cells/mL of medium used for standard 2D culture and fed-batch 3D cultures respectively. mTeSR™3D media used with an optimized fed-batch culture protocol enables efficient scale-up of hPSC production with greatly simplified workflow.

STEMCELL TECHNOLOGIES INC.

Level 2, Rooms 2009/2011
12:00 - 12:30

ROBUST AND CONSISTENT CONVERSION OF PRIMED HUMAN PLURIPOTENT STEM CELLS TO NAÏVE-LIKE PHENOTYPES

Arwen Hunter, *STEMCELL Technologies Inc.*

Traditional primed human pluripotent stem cell (hPSC) cultures correspond to late phase epiblast development and lack the core naïve state transcriptional circuitry observed in the mouse. Recent advances in the field have isolated and maintained naïve-like hPSCs with distinct developmental identities corresponding to earlier embryonic developmental phases. These advancements have allowed for the reversion of traditional primed hPSCs to these earlier states using

specialized cell culture media and protocols. Naïve-like PSCs can subsequently be re-primed and maintained using traditional methods. This presentation will describe the application of our RSeT™ product line and protocols to robustly and consistently revert primed hPSCs to naïve-like states. RSeT™ products also allow for the continuous maintenance of the cells with phenotypic and karyotypic stability. We will examine the distinct characteristics of these cells including their core transcriptional profiles as well as the capacity to toggle between primed and naïve-like phenotypes. This tutorial will highlight STEMCELL Technologies' integrated workflow for maintaining multiple pluripotent stem cell states and their subsequent downstream differentiation under defined culture conditions.

CORNING LIFE SCIENCES

Level 2, Rooms 2014/2016/2018
11:30 - 12:30

STEM CELL CULTURE, DIFFERENTIATION AND SCALE-UP – NOVEL TECHNOLOGIES ENABLING RESEARCH AND CELL PROCESSING APPLICATIONS

Paula Flaherty, *Corning Life Sciences*

A critical component for basic and clinical research are stem cells that maintain an undifferentiated phenotype during expansion followed by differentiation to specific cell types. In this session we will discuss robust, easy to use, reproducible, scalable systems, including feeder-free and novel animal-free platforms for pluripotent and adult stem cell expansion and differentiation, including Matrigel Matrix, pre-coated recombinant Laminin521, Fibronectin/ Collagen-I / Vitronectin peptide mimetic cultureware, hMSC expansion media, scalable vessel platforms and closed systems.

THERMO FISHER SCIENTIFIC

Level 2, Rooms 2020/2022
11:30 - 12:00

STANDARDIZED GENERATION AND CHARACTERIZATION OF PATIENT-SPECIFIC IPSC LINES AND GENE EDITING OF HESCS AND IPSCS

Emily Titus, *Centre for Commercialization of Regenerative Medicine (CCRM)*

CCRM is a translational centre based in Toronto, Canada, focused on the development and commercialization of regenerative medicine and cell therapy technologies. An early achievement was the establishment of an iPSC production facility focused on generating high quality PSC lines for academic researchers and clinicians. Fully operational for three years, CCRM has delivered over 100 patient-derived iPSC lines currently used for disease modelling, and in drug screening initiatives, . Specializing in non-integrative reprogramming technologies, CCRM has developed SOPs to reprogram many common cell types in feeder-free conditions, including dermal fibroblasts, bone marrow stromal cells, cord and peripheral blood, and endothelial cells. iPSC lines are thoroughly characterized and tested using directed differentiation protocols to screen for pluripotent potential. Most recently, CCRM has established gene editing in hESCs and iPSCs using both TALENs and CRISPR/Cas9 to generate reporter cell lines and perform gene correction on patient-derived iPSCs. This presentation will focus on the technical challenges and associated solutions implemented at CCRM to establish these workflows.

THERMO FISHER SCIENTIFIC

Level 2, Rooms 2020/2022
12:00 - 12:30

NEURONAL DIFFERENTIATION OF PARKINSON'S PATIENT-DERIVED IPSCS INTO FUNCTIONAL DOPAMINERGIC NEURONS

Birgitt Schuele, *Parkinson's Institute and Clinical Center*

Differentiation into dopaminergic neurons that show midbrain specificity and exhibit specific cellular characteristics is critical for disease modeling, drug screening, and regenerative medicine. However, there are several technical hurdles such as yield of desired

cell type, reproducibility of protocol, duration of differentiation, and cost.

We compared Gibco Pluripotent Stem Cell (PSC) Dopaminergic Neuron Differentiation Kit (Prototype, Thermo Fisher Scientific, Cat. No. A30416SA) to our dopaminergic differentiation protocol (Mak et al. 2012) for length of protocol, efficiency of DA neuron generation, and electrophysiological properties.

The Gibco PSC Dopaminergic Neuron Differentiation Kit showed a sharp increase in floorplate/mesencephalic markers such as FOXA2, CORIN, LMX1A, and EN1 at day 10 of neuronal induction. About 60% of total cells expressed the DA marker, tyrosine hydroxylase, after 35 days of differentiation and showed spontaneous activity on multielectrode arrays of ~3000 spikes and an average spike amplitude of 22μV (range of 17μV to 40μV).

In summary, the Gibco PSC Dopaminergic Neuron Differentiation Kit provides reproducible conditions, shorter differentiation time, and a high-yield of functional dopaminergic neurons.

MTI-GLOBALSTEM

Level 2, Room 2024
11:30 - 12:30

NEW TOOLS FOR IPSC REPROGRAMMING, DIFFERENTIATION AND CRISPR-CAS9 GENE-EDITING

Jens Durruthy -Durruthy, *Stanford University, Institute for Stem Cell Biology and Regenerative Medicine*

James Kehler, *MTI-GlobalStem*

Phillip Beske, *United States Army Medical Research Institute of Chemical Defense (USAMRICD)*

During this lunch hour session, MTI-GlobalStem is pleased to present three research programs generating and using induced pluripotent stem cells for functional human genetic experiments: 1) Dr. Jens Durruthy-Durruthy will describe efforts at Stanford University to create a diverse collection of patient iPSCs using mRNA reprogramming. 2) Dr. James Kehler at MTI-GlobalStem will present an integrated workflow for targeting human iPSCs from the efficient transfection of CRISPR/Cas9 to the subsequent clonogenic isolation, expansion and screening for generating allelic series of lines with defined genetic mutations. 3) Dr. Phil Beske, a member of Dr. Patrick McNutt's team at USAMRICD, will provide insights on the US Army's novel use of human iPS-derived neurons in synaptic assays for the development of treatments to counteract botulinum neurotoxins. With the emergence of these revolutionary technologies enabling human mechanistic studies, researchers require reliable tools for stem cell generation, differentiation and gene-editing, and MTI-GlobalStem is proud to work with scientists developing new applications to use stem cells in advancing basic and translational research.

WEDNESDAY, 22 JUNE, 13:00-15:15

PLENARY I

THE MCEWEN AWARD FOR INNOVATION LECTURE

ESCAPE FROM THE GROUND STATE

Smith, Austin G.

Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute, Cambridge, U.K.

Ground state pluripotency refers to a stable and homogeneous population of naïve pluripotent cells. This is exemplified by mouse embryonic stem (ES) cells shielded from differentiation cues by two inhibitors (2i) of ERK MAP kinase signalling and glycogen synthase kinase-3. Following release from ground state culture conditions, ES cells embark on the journey towards differentiation. I will discuss ongoing studies into how mouse ES cells exit the ground state propelled by the ERK pathway and begin to develop competence for multi-lineage specification. Our observations suggest that naive cells transition through a formative phase and only then to lineage priming.

PRESIDENTIAL SYMPOSIUM: STEM CELLS AND CANCER

THE ROLE OF CANCER STEM CELLS IN THERAPY FAILURE AND DISEASE RECURRENCE

Dick, John E.

Princess Margaret Cancer Centre, Toronto, ON, Canada

The functional heterogeneity of individual tumor cells can be due to genetic diversity and/or because the tumor is organized as a cellular hierarchy with some tumor cells possessing stemness programs (defining them as cancer stem cells-CSC). Three lines of evidence show that genetic and hierarchy models are highly integrated. Gene signatures specific to AML leukemia stem cells (LSC) have revealed a common stemness program that is highly predictive of patient response to therapy and overall survival. Thus, determinants of stemness influence clinical outcome of AML across a spectrum of mutations indicating that many genetic abnormalities coalesce around stem cell properties. Secondly, combined genetic and functional tumor-initiation studies point to the link between clonal evolution and CSC. LSC originate genetically diverse subclones that are related through a complex branching evolutionary process. Thus clonal evolution occurs within cells that are capable of long term clonal propagation. Finally, our studies have shown that it is possible to backtrack the genetic steps that the leukemia took within otherwise normal stem and progenitor cells prior to diagnosis; these ancestral cells can actually still be found in the blood cells that are still present in the leukemia blood sample taken at diagnosis. These pre-leukemic stem cells (pre-L HSC) with only single mutations represent the cell of origin. Now, by genetic tracking of pre-L HSC, LSC and bulk leukemia blast cells we have gained insight into the origin of relapse. In some patients, ultrarare LSC already present at diagnosis prior to any chemotherapy are already chemoresistant and have the capacity for regeneration. In other cases, relapse comes from rare leukemia blast cells that have acquired stemness properties. Overall we have gained unprecedented insight into the complex evolutionary processes that underlie leukemic progression and the role that stemness plays in disease recurrence.

Funding Source: Supported by Fate Therapeutics

STEM CELL COMPETITION AND CANCER

Weissman, Irving L.

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

Because stem cells both self-renew and interact with a limited number of niches, stem cell competition may result. We first noted stem cell competitions in colonial tunicates, protochordates that share an extracorporeal vasculature with histocompatible kin. The germline stem cells of the two genotypes compete, and when gonads arise, a heritable winner inhabits the gonads of all individuals in the shared circulation. We then found that within developing mice, germline stem cells also compete. We then demonstrated that mouse and human hematopoietic stem cells [HSC] also compete, and this plays a role in the clonal success of some HSC over others in young and old individuals. Preleukemic development in CML, in MPN, in MDS, and in AML occurs at the level of HSC clones. The initating events are usually in genes that regulate epigenetic events in allowing or preventing their differentiation and/or self-renewal. Each step in the leukemia pathway gives the HSC clone a competitive advantage over the others. We examined single HSC from AML patients to determine the stepwise succession of preleukemic clones. In our studies, all acute leukemia stem cells [LSC] are at the stage of downstream multipotent or oligopotent progenitors, cells that do not depend on the HSC niche for survival. In the AMLs we have studied, the final genetic events induce high level proliferation, e.g. with the activation of ras or flt3 or wnt-beta catenin pathway genes. We predict this will be true for all cancers that arise from tissues that are maintained by tissue stem cells. In the process of cancer development one or more events trigger programmed cell death [PCD] which is accompanied by programmed cell removal [PrCR] by phagocytes before the PCD leads to disintegration of the dying cells. Pre-

sumably this is a homeostatic process to prevent inflammation induced by disintegrating cells. All cancer clones overcome PrCR by overexpression of 'don't eat me' signals such as tumor cell CD47 interacting with phagocytic cell Sirp.alpha. One major 'eat me' signal is the appearance of cleaved calreticulin on the tumor cell surface, and this is a signal also for at least some dying cells to initiate PrCR. CD47 is therefore a prime example of a gene whose expression confers on a stem cell or cancer stem cell a competitive advantage.

SKIN STEM CELLS IN SILENCE, ACTION, AGING AND CANCER

Fuchs, Elaine

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

Balancing stem cell (SC) self-renewal and differentiation is essential for normal tissue maintenance and wound repair. Increasing evidence suggests that the regulatory circuitry governing this balancing act is at the roots of both aging and cancer. Hair follicles (HFs) undergo synchronized bouts of hair regeneration, making them an ideal model to dissect how its SCs transition from a quiescent state to an active period of hair growth. During normal homeostasis, HFSC behavior is controlled through cues received from their niche microenvironment, which can include signals emanating from nearby cells of both the SCs' own lineage and other lineages. We've been dissecting how these cues determine the behavior of SCs in their niche and how signaling changes shift the balance between quiescence and tissue regeneration. Our studies underscore the importance of WNT signaling in promoting SC activation and regeneration, while BMP signaling launches a cascade of transcription factors that work to restrict it. During aging, BMP levels rise along with their quiescence-promoting transcription factors, and bouts of hair growth diminish. We've recently addressed the consequences to aging when this molecular brake is perturbed, shortening intervals between hair growth. While some SC transcription factors govern quiescence, others maintain the undifferentiated state. We've shown that the two are integrated at the chromatin level, where they regulate ~400 genes whose expression defines the identity of the SCs within their native niche. We've shown that this landscape changes dramatically when SCs exit their niche in hair regeneration and in wound-repair. Our findings provide new insights into our understanding of the normal process of SC activation during homeostasis and wound-repair. Finally, we've examined how during tumorigenesis, SC regulation goes awry, as cells acquire new mutations and encounter marked changes in their microenvironment that shift their chromatin landscape.

THE NON-CODING RNA REVOLUTION IN BIOMEDICAL RESEARCH

Pandolfi, Pier Paolo

Beth Israel Deaconess Medical Center, Boston, MA, U.S.

We will discuss exciting new data regarding the role of pseudogenes, lincRNAs and miRNAs in the pathogenesis of human cancer as also studied in vivo in the mouse. We will also focus on competing endogenous RNAs (ceRNAs), circular (circ)-ceRNAs and pseudo-ceRNAs and give important attention to how understanding the code by which RNAs communicate (e.g. the ceRNA language) will facilitate efforts to deconvolute and functionalize non-coding RNA networks and their role in tumorigenesis.

WEDNESDAY, 22 JUNE, 16:00-18:00

PLENARY II: TISSUE GROWTH AND MORPHOGENESIS

THE ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE

CLONAL ANALYSIS OF NATIVE HEMATOPOIESIS

Camargo, Fernando

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

Tremendous progress has been achieved in the characterization of the hematopoietic system over the past two decades. Historically, the main experimental approach used to elucidate and define these cellular relationships in the bone marrow (BM) has been the transplantation assay. For this reason, most of our knowledge about the in vivo properties of hematopoietic stem cells (HSCs) and progenitor cells has been derived from studies in the transplant context. Because of the lack of tractable systems, the mechanistic nature of non-transplant hematopoiesis has remained largely unexplored. Over the past several years, my laboratory has developed novel genetic tools for the clonal tracing and imaging of hematopoietic populations in the unperturbed niche that aim to bring insight into the biology of stem and progenitor cells in situ. I will discuss our results performing clonal analyses to bring insight into the dynamics of stem and progenitor biology during embryonic hematopoiesis and in the severely aged hematopoietic system.

HIPPO SIGNALING IN GROWTH CONTROL AND BEYOND

Pan, Duojia D. J.

Johns Hopkins University School of Medicine, Baltimore, MD, U.S.

The Hippo signaling pathway regulates organ size and tissue homeostasis in diverse species from Drosophila to mammals. This pathway comprises several tumor suppressors acting in a kinase cascade that ultimately phosphorylates the oncoprotein Yorkie (Yki) or its mammalian counterpart YAP/TAZ. Much of the recent research on Hippo signaling has focused on identifying upstream inputs into the Hippo kinase cascade, elucidating the mechanisms of Yki/YAP/TAZ in transcriptional regulation, and developing small molecule probes and inhibitors targeting the Hippo pathway. Recent work has also expanded the physiological function of Hippo signaling to many biological processes beyond growth control. I will present recent progress in these areas at the ISSCR meeting.

A POSITIONAL CODE AND POLARIZED FORCES CONTROL TISSUE REMODELING IN DROSOPHILA

Zallen, Jennifer A.

Howard Hughes Medical Institute and Sloan Kettering Institute, New York, NY, U.S.

A major challenge in developmental biology is to understand how tissue-scale changes in organism structure arise from events that occur on a cellular and molecular level. My lab uses multidisciplinary approaches from cell and developmental biology, physics, engineering, and computer science to study how tissue architecture is dynamically established and remodeled throughout development. During development, the body axis elongates dramatically from head to tail through the rapid and coordinated movements of hundreds of cells, a process that is conserved throughout metazoans. We identified the force-generating machinery that drives polarized cell movements that elongate the body axis of Drosophila, and showed that this machinery is controlled by a combination of chemical and mechanical cues in the extracellular environment. In particular, we discovered a global spatial system that systematically orients cell movements throughout the embryo, and showed that this information is provided by an ancient family of receptors widely used by the innate immune system for pathogen recognition. Using time-lapse imaging, we showed that these signals drive collective behaviors in which groups of cells assemble into multicellular rosettes that form and resolve in a directional fashion, promoting efficient elongation. The rosette mechanism for tissue elongation is a mechanically regulated process, in which an initial asymmetry in actomyosin contractility is amplified by the force-sensitive activation of myosin in neighboring cells. Together, these studies have elucidated general principles that link intrinsic cellular asymmetries to global tissue reorganization.

POSTER TEASERS

W-2170
CANCER-ASSOCIATED TERT PROMOTER MUTATIONS ABROGATE TELOMERASE SILENCING

Hockemeyer, Dirk

University of California, Berkeley, CA, U.S.

W-2199
HUMAN PLURIPOTENT STEM CELL DERIVED ENTERIC NEURAL CREST LINEAGES FOR CELL THERAPY AND DRUG DISCOVERY IN HIRSCHSPRUNG DISEASE

Fattahi, Faranak[1,2], Steinbeck, Julius[1], Kriks, Sonja[1], Tchieu, Jason[1], Zimmer, Bastian[1], Kishinevsky, Sarah[1], Zeltner, Nadja[1], Mica, Yvonne[3], El-Nachef, Wael[4], Zhao, Huiyong[1], de Stanchina, Elisa[1], Gershon, Michael[5], Grikscheit, Tracy[4], Chen, Shuibing[2] and Studer, Lorenz[1],

[1]Memorial Sloan-Kettering Cancer Center Developmental Biology, New York, NY, U.S., [2]Weill Cornell Medicine, Weill Graduate School of Medical Sciences, New York, NY, USA, [3]Life Technologies, Inc., Carlsbad, CA, U.S.,

W-3064
TMJ PROGENITOR CELL MARKERS AND FATE SPECIFICATION

Casanovas, Guillem[1], Pylawka, Serhiy[1], Kalajzic, Ivo[2] and Embree, Mildred[1]

[1]Columbia University, New York, NY, U.S., [2]UConn Health, Farmington, CT, U.S.

W-1127
MIR205 CONTROLS MOUSE MAMMARY GLAND DEVELOPMENT THROUGH REGULATION OF WNT AND YAP STEM CELL SELF-RENEWAL SIGNALING

Lu, Yang[1], McManus, Michael[2] and Rosen, Jeffrey M.[1]

[1]Baylor College of Medicine, Houston, TX, U.S., [2] University of California, San Francisco, CA, U.S.

W-2019

LUNATIC FRINGE IS A SELECTIVE MARKER OF HIPPOCAMPAL NEURAL STEM CELLS, NECESSARY FOR THEIR MAINTENANCE

Semerci, Fatih[1,2], Choi, William Tin-Shing[1,2], Bajic, Aleksandar[2,3], Thakkar, Aarohi[2,3], Encinas, Juan Manuel[2,4], Depreux, Frederic[5], Segil, Neil[6], Groves, Andrew Kelton[1,7] and Maletic-Savatic, Mirjana[1,3]

[1]Graduate Program in Developmental Biology Baylor College of Medicine, Houston, TX, U.S., [2]Jan and Dan Duncan Neurological Research Institute at Texas Children's Hospital, Houston, TX, U.S., [3]Department of Pediatrics Baylor College of Medicine, Houston, TX, U.S., [4]The Basque Foundation for Science, Bizkaia, Spain, [5]Rosalind Franklin University of Medicine and Science, Chicago, IL, U.S., [6]Broad CIRM Center, Keck School of Medicine, University of Southern California, Los Angeles, CA, U.S., [7]Department of Neuroscience Baylor College of Medicine, Houston, TX, U.S.

THE ISSCR TOBIAS AWARD LECTURE

PATHWAYS REGULATING BLOOD STEM CELL SELF-RENEWAL AND MIGRATION: TRANSLATING DEVELOPMENT INTO CLINICAL THERAPIES

Zon, Leonard

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

Hematopoiesis is the process by which blood stem cells proliferate or differentiate into the peripheral blood lineages. We have used the zebrafish as a model system to study this process. Stem cells arise in the developing aorta of the zebrafish and sequentially colonize other sites of hematopoiesis similar to processes that happen in mammals. Given the transparency of the zebrafish, we witnessed interactions between stem cells and their niches in live animals. Such studies have led to the discovery that prostaglandin E2 can stimulate stem cell production in zebrafish. After showing activity of PGE2 in marrow transplantation in mice, PGE2 was tested in a clinical trial in patients with leukemia who were treated by cord blood transplantation. Using a competitive transplantation experiment akin to the mouse competitive repopulation assay, a clinical trial was designed in which patients with leukemia, but no matched marrow, receive two cord blood units as an alternative source of stem cells (single cords have insufficient stem cells to ensure engraftment): one unit was treated with dmPGE2, the other was untreated. Both were transplanted into patients. DNA polymorphisms in white blood cells revealed preferential engraftment and earlier return of neutrophils and platelets in 10 out of 12 patients with treated cord bloods. This work has progressed to a Phase II clinical trial with 60 patients. Other eicosanoid pathways also regulate stem cell engraftment. EETs, another lipid derived from arachidonic acid, stimulates hematopoiesis. We demonstrate that eicosinoids induce a long-term memory in stem cells. We also developed a clonal marking system to evaluate stem cell number. Our work has implications on therapies for blood diseases and cancer.

THURSDAY 23 JUNE, 9:00 – 11:20

PLENARY III: CELLULAR PLASTICITY AND REPROGRAMMING

RECENT PROGRESS IN IPS CELL RESEARCH AND APPLICATION

Yamanaka, Shinya

Gladstone Institutes, San Francisco, CA, U.S. and CiRA, Kyoto University, Kyoto, Japan

The appeal of induced pluripotent stem cells (iPSCs) is that they can proliferate almost indefinitely and differentiate into multiple lineages. As a result, cell-based therapies, disease mechanisms and new drug development are being studied worldwide using iPSC technology. We are currently establishing technologies for the efficient generation of safe iPSCs. The original iPSCs were made from retroviral transduction, which risks chromosomal damage. We have since reported integration-free methods that reduce the risk of tumorigenicity while maintaining iPSC induction at high efficiency. We have also modified the culture system to be consistent with regulatory requirements for medical practice. Regarding quality control, some marker genes for neural differentiation-defective clones were identified, indicating the possibility of screening out low-quality iPSCs before use. In 2014, the world's first clinical study using iPSCs was initiated. iPSC-based therapies for other disorders are also nearing clinical study, suggesting applicability to many diseases. To push these efforts, we are proceeding with an iPSC stock project in which iPSC clones are established from donors with a homologous HLA haplotype, which lessens the risk of transplant rejection, with the aim of quality-assured iPSCs for future cell therapies. We are already distributing iPSC stock clones to corporate and medical institutions and aim for HLA-homozygous iPSC clones that cover at least half of the Japanese population by 2018. Another application of iPSCs is drug screening, toxicity studies and the elucidation of disease mechanisms. In addition, iPSCs may be resourceful for preventative measures, as they make it possible to predict the patient condition and provide a preemptive therapeutic approach to protect against the onset of the disease. Additionally, accumulating evidence is demonstrating the benefits of iPSCs in drug repositioning.

PLASTICITY OF EPIDERMAL STEM CELLS

Watt, Fiona M.

King's College London, U.K.

Recent studies have highlighted the existence of multiple stem cell compartments within adult mouse epidermis and shown that epidermal stem cells exhibit striking plasticity in response to tissue damage, transplantation or tumour development. I will discuss the transcription factor networks that maintain epidermal stem cell identity and the extrinsic signals from connective tissue fibroblasts that contribute to stem cells plasticity.

POSTER TEASERS

T-2119
HUMANITY IN A DISH: UNCOVERING THE COMMON GENETIC BASIS FOR HUMAN METABOLIC DISEASE WITH IPSCS

Warren, Curtis Robert[1,2], Friesen, Max[2,3], Becker, Caroline[4], O'Sullivan, John[5], Choi, Jihoon[4], Xia, Fang[2,4], Zhang, Xiaoling[6], Peters, Derek[2,4], Wakabayashi, Yoshi[6], Florido, Mary H. C.[2,4], Shay, Jennifer[2,4], Daheron, Laurence M.[4], Zhu, Jun[6], Gerszten, Robert E.[5], Deo, Ph.D., Rahul[7], Ramachandran, Vasan[8,9], O'Donnell, Christopher J.[9] and Cowan, Chad[2,5]

[1]Harvard University, Somerville, MA, U.S., [2]Harvard University, Cambridge, MA, U.S., [3]Harvard Stem Cell Institute, Somerville, MA, U.S., [4]Harvard Stem Cell Institute, Cambridge, MA, U.S., [5]Massachusetts General Hospital, Boston, MA, U.S., [6]National Heart, Lung, and Blood Institute, Bethesda, MD, U.S., [7]University of California, San Francisco, San Francisco, CA, U.S., [8]Boston University, Boston, MA, U.S., [9]The Framingham Heart Study, Framingham, MA, U.S.

T-3061
SPECIFIED THY1+ FIBROBLASTS DIFFERENTIATES TO CARDIOMYOCYTES DURING HEART REGENERATION IN VIVO/IN VITRO

Morita, Yuika[1], Hotta, Akitsu[2], Qian, Li[3] and Takeuchi, Jun K.[1,4]

[1]The University of Tokyo, Bunkyo, Japan, [2]Department of Life Science Frontier, Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan, [3]University of North Carolina at Chapel Hill, Chapel Hill, NC, U.S., [4]the University of Tokyo, Bunkyo, Japan

T-2165
SPATIAL TRANSCRIPTOME OF MID-GASTRULA MOUSE EMBRYO: MOLECULAR ANNOTATION OF TRANSCRIPTIONAL ACTIVITY, LINEAGE FATES AND CELL IDENTITY

Peng, Guangdun[1], Suo, Shengbao[1], Chen, Jun[2], Chen, Weiyang[1], Liu, Chang[1], Tam, Patrick P.L.[3], Han, Jingdong[1] and Jing, Naihe[1]

[1]Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China, [2]National Institute of Biological Sciences, Beijing, Beijing, China, [3]Children's Medical Research Institute, Westmead, Australia

T-2155
TRANSLATION AND CELLULAR GROWTH IS REQUIRED FOR MAINTENANCE OF OPEN CHROMATIN IN MOUSE EMBRYONIC STEM CELLS

Karslioglu, Aydan, Macrae, Trisha, Diaz, Aaron, McManus, Michael and Ramalho-Santos, Miguel

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

T-1055
DIRECT CONVERSION OF FIBROBLASTS TO FUNCTIONAL MEGAKARYOCYTE PROGENITORS

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HOW TO MAKE A NEURON

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Cellular differentiation and lineage commitment are considered robust and irreversible processes during development. Challenging this view, we found that expression of only three neural lineage-specific transcription factors Ascl1, Myt1l, and Brn2 could directly convert mouse fibroblasts into functional in vitro. These induced neuronal (iN) cells expressed multiple neuron-specific proteins, generated action potentials, and formed functional synapses. Thus, iN cells are bona fide functional neurons. Unlike reprogramming towards other lineages such as iPS cell reprogramming, the iN cell reprogramming process is very efficient (up to 20%) and deterministic. We previously found a molecular explanation in that Ascl1, a transcriptional activator, can access its physiological targets in fibroblasts even though these sites are in a closed chromatin state, thus robustly inducing a neuronal transcriptional program and rearranging the local chromatin. Surprisingly, Ascl1 alone is sufficient to induce fully functional iN cells, but in the majority of cells activates also non-neuronal programs. We further show, that Myt1l, a zinc finger domain protein, primarily functions as transcriptional repressor suppressing the fibroblast and other non-neuronal programs. This suggests that the physiological role of Myt1l is to ensure maintenance of neuronal identity by repressing many transcriptional program except neuronal genes, thereby functioning in exactly the inverse way as REST which blocks neuronal genes in many non-neuronal cell types. In summary, our data suggest that for optimal reprogramming results it may be important to use a combination of specific activators of the target cell program and specific repressors of the donor and other non-target cell programs.

BRAIN REPAIR AND REPROGRAMMING

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The adult brain has a very limited capacity for generation of new neurons, and continuous neurogenesis only takes place in a few restricted regions. Experimental studies have shown that endogenous progenitors can sometimes be recruited to generate new neurons also in other regions in response to injury. However, the number of new neurons that are formed are low, their migration hard to control, and the therapeutic benefits that they can mediate is unclear. For decades, researchers have therefore developed a strategy for brain repair using exogenous cell sources for cell replacement by transplanting them into the adult brain. In Parkinson's disease, clinical trials using fetal cells have demonstrated that effective repair can indeed be achieved by cell transplantation of developing human fetal dopamine (DA) neurons. Current approaches using pluripotent stem cells to replace the scarcely available fetal tissue as a source for DA neurons is underway and are predicted to reach clinical trials within then next few years. Other strategies that by-pass the pluripotent stage and directly convert somatic cells into induced neurons (iNs) represent an interesting alternative to induced pluripotent stem cells (iPSCs) for obtaining patient specific neurons to be used in personalized cell therapy. In this talk, I will discuss the current state of direct conversion of human fibroblasts into mature and functional DA neurons in vitro, gauge how they compare to stem cell-derived DA neurons, and define the major road-blocks for iNs on their route to clinical transplantation. In addition to fibroblasts, various cell types of the brain have been used as a cellular substrate for direct neural conversion in vitro, and reprogramming directly in the brain in vivo has emerged as an attractive possibility. I will discuss how the approach

to reprogram the desired target cell type directly in vivo, by delivery of reprogramming factors into the brain, presents another promising future alternative for brain repair.

THURSDAY 23 JUNE, 13:15 – 15:15

CONCURRENT I: NEURAL STEM CELLS

Level 2, Rooms 2014/2016/2018

ROLE OF CLASSICAL IMMUNE MOLECULES IN REGULATING AGE-RELATED DECLINE IN ADULT NEUROGENESIS

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Aging drives regenerative and cognitive impairments in the adult brain, increasing susceptibility to neurodegenerative disorders in healthy individuals. It is imperative to gain mechanistic insight into what drives aging phenotypes in the brain in order to maintain functional integrity in the elderly, and counteract vulnerability to neurodegenerative disease. We, and others, have shown that systemic manipulations, such as heterochronic parabiosis (in which the circulatory system of a young and old animal are joined), can partially reverse age-related impairments in neural stem/progenitor cell (NPC) function and loss of cognitive faculties in the aged brain. Interestingly, heterochronic parabiosis studies have revealed an age-dependent bi-directionality in the influence of the systemic environment indicating anti-aging factors in young blood elicit rejuvenation while pro-geronic factors in old blood drive aging. It has been proposed that mitigating the effect of pro-geronic factors may also provide an effective approach to rejuvenate aging phenotypes, however functional investigation of individual pro-geronic factors is lacking. My lab has identified ß2-microglobulin (B2M), a component of major histocompatibility complex class 1 (MHC I) molecules, as a systemic pro-aging factor that negatively regulates regenerative and cognitive functions in the adult hippocampus. We have demonstrated involvement of global cell surface expression of MHC I molecules in mediating the negative effects of heterochronic parabiosis on adult neurogenesis. Moreover, at a mechanistic level, we identified classical MHC I molecules, H2-Kb and H2-Db, as negative regulators of NPC proliferation and neuronal differentiation. Collectively, our work identifies a non-canonical role for traditional immune molecules in the age-related decline in NPC function.

Funding Source: Supported by Innovative Cell Technologies

EFFICIENT CRISPR/CAS9-BASED GENE TARGETING IN MAMMALIAN NEURAL STEM CELLS ENABLES COMPLEX AND DIVERSE GENETIC MANIPULATIONS

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Targeted genetic manipulations are routinely used in mouse embryonic stem cells to create sophisticated new alleles, such knockouts, knockin reporters, and engineering of disease mutations. Mammalian neural stem (NS) cell cultures should similarly be amenable to such complex targeted genetic manipulations as they are: clonally expandable in adherent monolayer, genetically stable, and easily transfected. However, gene targeting directly in mammalian NS cells has not been reported to date. Here we deploy CRISPR/Cas technologies and demonstrate: 1) highly efficient gene targeting at safe harbor loci (Rosa26 and AAVS1); 2) efficient production of biallelic mutants for 14 different neurodevelopmental transcription factors; 3) facile biallelic 'knock in' of either epitope or fluorescent tags (e.g. Sox2-V5 and Sox2-mCherry); 4) engineering of glioblastoma-associated tumour suppressor (TP53) and oncogenic point mutations (H3F3A). The resources and methods we describe provide significant new opportunities for sophisticated and facile functional genetic analysis in mammalian neural stem cells.

Funding Source: SP is supported by a Cancer Research UK Senior Research Fellowship

HUWE1 PROMOTES THE QUIESCENCE OF ADULT NEURAL STEM CELLS VIA TARGETED ELIMINATION OF ASCL1

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Quiescence is a fundamental state of adult stem cells that ensures their long-term maintenance. However, little is known about how this state is regulated. We previously showed that the transcription factor Ascl1 is absolutely required for the activation of adult neural stem cells in the dentate gyrus of the hippocampus. We also showed that the levels of Ascl1 determine the activity of neural stem cells. Thus, we aim to investigate the mechanisms that control Ascl1 protein levels. Mass spectrometry analysis of cultured neural stem cells revealed that the E3-ubiquitin ligase Huwe1 strongly binds Ascl1. We performed a series of in vitro experiments to prove that Huwe1 controls Ascl1 stability. Conditional deletion of Huwe1 in hippocampal stem cells in vivo dramatically increases Ascl1 levels, promoting proliferation and blocking neuronal differentiation. Strikingly, Ascl1 stabilization upon loss of Huwe1 is not sufficient to activate stem cells, but prevents their return to

quiescence, thus leading to the exhaustion of the active stem cell population. These effects are mediated by the upregulation of CyclinD genes, which are direct targets of Ascl1.Our findings reveal a crucial function for Huwe1 in the re-acquisition of quiescence by activated adult neural stem cells. Thus, the quiescent state of adult stem cells is controlled by targeted proteasomal degradation of a key activator protein.

ADULT HIPPOCAMPAL NEURAL PROGENITORS REGULATE SEIZURE-INDUCED NEUROINFLAMMATION VIA SECRETED VEGF

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One of the most rapid and dramatic changes in the adult hippocampus after seizures is a surge in neural stem and progenitor cell (NSPC) proliferation, leading to a subsequent increase in new neurons weeks later. While the function of seizure-induced new neurons is intensely debated, the role of the undifferentiated NSPC population has received little attention. We recently demonstrated that adult hippocampal NSPCs can strongly influence hippocampal function via secretion of vascular endothelial growth factor (VEGF). We therefore asked whether NSPCs could regulate seizure-induced hippocampal damage in their undifferentiated state by secreting VEGF. To determine the cell phenotype of VEGF-expressing cells before and after a seizure, we injected adult (7-9 weeks old) VEGF-GFP reporter mice with kainic acid (KA) or vehicle then used confocal microscopy of fixed hippocampal sections taken after 1, 3 or 7d to determine the cell phenotype of VEGF-GFP+ cells. In the dentate gyrus (DG) and hilus, we found VEGF-GFP was expressed primarily in NSPCs and astrocytes and that both of those VEGF-GFP+ cell populations increased after KA. We next asked whether loss of VEGF from NSPCs in adulthood could impact seizure-related damage in the hippocampus. We created a tamoxifen(TAM)-inducible NSPC-VEGF knockdown by crossing NestinCreER^{T2} and VEGF$^{flox/flox}$mice. We found that total VEGF expression in the DG/hilus after KA-induced seizures was significantly blunted in VEGF knockdown mice compared to littermate controls. One week after KA, VEGF knockdown mice also showed significantly greater seizure-induced neuronal degeneration, astrogliosis and microgliosis. In contrast, seizure-induced NSPC proliferation and vascular reorganization were similar in knockdown and control mice. Our findings suggest that loss of VEGF from adult hippocampal NSPCs substantially reduces the VEGF surge after a seizure and results in exacerbation of hippocampal neuroinflammation. Adult hippocampal NSPCs may therefore have a functional role in injury recovery in their undifferentiated, non-neuronal state as important sources of VEGF.

AN IN VITRO MODEL OF LISSENCEPHALY: EXPANDING THE ROLE OF DCX DURING NEUROGENESIS

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Lissencephaly is characterized by a smooth cerebral surface, severe neurodevelopmentral delay and seizures. Lissencephaly is the result of mutations in one of several genes involved in cytoskeletal regulation and the most common cause are mutations in LIS1 or in the X-linked DCX gene. The proposed primary defect underlying the smoothening of the brain is impaired neuronal migration. In this study we demonstrate that mutated DCX is associated with defects in the neural differentiation and neurite outgrowth in addition to perturbed cell migration. We have established iPS cells and neuroepithelial stem (NES) cells from two patients with DCX mutations (p.Arg19* and p.Thr88Met) and from healthy individuals. Proliferating NES cells don't express DCX and, consequently, we could not detect any disease phenotypes in neural progenitors. However, upon differentiation the DCX expression increased dramatically and to detectable protein levels in control cells. In contrast, DCX protein remained undetectable in patient derived cells. Furthermore, mutated NES cells show perturbed differentiation and they appear to remain in the proliferative state longer than healthy cells upon differentiation. Transcriptome analyses supported impaired differentiation in cells with mutated DCX and genes connected to proliferation remained upregulated during differentiation in patient's cells when compared to healthy cells. Interestingly, DCX mutated cells showed sprouted neurites that were half the length of neurites from healthy neurons. Consistently, genes important for neurite outgrowth and synapse maturation were under-expressed in mutated cells. Interestingly, by knockdown targeting a highly over-expressed gene in mutated cells we could rescue the neurite outgrowth phenotype to resemble the neurites of healthy cells. Taken together, we have shown that neural progenitor cells from Lissencephaly patients, that fail to up-regulate DCX upon induction of differentiation, seem partly resistant to differentiation. Furthermore, the upregulation of DCX seems to be key not only for migration but also for proper differentiation and neurite outgrowth. The impaired differentiation results in continued proliferation, which might be the underlying cause of the defect in migration and underdeveloped neurites.

IMPACT OF ZIKA VIRUS ON HUMAN CORTICAL NEUROGENESIS

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The suspected link between infection by Zika virus (ZIKV), a re-emerging flavivirus, and microcephaly is an urgent global health concern. We recently established a human induced pluripoent stem cell (iPSC) model to investigate the impact of ZIKV on human brain development. We found that ZIKV efficiently infects human cortical neural progenitor cells (hNPCs) derived from human iPSCs. Infected hNPCs further release infectious ZIKV particles. Importantly, ZIKV infection increases cell death and dysregulates cell cycle progression, resulting in attenuated hNPC growth. Global gene expression analysis of infected hNPCs reveals transcriptional dysregulation, notably of cell cycle-related pathways. These results identify human cortical neural precursor cells as a direct ZIKV target, establish a tractable experimental model system to investigate mechanism of ZIKV on human brain development, and provide a platform to screen therapeutic compounds. I will present latest findings from our ongoing studies.

THURSDAY 23 JUNE, 13:15 – 15:15

CONCURRENT I: PARADIGMS FROM MODEL ORGANISMS

Level 2, Room 2024

THE NICHE LIGAND-RECEPTOR DIRECTLY ORIENTS THE SPINDLE IN DROSOPHILA MALE GERMLINE STEM CELLS

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Asymmetric cell division is critical for balancing self-renewal and differentiation in many stem cells. For those stem cells residing in the niche, spindle orientation with respect to the niche is crucial to achieve asymmetric stem cell division. Despite this relationship between the stem cell niche and spindle orientation, the niche's role in spindle orientation is poorly understood. Here we show that the niche ligand Upd and its receptor Dome, but not their downstream JAK-STST pathway, are required for spindle orientation in Drosophila male germline stem cells (GSCs). We found that Dome directly interacts with the plus-end microtubule binding protein Eb1 and they function together to anchor the spindle toward the niche, likely via regulation of microtubule dynamics. Our study reveals a novel mechanism by which the niche directly governs spindle orientation, integrating self-renewal and asymmetric division in stem cells.

PARENT-OF-ORIGIN DNA METHYLATION DYNAMICS DURING MOUSE DEVELOPMENT AT SINGLE-CELL RESOLUTION

Stelzer, Yonatan, Wu, Hao, Song, Yuelin, Shivalila, Chikdu S, Marloulaki, Styliani and Jaenisch, Rudolf

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DNA methylation is a broadly studied epigenetic modification that is essential for normal mammalian development. To enable real-time endogenous readout of DNA methylation, we have recently established a Reporter of Genomic Methylation (RGM) that relies on a synthetic imprinted gene promoter driving a fluorescent protein. We show that insertion of RGM proximal to promoter-associated CpG islands, or non-coding regulatory elements such as tissue-specific super-enhancers, allows faithful reporting on gain and loss of DNA methylation. Importantly, we demonstrate that RGM enables tracing of real-time DNA methylation dynamics during cell fate changes at single-cell resolution. In placental mammals, differential DNA methylation at imprinting control regions (ICRs) regulates the parent-of-origin monoallelic expression of multiple imprinted genes in clusters. To study methylation dynamics associated with ICRs during mouse development, RGM was targeted allele-specifically to the intergenic ICR located at the Dlk1-Dio3 locus. Targeted mouse embryonic stem cells elucidated the association between ICR methylation state and parent-of-origin expression of imprinted genes in this locus. Furthermore, isolation and expansion of rare cell populations that exhibit aberrant methylation allowed studying the effects of loss-of-imprinting on normal development. We show that RGM faithfully reflects parent-of-origin methylation inheritance throughout mouse generations, thus facilitating a systematic in-vivo analysis of methylation dynamics during embryonic development and in adult tissues. Surprisingly, we find the methylation levels associated with the Dlk1-Dio3 ICR to be highly regulated during mouse development, resulting in tissue- and cell-type specific differences in adult mice. We further demonstrate that these methylation changes persist during adult neurogenesis, thus contributing to epigenetic diversity and cellular mosaicism in the adult brain. Taken together, our results suggest that parent-specific imprints are not maintained in a strictly manner but are subjected to tissues and cell specific effects later in development. This results in loss or gain of methylation imprints with potential broad implications for cellular and inter-individual epigenetic diversity.

DROSOPHILA FOLLICLE STEM CELLS RESIDE IN LAYERS WITH POSITION-DEPENDENT SPECIFICATION OF DISTINCT DIRECT STEM CELL DERIVATIVES GUIDED BY A WNT SIGNALING GRADIENT

Reilein, Amy, Melamed, David, Park, Sophie, Berg, Ari, Cimetta, Elisa, Tandon, Nina, Finkelstein, Sarah, Toueg, Raphael, Veras, Yokarla and Kalderon, Daniel

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In Drosophila, stem cells reside in relatively simple environments where they can be readily visualized, tracked and genetically manipulated, affording exceptional opportunities to derive a detailed, comprehensive picture of stem cell behavior and regulation by extracellular signals. Here we present a drastically revised understanding of the epithelial stem cells in the ovary, named follicle stem cells (FSCs), which reveals that FSCs are a remarkably good model for highly proliferative epithelial cells including those in mammalian intestine. FSCs and germline stem cells are located at the anterior of the ovariole, in the germarium, where FSC derivatives encapsulate and provide developmental signals for the germline. Through multicolor lineage tracing we show that FSCs exist as a population of about 14-16 cells distributed among two to three rings lining the germarial wall. FSCs in the most posterior layer directly supply follicle cells (FCs) that proliferate further as they encapsulate germline cysts to form egg chambers. FSCs in the anterior layers divide less frequently and directly give rise to Escort Cells, which are quiescent and contribute to early germline cyst maturation. FSCs can exchange between layers, so that a single lineage can include both FCs and Escort Cells. Live imaging showed that FSCs constantly move and exchange positions radially and also in an anterior-posterior direction. Lineage tracing at a variety of time points following clonal marking showed that FSCs undergo frequent loss and amplification, consistent with population asymmetry. Moreover, an FSC can become an FC at any time, not just immediately after FSC division. Consequently, stem cell proliferation rate is necessarily a major determinant of competition among FSCs to produce the dominant lineage colonizing the entire niche. Niche factors regulate FSC proliferation but may also regulate FSC position and fate. By manipulating levels of Wnt in the FSCs, we found that high Wnt signaling biases FSCs strongly towards the anterior FSC layer and Escort Cell production, whereas loss of Wnt signaling biases FSCs towards the posterior layer and prevents Escort Cell formation. This new FSC paradigm provides a model system to understand how multiple signaling pathways interact to regulate epithelial stem cell identity and dynamics.

Funding Source: Funded by the NIH.

INDUCED IN VIVO REPROGRAMMING OF ZEBRAFISH MUSCLE INTO ENDODERM BY DIRECT TRANSDIFFERENTIATION

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The extent to which differentiated cells, while remaining in their native microenvironment, can be converted into unrelated cell types will reveal fundamental insight into cellular plasticity and impact regenerative medicine. We have identified two transcription factors that, when co-expressed in several non-endoderm lineages including skeletal muscle, are able to cell-autonomously induce the early endoderm program. Induced muscle cells can proceed to express key endoderm organogenesis genes including hnf1b and pdx1, and subsequently form organoids. Endoderm markers appearing prior to loss of muscle cell morphology, a lack of dependence on cell division, and a lack of pluripotency gene activation, together, suggests that lineage reprogramming occurred independent of a pluripotent intermediate. Importantly, lineage reprogramming can occur in oct4 mutants, providing functional evidence that lineage conversion is via direct transdifferentiation. Our work demonstrates that within a vertebrate animal, differentiated cells originating from one germ layer can be induced to directly adopt lineages of a different germ layer – suggesting that differentiated cells in vivo are more plastic than previously assumed. This discovery may pave the way towards a vast new in vivo supply of replacement cells for degenerative diseases such as diabetes.

Funding Source: NIH Director's New Innovator Award DP2

AN INTERCELLULAR E-CADHERIN-EGFR RELAY MAINTAINS ORGAN SIZE DURING RENEWAL BY COUPLING CELL DIVISION AND DEATH

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Self-renewing organs require balanced rates of cell production and loss to maintain a constant number of cells. Cellular imbalance leads to organ hyperplasia or degeneration, but how cellular balance is enforced during normal renewal remains poorly understood. Examining intestinal renewal in Drosophila, we find that feedback inhibition from mature enterocytes to stem cells serves to couple cell death and division and maintain constant cell number. In enterocytes, the adhesion receptor E-cadherin (E-cad) inhibits stem cell divisions not by binding stem cell E-cad,

but by repressing the EGF maturation factor rhomboid to limit secretion of enterocyte EGFs. Conversely, loss of E-cad upon physiological apoptosis derepresses rhomboid, triggering local activation of EGFR in nearby stem cells. EGFR activation induces stem cells to divide, generating new cells to replace apoptotic enterocytes. When enterocyte apoptosis is blocked, stem cells compensate by slowing their divisions. Disrupting E-cad-EGFR feedback inhibition impairs this compensatory response and leads to organ hyperplasia. Our results show that global inhibition of stem cell EGFR is locally relieved when an enterocyte apoptoses. This mechanism couples division and death, ensuring zero-sum cell replacement and constant organ size during renewal.

Funding Source: NSF Graduate Research Fellowship

STEM CELL POPULATION DYNAMICS, TISSUE HOMEOSTASIS AND REGENERATION

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Despite the importance of regeneration and tissue homeostatic processes to human biology and health, relatively little is known about how these adult processes are controlled. Numerous issues remain unaddressed including: How organ systems maintain their form and function while in a state of cell flux; How animals control and coordinate the size and cell number of multiple organ systems; How developmental genes re-express in the adult during tissue homeostasis. Answering any of these issues would set a baseline from which to try to enhance regenerative properties in multicellular organisms, particularly after injury. We have chosen the freshwater planarian Schmidtesa mediterranea as a model system to address these fundamental biological problems. The speed and robustness of both tissue homeostasis and regeneration, as well as the abundance of pluripotent stem cells in S. mediterranea, provide unique opportunities to address cellular and molecular problems associated with transform these animals into an experimentally accessible system to gain mechanistic insight on these problems at molecular and cellular levels. Here we will discuss the role of the planarian stem cells in homeostasis and regeneration as well as some of the factors and behaviors displayed by this cells as they carry out their restorative functions.

THURSDAY 23 JUNE, 13:15 – 15:15

CONCURRENT I: MECHANISMS OF PLURIPOTENCY

Level 2, Rooms 2001/2003/2005/2007

DECIPHERING THE PLURIPOTENCY OF RODENT AND NON-HUMAN PRIMATE STEM CELLS

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Pluripotent stem cells (PSCs) have the capacity of unlimited self-renewal and differentiation into almost all kinds of cells. Intriguingly, PSCs derived from different species or embryonic stages exhibit diverse pluripotency states. The chimera formation (2N), germline transmission and tetraploid complementation (4N) experiments provide the most stringent assays of pluripotency by directly assessing the in vivo developmental potency of PSCs. Furthermore, PSCs with different pluripotency levels provide resources to decipher the regulatory mechanisms or pluripotency markers. Following this principle, we previously evaluated the pluripotency levels of induced pluripotent stem cells (iPSCs) by 4N assay and identified the activation of Dlk1-Dio3 region as a marker for fully pluripotent iPSCs. Recently, we have evaluated the in vivo developmental potential of rat and monkey embryonic stem cells (ESCs) by 2N and 4N assays. We found that the rat ESCs could also produce viable rats by 4N as mouse ESCs, but this capability of rat ESCs was more unstable compared with mouse ESCs. Moreover, monkey ESCs can also form chimeric fetuses with contribution to all three germ layers after being converted to a “naïve-like” state, yet unlike the rodent ESCs with robust chimera contribution. To understand the species-specific differences in pluripotency of ESCs, we produced a new cell type, the so called “allodiploid ESCs” containing one set of mouse genome and another set of rat genome using the haploid stem cell technology, which can serve as new resources to study the species-specific differences. We found that the differential expression of Wnt3a and Bmp4 between mouse and rat ESCs may contribute to their differences of pluripotency maintenance. We hope that these PSCs with defined pluripotency levels can provide a step forward toward understanding the operating mechanisms of pluripotency, and can promote the translation of regenerative medicine.

NAIVE PLURIPOTENT STEM CELLS DISPLAY MOLECULAR SIGNATURES OF THE HUMAN PREIMPLANTATION EMBRYO

Theunissen, Thorold[1], Friedli, Marc[2], He, Yupeng[3], Planet, Evarist[2], Oneil, Ryan[3], Markoulaki, Styliani[1], Pontis, Julien[2], Wang, Haoyi[1], Iouranova, Alexandra[2], Imbeault, Michaël[2], Duc, Julien[2], Cohen, Malkiel[1], Wert, Katherine[1], Castanon, Rosa[3], Zhang, Zhuzhu[3], Huang, Yanmei[1], Nery, Joseph[3], Trono, Didier[2], Ecker, Joseph[3] and Jaenisch, Rudolf[1]

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Significant interest has been devoted to the isolation of human pluripotent stem cells displaying the naive state of mouse embryonic stem cells (ESCs). We previously took a systematic approach by screening a diverse library of kinase inhibitors for the ability to maintain activity of the distal enhancer of OCT4. Through iterative screening we identified a combination of five kinase inhibitors that, together with LIF and Activin A (5i/L/A), enabled the conversion of pre-existing human ESCs to the naive state in the absence of exogenous transgenes. These inhibitors generate human pluripotent cells in which transcription factors associated with the ground state of pluripotency are highly upregulated and bivalent chromatin domains are depleted. However, to what extent naive human cells isolated in culture resemble pluripotent cells in vivo remains unclear. Here we present three lines of evidence indicating that naive pluripotent stem cells generated in 5i/L/A share defining molecular signatures with the human preimplantation embryo. First, a comprehensive analysis of the transposcriptome shows that naive human ESCs share a unique retroelement expression profile with cleavage stage embryos, which differs substantially from both primed cells and previously reported naive-like cells. Second, base pair-resolution mapping of the methylome revealed that induction of naive pluripotency is accompanied by a genome-wide depletion in CpG and non-CpG methylation that is reversible upon differentiation except at imprinted regions. Third, allele-specific analysis demonstrates that female naive cells exhibit an X chromosome signature of the human preimplantation embryo. Finally, we use a sensitive assay for human mitochondrial DNA to show that naive human ESCs generated with various protocols rarely contribute to interspecies chimeras after injection into mouse morula or blastocyst stage embryos. In the absence of an in vivo assay for developmental competency, a rigorous comparison with the preimplantation embryo using unbiased genome-level transcriptional and epigenetic parameters provides the most stringent assessment of naive human pluripotency. Our work provides a set of molecular benchmarks for evaluating the developmental identity of distinct human pluripotent states captured in vitro.

Funding Source: Simons Foundation, NIH, Swiss National Science Foundation, European Research Council, Wellcome Trust, Foundation Bettencourt Award, Association pour la Recherche sur le Cancer (ARC) and the Fonds de la Recherche en Santé du Québec.

SINGLE-CELL RNA-SEQ REVEALS LINEAGE FORMATION AND X-CHROMOSOME DOSAGE COMPENSATION IN HUMAN PREIMPLANTATION EMBRYOS

Lanner, Fredrik, Petropoulos, Sophie, Edsgärd, Daniel, Reinius, Björn, Deng, Qiaolin, Panula, Sarita, Codeluppi, Simone, Plaza Reyes, Alvaro, Linnarsson, Sten and Sandberg, Rickard

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Mouse studies have been instrumental in forming our current understanding of early cell-lineage decisions, however similar insights into the early human development are severely limited. Here we present a comprehensive transcriptional map of human embryo formation, including the sequenced transcriptomes of 1,529 individual cells from 88 human preimplantation embryos. These data show that cells undergo an intermediate state of co-expression of lineage-specific genes, followed by a concurrent establishment of the trophectoderm, epiblast and primitive endoderm lineages, which coincide with blastocyst formation. Female cells of all three lineages undergo X-chromosome dosage compensation prior to implantation. In contrast to the mouse, XIST is transcribed from both alleles throughout the progression of this expression dampening, and X-chromosome genes maintain biallelic expression while dosage compensation proceeds. We envision broad utility of this transcriptional atlas in future studies on human development as well as in stem cell research.

Funding Source: Swedish Research Council, Ragnar Söderberg Foundation, Swedish Foundation for Strategic Research, European Research Council, Åke Wibergs Foundation and Mats Sundin Fellowship in Human Development.

HUMAN-MOUSE CHIMERISM VALIDATES HUMAN STEM CELL PLURIPOTENCY

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Pluripotent stem cells (PSCs) are defined by their capacity to differentiate into all three tissue layers that comprise the body and to renew themselves through unlimited proliferation. Chimera formation, generated by stem cell transplantation to the embryo, is a stringent assessment

of stem cell pluripotency. As such, mouse embryonic stem cells (mESCs) form chimeras with the pre implantation mouse embryo with high efficiency, demonstrating that mESCs can contribute to all tissues of the resulting mouse. However, the ability of human pluripotent stem cells (hPSCs) to form embryonic chimeras remained in question. A resolution of this key problem was critical to secure the utility of hPSCs for stem cell science and for regenerative medicine applications. Our experimental objective was to determine the capacity of human pluripotent stem cells (hPSCs) and their mesodermal progeny to participate in early mouse embryo development. We show using a stage-matching approach that human induced pluripotent stem cells (hiPSCs), human embryonic stem cells (hESCs), and their in vitro derived mesodermal progeny have the capacity to participate in normal mouse development when transplanted into gastrula stage embryos. Both hPSCs (hiPSCs and hESCs) and their in vitro differentiated progeny form interspecies chimeras with high efficiency, whereby they colonize the embryo in a manner predicted from classical developmental fate mapping. Pivotally, hPSCs integrate and differentiate into each of the three primary tissue layers; endoderm, mesoderm, ectoderm. Thus we show that hPSCs have the capacity to participate in normal development when transplanted into gastrula stage mouse embryos, providing in vivo functional validation of hPSC pluripotency. In sum, hPSCs and their mesodermal derivatives can incorporate into mouse embryos in a stage- and location-specific (synchronous, orthotopic) manner. This novel approach enables the study of cell fate decisions and plasticity of tissue specific progenitors during normal development. This faithful recapitulation of tissue-specific fate post-transplantation underscores the functional potential of hPSCs and provides evidence that human-mouse interspecies developmental competency can occur.

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SINGLE CELL RNA SEQUENCING UNCOVERS CELL CYCLING MARKERS OF LINEAGE SPECIFICATION DURING HUMAN EMBRYONIC STEM CELL DIFFERENTION

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Pluripotent stem cells provide a powerful system to dissect the underlying molecular dynamics that regulate cell fate changes during mammalian development. Here, we use single cell RNA sequencing during differentiation of human embryonic stem cells towards the three germ layers to study the population dynamics of cells during lineage specification. We analyzed the transcriptomes of more than a thousand individual cells and identify distinct subpopulations and markers during stem cell differentiation. Transcritome-wide single cell data further allowed us to study the relationship of thousands of cellular markers at unprecedented temporal resolution. We infer the cell cycle phase of individual cells and find that the fraction of early and late G1 cells increases during differentiation towards endoderm/mesoderm or ectoderm fate, respectively. These distinctly regulated phases of the cell cycle activate key regulatory programs for cell fate progression. Taken together our data shows that single cell RNA sequencing is a powerful tool for identifying the molecular markers that guide exit from human pluripotency and cellular specification in a cell cycle dependent manner.

HUMAN IPS CELLS, PLURIPOTENCY AND DEVELOPMENTAL POTENTIAL

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The development of the iPS cell technology has revolutionized our ability to study human diseases in defined in vitro cell culture systems. However, a number of issues need to be resolved and will be addressed in this talk. 1. State of pluripotency: Mouse ES and iPS cells appear to represent a naive state of pluripotency corresponding to the inner cell mass (ICM), whereas human ES or iPS cells represent the "primed" state corresponding to mouse EpiSCs. A major question is whether the naive state exists in the human system. We have, using an unbiased screening approach, generated ES cells that display a transcriptome similar to the human cleavage embryo. 2. Disease modeling and iPS cells: A major incentive of the iPS cell system is to model human diseases in the Petri dish. However, a serious concern is whether a 2D in vitro system can faithfully model complex human diseases. We are, therefore, using a 3D organoid system to study human brain development and CNS disorders. Ultimately, human diseases need to be studied under in vivo conditions. To this end we are establishing various approaches to generate mouse – human chimeras. 3. Neural Crest chimeras: To study the potential of committed stem to functionally integrate into the developing mouse embryos we have differentiated mouse, rat and human ESCs or iPSCs into NCCs that were injected in utero into E8.5 albino wild-type and c-Kit mutated W^{sh}/W^{sh} embryos. Both the mouse and human NCCs migrated laterally under the epidermis and ventrally into deeper regions of the embryo. Importantly, analysis of postnatal animals derived from mouse, rat or

human NCC-injected embryos displayed coat color pigmentation from the donor cells. Our results demonstrate that NCCs from different species can integrate into the developing mouse embryo, migrate through the dermis and differentiate into functional pigment cells in postnatal mice. The generation of postnatal mouse/human chimeras carrying differentiated and functional human cells allows for a novel experimental system in which to study human diseases in an in vivo, developmentally-relevant environment

THURSDAY 23 JUNE, 13:15 – 15:15

CONCURRENT I: DISEASE MODELING I

Level 2, Rooms 2020/2022

USING STEM CELL AND GENE EDITING TECHNIQUES TO STUDY AND TREAT AGING-ASSOCIATED DISORDERS

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Hutchinson-Gilford progeria syndrome (HGPS) and Werner syndrome (WS) are two human premature aging disorders with features that closely recapitulate the characteristics of human aging. Mutations in LMNA and WRN genes lead to aberrant splicing product progerin and protein loss in HGPS and WS, respectively. Study on how genetic alteration leads to the cellular and organismal phenotypes of premature aging will provide clues to the molecular mechanisms underlying physiological aging and facilitate our understanding of the molecular pathways contributing to healthy aging. We have generated induced pluripotent stem cells (iPSCs) from fibroblasts obtained from patients with HGPS, Parkinson's disease (PD), Amyotrophic lateral sclerosis (ALS), Fanconi Anemia (FA), and Xeroderma pigmentosum (XP). Further, using targeted gene correction technique, we successfully corrected the mutated LMNA in HGPS-iPSCs, mutated LRRK2 in PD-iPSCs, mutated FANCA in FA-iPSCs, and mutated SOD1 and FUS in ALS-iPSCs. Finally, by using targeted "knock-out" and "knock-in" techniques, we generated WS-, FA-, PD-, and Glioblastoma multiforme (GBM)-specific human stem cells with relevant pathogenic mutations. Upon differentiation of these disease-specific pluripotent stem cells to specific somatic cell types, the latter recapitulate aging/disease-associated and tissue-specific phenotypic defects. Altogether, these studies provide important platforms for studying aging/disease mechanisms and developing new therapies.

AN EPIDEMIOLOGICAL APPROACH TO IDENTIFY BIOMARKERS OF LEFT VENTRICULAR HYPERTROPHY USING AN HIPSC-CM COHORT

Li, Wenli[1], Aggarwal, Praful[1], Turner, Amy[1], Matter, Andrea[1], Arnett, Donna[2], Lewis, Cora[3], Hunt, Steven[4,5], Gu, Charles[6] and Broeckel, Ulrich[1]

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Human iPSC (hiPSC) derived cells have become an important tool to study molecular disease mechanisms. For complex disease modeling using hiPSCs, there is still uncertainty regarding sample selection and analysis methods. Here, we report an innovative approach to identify biomarkers of left ventricular hypertrophy (LVH) using a collection of hiPSC derived cardiomyocytes (hiPSC-CMs). As an independent risk factor for cardiovascular diseases, LVH represents pathological increase of LV mass with high prevalence in African Americans (AA). Given the limited understanding of molecular mechanism of LVH, novel biomarkers will most likely lead to improved diagnosis and future drug development. Our study is built on a large family-based epidemiology cohort (NHLBI HyperGEN) with 2407 participants designed to identify variant and biomarkers of LVH. With a genetic and phenotypic prioritization strategy, we generated hiPSC-CM lines from 250 donors. We established an in vitro assay of LVH by stimulation with Endothelin-1. To identify biomarkers linked to donor LV mass, we performed RNA-seq analysis combined with multivariate linear regression and mixed model regression analyses. We present the analysis of 23 hiPSC donors from the AA participants with either high or low LV mass as determined by echocardiography.First, we identified 407 differentially expressed genes ($p<0.05$) between the two LV phenotype groups. With donor LV mass as the response variable, our predictor variables included established donor risk factors as well as cellular experimental factors (ET1-stimulation status and iPSC-CM cell plating density). We identified seven novel biomarkers with significant association to the donor LV mass (p-value <=0.0001). Interestingly, four of these genes (MYH11, PGM2, TMEM198 and ENOX2) showed robust response to ET-1 stimulation. Our study demonstrated an innovative method for complex disease modeling using hiPSC technology. We identified novel biomarkers characteristic of both the cellular features of an hiPSc-CM model and donor LV mass. While functional follow up on these genes will be necessary, our method can be applied to identification of novel cellular biomarkers for complex diseases.

IDENTIFICATION OF THERAPEUTIC TARGETS AND PATHOGENIC MECHANISMS FOR C9ORF72 ALS USING PHENOTYPIC CHEMICAL SCREENING

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Expansion of a GGGGCC repeat in C9orf72 recently emerged as the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), making it a key therapeutic target. However, the neurodegenerative mechanisms underlying C9orf72 ALS/FTD are unclear, limiting the identification of therapeutic strategies. To identify potential therapeutic targets and delineate pathogenic mechanisms, we established a model of C9orf72 ALS using induced motor neurons (iMNs) generated by transcription factor-based reprogramming and performed a chemical genetic screen using neuron survival as a readout. C9orf72 patient iMNs, but not induced dopaminergic neurons, undergo accelerated degeneration (3 patients, 3 controls, p=.002) and possess the hallmark pathology of C9orf72 ALS. Removing the repeat expansion CRISPR/Cas9 editing fully rescues iMN survival. Thus, C9orf72 iMNs faithfully model ALS disease processes. From a screen of 1000 bioannotated small molecules, we identified three classes of molecules that rescue C9orf72 patient iMN survival without affecting the survival of controls (PDGF inhibitors, S1P1 receptor agonists, and PIKFYVE kinase inhibitors), as well as one class that specifically accelerates C9orf72 iMN degeneration (PI3-kinase inhibitors). We find that PDGF inhibition, S1P1 receptor activation, and PIKFYVE inhibition rescue C9orf72 iMN survival by reversing a defect in endocytosis that causes aberrant upregulation of glutamate receptors on iMNs. By restoring proper glutamate receptor homeostasis, which is maintained in neurons through endocytosis, these three classes of molecules prevent C9orf72 iMN degeneration by excitotoxicity, which we find to be the major cause of neurodegeneration in our model. Interestingly, all three small molecules exert their effect by activating PI3-kinase, which directly stimulates endocytosis. Verifying the relevance of these findings to patients, glutamate receptors are significantly upregulated on motor neurons in postmortem tissue from both patients and C9orf72 mutant mice, and neurons in C9orf72 mice undergo hyperactivation when exposed to glutamate in vivo. Thus, our results highlight the importance of early endosomal trafficking in C9orf72 ALS pathogenesis, and identify several potential therapeutic targets.

DEVELOPMENTAL AND TUMORIGENIC ASPECTS OF TRILATERAL RETINOBLASTOMA MODELED IN HUMAN EMBRYONIC STEM CELLS

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Human embryonic stem cells (hESCs) have been successfully used to model genetic disorders, providing an in vitro platform for understanding mechanisms underlying diseases and finding ways to treat them. Trilateral retinoblastoma is a genetic condition in which bilateral retinoblastoma, the most common primary malignant intraocular tumor in children, is associated with an intracranial primitive neuroectodermal tumor. This mostly fatal disease is caused by a combination of a somatic mutation and a germline mutation in the retinoblastoma 1 (RB1) gene. Using CRISPR-Cas9 we generated RB1 homozygous null hESCs, a condition that is thought to be embryonic lethal. Despite having a normal karyotype and typical morphology, these pluripotent cells displayed a distinct gene expression pattern with alterations in RB1 targets. RNA-sequencing also revealed a substantial downregulation of mitochondrial gene expression, which was traced back to a severe lack of functional mitochondria in mutant cells, which is similarly observed in poorly differentiated retinoblastoma tumors. Teratomas derived from RB1-null hESCs are significantly larger than control tumors, with a remarkable expansion of neural tissues, mimicking the generation of neural tumors in trilateral retinoblastoma patients. In parallel, RNA-sequencing and immunofluorescence staining of these teratomas showed an abolishment of epidermal tissues, another ectodermal descendent. Using transcription-factor binding site analysis of the genes altered by RB1 deletion, we found that this ectodermal-developmental shift might be mediated by ZEB1, a key regulator of the epithelial-mesenchymal transition found to be regulated by RB1. This observation could explain, at least in part, the embryonic lethality of biallelic RB1 deletion. We also used our model to screen for compounds specifically targeting RB1-null mutants. A large toxicity screen of FDA approved chemotherapies revealed that RB1 mutant hESCs are resistant to several currently used cancer treatments. In contrast, these cells were more susceptible to one compound, suggesting it might be useful in treating trilateral retinoblastoma patients. Our work sheds light on both developmental and tumorigenic aspects of trilateral retinoblastoma and suggests a new platform to develop drugs to cure it.

MODELING OF SEVERE METABOLIC GENETIC DISEASES IN VITRO USING GENOME EDITING AND HUMAN PLURIPOTENT STEM CELL DIFFERENTIATION TO VASCULAR ENDOTHELIAL CELLS

Roudnicky, Filip[1], Zhang, David Jitao[1], Dernick, Gregor[1], Christensen, Klaus[1], Staempfli, Andreas[1], Bordag, Natalie[2], Wagner Golbs, Antje[2], Graf, Martin[1], Meyer, Claas Aiko[1], Cowan, Chad[3] and Patsch, Christoph[1]

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The use of human pluripotent stem cells (hPSCs) for in vitro disease-modeling is limited by the lack of robust and efficient protocols for the differentiation of relevant adult cell types. Recently, we have reported a method to generate vascular endothelial cells from hPSCs. This novel and robust protocol in conjunction with use of programmed nucleases allowed us to model severe metabolic genetic disease in vitro. Vascular endothelium is considered to have an important role in development of metabolic insulin resistance. Therefore we have focused on two rare genetic diseases, showing insulin resistance, with mutations in AKT2: loss of function mutation or dominant active mutation (Glu17Lys (E17K)). Using TALENs we have previously generated an allelic series of isogenic hPSC lines with wild-type AKT2, knockout of AKT2, or a single $AKT2^{E17K}$ allele. We have successfully differentiated those hPSC lines to vascular endothelial cells in vitro. We have evaluated the RNA expression, metabolome and secretome of these lines and identified an increase in inflammation in knockout of AKT2 and $AKT2^{E17K}$ lines. Using leukocyte adhesion assay we could show an increase in leukocyte binding to AKT2 and $AKT2^{E17K}$ lines compared to wild-type AKT2. $AKT2^{E17K}$ line showed striking increase in secretion of inflammatory mediators: IL-6 (5-fold), IL-8 (2.2-fold), MCP-1 (2.8-fold) and PAI-1 (1.8-fold) compared to wild-type AKT2. These results could suggest that vascular dysfunction due dysregulated insulin signaling may contribute to coronary artery disease. Our further studies will be designed to elucidate this connection.

CHALLENGES OF IMMATURITY AND PROLIFERATION IN USING HPSC-DERIVED CARDIOMYOCYTES AS DISEASE MODELS

Mummery, Christine L., Birket, Mathew, van Meer, Berend, Ribeiro, Marcelo, Passier, Robert, Bellin, Milena, Orlova, Valeria, Davis, Richard, Freund, Christian, Kosmidis, George and Tertoolen, Leon

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The first beating cardiomyocytes were derived from human embryonic stem cells in 2002 and the differentiation protocols proved directly transferable to induced pluripotent stem cells (hiPSC). Understanding the underlying developmental mechanisms that control differentiation of pluripotent cells to their derivatives and mimicking these in defined culture conditions in vitro has proven essential for moving the field forward. This has been aided by a valuable series of transgenic lineage reporter hPSC lines. From initial methods that yielded only ventricular like cells, we can now specify atrial and pacemaker fates and derive epicardial-like cells that normally cover the outer surface of the heart. Heart cells from hPSC are an area of growing interest as a way of modelling cardiac and vascular diseases with view to understanding underlying mechanism for drug target identification. Challenges to applications of these cells in disease modelling, drug discovery and safety pharmacology however remain their limited expansion in culture and immature phenotype after differentiation. We discuss approaches to addressing this through culture modification, complex cell combinations and biophysical strain and show examples of the impact on determining the phenotype of hiPSC-derivatives in genetic diseases of the cardiovascular system.

THURSDAY 23 JUNE, 13:15 – 15:15

CONCURRENT I: STEM CELL PLASTICITY

Level 2, Room 2004

STEM CELLS AND PLASTICITY IN THE TESTIS

Matunis, Erika L.[1], Akeju, Miriam[1], de Cuevas, Margaret[1], Greenspan, Leah[1], Hasan, Salman[1], Hetie, Phylis[2], Li, Yijie[1] and Ma, Qing[1]

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Tissue or adult stem cells reside in specific local microenvironments, or niches, where signals from nearby cells and substrates promote stem cell maintenance. Spermatogonial stem cells in the testis provide a lifetime supply of sperm, making this tissue an excellent model for studying stem cells in vivo. Each Drosophila testis contains a well-characterized niche comprised of a cluster of quiescent somatic cells called the hub, to which spermatogonial (or germline) and somatic stem cells adhere. Some of the first descriptions of the types of stem cell plasticity in vivo, such as dedifferentiation and transdifferentiation, were demonstrated in this system, and are now known to occur more generally. For example, hub cells are also a reserve pool of somatic stem cells that are activated upon damage to the niche: genetic ablation of somatic stem cells causes hub cells to transdifferentiate into new, functional somatic stem cells to replace the missing cells. Damage-induced transdifferentiation is transient, however, and hub cells return to quiescence when the niche regains a full complement of stem cells. This suggests that

local signals, likely from somatic stem cells, converge with the cell cycle machinery in hub cells to actively promote quiescence under normal conditions. Consistent with this hypothesis, hub cell transdifferentiation is not observed during normal aging. However, testes where transdifferentiation has occurred develop a surprising age-related phenotype: multiple ectopic niches full of proliferating stem cells appear throughout the tissue, disrupting it entirely. Our work suggests that the ability of quiescent cells to transdifferentiate into stem cells in response to damage may be a general property of niches, and provides a novel paradigm to study mechanisms regulating the maintenance of cell identity and niche numbers with age in adult stem cell-based tissues.

MATRIX TENSION DIRECTS WNT-DEPENDENT MESODERM DIFFERENTIATION OF HUMAN EMBRYONIC STEM CELLS

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Regenerative medicine is predicated on understanding the mechanisms regulating development and applying these conditions to direct stem cell fate. Embryogenesis is dictated by morphogen gradients and guided by cell-cell and cell-matrix interactions, however, our understanding of the microenvironmental signals that are required to create and shape the developing embryo is far from complete. By growing hESCs on extracellular matrices with defined elastic moduli and specified tissue geometries, we have identified physical and mechanical parameters that, combined with biochemical cues, dramatically enhance Wnt-dependent mesoderm differentiation and the EMT associated with mesoderm specification during gastrulation. The organization of hESC colonies and the cytoarchitecture of individual cells vary as a function of stiffness, which affects the stabilization and localization of proteins associated with adherens junctions and focal adhesions. We found that hESCs grown on a compliant matrix exhibited reduced focal adhesion-mediated integrin signaling and stabilized cell-cell adhesions to increase the intracellular ß-catenin pool, enabling cells to become effectively primed for differentiation. Upon morphogen-stimulated induction of mesoderm differentiation, Src-driven ubiquitination of E-cadherin by Cbl-like ubiquitin ligase enabled ß-catenin transcriptional activity to initiate and reinforce mesoderm specification. Differentiation was compromised in hESCs grown on a stiff matrix due to elevated integrin-dependent Src activity that precociously stimulated E-cadherin endocytosis and ß-catenin proteasomal degradation. Striking compliance-based changes in cytoarchitecture thus regulate functional synergy between mechanical cues and morphogen gradients, providing a mechanism for how mechanical perturbations can translate into a dramatically altered transcriptional profile in the context of embryonic stem cell differentiation. This indicates a tunable parameter that can be used to enhance pluripotent cell-based differentiation protocols, while also providing insights into the biophysical mechanisms underlying the cell fate specification and spontaneous self-organization required for coordination of embryonic development.

Funding Source: We would like to acknowledge funding from CIRM grant RB5-07409 and CIRM training grant TG2-01153.

ATM-P53 ACTIVATION BLOCKS HEPATIC CONVERSION BY SENSING CHROMATIN OPENING

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Lineage conversion by expression of lineage-specific transcription factors is a process of epigenetic remodeling that has low efficiency. The mechanism by which a cell resists lineage conversion is largely unknown. Using hepatic-specific transcription factors Foxa3, Hnf1a and Gata4 (3TF) to induce hepatic conversion in mouse fibroblasts, we showed that 3TF induce strong activation of the ATM-p53 pathway, which leads to proliferation arrest and cell death, and it further prevents hepatic conversion. Notably, ATM activation, independent of DNA damage, responds to chromatin opening during hepatic conversion. By characterizing the early molecular events during hepatic conversion, we found that the SWI/SNF chromatin remodeling complex mediates chromatin opening and ATM activation by facilitating ATM recruitment to the open chromatin regions. These findings shed light on cellular responses to hepatic conversion by revealing a function of the ATM-p53 pathway in sensing chromatin opening.

INFLUENCE OF CHOLESTEROL/ CAVEOLIN-1/CAVEOLAE HOMEOSTASIS ON HUMAN MESENCHYMAL STEM CELL MEMBRANE PROPERTIES AND ADHESIVE CHARACTERISTICS

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Adult mesenchymal stem cells (MSCs) are considered an important resource for tissue repair. Their utilization in regenerative medicine depends on understanding the mechanisms driving their responsiveness to external stimuli. It is likely that an initial determinant of stem cell responsiveness to external stimuli is the organization of signaling molecules in cell membrane rafts. Membrane rafts fall into two broad categories, non-caveolar and caveolar, based on the absence or presence, respectively, of caveolin proteins. We have previously demonstrated that expression of caveolin-1 (Cav-1) increases in MSCs induced to undergo osteogenic differentiation, and knockdown of Cav-1 expression significantly enhances MSC proliferation and osteogenic differentiation. These results suggest that Cav-1 may act to regulate the differentiation and self-renewal of MSCs. In this study, we investigated the effects of perturbations in cholesterol/Cav-1/caveolae homeostasis on membrane properties and adhesive characteristics of human bone marrow-derived MSCs. We have generated 5 different MSC sub-populations: (i) control MSCs, (ii) cholesterol-depleted MSCs, (iii) cholesterol-enriched MSCs, (iv) MSCs transfected with control, non-specific siRNA, and (v) MSCs transfected with Cav-1 siRNA. Each cell group was analyzed for perturbation of cholesterol status and Cav-1 expression. Our results demonstrated that perturbations in cholesterol/Cav-1 levels affected the membrane properties of MSCs. Cholesterol supplementation resulted in increased cell membrane cholesterol and decreased membrane fluidity, and elevated localization of caveolae and Cav-1 to the cell membrane, with changes in surface levels of ß1 integrin, an important mediator of cell adhesion function. Conversely, knockdown of Cav-1 expression caused a parallel decrease in the number of cell surface caveolae, and decreased delivery of cholesterol to the cell membrane, thus increasing membrane fluidity. Cells with depleted Cav-1 expression exhibited elevated cell surface integrins. These preliminary results suggest that cholesterol/Cav-1/caveolae in MSC homeostasis regulates aspects of the cell membrane important to substrate sensing and cell adhesion, and influences MSC response to its microenvironment and external stimuli.

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MICROENVIRONMENT ENGINEERING TO AUGMENT MESENCHYMAL TO EPITHELIAL TRANSITIONS AND CELLULAR REPROGRAMMING

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The derivation of cells from earlier developmental states through reprogramming a patient's cells could transform medicine by enabling genetic correction, and autologous cellular therapies. However, current reprogramming strategies continue to suffer from inefficiency, and very little is known about the influence of the cell culture substrate. Most methods are performed on rigid plastic which leads to heterogeneity in cellular organization and proliferation. Motivated by the architecture of the early embryo where pluripotency is first established, we engineered designer cell culture materials to explore how matrix composition, substrate mechanics and tissue geometry would influence de-differentiation. Soft hydrogels conjugated with a combination of laminin and collagen were found to promote the expression of markers associated with a mesenchymal-to-epithelaial transition within one week, and changes in the acetylation and methylation state at H3K9. Constraining tissue geometry using micropatterning led to the formation of colony-like 3D structures with enhanced epithelial character, which depended on perimeter geometric features. Introduction of embryonic stem cell media to the microengineered colonies initiated pluripotency signaling networks as determined through nuclear morphology, proliferation rates, and endogenous Oct4 and Sox2 expression. Interestingly, with some combinations of matrix protein and stiffness, MEFs adopted a neuronal like morphology accompanied by expression of ß3-tubulin and microtubule associated protein 2 (MAP2), suggesting that initiation of direct reprogramming may occur through tuning matrix properties alone in the absence of lentivirus. In addition to evidence of de- and trans-differentiation, we will discuss other ongoing investigations using this platform to de-differentiate cancer cells through controlled biochemical and biophysical cues. Taken together, our studies demonstrate plasticity in response to extracellular matrix parameters, which may be harnessed to steer somatic cells to earlier developmental states and across germ layers.

ESTABLISHMENT OF HISTONE MODIFICATIONS IN PRE-IMPLANTATION MOUSE EMBRYOS

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Histone modifications play critical roles in regulating the expression of developmental genes during embryo development in mammals. However, genome-wide analyses of histone modifications in pre-implantation embryos have been impeded by technical difficulties and scarcity of the required materials. By using a small-scale chromatin immunoprecipitation sequencing (ChIP-seq) method, for the first time, we mapped the genome-wide profile of histone H3 lysine 4 trimethylation (H3K4me3) and histone H3 lysine 27 trimethylation (H3K27me3), which are associated with gene activation and repression, respectively, in mouse pre-implantation embryos. We found that the re-establishment of H3K4me3, especially on promoter regions, occurs much more rapidly than that of H3K27me3 following fertilization, which is consistent with the major wave of zygotic genome activation (ZGA) at the 2-cell stage. Furthermore, H3K4me3 and H3K27me3 possess

distinct features of sequence preference and dynamics in pre-implantation embryos. Although H3K4me3 modifications exist constantly on transcription start site (TSS) regions, the breadth of the H3K4me3 domain is a highly dynamic feature. Interestingly, the broad H3K4me3 (wider than 5 kb) is associated with higher transcription activity and cell identity not only in pre-implantation embryos but also in the process of deriving embryonic stem cells (ESCs) from the inner cell mass (ICM) and trophoblast stem cells (TSCs) from the trophectoderm (TE). Down-regulation of a H3K4me3 demethylase Kdm5b can greatly widen H3K4me3 peaks and causes embryo developmental defects. Compared to ESCs, we found that the bivalency (co-occurrence of H3K4me3 and H3K27me3) in early embryos is much less and unstable. In addition to H3K4me3 and H3K27me3, we also mapped H3K9me3 in both normal fertilization-derived embryos and somatic cell nuclear transfer (SCNT)-derived embryos. We found that the successful removal of H3K9me3 plays an important role in zygotic genome activation during 2-cell stage.

THURSDAY 23 JUNE, 13:15 – 15:15

CONCURRENT I: MUSCLE STEM CELLS

Level 2, Room 2002

DEFINING THE DEVELOPMENTAL AND FUNCTIONAL POTENTIAL OF HUMAN PLURIPOTENT STEM CELL DERIVED SKELETAL MUSCLE PROGENITOR CELLS

Pyle, April

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Human induced pluripotent stem cell (hiPSC) derived skeletal muscle offers enormous potential for disease modeling, screening and use in cell-based therapy for muscle wasting disorders. Adult skeletal muscle contains self-renewing stem cells called satellite cells (SCs), whose function is to repair damaged tissue. In the most common pediatric muscle wasting disorder Duchenne Muscular Dystrophy (DMD), the endogenous muscle stem cells become exhausted or non functional due to continuous rounds of degeneration and regeneration. This results in progressive muscle wasting and eventually patient death. We have developed approaches to generate CRISPR corrected skeletal muscle progenitor cells (SMPCs) derived from DMD-hiPSCs. Delivery of corrected SMPCs could be used to reconstitute the endogenous SC niche and provide an autologous source of self-renewing stem cells for patients with DMD. One obstacle is that hiPSC-SMPCs likely represent an early stage in muscle development and have poor in vitro differentiation and in vivo engraftment potential. Generation of SMPCs from hiPSCs requires specification through the somite, the origin of most skeletal muscle cells in the body. SMPCs are generated in waves of myogenic progenitor cells that eventually give rise to SCs in the adult. We have performed RNA-sequencing of progenitor cells during human somitogenesis to improve hiPSC derived somite generation. Further we have profiled hiPSC-SMPCs to fetal and adult SCs to identify candidates important for myogenic specification and maturation of hiPSC-SMPCs with improved in vitro and in vivo differentiation potential. Improving our understanding of hiPSC myogenic differentiation will enhance our ability to generate an engraftable SC with potential for use in muscle wasting disorders including muscular dystrophy and aging.

NOVEL INDUCER OF QUIESCENCE THAT AUGMENTS MUSCLE STEM CELL ENGRAFTMENT AND REGENERATION REVEALED BY PROTEIN LIBRARY SCREEN

Blau, Helen M.[1], Sampath, Srinath[1,2], Sampath, Srihari[1,2], Ho, Andrew[3], Corbel, Stephane[1,2] and Schmedt, Christian[1,2]

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Knowledge of the regulators that maintain a quiescent state is lacking, yet such cues are crucial to maintaining a muscle stem cell reservoir that can meet the needs of regeneration throughout life. Regeneration of skeletal muscle is dependent on the function of tissue-resident muscle stem cells (MuSC), known as satellite cells. MuSC dysfunction is central to muscle pathophysiology, including in age-associated loss of muscle regenerative capacity and congenital disorders such as Duchenne muscular dystrophy. Despite the central role of satellite cells in muscle regeneration, the signals controlling the balance between muscle stem cell quiescence, proliferation, and differentiation remain incompletely understood. To discover regulators of quiescence we developed a novel in vivo imaging-based screening strategy allowing identification of proteins that do not induce in vitro proliferation, but instead maintain MuSCs in a non-mitotic state, poised for rapid and robust expansion upon transplantation. We demonstrate that Oncostatin M, a member of the IL6 family of cytokines, induces reversible exit from the cell cycle and induction of a global transcriptional program significantly enriched within a newly established satellite cell "quiescence signature". Genetic ablation of the Oncostatin M receptor in mice demonstrates that signaling via this Gp130 receptor family member is essential for maintenance of satellite cell quiescence, and for proper skeletal muscle regeneration in vivo. Given that aberrant

activation and exhaustion of stem cells is seen in a variety of disorders, this cytokine constitutes an attractive therapeutic target in muscle disease states.

INDUCIBLE DEPLETION OF SATELLITE CELLS ACCELERATES AGE-RELATED MOUSE NEUROMUSCULAR JUNCTION DETERIORATION

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Aging is accompanied by a gradual loss of skeletal muscle size and function, known as sarcopenia. Although sarcopenia profoundly contributes to frailty and loss of mobility in the elderly, the reasons for age-related skeletal muscle decline remain elusive. Skeletal muscle maintenance depends on the integrity of neuromuscular junctions (NMJs), sites of motor innervation that deteriorate with age. Aging is also associated with loss in muscle resident stem cell, satellite cell (SC) number and function. However, any interrelationship between age-related SC and NMJ decline remains ambiguous. To elucidate the fates and roles of SCs and derived progenitors at deteriorating NMJs with age, we employed an inducible Cre recombinase under the control of Pax7 regulatory elements to genetically label or deplete SCs. We found contribution of indelibly labeled SCs to muscle fibers in the vicinity of aging NMJs. Although SC depletion did not lead to additional loss of skeletal muscle mass, it was sufficient to accelerate age-associated decline of nerve evoked muscle twitch responses. Moreover, the depletion of SCs from aging skeletal muscle resulted in an earlier onset of 1) deficits in NMJ innervation, and 2) NMJ-associated matrix deposition, consistent with fibrosis. Collectively our findings reveal that loss of SC derived contributions at aging NMJs accelerates age-related NMJ deterioration.

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SYSTEMIC REGULATION OF QUIESCENT STEM CELL FUNCTION AND REGENERATIVE POTENTIAL

Rodgers, Joseph T. [1] and Rando, Thomas A.[2]

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Adult stem cells possess a unique ability to exist a non-cycling, quiescent state. The primary role of quiescence is to preserve stem cell function until the stem cell is activated to participate in tissue repair or homeostasis. We have recently found that quiescent stem cells dynamically regulate their functional properties in response to environmental cues and that this regulation controls how stem cells respond to subsequent stimuli. Adult stem cells can cycle between at least two functionally distinct phases within quiescence; $G_{0,}$ a phase in which stem cells are deeply quiescent and resistant to activation cues, and $G_{Alert,}$ a phase in which quiescent stem cells are highly responsive to activation stimuli and have enhanced capacity to repair tissue damage. Within a stem cell, the transitioning between G_0 and G_{Alert} is controlled by mTORC1 signaling. Here, we report that systemic regulation of the Hepatocyte Growth Factor (HGF)-processing pathway is a mechanism that links physiologic stresses to the regulation of stem cell quiescence. Injecting animals with a component of the HGF-processing pathway, an active form of the serum protease Hepatocyte Growth Factor Activator (HGFA), is sufficient to induce the transition of stem cells from G_0 into G_{Alert}. Administering HGFA to animals prior to inducing a tissue injury dramatically reduces healing time and improves functional recovery. We propose that using stem cell Alerting factors to directly control quiescent stem cell function may be a therapeutic approach to improve tissue repair and recovery and to restore impaired healing in diabetes and aging.

Funding Source: NIA K99/R00 AG041764

PRESENTATION FROM LATE BREAKING ABSTRACTS

DEVELOPMENTAL PROGRESSION OF SKELETAL MUSCLE STEM CELLS IS MEDIATED BY AUTONOMOUS EXTRACELLULAR MATRIX REMODELING

Sacco, Alessandra[1], Tierney, Matthew[1], Gromova, Anastasia[2], Boscolo, Francesca[1], Sala, David[1], Spenle', Caroline[3] and Orend, Gertraud[3]

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Skeletal muscle stem cells (MuSC) exhibit distinct behavior during successive phases of developmental myogenesis. However, how their transition to adulthood is regulated is poorly understood. We show that fetal MuSC resist progenitor specification and exhibit altered division dynamics, intrinsic features that are progressively lost postnatally. Following transplantation, fetal MuSC more efficiently expand and contribute to muscle repair. Conversely, niche colonization efficiency increases in adulthood, indicating a balance between muscle growth and stem cell pool repopulation. Gene expression profiling identified several extracellular matrix (ECM) molecules preferentially expressed in fetal MuSC, including tenascin-C, fibronectin and collagen VI. Loss-of-function experiments confirmed their essential and stage-specific role in regulating MuSC function. Finally, fetal-derived paracrine factors were able

to enhance adult MuSC regenerative potential. Together, our studies revealed that fetal MuSC possess a remarkable regenerative potential through more efficient expansion, intrinsically regulating their behavior through the selective expression of ECM proteins to remodel their local microenvironment. The identified components of the fetal MuSC niche can be exploited as novel tools to direct adult muscle stem cell activity towards the immediate or long-term aspects of tissue repair, thus facilitating the development of novel regenerative medicine approaches for muscle wasting diseases.

Funding Source: SBPMDI start-up funds, Muscular Dystrophy Association MDA Grant 200845, NIH grants P30 AR06130303 and F31 AR065923-01, CIRM TG2-01162, and INSERM, University Strasbourg, INCa.

MUSCLE STEM CELL REGENERATIVE DECLINE WITH AGING

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Our group aims to understand the mechanisms regulating stem cell homeostasis and regenerative functions. Research is specially centered on stem cells of skeletal muscle (i.e., satellite cells). Recently, we have focused on two areas: 1) the functional decline of satellite cells with aging; and 2) the physiopathology of muscular dystrophies, with a specific interest in the contribution of inflammation and fibrosis to dystrophy progression. Concerning the first area, work from different laboratories has demonstrated that both environmental and cell-autonomous signals alter satellite cell regenerative potential with aging. I will discuss our latest results showing that satellite cells in their homeostatic quiescent state are equipped with quality control mechanisms to preserve their fitness, and how age-associate alterations in these protective mechanisms lead to stem cell loss of function and regenerative capacity.

THURSDAY 23 JUNE, 13:15 – 15:15

CONCURRENT I: CARDIAC DEVELOPMENT AND REGENERATION

Level 2, Rooms 2009/2011

MAKING ADULT CARDIOMYOCYTES FROM PLURIPOTENT STEM CELLS

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It has been a decade since Yamanaka and colleagues found a way to turn adult cells all the way back to pluripotent stem cells (PSCs), named induced PSCs (iPSCs). iPSCs can become any type of body cell in principle so there is tremendous enthusiasm for their use in disease modeling, drug discovery, and regenerative medicine. However, making iPSCs back to adult cells has been a tall order; although studies reported successful differentiation of iPSCs into specific cell types with their potential to model and treat human diseases, PSC-derived cells exhibit fetal-like characteristics and remain immature in a dish. This has emerged as a key obstacle for their application for late-onset disorders such as cardiomyopathy and Alzheimer's disease. To gain insights into cell maturation, my lab recently analyzed a large number of microarray datasets from early embryonic to adult hearts and established an atlas of gene expression, biological pathways, transcriptional regulators, and gene regulatory networks (GRNs). Moreover, using an in-vivo system, we were able to generate adult-like cells from PSCs and to model cardiomyopathy. This knowledge is expected to contribute our mechanistic understanding of cell maturation and may be used for PSC-based modeling of adult diseases.

TRANSGENE INDEPENDENT GENERATION AND ISOLATION OF FUNCTIONAL SINOATRIAL NODE PACEMAKER CELLS FROM HUMAN PLURIPOTENT STEM CELLS

Protze, Stephanie[1], Nussinovitch, Udi[2], Liu, Jie[3], Ohanna, Lily[3], Backx, Peter H.[3], Gepstein, Lior[2] and Keller, Gordon M.[4]

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The human heart rate is established by the sinoatrial node (SAN) that functions as primary pacemaker throughout life. Dysfunction of the SAN results in arrhythmias, and is routinely treated by implantation of an electronic pacemaker that has disadvantages including limited adaption to growth in pediatric patients and lack of autonomic responsiveness. Biological pacemakers derived from human pluripotent stem cells (hPSCs) represent a promising alternative. In this study, we have generated SAN-like pacemaker cells (SANLPCs) from hPSCs using a developmentally guided differentiation strategy that involves activation of BMP and RA signaling at the cardiac mesoderm stage. The derivative cardiac populations contained up to 35% SANLPCs that were identified by the lack of expression of the pan-cardiomyocyte marker NKX2-5. When generated from the HES3-NKX2-5:GFP reporter hPSC line, SANLPCs could be isolated from the differentiated population as NKX2-5^{-}SIRPA^{+} cardiomyocytes. These SANLPCs expressed significant higher levels of

SAN markers including TBX3, TBX18, SHOX2, HCN4 and lacked expression of the ventricular markers MLC2V and IRX4 compared to hPSCs-derived ventricular cardiomyocytes (VLCM). Furthermore, SANLPCs displayed typical pacemaker action potentials and responses to autonomic signals. When engrafted to the apex of the rat heart the NKX2-5^{-}SIRPA^{+} SANLPCs demonstrated the ability to pace the ventricle following induction of transient atrioventricular block. In contrast, transplanted VLCM showed no pacemaker capacity. To be able to isolate SANLPCs from non-genetically modified hPSC lines, we next optimized our differentiation strategy to promote the development of these cells under conditions that block the differentiation of NKX2-5^{+} cardiomyocytes. The resulting populations contained up to 50% SANLPCs with the remaining cells representing non-cardiomyocytes. We succeeded to purify highly enriched populations of SANLPCs (80%) from the non-cardiomyocytes by selection for SIRPA^{+}CD90^{-} cells. The ability to generate hPSC-derived SANLPCs independent of a transgenic reporter represents an important advancement, as it will enable to model diseases that affect SAN function using patient specific iPSCs and to develop functional biological pacemakers for future therapeutic applications.

SMALL MOLECULE COCKTAIL ENHANCEMENT OF IN VITRO AND IN VIVO DIRECT CARDIAC REPROGRAMMING OF POSTNATAL CARDIAC FIBROBLASTS

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The ability to directly trans-differentiate fibroblasts into cardiomyocytes through overexpression of three core transcription factors, Gata4, Mef2C and TBX5 (GMT), has been demonstrated by our group and others. Direct cardiac reprogramming is a promising approach to treat cardiac dysfunction; however clinical application remains limited due to inefficiencies in the reprogramming process. Using a chemical approach we aimed to increase the efficiency, speed and maturation of these directly reprogrammed cardiomyocytes. We screened 5500 compounds and identified 19 hits that increased reprogramming efficiency by 2–6 fold compared to controls. Among these, 4 TGF-ß inhibitors (DS 1-4) and 4 WNT inhibitors (DS 5-8) enhanced cardiac reprogramming. A combination of the TGF-ß inhibitor DS1 and the WNT inhibitor DS5 increased reprogramming efficiency 8–9 fold when added on the first day of reprogramming to the fibroblasts overexpressing GMT. This combination of small molecules also enhanced the maturation of the reprogrammed cells, as we observed beating cells after only 1 week of reprogramming compared to 6–8 weeks without the small molecules. Activation of canonical WNT signaling or TGF-ß signaling significantly abrogated the improvement in cardiac reprogramming by DS1 and DS5, indicating the specificity of the action of these inhibitors through the canonical WNT and TGF-ß pathways. We observed similar enhancement for human cardiac reprogramming. In a translational effort, in vivo exposure of mice to the TGF-ß and WNT inhibitors for 2 weeks in combination with GMT following myocardial infarction (MI) resulted in significant improvement in cardiac function compared to GMT alone as measured by ejection fraction 12 weeks after MI (GMT + compounds: 38.74% ±1.39%; GMT only: 28.49 ± 3.08%; compounds only: 22.72 ± 3.78%; DMSO only 21.36 ± 3.37%; $p<0.05$ for GMT compared to control and for GMT+compound compared to GMT; n=6-7 in each group). Lineage tracing revealed thick bands of newly generated induced cardiomyocytes in the area of damaged myocardium. In conclusion, a combination of TGF-ß inhibitors and WNT inhibitors, greatly enhanced the speed and quality of direct reprogramming in vitro and in vivo and resulted in significantly improved cardiac repair.

Funding Source: NIH and CIRM

REGENERATE WHOLE HEART USING HUMAN IPS CELL-DERIVED CARDIOVASCULAR PROGENITOR CELLS

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Heart disease is the leading cause of death in the world. Heart tissue engineering holds a great promise for the future heart disease therapy by building personalized heart tissues. We decellularized whole mouse hearts to obtain intact 3D heart scaffolds. The acellular heart scaffold was repopulated with human induced pluripotent stem cell-derived multipotential cardiovascular progenitor cells to create heart constructs. We found that the seeded multipotential cardiovascular progenitor cells migrate, proliferate and differentiate in situ into cardiomyocytes, smooth muscle cells and endothelial cells to reconstruct the whole decellularized hearts with muscle and vessle-like structures. After twenty days perfusion, the engineered heart tissues exhibit spontaneous contractions, generate mechanical force and are responsive to drugs. In addition, we observe that heart extracellular matrix promoted cardiomyocyte proliferation, differentiation and myofilament formation from the repopulated human multipotential cardiovascular progenitor cells. Here we provide a novel strategy to engineer whole personalized heart constructs using a single patient-specific cell resource.

UNDERSTANDING THE REGULATION OF CARDIAC CALCIUM CHANNELS USING IPSC-DERIVED CARDIOMYOCYTES

Song, LouJin and Yazawa, Masayuki

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

Cardiac calcium channels play important roles in heart development and function. Missense mutations in calcium channel alpha1c subunit have been reported to be associated with several types of cardiac arrhythmias including long QT syndrome (LQTS). Previously, we have used human induced pluripotent stem cells (iPSCs) to generate human cardiomyocytes (CMs) from LQTS patients and characterized those CMs. Our previous study demonstrated that the gain-of-function mutation (G406R) affected calcium channel inactivation, action potentials, calcium handling and contraction in human CMs. We found that roscovitine (Ros), a cyclin-dependent kinase (cdk) inhibitor, could rescue the phenotypes in LQTS CMs. However, how Ros restores the physiological functions in the patient CMs remains elusive. Our preliminary results using Ros analogs and cdk inhibitors suggested that cdk5/p35 pathway could be involved in the molecular bases of cardiac calcium channelopathy caused by the G406R mutation in the alpha1c subunit of cardiac calcium channels. We further confirmed our observation by expressing a dominant negative form of cdk5 or knocking down the expression of endogenous cdk5 using shRNAs in LQTS CMs with G406R mutation in the alpha1c subunit of cardiac calcium channels and the result suggested that cdk5 inhibition alleviated the phenotypes of those patient-specific CMs. We next furthered our study to understand the mechanisms underlying the effects of cdk5 inhibition on the patient-specific CMs. Gene expression and western blot analyses demonstrated that the mRNA and protein expression of several molecules in the cdk5/p35 pathway significantly increased in the patient-specific CMs. Co-immunoprecipitation analysis and in vitro phosphorylation assay also supported a direct binding and phosphorylation of the alpha1c subunit of the cardiac calcium channels by cdk5. Overall, the results demonstrated that there could be a direct regulation of cardiac calcium channels by cdk5 and the inhibition of cdk5 could be a novel therapeutic for LQTS patients caused by calcium channelopathy. This study is the first to examine the role of cdk5/p35 pathway in cardiac physiology and the pathogenesis of cardiac arrhythmias. The outcome of this study will provide new insights into the molecular bases of cardiac calcium channel regulation.

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REINFORCEMENT OF CELL FATE DECISIONS IS CRUCIAL FOR MAINTAINING CARDIAC CHAMBER INTEGRITY

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The atrial and ventricular chambers of the heart behave as distinct subunits with unique morphological, electrophysiological, and contractile properties. Proper maintenance of atrial and ventricular features is therefore essential for the development and homeostasis of a functional heart. However, chamber fate assignments seem relatively plastic: for example, work in zebrafish has demonstrated that cells retain the potential to alter their chamber-specific traits, even after initiating differentiation. Our recent studies of zebrafish nkx2.5 and nkx2.7 mutants has shown that these transcription factors play key roles in enforcing chamber-specific gene expression programs, but the signaling pathways that function upstream of these factors are less well understood. Here, we show that the FGF signaling pathway, which facilitates ventricular specification, is required to preserve ventricular identity. We find that inhibition of FGF signaling with the FGFR antagonist SU5402 can generate ectopic atrial cardiomyocytes within the already differentiated ventricle; similar phenotypes are evident in fgf8 mutants and in embryos overexpressing a dominant-negative FGF receptor. Additionally, temporally restricted manipulation of the FGF pathway reveals a specific time window during which ventricular chamber identity is vulnerable to the loss of FGF signaling. Analysis using photoconvertible reporter transgenes indicates that the ectopic cells in SU5402-treated embryos are not derived from the atrium. Instead, examination of the dynamic localization of atrial and ventricular proteins suggests that ectopic atrial cells are produced through transformation of ventricular cardiomyocytes. Furthermore, we find that FGF signaling is required for normal maintenance of nkx2.5 and nkx2.7 expression. Overexpression of nkx2.5 can improve the preservation of ventricular character in SU5402-treated embryos, suggesting that FGF signaling functions upstream of Nkx factors to promote retention of ventricular identity. Together, our data suggest a model in which continuous FGF signaling acts to suppress the plasticity of differentiated cardiomyocytes and to preserve the integrity of the ventricular chamber.

THURSDAY 23 JUNE, 16:00 – 18:00

CONCURRENT II: MECHANISMS OF ASYMMETRIC CELLULAR DIVISION

Level 2, Room 2004

BREAKING SYMMETRY ASYMMETRIC EPIGENETIC INHERITANCE DURING DROSOPHILA GERMLINE STEM CELL ASYMMTERIC DIVISION

Chen, Xin

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Many types of stem cells undergo asymmetric cell divisions to give rise to daughter cells with distinct cell fates: one that retains stem cell identity and another that differentiates. During asymmetric cell division, the genomic information is preserved through DNA replication followed by equal partition to the two daughter cells. A long-standing question has been how the epigenetic information of a stem cell is transferred to the daughter cells. Using the Drosophila male germline stem cell lineage, our recent studies showed that epigenetic information is inherited asymmetrically during asymmetric stem cell divisions. Our ongoing research is to elucidate how stem cells maintain their epigenetic memory through many divisions and whether the loss of stem cell epigenetic memory leads to diseases.

PRIMARY NEURAL PROGENITOR CELLS IN THE ADULT MOUSE V-SVZ UNDERGO SYMMETRIC CONSUMING DIVISIONS AND LIMITED SELF-RENEWAL

Obernier, Kirsten, Thomson, Matthew, Guinto, Cristina, Rodas Rodriguez, Jose, Parraguez Garcia, Jose and Alvarez-Buylla, Arturo

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GFAP+ primary neural progenitor cells (B1 cells) in the ventricular-subventricular zone (V-SVZ) sustain neurogenesis throughout life generating young migratory interneurons destined for the olfactory bulb. Whereas the lineage from B1 cells to transient amplifying C cells to young interneurons is known, the modes of division that allow life-long neurogenesis remain elusive. Here we have studied the behavior of GFAP+ B1 cells in vivo by using retroviruses, thymidine analog BrdU and Cre/loxP strategies. Our data suggest that C cells are not generated by asymmetric self-renewing divisions as often assumed but rather by consuming divisions of B1 cells. As this seem to be the predominant mode of division, the number of B1 decreases with age. While we did not observe evidences of asymmetric cell division, few B1 cells self-renew through symmetric divisions in vivo to maintain the population of primary progenitor cells. Ex vivo time-lapse microscopy on whole-mount preparations of the V-SVZ revealed that self-renewing B1 cells maintain their basal process during cell division, reminiscent of radial glia, and outgrow a second process that will be inherited by the other daughter B1 cell. While both daughter cells did not undergo further divisions during an imaging period of up to 4 days, our in vivo data suggest that daughter cells of self-renewing B1 cells get activated stochastically later in life and generate olfactory bulb interneurons likely via consuming divisions. Thus, neurogenesis is sustained via symmetric self-renewing and consuming divisions.

LETHAL GIANT LARVAE 1 (LGL1) REGULATES CELL FATE, POLARITY, PROLIFERATION AND MIGRATION OF CORPUS CALLOSUM PROGENITOR CELLS

Daynac, Mathieu, Meyers, Ian, Kadhkodaei, Banafsheh, Collins, Hannah, Gomez-Lopez, Sandra, Truffaux, Nathalene, Murphy, Nicole Elizabeth, Niu, Jianqin, Fancy, Stephen and Petritsch, Claudia

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

Embryonic neural stem cells and adult oligodendrocyte progenitor cells (OPC) undergo asymmetric cell division (ACD) to self-renew and generate functional cells. ACD is a fundamental process to restrict proliferation and balance it with self-renewal. Loss of ACD at the expense of symmetric, self-renewing divisions is observed when OPC turn into glioma cells. The majority of ACD regulators in Drosophila neuroblast are conserved in the mammalian genome. Lgl1 has been implicated in the asymmetric localization of cell fate determinants in neural progenitor cells. Functional characterization of mammalian ACD homologues is incomplete, especially in OPC. The objective of this project is to determine whether Lethal giant larvae 1 (Lgl1), a gene that was initially identified as a tumor suppressor in Drosophila, regulates ACD in corpus callosum progenitor cells. We propose that Lgl1 regulates ACD and thereby restricts proliferation and promotes differentiation in OPC. Indeed, in murine OPC carrying conditional null alleles of Lgl1, depletion of Lgl1 in vivo increases frequency of proliferative NG2+ OPC and decreases CC1+ pre-myelinating oligodendrocytes cells. In a murine model of spinal cord demyelination, Lgl1 ablation in NG2+ OPC in vivo increases their proliferation during re-myelination. We confirmed in vitro that Lgl1 loss increases proliferation and migration of OPC, disrupting cell polarity and asymmetric divisions. Our data suggest that loss of Lgl1 disrupts ACD and contribute to neoplastic transformation. We expect that our data will provide a better understanding of how ACD is established and regulated and will determine if disruption of ACD is causal to neoplastic transformation

ALPHA-KETOGLUTARATE ACCELERATES THE INITIAL DIFFERENTIATION OF PRIMED HUMAN PLURIPOTENT STEM CELLS

TeSlaa, Tara, Chaikovsky, Andrea C., Escobar, Sandra L., Graeber, Thomas G., Braas, Daniel and Teitell, Michael A.

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Production of α-ketoglutarate (αKG) at high rates has been shown to maintain low levels of DNA and histone methylation and promote ground state or naïve pluripotency in mouse pluripotent stem cells (mPSCs) by supporting the activity of αKG-dependent dioxygenases. However, JmjC-domain containing histone demethylases (JHDMs) and the TET family of 5-methylcytosine hydroxylases, which are both families of αKG dependent dioxygenases, are required for both pluripotency and differentiation. The role of αKG during differentiation of human pluripotent stem cells (hPSCs), which are in a more mature, or primed pluripotent state than naïve mPSCs, remains unexplored. We investigated the role of αKG in both hPSCs and mouse primed pluripotent stem cells. Despite low levels of oxidative phosphorylation in hPSCs, αKG and other TCA cycle metabolites are robustly produced. Addition of a cell permeable derivative of αKG, dimethyl αKG (dm- αKG), to differentiating hPSCs accelerated differentiation into multiple lineages. Furthermore, mouse epiblast stem cells (mEpiSCs), which are derived from more developmentally mature post-implantation embryos, also differentiated at a higher rate when treated with dm-αKG. Consistent with these findings, decreased levels of αKG, or increased levels of succinate, an inhibitor of αKG dependent dioxygenases, delayed differentiation of hPSCs. To determine whether αKG accelerates differentiation through activation of the JHDM and TET families of αKG-dependent dioxygenases, histone and DNA methylation marks were assayed. DNA 5-hydroxymethylcytosine levels increased and histone trimethylation levels decreased in differentiating hPSCs when dm-αKG was added. The data strongly support that αKG promotes the differentiation of pluripotent stem cells from the primed state by increasing the activity of αKG dependent dioxygenases, which stimulates epigenetic remodeling that is required for the activation of differentiation gene programs.

Funding Source: Supported by NRSA GM007185 and by the Broad Stem Cell Research Center (BSCRC) at UCLA Training Program (TT), by the BSCRC at UCLA, CIRM RB1-01397 and RT3-07678 awards, and by NIH Awards GM073981, CA156674, CA90571, GM114188, and CA185189.

TISSUE ENGINEERING PREVIEW FROM LATE BREAKING ABSTRACTS

GENERATION OF TISSUE-ENGINEERED SMALL INTESTINE WITH AN ENTERIC NERVOUS SYSTEM DERIVED EXCLUSIVELY FROM HUMAN PLURIPOTENT STEM CELLS

Schlieve, Christopher Ross[1], Fowler, Kathryn[1], Hajjali, Ibrahim[1], Hou, Xiaogang[1], Huang, Sha[2], Spence, Jason[2] and Grikscheit, Tracy[1]

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Loss of intestine from infection, ischemia, or injury can lead to the inability to absorb enough nutrients to sustain life, a condition called short bowel syndrome (SBS). Chronic medical management and surgical interventions provide little success in increasing intestinal function. Given the high rates of morbidity and mortality in SBS patients, development of patient-specific intestinal tissue for transplantation is essential. We have generated human intestinal organoid-derived tissue-engineered small intestine (HIO-TESI) from embryonic stem cells. However, HIO-TESI fails to develop an enteric nervous system (ENS). The purpose of our study is to establish an enteric nervous system in HIO-TESI derived exclusively from human pluripotent stem cells (hPSCs). H9 hESCs or WTC hiPSCs were maintained in mTeSR. H9 cells were temporally exposed to Activin A, CHIR99021, and FGF4 as previously described to generate HIOs. Enteric neural crest (ENC) progenitor cells were derived from hPSCs exposed to LDN193189, SB431542, CHIR99021 and Retinoic Acid as previously described. HIOs and unsorted ENC progenitor cells were seeded onto biodegradable scaffolds, wrapped in the omentum of adult NSG mice, and allowed to mature for 3 months. ENS-HIO-TESI was immunostained for neuronal, glial, and smooth muscle cell markers: EDNRB, RET, TrkC, Tuj1, GFAP, s100b, ChAT, Calbindin, Calretinin and SMA. H&E analysis of ENS-HIO-TESI demonstrates mature villus formation with the presence of underlying smooth muscle and ganglia within the submucosal and muscular layers. Excitatory neurons (Tuj1/ChAT/Calretinin or Tuj1/ChAT/Calbindin), glia (GFAP/s100b) and ganglia (EDNRB/RET/TrkC) were identified. These data demonstrate that supplementation of HIO-TESI with hPSC-derived ENC progenitor cells gives rise to essential components of the ENS.

Funding Source: CIRM TG2-01161

BALANCING SELF-RENEWAL AND DIFFERENTIATION THROUGH REGULATING MODES OF DIVISION IN VERTEBRATE NEURAL STEM CELLS

Guo, Su

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Generation of distinct daughter cell fate through asymmetric cell division (ACD) is a conserved phenomenon from single-cell protozoans to complex multi-cellular organisms. In metazoans, a set of evolutionarily conserved polarity regulators, the PAR (PARtitioning defective) proteins, themselves polarized in the mother cell, play a critical role in orchestrating ACD, resulting in daughter cells with distinct fates. We have established radial glia progenitors, the principal neural stem cells (NSC) in the developing zebrafish forebrain as an in vivo model for understanding stem cell division modes, owing to their amenability for molecular genetic analysis and time-lapse imaging. Two general questions of interest are: 1) How does a NSC choose to undergo symmetric cell division (SCD) versus ACD? 2) Once a NSC enters the ACD mode, what is the nature of asymmetry that is critical to determine daughter cell fate? In this talk, I will discuss the role of cortical polarity regulator Par-3 in establishing Notch signaling asymmetry, which is critical to stem cell fate decisions.

THURSDAY 23 JUNE, 16:00 – 18:00

CONCURRENT II: NUTRITIONAL EFFECTS ON STEM CELLS

Level 2, Room 2024

UNDERSTANDING HOW WE GET FAT: DIETARY REGULATION OF ADIPOCYTE PRECURSORS

Rodeheffer, Matthew S.

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We are in the midst of a global obesity epidemic; however, the cause of this recent widespread increase in adiposity remains a matter of debate and our knowledge of the basic biology of white adipose tissue (body fat) remains poor. Our lab recently identified and characterized the adipocyte cellular lineage in vivo. Directed studies of the regulation of the adipocyte precursors in vivo have shown that within some fat depots adipocyte precursors are transiently activated at the onset of obesity, leading to an increase in the number of fat cells (adipocytes) and fat mass. Furthermore, we have shown that there is an obesity-specific mechanism of adipocyte formation that is driven by dietary change. Here we show that high fat diets high in oleic acid, such as lard-based diets, result in increased fat cell number, while high fat diets low in oleic acid, such as coconut oil, do not stimulate increases in adipocyte number and gain less weight. Oleic acid is also sufficient to activate adipocyte precursors in vivo and stimulates adipogenesis in vitro. These findings suggest that the recent, drastic changes in types of fats in our diets have directly contributed to increased obesity rates.

AUTOPHAGY IS ACTIVATED DURING AGING TO MAINTAIN MOUSE HEMATOPOIETIC STEM CELL METABOLISM AND FUNCTIONAL CAPACITY

Ho, Theodore T, Warr, Matthew R and Passegue, Emmanuelle

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

With age, hematopoietic stem cells (HSCs) lose their ability to produce all blood cells, resulting in a decline in immune responses and increased rates of blood diseases in the elderly. We previously showed that autophagy is crucial for protecting HSCs from metabolic stress and that old HSCs have increased autophagy levels. Subsequent analyses of aged GFP-LC3 autophagy-reporter mice revealed a striking heterogeneity in old HSCs, with only ~ 30% having high autophagy levels. To understand how autophagy regulates HSC function, we generated mice with conditional deletion of the essential autophagy gene Atg12 (Atg12cKO) in the blood system. We observed premature aging phenotypes in Atg12cKO HSCs that resemble old HSCs, including similar differentially methylated regions, enhanced myeloid differentiation, rapid loss of self-renewal potential and HSC depletion under regenerative challenges such as transplantation. Analyses of Atg12cKO HSCs by electron microscopy also revealed an excess of mitochondria, similar to the ~ 70% old HSCs that do not show high autophagy levels. In both cases, this resulted in increased OXPHOS, ROS production, cell cycle activation, and precocious myeloid differentiation. In addition, only old HSCs with low levels of autophagy showed functional exhaustion after transplantation, while old HSCs with high levels of autophagy resembled young healthy HSCs and displayed robust long-term regenerative capacity. Our results demonstrate that HSCs require autophagy to maintain a low metabolic, quiescent state that preserves their regenerative capacity, and that during aging HSCs become increasingly dependent on autophagy activation for their functional maintenance. Old HSCs with low autophagy levels are severely impaired, likely causing age-associated declines in regenerative potential and blood production. This suggests that increasing autophagy in old HSCs could help promote HSC fitness and rejuvenate the aging blood system.

Funding Source: American Heart Association

DIETARY CONTROL OF THE INTESTINAL STEM CELL NICHE IN CANCER INITIATION

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Massachusetts Institute of Technology (MIT), Cambridge, MA, U.S.

An unresolved question in stem cell biology is how organismal diet influences tumor initiation and growth. We previously demonstrated that calorie restriction (CR) in mice augments ISC numbers and function by reducing mechanistic target of rapamycin complex 1 (mTORC1) signaling in Paneth cells, and that these effects of CR can be mimicked by rapamycin (an mTORC1 inhibitor). An implication of this work is that CR may increase intestinal tumor incidence as it increases the number of stem cells that can become transformed. Indeed, in preliminary work we find that this is the case. CR increases the frequency and size of adenomas after loss of the tumor suppressor Apc. Within adenomas, stem and Paneth cell numbers expand in mice under CR. Interestingly, the enhanced capacity of adenoma stem cells to form organoids occurs in a non cell-autonomous fashion, by co-culturing with CR or rapamycin-treated Paneth cells. Mechanistically, CR induces a PPAR-delta program in paneth cells and pharmacologic activation of PPAR-delta recapitulates the functional increase of stem cell clonogenicity observed in CR. We hypothesize that the transcription factor PPAR-delta mediates increased activity in the stem cell niche in response in CR Paneth cells**.** These findings highlight that a CR dietary intervention increases tumor incidence and that the reason this has not been recognized before is that the inhibitory effects of CR on tumor growth has masked the increase in tumor incidence.

INSULIN SIGNALING AND RESISTANCE IN HUMAN PLURIPOTENT STEM CELL-DERIVED MODELS OF METABOLIC DISEASE

Friesen, Max[1], Warren, Curtis Robert[1], Florido, Mary HC[1] and Cowan, Chad[1,2]

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We are in the midst of a worldwide epidemic of type 2 diabetes (T2D) and closely related problems of obesity and metabolic syndrome. These disorders represent a complex interaction between genes and environment. In the case of T2D there is a well-defined progressive pathogenesis of disease, beginning with insulin resistance in peripheral tissues such as muscle, fat and liver. This is initially compensated for by increased insulin secretion, but eventually beta cells exhaust and there is a gradual decline in insulin level leading to clinical onset of hyperglycemia. While some alterations in insulin action leading to insulin resistance have been defined and genome wide association studies have identified many genes associated with risk of T2D, the primary defect(s) in peripheral tissues leading to the insulin resistance remains unclear. To elucidate the molecular basis of insulin resistance, we generated several genetic models in human pluripotent stem cells. These models replicate both impaired and constitutively activated insulin signaling through the knockout or modification of genes involved in the insulin signaling pathway. To mimic impaired signaling, we knocked out the insulin receptor INSR, AKT2, the main intracellular insulin signaling node, as well as FOXO1, a major insulin-regulated metabolic transcription factor. In addition, to model activated insulin signaling we have knocked out PTEN and knocked-in the E17K mutation in AKT2. We are currently characterizing these genetic models in a number of relevant metabolic cell types differentiated from human pluripotent stem cells. These include the major metabolic tissue; adipocytes, hepatocytes and skeletal muscle, as well as the cells tasked with transport of insulin from the bloodstream to underlying organs, namely endothelial and vascular smooth muscle cells. The differentiated cells are comprehensively analyzed via RNA-seq, metabolomics profiling and insulin stimulation assays to generate a global picture of the effects of altered insulin resistance on the behavior of metabolically important cells. Ultimately we hope to illuminate novel mechanisms and identify targets in the insulin signaling pathway that would be of value in understanding and treating insulin resistance in the setting of human metabolic disease.

ROAD TO THE CLINIC PREVIEW FROM LATE BREAKING ABSTRACTS

MOTOR AND FUNCTIONAL GAINS DEMONSTRATED IN A DOSE-ESCALATION ARM OF A PHASE II NEURAL STEM CELL TRANSPLANTATION STUDY IN CERVICAL SPINAL CORD INJURY

Huhn, Stephen[1], Gage, Allyson[1], Kalsi-Ryan, Sukhvinder[2], Levi, Allan[3], Bryce, Thomas[4], Park, Paul[5] and Munin, Michael[6]

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The effect of human neural stem cell transplantation on motor recovery in chronic cervical spinal cord injury (SCI) is currently being tested in a randomized controlled multicenter Phase II study. The study includes an open-label dose-escalation arm (Cohort 1) that was designed to select the dose for the randomized controlled arm (Cohort 2). In Cohort 1, doses of 15, 30, and 40 million cells were sequentially administered to 6 subjects (2 subjects/dose). Neural stem cells were transplanted directly into the spinal cord above and below the injury epicenter and all subjects underwent a 6-month course of immunosuppression. To interrogate motor benefit, two standardized upper extremity assessments were utilized, the International Standards for the Neurological Classification of Spinal Cord Injury (ISNCSCI) and the Graded and Redefined Assessment of Strength, Sensibility, and Prehension (GRASSP). Each was administered at baseline and at 3 month intervals for one-year post-transplant. Six subjects with complete motor injury enrolled in Cohort 1 and time from injury ranged from 10 to 23-months. One-year data demonstrated overall improvement of motor strength and function in 4 subjects; 2 subjects had either stable or slightly reduced motor outcomes. Gains in the upper extremity motor score over 12 months were observed in 3 subjects as measured by the ISNCSCI. Four subjects had improved unilateral motor levels at multiple time points and one subject converted from a complete to an incomplete injury. Overall, 4 subjects had gains in both upper extremity strength and function as measured by 3 domains of the GRASSP; strength domain, Manual Muscle Testing (MMT) and the two functional domains, the Prehension Ability (PA) and Prehension Performance (PP). These parallel gains in strength and function are unexpected in chronic patients and represent the first demonstration of motor benefit following neural stem cell transplantation in SCI.

DIETARY CONTROL OF STEM CELLS IN PHYSIOLOGY AND DISEASE

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Little is known about how pro-obesity diets regulate tissue stem and progenitor cell function. Here we show that high-fat diet (HFD)-induced obesity augments the numbers and function of Lgr5+ intestinal stem cells of the mammalian intestine. Mechanistically, a HFD induces a robust peroxisome proliferator-activated receptor delta (PPAR-ð) signature in intestinal stem cells and progenitor cells (non-intestinal stem cells), and pharmacological activation of PPAR-ð recapitulates the effects of a HFD on these cells. Like a HFD, ex vivo treatment of intestinal organoid cultures with fatty acid constituents of the HFD enhances the self-renewal potential of these organoid bodies in a PPAR-ð-dependent manner. Notably, HFD- and agonist-activated PPAR-ð signalling endow organoid-initiating capacity to progenitors, and enforced PPAR-ð signalling permits these progenitors to form in vivo tumours after loss of the tumour suppressor Apc. These findings highlight how diet-modulated PPAR-ð activation alters not only the function of intestinal stem and progenitor cells, but also their capacity to initiate tumours.

THURSDAY 23 JUNE, 16:00 – 18:00

CONCURRENT II: STEM CELL NICHES

Level 2, Rooms 2009/2011

STEM CELL-NICHE INTERACTIONS IN THE ADULT MOUSE BRAIN: THE ROLE OF CYTOKINE TNF ALPHA

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Adult stem cells are found at specific locations and their behavior and lifelong maintenance is regulated by both cell intrinsic factors and signals from the microenvironment or niche in which they reside. However, stem cell niches are still poorly characterized due to the complexity of the interactions between stem cells and their neighbors and to the dynamic changes required for the continuous production of new cells. In the adult brain subependymal zone (SEZ), radial glia/astrocyte-like neural stem cells (NSC) continually produce new neurons and oligodendrocytes, via a population of rapidly-diving transit-amplifying progenitor cells. In the adult SEZ, different elements, including innervation, irrigation and the cerebrospinal flu-

id of the brain lateral ventricles, appear to play important roles in the regulation of NSC behavior, but the signalling pathways involved are still under investigation. Increasing evidence indicates that immune cells and immunological mediators could also modulate NSC behavior. Effects on neurogenesis of pro-inflammatory cytokines that are produced under non-physiological conditions, such as irradiation, inflammation, status epilepticus or stroke, have been described. However, their effects appeared sometimes contradictory, suggesting potentially distinct effects depending on the cell or receptor type involved. Tumor necrosis factor alpha (TNFα), a pro-inflammatory cytokine, is a multifunctional protein with a broad range of activities in different systems. We have evaluated potential roles of TNFα and its receptors in SEZ remodeling/regeneration analyzing direct effects of this cytokine on the proliferation/self-renewal of NSCs in culture and assessing its relevance in different in vivo scenarios where SEZ homeostasis is compromised. We have also analyzed the role of the two TNFα receptors using specific TNFR1 and TNFR2 agonists and TNFR knock-out mice. We found that TNFα modulates proliferation, self-renewal and the balance of symmetrical/asymmetrical divisions of NSCs and that each receptor mediates a distinct biological response.

Funding Source: MINECO (SAF, CIBERNED, and TerCel Programs), Generalitat Valenciana (Prometeo Program), and Botín Foundation-Santander Bank.

GENOME-WIDE RNA TOMOGRAPHY OF THE HEMATOPOIETIC STEM CELL NICHE IN ZEBRAFISH REVEALS UNEXPECTED FUNCTIONAL MACROPHAGE-STEM CELL INTERACTIONS

Hagedorn, Elliott[1], Junker, Jan Philipp[2], Perlin, Julie[1], D'Amato, Christopher[1], Collins, Samantha[1], Li, Brian[1], Riquelme, Raquel[1], van Oudenaarden, Alexander[3] and Zon, Leonard[1]

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The challenges of visualizing the bone marrow have precluded a rigorous analysis of the dynamic cell-cell interactions that control hematopoietic stem and progenitor cell (HSPC) engraftment. The zebrafish provides an unparalleled opportunity to directly visualize HSPC-niche cell interactions in live animals. Using a new technique called tomo-seq (RNA tomography) we identified ~300 genes showing enriched expression in the zebrafish caudal hematopoietic tissue (CHT) – an embryonic HSPC niche akin to the mammalian fetal liver. In situ hybridization for 68 of 84 tested genes confirmed CHT expression. In parallel we performed RNA-seq on isolated cell populations, including endothelial cells, macrophages, neutrophils and erythrocytes. By cross-referencing these datasets we determined the cell types in which many of the 300 CHT-enriched genes were expressed. This analysis revealed several cell surface adhesion receptors enriched on macrophages in the CHT, including the integrin heterodimers itgam/itgb2, itgae/itgb7, itga4/itgb1b and itga4/itgb7. We examined whether known ligands for these integrins were present on the HSPCs. In situ hybridization to vcam1 (ligand for itga4/itgb1b) showed punctate HSPC-like staining in the CHT. Further analysis of a vcam1:GFP promoter fusion revealed GFP expression in HSPCs (runx1:mCherry). Using spinning disk confocal microscopy we imaged HSPCs and macrophages in the CHT and observed direct and specific physical interactions that preceded the engraftment of HSPCs. In a grooming-like behavior that lasts for 30-45 min., the HSPC is engaged by the macrophage, which moves all over the surface of the cell, before disengaging the HSPC, which then remains in the CHT. Between 48-72 hpf, 20% of HSPCs were engaged in this behavior with a macrophage. To functionally evaluate these interactions, we depleted macrophages at 55 hpf using clodronate liposomes and observed circulating HSPCs with a significant reduction in HSPC engraftment in the CHT (11/15 embryos, compared to the control where 14/14 embryos showed normal CHT engraftment). Together these studies establish a role for macrophages in promoting the niche engraftment of HSPCs. These results could have important implications for the design of new therapies to improve engraftment during stem cell transplantation.

THE CELLULAR COMPOSITION OF THE HEMATOPOIETIC STEM CELL NICHE CHANGES DURING REGENERATION AFTER IRRADIATION

Zhou, Bo and Morrison, Sean J.

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

The hematopoietic system is a paradigm for understanding stem cell biology. Yet little is known about how the hematopoietic stem cell (HSC) niche regenerates after injury. Under homeostatic conditions, HSCs reside in a perivascular niche in the bone marrow where endothelial cells and LepR$^+$ perivascular cells express key niche factors, such as Stem Cell Factor (SCF, also known as KITL), that promote HSC maintenance. Irradiation decimates the HSC pool in the bone marrow and causes hematopoietic failure but hematopoiesis can be rescued by bone marrow transplantation. Here, we investigated how the bone marrow HSC niche changes in response to irradiation and bone marrow transplantation. Two weeks after irradiation and bone marrow transplantation, we observed in the bone marrow a 30-fold reduction in the number of LepR$^+$ stromal cells, a 40-fold reduction in the number of endothelial cells, and a 200-fold increase in the number of adipocytes. Scf was expressed at high levels by LepR$^+$ stromal cells and bone marrow adipocytes and at low lev-

els by endothelial cells. Scf expression was not detectable in osteoblasts or hematopoietic cells. Conditional deletion of Scf from endothelial cells, osteoblasts or hematopoietic cells did not significantly affect bone marrow cellularity or the number of Lineage$^-$Sca-1$^+$c-kit$^+$ (LSK) hematopoietic progenitors in the bone marrow at two or four weeks after irradiation and bone marrow transplantation. However, conditional deletion of Scf from LepR$^+$ stromal cells or bone marrow adipocytes significantly reduced bone marrow cellularity and LSK cell number in the bone marrow at two and four weeks after irradiation and bone marrow transplantation, leading to severe anemia and reduced mouse survival. The cellular composition of the HSC niche thus changes after irradiation as adipocytes become a significant new source of factors for HSC maintenance and hematopoiesis.

MYELOID PROGENITOR CLUSTER FORMATION DRIVES REGENERATIVE AND LEUKEMIC MYELOPOIESIS IN MICE

Herault, Aurelie[1], Binnewies, Mikhail[1], Leong, Stephanie[1], Calero-Nieto, Fernando[2], Zhang, Si Yi[1], Pietras, Eric[1], Chu S, Haihua[3], Barry-Holson, Keegan,[1], Armstrong, Scott[3], Göttgens, Berthold[2] and Passegue, Emmanuelle[1]

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Myelopoiesis is transiently induced in response to injury and is constitutively deregulated in leukemia. Both conditions are characterized by increased production of myeloid progenitors such as granulocyte/macrophage progenitors (GMP), and mature myeloid cells. However, little is known about how myeloid differentiation occurs spatially in the bone marrow (BM) cavity. Here, we use a novel immunofluorescence imaging approach to track the in situ behavior of GMPs during regenerative and leukemic myelopoiesis. In steady state conditions, we identify GMPs as single cells scattered throughout the BM cavity. In contrast, we find that regenerating GMPs transiently form self-renewing GMP patches that build differentiating GMP clusters, which, in turn, give rise to a temporally limited myeloid cell outburst. At the mechanistic level, we establish how the timed releases of several BM niche signals and the transient activation of an amplification self-renewal network involving Irf8 and ß-catenin, control GMP cluster formation during myeloid regeneration. In particular, we show that the early release of SCF and IL-1ß by the damaged vasculature activate hematopoietic stem cells (HSC) to undergo myeloid regeneration, and that a following spike in G-CSF production, in turn, dictate the kinetics of GMP cluster formation. We also find that the late secretion of TGF-ß and CXCL4 by megakaryocytes, which are surrounding the GMP clusters, finally restore HSC quiescence and terminate the regenerative response. Moreover, we show that leukemic GMPs constantly produce differentiating GMP clusters due to the combine effects of persistent activation of transformed HSCs by the pro-inflammatory leukemic niche and constitutive triggering of the Irf8/ß-catenin self-renewal network by the involved oncogenic events, and the lack of production of quiescence-enforcing termination cytokines by defective leukemic megakaryocytes. Taken together, our results uncover a previously unrecognized dynamic behavior of GMPs in the BM cavity that tunes emergency myelopoiesis and is hijacked in leukemia. They identify several new mechanisms by which the BM niche microenvironment controls myeloid differentiation that could be harnessed to activate or prevent myeloid cell expansion for translational applications.

DYNAMIC REGULATION OF INTESTINAL STEM CELL NICHE RECOVERY IN REAL-TIME

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The stem cell niche regulates tissue homeostasis and regeneration. Yet, how precisely the niche replaces lost cells and recovers from damage remains largely unknown. Here, we developed a systems biology approach combining in vivo laser ablation followed by chronic imaging and in silico dynamic models to study this spatiotemporal process in the intestinal epithelium. We ablated individual stem or Paneth cells in the mouse intestinal crypt with high-precision photodisruption using a femtosecond laser, and monitored the in vivo dynamics of intestinal niche recovery in real-time, stabilized by a surgically implanted 3D-printed scaffold. The niche recovers immediately after cell loss by rearranging stem/Paneth cell patterns rather than waiting for new cell division to fill the vacancy. Distinct from classic lateral inhibition, intestinal stem cells employ a unique positive feedback mechanism via direct Notch1 binding to sustain the niche. Inactivation of the positive feedback by CRISPR/Cas9 mutation disrupts the niche pattern, limits self-renewal, and renders the niche incapable of recovery in organoids. Dynamical system analysis and agent-based multiscale stochastic modeling demonstrated that this regulation scheme enhances the robustness of Notch-mediated patterning when cell turnover rate is high. This study highlights a systems approach that integrates in vivo, in vitro, and in silico models coupled with technology of precise perturbation to comprehend spatiotemporal regulation of mammalian tissue.

Funding Source: NIH R01GM095990, R01 GM114254

THE MICROENVIRONMENTAL NICHES FOR HEMATOPOIETIC STEM CELLS IN THE BONE MARROW

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Niches for hematopoietic stem cells (HSCs) are restricted microenvironments that are required for the maintenance of HSCs, which are in contact with these microenvironments. However, the identity of cells creating HSC niches has been a subject of longstanding debate. We focused our analysis on the chemokine CXCL12, which is essential for homing and maintenance of HSCs and development of immune cells in the bone marrow, and identified a population of mesenchymal cells with long processes, expressing high amounts of CXCL12, termed CXCL12-abundant reticular (CAR) cells. We revealed that most HSCs adjoined the processes of CAR cells and that ablation of CAR cells *in vivo* severely impaired the adipogenic and osteogenic differentiation potential of marrow cells and production of SCF as well as CXCL12, and led to a marked reduction in the numbers of hematopoietic stem and progenitor cells (HSPCs), indicating that CAR cells are adipo-osteogenic progenitors, which create a HSC niche. Recently, we found that the transcription factor Foxc1 was preferentially expressed in CAR cells in the marrow and was essential for development and maintenance of the HSPC niche, enhancing CXCL12 and SCF expression, and inhibiting adipogenic processes in CAR cells. The features of cells, which play a dominant role in creating HSC niches in the mouse and human bone marrow will be discussed.

THURSDAY 23 JUNE, 16:00 – 18:00

CONCURRENT II: STEM CELLS AND SOLID CANCERS

Level 2, Rooms 2014/2016/2018

THE SWI/SNF COMPONENT ARID1A REGULATES REGENERATIVE CAPACITY AND CARCINOGENESIS IN A DOSE-DEPENDENT FASHION

Zhu, Hao

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

It is widely assumed that cancer risk increases with regenerative capacity, but the relationship is likely more complicated. In mammals, chronic damage to the skin, intestine and liver is strongly associated with cancer, but it is possible that the regenerative abilities of these organs serve to preserve tissue integrity, reduce inflammation, and resist transformation during injury. Causative mechanisms have been intractable because animals with contrasting regenerative abilities are often evolutionarily distant. Thus, it is unknown if enhancing mammalian regeneration would influence cancer formation. Mice without the SWI/SNF component Arid1a possessed improved healing abilities after an array of injuries. After liver resection, chemical hepatocyte injury, and toxic bile duct injury, Arid1a deficient livers exhibited increased regeneration, reduced tissue damage, and improved organ function. Moreover, global homozygous Arid1a loss potentiated soft tissue healing after ear hole punch and ß-cell regeneration after pancreatectomy. The chromatin state as reprogrammed by Arid1a loss restricted access to promoters by lineage-specific transcription factors that ordinarily suppress cell cycle reentry, thus increasing regeneration after injury. Intriguingly, the homozygous Arid1a deficient state protects from chemical injury induced hepatocellular carcinoma (HCC) and extends survival in a MYC-driven hepatoblastoma model. Since Arid1a mutations are most frequently heterozygous in human HCC genome studies, we examined the haploinsufficient state in these mouse models and observed accelerated carcinogenesis and metastasis. Transcriptome analysis revealed dysregulated differentiation, proliferation, and metastasis genes. Our models show that full deletion of Arid1a can enhance mammalian regeneration without increasing cancer risk, but that its tumor suppressor functions are extremely sensitive to dose.

THE HIPPO PATHWAY REGULATES MAMMARY EPITHELIAL CELL PROLIFERATION THOUGH H4K20ME1

Zabala, Maider[1], Lobo, Neethan[1], Luong, An V.[1], Isobe, Taichi[1], Zarnegar, Mark A[1], Watanabe, Nicholas[1], Darmanis, Spyridon[1], Antoñana, Sonia[1], Lam, Jessica[1], Qian, Dalong[1], Somlo, George[2], Dirbas, Frederick M[1], Sahoo, Debashis[3] and Clarke, Michael F[1]

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The Hippo pathway regulates proliferation and its alteration has been described in a broad spectrum of human tumor types. However, little is known about the regulation of this pathway and its link with cancer. Here, we describe a novel mechanism by which genomic imprinting regulates the Hippo pathway. We observed that the expression levels of an imprinted miR-127 belonging to the DLK1-DIO3 cluster is consistently highest in normal and cancer stem cells isolated from 23 different breast cancer patients. This was explained by the hypomethylation status of the DLK1-DIO3 imprinted control region (IG-DMR) and miR-127 CpG island. We demonstrated that miR-127 regulates SETD8's translation and subsequent H4K20me1

deposition at the intergenic region of LATS2, a HIPPO pathway kinase. In this context H4K20me1 acts as activator of LATS2 expression. In consistency with those findings, we observed that SETD8, H4k20me1 and LATS2 protein levels are highest in more differentiated luminal cells whereas YAP1 and HIPPO pathway target genes are highest in basal/stem cell compartment. Single cell/colony transplantation assays demonstrated that enforced miR-127 expression enhances mammary outgrowth formation of mammary repopulating units (MRUs), whereas Setd8 impairs their engraftment potential. Furthermore, miR-127 also endows long-term proliferation to early progenitor cells as measured by serial passages in vivo. Conversely, inhibition of miR-127 impaired colony formation in organotypic assays and tumor growth in vivo from cells isolated from six well-characterized PDX models. We used Verteporfin or genetic knock-down of the HIPPO effector, YAP1, in order to demonstrate how miR-127 modulates the long-term proliferation of undifferentiated mammary and breast cancer stem cells through HIPPO pathway. This discovery opens an alternative option to design therapeutics to affect the Hippo pathway through epigenetic modulators.

Funding Source: M.Z. was supported by Fulbright Program and Susan G. Komen for the Cure/ Princess Cruises Community Foundation

H3K9 METHYLTRANSFERASES REGULATE LUNG TUMOR PROPAGATING CELLS AND LUNG STEM CELLS

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A significant gap in our understanding of stem cells in cancer is the extent to which their regulatory mechanisms are conserved or dysregulated compared to stem cells of the same healthy tissue. We have sought to directly address this by searching for potential common regulators of murine lung stem cells and cancer stem cell-like tumor propagating cells (TPCs). We have identified the H3K9me1/2 methyltransferases G9a/Glp as negative regulators of TPCs by screening lung adenocarcinoma cells for small molecules that modulate the TPC surface antigens CD24 and Sca-1. Gene expression analyses of primary adenocarcinomas confirm that G9a/Glp are down-regulated in Sca-1+ TPCs. Chemically inhibiting G9a/Glp promotes TPC phenotypes in lung adenocarcinoma cells, increasing their in vitro organoid forming efficiency and widening the distribution of tumors formed by inhibited cells after intravenous transplantation. Depleting G9a during tumorigenesis significantly alters the tumor population dynamics, enriching for TPCs and consequently accelerating disease progression and metastasis. Furthermore, inhibition of G9a/Glp in 3D multipotent lung stem cell cultures disrupts the normal formation of differentiated organoids, specifically impairing alveolar lineage organoids. This suggests a potential parallel role for H3K9me1/2 in controlling the dynamic between stem cells and certain differentiated cells in both the healthy lung and in lung cancer. Analysis of 400+ early stage patient lung adenocarcinomas reveals that low G9a expression and high expression of KDM3A, an H3K9me1/2 demethylase (KDM), significantly correlate with worse survival (P=0.008, P=0.002), implying that dysregulation of H3K9me1/2 is also a significant factor in human disease. Preliminary data suggest that depleting H3K9 KDMs downregulates TPC markers in lung adenocarcinoma cells and decreases their organoid forming efficiency, raising the possibility that targeting these molecules in lung adenocarcinoma patients may be therapeutically beneficial.

AN UNEXPECTED METASTASIS-INITIATING SUBSET OF HUMAN PRIMARY CARCINOMA CELLS DEFINED BY ROBUST EPITHELIAL DIFFERENTIATION AND STEM CELL PROPERTIES

Saini, Massimo[1], Klein, Corinna[2], Falcone, Mattia[2], Scheel, Christina[3], Weichert, Wilko[4], Sprick, Martin[1], Marme, Frederick[5], Wuchter, Patrick[5], Schneeweiss, Andreas[5] and Trumpp, Andreas[2]

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The potential of metastatic carcinoma cell to seed metastases has been linked to stem cell characteristics in mouse models and in vitro transformation models. However functional evidence in human primary cancers remains elusive. Survival in the circulation and disease propagation is though to be associated with loss of epithelial differentiation and transdifferentiation to a mesenchymal fate through an epithelial-to-mesenchymal transition (EMT). This hypothesis has influenced the design of clinical assays for metastatic circulating tumor cells (CTCs) and the search for therapeutic targets. It assumes that stem cell specific pathways rather than mature cell traits would lie beneath metastatic relapse. We made use of liquid biopsies from pleural effusions and peripheral blood apheresis to characterize disseminated cancer cell subsets defined by the surface marker EpCAM (Epithelial Cell Adhesion Molecule) in more than 20 metastatic breast cancer patients. We report succesfull RNA-sequencing and in vivo engratment of EpCAM-high, EpCAM-low and EpCAM-negative cancer cells displaying a progressive gradient of epithelial de-differentiation. Unexpectedly, the in vivo tumor-initiating potential was found to be higher in EpCAM-high cells than in any other subset, and this was true in all the engrafters. EpCAM-high cells displayed a robust epithelial differentiation program rather than a stem

cell gene expression profile, and this was remarkably true also in aggressive disease subtypes such as basal-like and triple negative. In collagen-based 3D cultures, single cell clonogenicity enriches in EpCAM-high cells, while in the bloodstream of mice the EpCAM-high fraction is more proficient in seeding metastatic lesions upon direct injection in the circulation. Consistently, a group of surface epithelial adhesion molecules including EpCAM are found co-expressed with the CSC marker CD47 and the tyrosine kinases MET and HER2 in RNAseq data from primary liquid biopsies of breast cancer. Early-stage (M0) appearance of the CD47+MET+ phenotype on breast cancers is an independent prognosticator of disease outcome in a cohort of 300 stage-adjusted ER+ invasive breast carcinoma patients. Altogether, these data unveil that metastases could be initiated and driven by a self-renewing epithelial differentiated cell.

DEFINING THE ROLE OF POLYPLOIDY IN MOUSE LIVER

Zhang, Shuyuan[1,2], Zhou, Kejin[1], Li, Lin[1], Nyguen, Liem[1], Goodman, Joshua[2], Sun, Xuxu[1], Zhang, Yu[1], Siegwart, Daniel[1] and Zhu, Hao[1]

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The liver is made of up to 70% polyploid cells, but the functional role of polyploidy is completely unknown. Hepatocyte polyploidization occurs through cytokinesis failure around the time of weaning and increases with age. A recent study found that a subset of diploid hepatocytes serve a stem cell function, suggesting that polyploid hepatocytes are less able to participate in regeneration. Since the genes that regulate polyploidy also control the cell cycle and cytokinesis, a fundamental difficulty in studying mice with differing levels of ploidy is that these models are permanent knockouts that impair our ability to examine any long-term regenerative or oncogenic consequences of altered ploidy. To create more polyploid and more diploid liver models without permanent defects in cell proliferation machinery, we delivered in vivo siRNAs to transiently target Anillin and E2f8, genes required for liver diploidization and polyploidization, respectively. These tools allowed us to substantially increase and decrease liver ploidy in vivo. Notably, differing levels of ploidy did not impact regeneration after partial hepatectomy, but did influence chemical (CCl4) liver injury. Most importantly, we found that increasing levels of polyploidy acts to suppress tumorigenesis in chemical (DEN) and genetic (MYC-induced) liver cancer models. Interestingly, this was not associated with differences in proliferation. Polyploid hepatocytes did exhibit reduced levels of reactive oxygen species when compared with diploid hepatocytes. Since antioxidants inhibit injury and cancer in many liver models, this suggests one possible means by which increasing ploidy suppresses carcinogenesis. This is one of the first lines of evidence that polyploidy serves to suppress oxidative stress and tumorigenesis, adding functional importance to a deeply mysterious observation in the liver.

TARGETING INTESTINAL STEM CELLS IN CANCER

de Sauvage, Frederic

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The Wnt signaling pathways plays critical roles during embryonic development and in adults through modulation of proliferation, cell migration and differentiation. Inappropriate activation of the Wnt pathway through mutation or misexpression can result in tumorigenesis, in particular in the gastrointestinal tract where Wnt pathway activation is observed in most colorectal tumors. The intestinal epithelium is turned over every 5 days on average and is very dependent on stem cell activity. Crypt based columnar cells (cbc) expressing the Lgr5 receptor have been identified as intestinal stem cells and play a key role in intestinal homeostasis and/or regeneration. We previously demonstrated, using the $Lgr5^{DTR}$ mouse model, that intestinal homeostasis can be maintained, at least in the short term, following the ablation of the cbc stem cell population. Here, we will detail the consequences of depleting Lgr5+ stem cells in models of colorectal cancer and potential strategies for targeting these cells in patients.

THURSDAY 23 JUNE, 16:00 – 18:00

CONCURRENT II: DEVELOPMENT AND REGENERATION IN ENDODERMAL DERIVATIVES

Level 2, Room 2002

THE INHIBITION OF HEPATOCYTE PROLIFERATION IN MOUSE TRIGGERS BILIARY CELLS TO BECOME FACULTATIVE STEM CELLS FOR HEPATOCYTES

Forbes, Stuart

University of Edinburgh, U.K.

Following injury the normal liver regenerates through hepatocyte proliferation. In human liver disease, when hepatocyte replication is impaired, ductular reactions proliferate and expand through the parenchyma. These ductular reactions are thought to containing putative hepatic progenitor cells (HPCs). The regenerative potential of HPCs has been controversial. Using current mouse models, the significant endogenous repopulation of hepatocytes by HPCs has not been shown. However, the models used do not produce significant inhibition of

hepatocyte replication. We have used independent techniques to investigate the regenerative potential of HPCs in mouse models of liver injury when hepatocyte proliferation is inhibited- a clinically relevant scenario. We have used the AAV8.TBG.Cre system to efficiently label and lineage trace all hepatocytes with RFP. These mice were crossed with ß1 integrin$^{fl/fl}$ mice resulting in impairment of hepatocyte replication at the same time as RFP labelling. Liver injury was induced with thioacetamide toxin or dietary models (CDE, DDC) for 1-2 weeks followed by recovery up to 4 weeks. Hepatocyte deletion of ß1 integrin resulted in reduced hepatocyte proliferation, hepatocyte senescence, marked ductular reactions and the development of non-hepatocyte derived regenerative nodules accounting for 25% of the hepatocytes by 2 weeks recovery. These unlabelled hepatocytes were more proliferative and had smaller nuclei than the original RFP labelled hepatocytes. A novel mouse model system was used to show the fate mapping of ductular cells/HPCs into hepatocytes using Krt19CreER^{T}LSL^{tdTomato} mice and p21 mediated inhibition of hepatocyte replication. In this system the large-scale differentiation of the ductular cells/HPCs into hepatocytes was seen and was dependent upon both hepatocyte injury and the inhibition of hepatocyte replication. These systems model clinical liver disease where hepatocyte proliferation is impaired and hepatocyte senescence is a frequent feature. These models are suited to unpicking the mechanisms of HPC activation and differentiation for therapeutic targeting.

INDUCTION OF HEPATIC PROGENITOR CELLS FOR THE HIGHLY EFFICIENT EX VIVO EXPANSION OF PRIMARY HUMAN HEPATOCYTES

Unzu, Carmen[1], Friedli, Marc[2], Planet, Evarist[2], Brandenberg, Nathalie[3], Rougemont, Anne-Laure[4], Lutolf, Matthias P.[3], Wildhaber, Barbara[4] and Trono, Didier[2]

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The only cure for many inherited metabolic liver diseases with severe extra-hepatic manifestations is liver transplantation, a high-risk procedure and limited by shortage of donors. The transplantation of genetically corrected hepatocytes is an attractive alternative, but is hampered by the low amplification potential of these cells in vitro. The derivation of liver cells from induced pluripotent stem cells (iPSC) holds promises to circumvent this difficulty. However, the generation of iPSC induces epigenetic anomalies resulting notably in improper resetting of transposable elements control. This both decreases the efficiency of reprogramming and re-differentiation of these cells and could potentially result in long-term complications, including oncogenic transformation after re-implantation. Here, we describe a method for generating highly proliferative hepatic progenitor cells (iHPC) by ex vivo pharmacological manipulation of human liver cells. Dedifferentiation of primary hepatocytes to iHPC was achieved in less than 7 days by culturing the cells in medium with a cocktail of growth factors and small molecules. In culture, iHPC expressed a combination of endoderm hepatic progenitor and mesenchymal stem cell markers and proliferated vigorously, allowing for their expansion by at least 10^4 times. In vitro 2D and 3D co-cultures of iHPC with adult primary hepatocytes induced their re-differentiation to hepatocytes. Transplantation of iHPC into the liver of an immune-deficient mouse confirmed their differentiation potential in vivo, without triggering detectable tumor. Finally, RNA sequencing of iHPC demonstrated that they displayed far more subtle changes in both transcriptome and transposcriptome, compared to hepatocyte-derived iPSC. Our results confirm the remarkable plasticity of human hepatocytes and provide a very promising methodological lead for the treatment of inborn hepatic diseases and for the development of a bio-artificial liver.

Funding Source: This work has been funded by the FP7 Marie Skłodowska-Curie Actions Project UE7- CN-I LIVE-625689 and with contributions of the Clinical Research Center and the Louis-Jeantet Foundation from Geneva.

MODELING PANCREATIC FATE DECISIONS USING A DESIGN-OF-EXPERIMENT (DOE) METHOD FOR THE DIRECTED DIFFERENTIATION OF PLURIPOTENT CELLS

Bukys, Michael[1,2], Finney, Krystal[2,3] and Jensen, Jan[1]

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The in vitro generation of insulin producing cells from pluripotent cells is of clinical interest. In an effort to optimize the directed differentiation of pluripotent cells toward endocrine fates we used a novel technology platform to address recalcitrant protocol optimization problems. We performed a series of design of experiment (DoE) based optimizations testing classical morphogen pathways in a simultaneous manner (BMP, WNT, SHH, FGF, RA, ACTIVIN) each design representing a >3000 experimental design space. To ascertain specific effects on cell fate, we measured > 100 lineage reporter genes for each condition. The resulting data matrix (>10,000 datapoints/experimental design) underwent mathematical fitting resulting in an effector/response matrix which could be explored for predictive analysis. We used such model data to predict specific morphogen/growth factor concentrations that should lead to maximal induction of cellular states representative of pancreatic development, using

suitable markers. Initial perturbations of the pluripotent space established several novel approaches for generating endodermal cells through maximizing for the expression of HNF1B, ONECUT2, NR5A2, and SOX17 respectively, indicating that a classical ACTIVIN A/WNT exposure is not mandatory for DE induction. We tested various endodermal populations for pancreatic competence using both established protocols for generating multipotent pancreatic progenitor cells (MPC) and a novel protocol we developed for pancreatic progenitor induction and endocrine conversion, contrasting previous published work (Pagliuca et al., Cell, 2014, Rezania et al., Nat. Biotech. 2014). Our current findings strongly demonstrate the strength of a Systems Developmental Biology approach in directing the differentiation of pluripotent cells, emphasizing the possibility of mathematically modeling optimal conditions for multiple lineages simultaneously.

TOWARDS GENERATION OF PURE AND AUTHENTIC HUMAN LIVER CELLS FROM PLURIPOTENT STEM CELLS

Ang, Lay Teng[1], Loh, Kyle[2], Goh, Suhua[1], Tan, Antson KY[1], Weissman, Irving L[2] and Lim, Bing[1]

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Multiple challenges surround the clinical or industrial application of embryonic stem cell (ESC)-derived human liver cells. Firstly, it is not yet possible to obtain homogeneous and authentic ESC-derived human liver cells that are the molecular and functional equivalent of primary liver cells. Secondly, the repertoire of extracellular signals that developmentally specify liver fate and the temporal sequence with which they act remains ambiguous. Here we defined various signaling pathways that regulate consecutive stages of liver differentiation, including patterning of human endoderm into foregut, liver bud specification and segregation of hepatocyte versus biliary fates. This knowledge allowed us to sequentially differentiate human ESCs (H1, H7, H9) into a >90% pure AFP+TBX3+ liver bud progenitor population and later, an >80% pure ALB+GS+ more downstream liver precursor population. These ESC-derived ALB+ human liver precursors repopulated the damaged liver of immunodeficient Fah-/- mice, improving the survival of these mice and reducing bilirubin levels. Next, we further used RNA-seq to define global transcriptional dynamics during in vitro hepatic differentiation by comparison to primary human liver cells at different developmental stages (in fetal and adult life) to compare in vivo and in vitro derived hepatocyte lineages. Thus, this study provided insights into the signaling regulation of different phases of liver differentiation in vitro and contributed to the generation of human liver progenitors that may be potentially useful for therapeutic or industrial applications.

Funding Source: This research is funded by Agency for Science, Technology and Research (A*STAR) and Exploit Technologies Pte Ltd.

A UNIQUE SYSTEM TO ASSESS THE IN VIVO LINEAGE POTENTIALS OF DEVELOPMENTALLY-ADVANCED CELLS BY BLASTOCYST INJECTION

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Embryonic stem cells (ESCs) established from non-rodent animals reflect the characteristics of post-implantation epiblasts, equivalent to mouse epiblast stem cells (EpiSCs), and fail to form chimeras with pre-implantation embryos. This underlies difficulty in deriving genetically modified animals using ESCs in non-rodents. Based on our serendipitous finding that an EpiSC subline that had acquired resistance to apoptosis could contribute to chimera formation, we tested if cell survival is transiently promoted by expressing anti-apoptotic gene BCL2, EpiSCs and even lineage-committed progenitors are capable of integrating into blastocysts. Upon blastocyst injection, such EpiSCs seemingly contribute to all bodily tissues in chimeric animals whereas Sox17^{+} endoderm progenitors contribute only to gut tissues. Thus, overriding apoptosis enables the developmental competence of even gastrulation-stage tissue progenitors to be manifested upon blastocyst injection. The lineage potentials of many embryonic tissue progenitors in intermediate stages of organogenesis have yet to be rigorously characterized. Our system provides an ideal platform to systematically chart these lineage potentials via blastocyst injection, yielding an informative reference map for developmental biology and enabling targeted generation of specific organs in vivo for regenerative medicine.

TISSUE REGENERATION IN LIVER: PLASTICITY OR STEM CELLS?

Grompe, Markus[1], Li, Bin[2] and Tarlow, Branden[1,2]

[1]Oregon Health & Science University, Portland, OR, U.S., [2]Oregon Stem Cell Center, Oregon Health Science University, Portland, OR, U.S.

Cell replacement in adult organs can be achieved through differentiation of stem cells, replication, or transdifferentiation of existing cells. In the adult liver stem cells have been proposed to replace tissue cells, especially upon in-

jury. Here we will present how specialized cell types are produced in the adult liver during homeostasis and injury. The origin and role of clonogenic biliary cells (Lgr5+ and others) will be discussed. Based on current evidence, we propose that plasticity of differentiated cells rather than stem cells account for most tissue repair in the adult mouse liver.

THURSDAY 23 JUNE, 16:00 – 18:00

CONCURRENT II: NEURAL DISEASE

Level 2, Rooms 2001/2003/2005/2007

MYELINOGENIC AND NERVE REGENERATING INDUCED SCHWANN CELLS DERIVED BY TWO-FACTOR SKIN FIBROBLAST REPROGRAMMING

Broccoli, Vania[1], Mazzara, Pietro Giuseppe[1], Massimino, Luca[1], Pellegatta, Marta[1], Ronchi, Giulia[2], Ricca, Alessandra[1], Iannielli, Angelo[1], Giannelli, Serena Gea[1], Cancellieri, Cinzia[1], Gritti, Angela[1], Geuna, Stefano[2] and Taveggia, Carla[1]

[1]San Raffaele Scientific Institute, Milan, Italy, [2]University of Turin, Ospedale San Luigi, Turin, Italy

Schwann cells (SCs) generate the myelin enwrapping the peripheral nerves. Transplantations of SCs might become an interesting therapeutic opportunity for the treatment of peripheral nerves injuries and demyelinating diseases of the peripheral nervous system (PNS). However, to date is lacking a renewal source of SCs. In this study we established a genetic system identifying the minimal combination of only two transcription factors (TFs) supporting the direct conversion of skin fibroblasts into induced Schwann cells (iSCs). Transcriptome profiling confirmed a substantial molecular convergence of somatic and induced SCs. In vitro studies showed that iSCs strongly resemble primary SCs in myelinating axons with a regular internode pattern. In vivo studies on a rat model of peripheral nerve injury indicated that grafted autologous iSCs sustain nerve regeneration. Moreover iSCs generated from globoid cell leukodystrophy fibroblasts recapitulate the pathophysiological defects associated with this disease. Generating iSCs through direct conversion of somatic cells might disclose significant opportunities for in vitro disease modelling as well as cell regenerative therapies.

HUMAN NEUROPSYCHIATRIC DISEASE MODELING USING CONDITIONAL DELETION REVEALS SYNAPTIC TRANSMISSION DEFECTS CAUSED BY HETEROZYGOUS MUTATIONS IN NRXN1

Pak, ChangHui, Tamas Danko, Yingsha Zhang, Jason Aoto, Garret Anderson, Stephan Maxeiner, Fei Yi, Marius Wernig and Thomas C. Südhof

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Heterozygous mutations of the NRXN1 gene, which encodes the presynaptic cell-adhesion molecule neurexin-1, were repeatedly associated with autism and schizophrenia. However, diverse clinical presentations of NRXN1 mutations in patients raise the question of whether heterozygous human NRXN1 mutations alone directly impair synaptic function. To address this question under conditions that precisely control for genetic background, we generated human ESCs with different heterozygous conditional NRXN1 mutations, and analyzed two different types of isogenic control and NRXN1 mutant neurons derived from these ESCs. Both heterozygous NRXN1 mutations selectively impaired neurotransmitter release without changing neuronal differentiation or synapse formation. Moreover, both NRXN1 mutations increased the levels of CASK, a critical synaptic scaffolding protein that binds to neurexin-1. Our results show that, unexpectedly, heterozygous inactivation of NRXN1 directly impairs synaptic function in human neurons, and they illustrate the value of this conditional deletion approach for studying the functional effects of disease-associated mutations.

GENE-EDITED HUMAN STEM CELL MODELS OF TUBEROUS SCLEROSIS EXHIBIT TREATABLE DISEASE PHENOTYPES UPON 2D AND 3D NEURONAL DIFFERENTIATION

Salick, Max R, Ihry, Robert John, Ho, Daniel J, Chen, Julie T, Biag, Jonathan D, Bilican, Bilada, Ye, Chaoyang, Dolmetsch, Ricardo E, Goold, Carleton P and Kaykas, Ajamete

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

Tuberous sclerosis complex (TSC) is a disease of the mTOR pathway caused by heterozygous mutations in the TSC1 or TSC2 genes, which occurs in 1 in 6,000 live births. Patients with TSC have an elevated risk of autism, and experience symptoms affecting several tissues, including the formation of non-malignant tumors in the brain, kidneys, heart, lungs, and skin. While all such symptoms are harmful, the cognitive impairment and seizures associated with brain involvement most significantly impact patient quality of life. Cortical tubers, which initiate epilepsy in TSC, are thought to form after a somatic loss of heterozygosity in the unaffected TSC1 or TSC2 allele. This

disrupts the formation of the TSC1-TSC2 complex, leading to hyperactivation of mTORC1. This activation results in increased protein synthesis and cell growth, and together with as-yet incompletely understood downstream actions of mTOR in the brain, leads to abnormal brain development, disrupted cortical architecture, and the presence of the characteristic balloon cell type. Here we describe the utilization of an inducible-CRISPR/Cas9 system to develop TSC2 knockout human embryonic stem cell (hESC) lines capable of long-term culture and subsequent differentiation. NGN2-based differentiation techniques were used to produce excitatory neurons from healthy and TSC hESCs, producing distinct phenotypic differences between the disease and control lines. Cell size is increased, dendritic morphology is altered, and S6 phosphorylation, a characteristic marker of mTOR activity, is highly upregulated in TSC2 mutant neurons. Preliminary tests of mTOR inhibitors indicate a reduction in S6 phosphorylation and soma size after only 5 days of treatment. Since neural stem cell differentiation, migration, and cortical layering are strongly affected by TSC, we developed cerebral organoid assays to examine these phenomena. These organoid-based assays revealed striking phenotypes in the form of large growths that emerged from TSC organoids after 12 days compared to control. This study shows the first known implementation of a stem cell line to exhibit 3D tuberous sclerosis phenotypes in a purely human in vitro environment. Further steps include functional assays, next-gen sequencing, and compound screening to find new treatments for this devastating disease.

Funding Source: Neuroscience Department, Novartis Institutes for Biomedical ResearchEducation Office, Novartis Institutes for Biomedical Research

SEAMLESS GENE CORRECTION IN HUNTINGTON DISEASE PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS USING CRISPR-CAS9 AND PIGGYBAC

Xu, Xiaohong[1], Huang, Yihui[1], Ooi, Jolene[1], Utami, Kagistia H.[1], Sim, Bernice[1], Tay, Yilin[1], Ginhoux, Florent[2] and **Pouladi, Mahmoud**[1,3]

[1]Agency for Science, Technology and Research, Singapore, [2]Singapore Immunology Network, Singapore, [3]National University of Singapore, Singapore,

Huntington disease (HD) is an autosomal-dominant neurodegenerative disease caused by a CAG trinucleotide expansion in the Huntington (HTT) gene. Despite extensive efforts being devoted to the discovery and evaluation of therapeutic targets for HD in animal models, no effective treatments have been developed to date. A major caveat of animal based-studies is the potential for species-specific effects that limits their construct and predictive validity for human diseases, including HD. In this context, human induced pluripotent stem cells (iPSCs) derived from HD patients provide a more physiologically relevant cellular platform for disease modelling and drug screening studies. However, iPSCs reprogramed from different individuals may exhibit variability in differentiation potential and cellular phenotypes that are independent of the HTT mutation due to variations in genetic background. Thus, in order to accurately detect authentic disease phenotypes and subtle alterations in cell function in iPSC-based models, the establishment of isogenic controls is necessary. Here we report the seamless correction of an HD iPSC line carrying an expansion of 180 CAG repeats using a CRISPR-Cas9 and PiggyBac transposon-based homologous recombination approach. Our results suggest that some molecular changes and phenotypes observed in HD iPSC models compared with non-related healthy controls in fact reflect differences in the genetic background of the respective lines rather than disease-specific mutant HTT effects, as indeed these changes are not rescued in the corrected counterparts. Therefore, our study provides an example of seamless correction of iPSCs from neurodegenerative disease patients and also demonstrates the importance of isogenic controls for disease modelling using iPSCs.

Funding Source: Agency for Science, Technology and Research (A*STAR, Singapore); National University of Singapore; Ministry of Education (Singapore)

MODELLING THE PHARMACOLOGICAL AND CLINICAL RESPONSE IN PRIMARY ERYTHROMELALGIA USING INDUCED PLURIPOTENT STEM CELLS

Nitzsche, Anja[1], Cao, Lishuang[1], McDonnell, Aoibhinn[1], Alexandrou, Aristos[1], Saintot, Pierre-Philippe[1], Loucif, Alexandre[1], Brown, Adam R[1], Young, Gareth[1], Mis, Malgorzata[2], Randall, Andrew[2], Waxman, Stephen G.[3], Stanley, Philip[1], Kerby, Simon[1], Tarabar, Sanela[1], Gutteridge, Alex[1], Allsopp, Timothy[1], Butt, Richard[1], McKernan, Ruth[1], Whiting, Paul[1], Ali, Zahid[1], Bilsland, James[1] and Stevens, Edward B[1]

[1]Pfizer Ltd, Neuroscience & Pain RU, Cambridge, U.K., [2]University of Bristol, Bristol, U.K., [3]Yale Centre for Neuroscience & Regeneration Research, Veterans Affairs Medical Centre, West Haven, CT, U.S.

Patient derived induced pluripotent stem cells (iPSC) largely recapitulate disease pathophysiology and hold great promise for novel drug target validation. The technology has significant potential enabling novel therapeutics testing on individual patients and their cognate iPSC-derived cells, to better predict efficacy. However, there are few clear examples of a candidate therapeutic response in patient iPSC disease models actually correlating to an effect in the clinic, particularly for chronic neuropathic pain. Inherited Erythromelalgia (EM) is associated with gain-of-function mutations in the peripheral nerve

sodium channel subunit Nav1.7 largely triggered by heat. In this study, the response of a potent small molecule to specifically inhibit the channel was investigated. Five EM patients, with unique mutations and well documented clinical history, received the channel inhibitor. There was an overall statistically significant treatment response, in a range correlating to a mechanistic effect described by the individual mutations. iPSC generated from these patients together with those from four healthy donors were differentiated into sensory neurons. Electrophysiological characterisation demonstrated spontaneously firing neurons, increased excitability and aberrant response to heat in the patient neurons. Careful analysis revealed a range of hyper-excitability linked to individual mutations, an effect normalised with the Nav1.7 inhibitor. EM is a complex clinical pain phenotype and no direct cellular to clinical response relationship was discernible, though a correlation of the mildest to most severe clinical phenotype did correspond with the pre-clinical hyper-excitability in cognate iPSC sensory neurons. This bench to beside approach is a proof-of-concept to illustrate the translational power of iPSC technology. iPSC derived sensory neurons enable recapitulation of sensory nerve fibre dysfunction in vitro, validation of the Nav1.7 channel as pivotal in the underlying disease mechanism and support the characterisation of a novel selective channel blocker as a putative treatment option. Future studies will verify if iPSC derived sensory neurons can be suitable for predicting treatment response in larger patient cohorts in a personalised medicine approach.

Funding Source: Pfizer Ltd.

NEURAL STEM CELL THERAPY IN SPINAL CORD INJURY: SPINAL CORD "REPLACEMENT" ENABLES HOST AXONAL REGENERATION

Tuszynski, Mark[1,2], Kadoya, Ken[1,3], Poplawski, Gunnar[1], Lu, Paul[1,2], Rosenzweig, Ephron[1], Lee, Corinne[1], Kimamaru, Hiromi[1], Koffler, Jacob[1], Gibbs, Dan[1], Adler, Andrew[1], Collyer, Eileen[1], Dulin, Jennifer[1] and Hunt, Matt[1]

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The injured adult central nervous system exhibits very little capacity to regenerate after spinal cord injury. In contrast, grafts of neural stem cells to sites of spinal cord injury extend extremely large numbers of axons over very long distances (at least 50 mm). Notably, while regeneration of injured adult axons is severely restricted in spinal cord white matter, myelin actually stimulates the growth of axons emerging from neural stem cell grafts, a finding that is related to the expression of specific cell surface antigens on myelin that interact with stem cell-derived axons. We have recently found that implants of neural stem cells also enable the regeneration of injured host axons into the spinal cord lesion site (filled with a neural stem cell graft). The most important axonal system for the control of voluntary movement in humans is the corticospinal projection, yet this system that has been refractory to most efforts to promote its regeneration. However, when neural stem cells are driven to caudal neural (i.e., spinal cord) fates and implanted into sites of spinal cord injury, corticospinal axons regenerate in large numbers into the lesion site. Mouse, rat and non-human primate corticospinal axons all exhibit similar responses to implants of caudalized neural stem cell grafts. Within the lesion, regenerating corticospinal axons form synaptic connections with grafted neural stem cells; these grafts in turn extend axons caudal to the injury site and form synapses with the host. In this manner, a synaptic relay is formed across the injury site that in some models supports improvement in functional outcomes. We are currently exploring cellular and molecular mechanisms underlying this extraordinary degree of axonal growth, while attempting to develop practical methods for possible application to human clinical trials.

Funding Source: CIRM, Veterans Administration, NIH, Craig H. Neilsen Foundation, Wings for Life

THURSDAY 23 JUNE, 16:00 – 18:00

CONCURRENT II: STEM CELLS IN ORGAN DEVELOPMENT AND MAINTENANCE

Level 2, Rooms 2020/2022

LGR5 STEM CELL-BASED ORGANOIDS IN HUMAN DISEASE

van de Wetering, Marc

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.

SINGLE-CELL RNA-SEQ ENABLES SPATIAL ALIGNMENT OF CHICK PRIMITIVE STREAK CELLS TO REVEAL NOVEL MARKERS OF ENDODERM AND MESODERM DIFFERENTIATION

Vermillion, Katie L., Leng, Ning, Thomson, James and Vereide, David

Morgridge Institute for Research, Madison, WI, U.S.

In the developing vertebrate embryo, the foundation of a body plan is established during gastrulation, a complex process that involves the precise choreography of the migration, proliferation, and differentiation of thousands of cells. Gastrulation initiates with the formation of the primitive streak, the site at which epiblast cells ingress to form the endoderm and mesoderm. By stage four in the chicken embryo, the primitive streak contains cells specified to become particular tissues. For example, fate maps reveal that the anterior primitive streak contains cells destined to become the axial mesoderm, including the notochord, somites and heart, while the posterior primitive streak contains cells that will give rise to the lateral mesoderm including blood, blood vessels and the coelomic cavity. In this study, we employed single-cell RNA-seq to further resolve the complexity of the primitive streak. Using a novel statistical tool named Wave-Crest, the spatial alignment of single primitive streak cells was reconstructed along the anterior-posterior axis. The accuracy of Wave-Crest was confirmed by published gene expression databases. Using the reconstructed alignment, we identified novel markers of endoderm and mesoderm. Several of the novel markers are involved in cell signaling including SKAP2, which plays an essential role in the Src signaling pathway, and MICAL2, which is a key regulator of SRF signaling. We hypothesize these markers can be employed to identify distinct progenitors within the primitive streak and guide the generation of tissues from pluripotent stem cells in vitro.

BREAKDOWN OF GAP JUNCTIONAL COMMUNICATION RESULTS IN BLOCK OF PRIMITIVE ENDODERM FORMATION

Edenhofer, Frank[1], Wörsdörfer, Philipp[2], and Willecke, Klaus[3]

[1]University of Innsbruck, Innsbruck, Austria, [2] Institute of Anatomy and Cell Biology, University of Würzburg, Würzburg, Germany [3]University of Bonn, Germany

Gap junctional intercellular communication (GJIC) has been suggested to play a role during early embryonic development but the particular function remain largely unknown. Connexin (Cx) 43 and Cx45 are co-expressed in embryonic stem (ES) cells, form gap junctions and are considered to exhibit adhesive function and/or to contribute to the establishment of defined communication compartments. Here we describe the generation of Cx43/Cx45-double deficient mouse ES cells to achieve almost complete loss of GJIC. Deletion of both, Cx43 and Cx45, results in a global block of differentiation without affecting pluripotency markers and proliferation. Employing embryoid body formation as an in vitro model we demonstrate that GJIC-incompetent ES cells fail to form primitive endoderm, representing the inductive key step of gastrulation. Lentiviral overexpression of either Cx43 or Cx45 in Cx43/45 mutants rescued the observed phenotype, confirming the specificity and indicating a redundant function of both connexins. GJIC-incompetent ES cells exhibit a strikingly altered subcellular localization pattern of the transcription factor NFATc3 indicating Calcineurin-NFTA signaling affected by Cx depletion. In fact, chemical inhibition by Cyclosporin A , a known Inhibitor of Calcineurin-NFTA signaling, phenocopies loss of GJIC in wild type control cells. Our study shows that intercellular communication via gap junction channels is essential for global differentiation via the synchronized formation of well-structured primitive endoderm, representing the key step of early development.

UNVEILING LINEAGE DECISIONS IN DEVELOPING TISSUES

Rulands, Steffen[1], Chabab, Samira[2], Lescroart, Fabienne[2], Blanpain, Cedric[2] and Simons, Benjamin David[2]

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While lineage tracing has greatly advanced our understanding of stem cell fate choice in adult tissues, in development the application of clonal analysis remains a major problem. Due to cell dispersal or mechanical deformations labeled clones often fragment into disconnected clusters or merge to compounds of clones. Naturally, the analysis of these lineages is highly ambiguous. But how can we learn from lineage tracing studies about these kinds of developing tissues? We answer this question in the context of heart development. We combined lineage tracing experiments with biophysical modelling to reconstruct the fragmented lineages. With this we are able to unveil the behavior of the earliest precursors of the heart. We identify the time points of differentiation of these precursors and characterize their division modes and regional specification. However, our results are not restricted to heart development: we find that fragment sizes follow simple, universal distributions which do not depend on the specific biological context. This suggests that there are simple laws that generate the outcome of these experiments. Indeed, drawing upon the physics of aerosols

we define a generic framework for the interpretation of clonal fate data in developing tissues.

Funding Source: S.C. is supported by fellowship of the FRS/FRIA. F.L has been supported by the EMBO long-term fellowship. B.D.S. and S.R. are supported by Wellcome Trust (grant number 098357/Z/12/Z). C.B. is an investigator of WELBIO.

MODELING DIABETIC BETA CELL FAILURE USING HUMAN MULTIPOTENT PANCREATIC PROGENITORS

Trott, Jamie[1], Tan, Jennica[1], Ong, Sheena[1], Bonnard, Carine[2], Al-Shboul, Mohammad[2], Reversade, Bruno[2] and Dunn, Ray[2]

[1]Institute of Medical Biology, Singapore, [2]Institute of Medical Biology, Singapore, Singapore

A major objective of regenerative medicine is to generate specialised cell types for modelling and treating degenerative illnesses. Of particular interest are the Insulin secreting pancreatic beta cells that are responsible for maintaining normal blood glucose levels, and whose failure leads to diabetes. Human Pluripotent Stem Cells (hPSC) have been proposed as an unlimited source of beta cells for studying and treating diabetes. However, the complex, multi-step differentiation protocols used to derive functional beta cells from hPSC inevitably exhibit considerable batch-to-batch variability, particularly when applied to PSC from different genetic backgrounds. We have developed conditions for culturing multipotent pancreatic progenitors, which are also capable of long-term expansion but are developmentally much closer to beta cells. These cells express markers characteristic of pancreatic progenitors, including the key transcription factors PDX1 and SOX9. Exposure to differentiation cues induces upregulation of markers of the exocrine, endocrine and ductal pancreatic lineages indicating multi lineage potency. Cultured pancreatic progenitors are currently being used to generate models of diabetic beta cell failure. We have identified 12 consanguineous families in which inheritance of beta cell failure enables studies of the fundamental mechanisms underlying diabetes. A variety of genetic approaches have been used to identify pathogenic mutations in genes associated with beta cell function. We are currently using a 3D differentiation system to identify physiological differences between beta cells generated from diabetic and sibling control pancreatic progenitors.

REPROGRAMMING NEURONAL DIVERSITY IN VIVO

Arlotta, Paola

Harvard University, Cambridge, MA, U.S.

Neurons of the mammalian central nervous system (CNS) are a classic example of a stable, terminally differentiated cell type. With the exception of the adult neurogenic niches, where a limited set of neuronal subtypes continues to be generated throughout life, CNS neurons are only born during embryonic development. Once generated, neurons become permanently postmitotic and do not change their identity for the lifespan of the organism. Focusing on pyramidal neurons of the cerebral cortex, I will present data showing that during a defined window of time ("critical window of nuclear plasticity") postmitotic neurons can still change their class-specific identity, and that this reprogramming event can be induced in vivo. I will then discuss recent work indicating that reprogramming the class identity of pyramidal neurons is in turn sufficient to change the afferent inhibitory input onto the reprogrammed neurons, suggesting that reprogramming pyramidal neuron class-specific identity can actively rewire the cortical local circuit. All together, the work suggests that direct neuronal reprogramming is a new tool to probe the normal plasticity of the brain, and inspires its application to change circuit connectivity in psychiatric and neurodevelopmental pathologies.

FRIDAY, 24 JUNE

PLENARY IV: GENE NETWORKS AND EPIGENETICS

PERSONAL REGULOME NAVIGATION

Chang, Howard Y.

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In biology as in real estate, location is a cardinal organizational principle that dictates the accessibility and flow of informational traffic. An essential question in nuclear organization is the nature of the address code—how objects are placed and later searched for and retrieved. Long noncoding RNAs (lncRNAs) have emerged as key components of the address code, allowing protein complexes, genes, and chromosomes to be trafficked to appropriate locations and subject to proper activation and deactivation. LncRNA-based mechanisms control cell fates during development, and their dysregulation underlies some human disorders caused by chromosomal deletions and translocations. I will describe a new technology based on DNA transposition that reveals the epigenomic profiles of single cells or from clinical biopsies of disease states. Together these insights are enabling the personal navigation of the gene regulatory landscape in health and disease.

DISSECTING CHROMATIN TO ENHANCE CELL REPROGRAMMING

Zaret, Kenneth S.

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

Cell fate changes involve dramatic and discrete switches in gene expression repertoires. Such changes are initiated by pioneer transcription factors, which can access genes in silent chromatin that are unmarked for activation or repression. Yet most directed cell differentiation, e.g., cell reprogramming, is inefficient, and the inefficiency traces back to highly compacted, heterochromatic domains that are actively repressed and can block pioneer factor access. It has been possible to overcome heterochromatic barriers by broadly impeding general chromatin components, which also helps cellular reprogramming. However, heterochromatin occurs at highly repeated sequences at centromeres, telomeres, and retrotransposons, helping to keep the domains silent and non-recombinogenic. Thus disrupting all heterochromatin, to facilitate reprogramming, could have undesired consequences on genome stability. I will discuss our new analysis of diverse proteins that are embedded in heterochromatin, to understand how heterochromatin barriers can be overcome in a specific fashion and promote high-fidelity cell fate changes.

ESTABLISHING ENHANCER LANDSCAPES REQUIRES COLLABORATION BETWEEN TRANSCRIPTION FACTORS, CHROMATIN MODIFIERS AND PAUSED POL II

Scruggs, Benjamin, Henriques, Telmo, Khan, Abid, Sharma, Vineet, Burkholder, Adam, Fargo, David and **Adelman, Karen**

NIEHS - NIH, Research Triangle Park, NC, U.S.

Differentiation of pluripotent cells involves coordinated changes in gene expression and chromatin architecture. Paramount to this process is the evolution of specific enhancer landscapes that direct cell-type specific patterns of transcription activation and repression. Importantly, enhancers are characterized by the binding of lineage-specifying transcription factors to regions of accessible chromatin and are marked with certain histone modifications. Moreover, enhancers recruit the transcription machinery and are actively transcribed by Pol II, with levels of enhancer RNA synthesis reflecting enhancer strength. I will describe our investigations of enhancers in pluripotent embryonic stem cells, and how the location and activity of enhancers is altered during differentiation to achieve a particular cell state. We find that events governing the appearance and potency of enhancers during development include regulated recruitment of RNA polymerase II to enhancers, as well as the pausing of Pol II during early transcription elongation. We provide evidence that paused Pol II is key for maintenance of open chromatin within enhancer loci and for stabilization of transcription factor occupancy. Thus, in addition to synthesizing enhancer RNA species, the occupancy of enhancers by Pol II sculpts local chromatin architecture, enabling cell-type specific profiles of gene expression.

TRANSCRIPTIONAL REGULATION OF CARDIAC DIFFERENTIATION AND CHROMATIN STRUCTURE

Bruneau, Benoit

Gladstone Institutes of Cardiovascular Disease, San Francisco, CA, U.S.

Complex networks of transcription factors regulate cardiac cell fate and morphogenesis, and dominant mutations in transcription factor genes lead to most instances of inherited congenital heart defects (CHDs). The mechanisms underlying CHDs that result from these mutations is not known, but regulation of gene expression within a relatively narrow developmental window is clearly essential for normal cardiac differentiation and morphogenesis. We have detailed the interactions between CHD-associated cardiogenic transcription factors, their interdependence in regulating cardiac gene expression and morphogenesis, and their function in establishing early cardiac lineage boundaries that are disrupted in CHD. We have

also delineated an essential role of CTCF in regulating genome-wide three-dimensional chromatin organization.

POSTER TEASERS

F-1061
INDUCTION OF HEMATOPOIETIC STEM AND PROGENITOR CELLS FROM HUMAN PLURIPOTENT STEM CELLS VIA IN VIVO SCREENING OF DEFINED FACTORS

Sugimura, Ryohichi and Daley, George Q.

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

F-2082
INDUCED PLURIPOTENT STEM CELL-DERIVED REJUVENATED T-CELL THERAPY WITH SUICIDE GENE-BASED SAFEGUARD SYSTEM

Ando, Miki[1], Nishimura, Toshinobu[2], Yamazaki, Satoshi[1], Yamaguchi, Tomoyuki[1], Brenner, Malcolm[3] and Nakauchi, Hiromitsu[1,2]

[1]The University of Tokyo, The Institute of Medical Science, Tokyo, Japan, [2]Stanford University, Stanford, CA, U.S., [3]Baylor College of Medicine, Houston, TX, U.S.

F-3033
LARGE SCALE, EFFICIENT PRODUCTION OF HPSC-DERIVED MIDBRAIN DOPAMINERGIC NEURONS IN A DEFINED, 3D BIOMATERIAL PLATFORM

Adil, Maroof M.[1], Rodrigues, Goncalo M. C.[2], Kulkarni, Rishikesh U.[1], Rao, Antara T.[1], Chernavsky, Nicole E.[1], Miller, Evan W.[1] and Schaffer, David V.[1]

[1]University of California Berkeley, Berkeley, CA, U.S., [2]SCBL-RM, Lisbon, Portugal

F-2153
COMPARATIVE EPIGENOMIC PROFILING OF REGULATORY ELEMENTS IN HUMAN AND CHIMPANZEE STEM CELLS REVEALS SPECIES-SPECIFIC ENDOGENOUS RETROVIRUS ACTIVITY

Narvaiza, Iñigo[1], Benner, Christopher[1], Wang, Meiyan[1], Marchetto, Maria Carolina[1], Ku, Manching[1], Japelli, Roberto[1], Swigut, Tomasz[2], Wysocka, Joanna[2] and Gage, Fred H.[1]

[1]Salk Institute for Biological Studies, La Jolla, CA, U.S., [2]Stanford University, Stanford, CA, U.S.

THE ANNE MCCLAREN MEMORIAL LECTURE

THE DYNAMICS OF THE EPITHELIAL-TO-MESENCHYMAL TRANSITION DURING MOUSE GASTRULATION

Ramkumar, Nitya, Hernández-Martínez, Rocío, Omelchencko, Tatiana and **Anderson, Kathryn V.**

Sloan Kettering Institute, New York, NY, U.S.

The epithelial epiblast of the post-implantation mouse embryo gives rise to all the lineages of the mouse embryo. The gastrulation epithelial-to-mesenchymal transition (EMT) transforms this pluripotent epiblast into the lineage-committed cells of the mesoderm and definitive endoderm. Genetic studies have shown that Wnt, Nodal and BMP signaling pathways are required for the EMT, but the cellular mechanisms that mediate the EMT have not been defined. Using genetic approaches to dissect the process of mouse gastrulation, we find that Crumbs2 (CRB2), an apical polarity protein, is required for the transcriptional switch from SOX2 to SNAIL1 that controls the EMT. In addition, anisotropic distribution of CRB2 appears to define which of the cells within the streak region will undergo EMT. In other studies, we find that regulation of adherens junctions by p120-catenin controls the size of the region undergoing EMT, in part through regulation of Wnt signaling. Our goal is to combine analysis of embryonic phenotypes, live imaging and experiments in mutant ES cells in order to define cellular mechanisms required for the transition from pluripotency to lineage commitment in vivo.

FRIDAY 24 JUNE, 13:15 – 15:15

CONCURRENT III: NEURODEVELOPMENT AND REGENERATION

Level 2, Rooms 2001/2003/2005/2007

STEM CELL HETEROGENEITY IN THE ADULT NAIVE AND INJURED BRAIN: LESSONS FROM SINGLE CELL TRANSCRIPTOMICS

Martin-Villalba, Ana, Zhao, Sheng, Llorens-Bobadilla, Enric, Baser, Avni and Kalamakis, Georgios

German Cancer Research Center (DKFZ), Heidelberg, Germany

Adult mammalian neurogenesis is best characterized in the neurogenic niche of the subventricular zone of the lateral ventricles and the subgranular zone of the dentate gyrus. The process of neurogenesis includes activation of neural stem cell to generate neurogenic progenitors that

differentiate in preset glial and neuronal lineages. This process can be influenced by signals present within the microenvironment of the niche that are regulated by environmental factors such as physical exercise, mood disorders, injury, and others. The study of heterogeneity in the response of neural stem cells to these events has not fully been addressed yet. In my talk I will discuss what we have learned about neural stem cell heterogeneity in the adult brain during homeostasis and following injury to the CNS and how they compare to stem cells in other organs.

MOLECULAR ANATOMY OF MIDBRAIN AND DOPAMINE NEURON DEVELOPMENT IN MOUSE, HUMAN AND STEM CELLS

Arenas, Ernest[1], La Manno, Gioele[1], Gyllborg, Daniel[1], Codeluppi, Simone[1], Salto, Carmen[1], Zeisel, Amit[1], Stott, Simon[2], Borm, Lars E[1], Toledo, Enrique M[1], Villaescusa, J Carlos[1], Lönnerberg, Peter[1], Ryge, Jesper[3], Barker, Roger A[2] and Linnarsson, Sten[1]

[1]Karolinska Institutet, Stockholm, Sweden, [2]University of Cambridge, U.K., [3]Ecole Polytechnique Federale de Lausanne, Lausanne, Switzerland

A better molecular understanding of human midbrain development is necessary in order to guide efforts to engineer dopaminergic neurons for cell replacement therapy in Parkinson's disease. Here we define ventral midbrain cell types in both human and mouse, based on single-cell RNA-seq, and reveal the temporal dynamics of key lineages across mouse and human development and in adult mouse dopaminergic neurons. Development was strikingly conserved across species, but key differences in timing and transcription factors were observed. Our study identifies five distinct types of ventricular zone cells in ventral midbrain development, three radial glia-like cell types, one neuronal progenitor and one ependymal cell type. Multiple intermediate neuroblasts with transcription factors later found in GABAergic, serotonergic, cholinergic and dopaminergic neurons were also identified. Surprisingly three types of dopaminergic neurons were detected during embryonic development. These cells diversified and developed into five distinct classes of postnatal dopaminergic neurons. This comprehensive mouse and human reference dataset was subsequently used to assess the content and quality of human pluripotent stem cells differentiated into dopaminergic neurons. Single-cell analysis of these cells revealed a variety of cell types corresponding to those found during human fetal midbrain development in vivo,including authentic dopaminergic neurons, but also partially differentiated cells. In sum, the identification and characterization of ventral midbrain cell types in mouse and human development has allowed us to establish a rigorous and quantitative method to assess stem cell preparations. Moreover our analysis can guide future efforts towards improving the quality and safety of human pluripotent stem cell-derived midbrain dopaminergic cells intended for cell replacement therapy in Parkinson's disease.

Funding Source: This project was supported by EU-FP7 (DDPD-Genes and NeuroStemCellRepair), ERC, Swedish Research Council and Swedish Foundation for Strategic Research.

HARNESSING WNT/BETA-CATENIN SIGNALING TO ENABLE HIGHLY EFFICIENT DERIVATION OF HUMAN MOTOR NEURONS FROM ANY SPINAL CORD REGION

Ashton, Randolph S.[1], Lippmann, Ethan[1,2], Sehgal, Neha[1,2], Estevez-Silva, Maria[1,2], Williams, Clay[2,3], Ruhl, David[2,4], Bakooshli, Mohsen[5], Knight, Gavin[1,2], Lemke, Kristen[1], Plantz, Joshua[1], Chapman, Edwin[2,4], Gilbert, Penney[6] and Coon, Joshua[2,3]

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Wnt/ß-catenin signaling plays a critical role in both caudalizing and ventralizing spinal cord tissues during development to pattern a diverse spectrum of efferent motor neuron (MN) phenotypes. This diversification of MN phenotype regulates their connectivity with distinct peripheral tissues and conveys variable susceptibility to degenerative diseases. Gaining a comprehensive, molecular understanding of MN diversity is limited by the fact that current derivation protocols only generate a single, predominantly cervical regional MN phenotype. Hence, we sought to develop a singular protocol capable of efficiently deriving the vast spectrum of spinal MN phenotypes from human pluripotent stem cells (hPSCs). This will facilitate elucidation of their molecular diversity, mechanisms underlying variable disease susceptibility, and potential use in regenerative therapies. Building on our chemically defined culture system to rapidly differentiate hPSCs into >90% $Pax6^+/Sox2^+$ neuroectoderm, we first developed a biphasic morphogen regimen, which recapitulates Wnt/ß-catenin's caudalizing role, to deterministically pattern HOX gene expression within human neuroectoderm. This enables derivation of >83% $Pax6^+/Sox2^+$ neuroectoderm cultures possessing HOX gene and transcription factor profiles indicative of distinct cervical, thoracic, and lumbar spinal cord domains. Secondly, we discovered that during hPSC motor neuron differentiation Wnt/ß-catenin signaling efficiently induces expression of the ventral transcription factor NKX6.1 (>90%), which is critical for subsequent induction of Olig2 by Sonic Hedgehog signaling. Thus, we integrated the dual patterning

roles of Wnt/ß-catenin to create a singular, chemically defined protocol capable of highly efficiently derivation of OLIG2$^+$ progenitors (>80%) and post-mitotic spinal MNs (~55-70%) from any cervical, thoracic, or lumbosacral spinal cord region. Furthermore, we demonstrate that the MNs mature to become electrophysiologically active and capable of forming neuromuscular junctions. Access to a spectrum of regional, human spinal MNs and progenitors will be broadly useful for drug discovery, disease modeling, and potentially as regenerative therapies.

WIDESPREAD MIGRATION AND INTEGRATION OF NEURONS IN THE EARLY POSTNATAL HUMAN FRONTAL CORTEX

Paredes, Mercedes

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

The first months of life are key to human brain development as a child begins interacting with its environment. The human frontal lobe has greatly increased in size and complexity compared to other mammals or non-human primates. To study the manner in which this region continues to develop postnatally, we followed young neurons from the walls of the lateral ventricles and sub-ventricular zone (V-SVZ) to their final cortical destinations using high-resolution MRI, histology, and time-lapse confocal microscopy. We discovered a prominent and transient population of Doublecortin (DCX)+ migrating young neurons in a stream we refer to as the Anterior Arch. These cells were distributed widely throughout the frontal lobe invading multiple cortical areas in the first three months of life. DCX+ cells within the Arch were organized into four distinct regions (or tiers): 1) subventricular I, 2) subventricular II, 3) perivascular, and 4) in the developing white matter. The orientation of elongated DCX+ cells suggested that migratory neurons closer to the ventricular wall, in Tiers 1 and 2, were largely dispersing tangentially, while those in Tiers 3 and 4 have a more radial orientation. These young neurons expressed markers of interneurons and their entry into the anterior cingulate cortex (a major target of the Arch used for quantification) was correlated with the emergence of specific subtypes of GABAergic interneurons (NPY, Somatostatin and Calretinin). The distribution of Calbindin and Parvalbumin subtypes did not change with age in a similar fashion. DCX+ cells also expressed transcription factors associated with the ventral progenitor regions, the medial and caudal ganglionic eminences (MGE and CGE). Altogether, these data reveal a major migration of young neurons into the frontal lobe at periods of brain development that may contribute to changes to the neural circuit composition and its maturation during early infancy. The late development of neurons in the Arch may be related to plasticity in the developing human frontal lobe and defects in this migration could result in circuit defects that underlie neurodevelopmental disorders.

Funding Source: CIRM (California Institute of Regenerative Medicine) Training GrantK08 Clinical Scientist Training Grant

CHARACTERIZATION OF LONG NON-CODING RNAS EXPRESSED DURING CELL TYPE TRANSITIONS IN CORTICAL NEURON DIFFERENTIATION FROM HUMAN, CHIMPANZEE, ORANGUTAN, AND RHESUS MACAQUE PLURIPOTENT STEM CELLS

Field, Andrew[1], Jacobs, Frank[1], Ewing, Adam[1], Rosenkrantz, Jimi[1], Harte, Rachel[1], Katzman, Sol[1], Salama, Sofie[1] and Haussler, David H.[1,2]

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The cerebral cortex has undergone rapid changes in size and complexity in the primate lineage, yet the molecular processes underlying primate brain development are poorly understood. We have developed a common protocol for cortical neuron generation from human, chimpanzee, orangutan, and rhesus pluripotent stem cells that recapitulates early neural development and enables us to do comparative molecular analysis. Here we focus on long non-coding RNAs (lncRNAs), which as a class have been implicated in gene regulation, differentiation of specific tissues, and, in some cases, play a role in the fine-tuning of developmental processes. Despite their potential importance in driving the development of tissues, studies focusing on lncRNAs have been impeded by the low sequence conservation and extremely tissue-specific expression patterns of functionally relevant lncRNAs. For this reason, we developed a new approach focusing on both the sequence and expression conservation of lncRNAs in equivalent developing tissues among closely related primate species. Using our protocol for neuron differentiation from human and non-human primate pluripotent stem cells to model early brain development, we collected RNA for high throughput total transcriptome sequencing at weekly time points and identified thousands of lncRNAs induced during cortical neuron formation in each species. Out of 2,684 putative lncRNA loci identified in our human samples, 88% share a homologous loci in rhesus. 57% of these loci are also expressed during rhesus neural differentiation. A higher proportion of these transcripts are expected to have conserved expression in chimpanzee and orangutan though the analysis of these tissues is not yet complete. Overall, cortical neuron associated lncRNAs are more conserved in both sequence and expression over the primate lineage than mammals as a whole, which may indicate that they contribute to primate-specific phenotypes. Functional studies using CRISPR based endogenous activation of the top human

lncRNA candidates are currently underway. These experiments will evaluate their importance during neurogenesis, provide insight to primate- and human-specific features of cortical development, and may also reveal the role of many disparate genetic lesions that contribute to human neurological diseases.

Funding Source: Howard Hughes Medical Institute, National Institutes of Health, California Institute for Regenerative Medicine

ORIGIN AND MAINTENANCE OF ADULT NEURAL STEM CELLS; NOT WHAT WE IMAGINED

Alvarez-Buylla, Arturo

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

The largest population of neural stem cells (NSCs) in the adult rodent brain are in the Ventricular-Subventricular Zone (V-SVZ). These primary progenitors correspond to a subpopulation of astroglial cells called B1 cells. In addition to oligodendroglias, B1 cells generate more than ten different subtypes of inhibitory interneurons that migrate to the olfactory bulb. B1 cells in different sub-regions of the V-SVZ are specialized for the production of these different subtypes. Surprisingly, regional specification is stablished very early in embryonic development. Recent findings indicate that B1 cells derive from RG that divide in the embryo and then remain largely quiescent for extended periods of time before becoming re-activated. This raises the basic question of how neurogenesis is maintained over long periods of time. The new data changes current views about the normal in vivo behavior and origins of adult NSCs.

FRIDAY 24 JUNE, 13:15 – 15:15

CONCURRENT III: GERMLINE STEM CELLS

Level 2, Rooms 2020/2022

USING CRISPR/CAS9 TO INTERROGATE GERM CELL FORMATION AND FUNCTION

Buszczak, Michael, Bhargava, Varsha, Goldstein, Courtney, Pineider, Juliana and Gonzalez, Kevin

UT Southwestern Medical Center, Dallas, TX, U.S.

While germ cells share many common features across species, fundamental aspects of germ cell biology remain poorly understood. To gain further insights into the mechanisms that regulate the function and activity of germline stem cells and their differentiating progeny, we have initiated an in vivo CRISPR-Cas9 screen to knockout over 100 uncharacterized genes that exhibit enriched expression in the Drosophila female germ line. Many of these genes have clear human orthologs, which also exhibit enriched expression in the germline. To date we have generated over 35 mutants, some of which exhibit a range of different germ cell specific phenotypes. We have recently begun to further characterize several of these mutants in more detail. One mutation of particular interest deletes a gene we call bedlam. Loss of bedlam results in a number of different phenotypes, including cell cycle defects and germ cell tumor formation. Bedlam belongs to a family of putative metallopeptidases that help to regulate DNA-protein adduct repair. Preliminary data using an immunofluorescence-based assay suggest that loss of bedlam results in increased DNA damage in germ cells. Given homology between Bedlam and its human ortholog, we anticipate the further molecular and biochemical characterization of Bedlam function will provide key insights into germ cell differentiation and the mechanisms that protect the integrity of the germline genome in multicellular organisms.

GERM CELL SELECTION IN DROSOPHILA EMBRYO

Slaidina, Maija[1] and Lehmann, Ruth[2]

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Selection of the fittest germ cells is essential for optimal reproduction and propagation of species. Here we uncover a novel genetic mechanism that ensures the selection of the fittest primordial germ cells in Drosophila embryo. These primordial germ cells will further contribute to the germline stem cell pool. In many animal species an excess number of germ cells are formed early during embryogenesis but only a fraction of these germ cells are incorporated in the gonad and contribute to the next generation, while the rest die. Here we explore whether germ cell survival vs. death fate decision is stochastic or predetermined and how it is regulated. We first identified that among early germ cells (stage 5) there are quantitative differences in inheritance of maternally provided factors depending on their localization (central vs. lateral) at the posterior pole of the embryo. By single cell labeling and tracking we demonstrated that germ cell fate decision – survival vs. death – is predetermined as early as the cells are specified. Moreover, higher inheritance of maternally provided germ cell determinants and the mRNA of a lipid phosphate phosphatase Wunen-2 (Wun2) correlated with higher survival. Wun and Wun2 are previously known regulators of germ cell migration and death. By genetic manipulations, we show that Wun2 expression level in germ cell determines their fate. Moreover, Wun2 regulates germ cell death independently of the tumor suppressor p53, which has been previously implicated in germ cell

death regulation. Thus germ cells are eliminated through at least two independent cell death pathways. We propose that both pathways together ensure selection of germ cells with the highest levels of maternally inherited germ cell determinants and the least cellular damage.

Funding Source: Maija Slaidina was a Howard Hughes Medical Institute Fellow of the Life Sciences Research Foundation.

DERIVATION AND DIFFERENTIATION OF HAPLOID HUMAN EMBRYONIC STEM CELLS

Sagi, Ido[1], Chia, Gloryn[2], Golan-Lev, Tamar[1], Peretz, Mordecai[1], Weissbein, Uri[1], Sui, Lina[2], Sauer, Mark[2], Yanuka, Ofra[1], Egli, Dieter[2,3] and Benvenisty, Nissim[1]

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Diploidy is a fundamental genetic feature in mammals, in which haploid cells normally arise only as post-meiotic germ cells that serve to insure a diploid genome upon fertilization. However, haploid cells provide valuable tools for delineating genome function through loss-of-function genetic screening. Gamete manipulation has yielded haploid embryonic stem (ES) cells from several mammalian species, but as of yet not from humans. Here we generated and analyzed a collection of 14 human parthenogenetic ES cell lines originating from haploid oocytes, leading to the successful isolation and maintenance of human ES cell lines with a normal haploid karyotype. Haploid human ES cells exhibited typical pluripotent stem cell characteristics, such as self-renewal capacity and a pluripotency-specific molecular signature. Although haploid human ES cells resembled their diploid counterparts by several aspects, they also displayed distinct properties including differential regulation of X chromosome inactivation and genes involved in oxidative phosphorylation, alongside reduction in absolute gene expression levels and cell size. Most surprisingly, while studies on mouse haploid ES cells showed that haploidy is lost upon differentiation, we found that a haploid human genome is compatible not only with the undifferentiated pluripotent state, but also with differentiated somatic fates representing all three embryonic germ layers both in vitro and in vivo. Importantly, differentiation occurred despite persistent dosage imbalance between the autosomes and X chromosome. The surprising differentiation potential of haploid human genomes suggests that diploidy-dependent adaptations, rather than haploidy, pose the predominant barriers for human development. Finally, we demonstrated the utility of haploid human ES cells for loss-of-function genetic screening by analyzing a haploid gene-trap mutant library for genes conferring resistance to the purine analog 6-thioguanine. Thus, haploid human ES cells hold a great potential for biomedically-relevant functional genomics by forward genetic screening, and will provide novel means for studying human genetics and development.

A NOVEL NICHE–STEM-CELL SIGNALLING MACHINERY IN THE DROSOPHILA TESTIS

Inaba, Mayu[1,2], Yamashita, Yukiko[2] and Buszczak, Michael[1]

[1]UT Southwestern Medical Center, Dallas, TX, U.S., [2]University of Michigan, Ann Arbor, MI, U.S.

Stem cells reside in the local microenvironments called "niches". Niches keep resident stem cells in an undifferentiated and self-renewing state. Stem cells and their differentiating daughters are often immediately juxtaposed to one another, raising the question of how niche signaling is spatially confined only to stem cells. Many of the same molecules used by niches are broadly used in other contexts for long-range signaling. For example, Drosophila BMPs, Hh, Wnt/Wg proteins function in embryonic patterning where they are thought to "diffuse" over relatively long distances. The mechanism how these same signals are used in the confined space of the niche remains poorly understood. Drosophila germline stem cells (GSCs) provide a powerful model for studying stem cells, because individual stem cells and niche components are easily identified and abundant genetic tools are available for functional analysis. Male GSCs are directly attached to the hub cell cluster, a major niche component, and divide asymmetrically to produce one stem cell and the other differentiating daughter gonialblast (GB). Hub cells secrete Dpp, a Drosophila BMP ligand, toward GSC, activating the signaling only in GSCs, but not in GBs. We recently discovered previously unrecognized cellular protrusions, termed MT (microtubule-based)-nanotubes, that are specifically formed by GSCs and integrate into deep inside of the niche tissue (hub cell cluster). MT-nanotubes transport Tkv, the receptor for BMP ligand, into the hub where it interacts with ligand produced by the hub cells. Disruption of MT-nanotubes impaired activation of BMP signaling and thus stem cell maintenance. Our data collectively suggest a novel mechanism of specific niche signaling, where the stem cells acquire niche ligand by extending MT-nanotubes directly into the niche cells instead of relying on passive diffusion of ligand from the source. This also explains how differentiating cells are excluded from the niche signaling, providing a mechanistic basis for the short-range nature of the niche signaling.

Funding Source: a DeLill Nasser Travel Award for Professional Development in Genetics for 2016

CELLULAR ORGANELLE REPLACEMENT FOR PREVENTION OF INCURABLE MITOCHONDRIAL DISEASES

Zhu, Jianhong

Fudan University Huanshan Hospital, Shanghai, China

The field of stem cell therapy and organelle replacement is rapidly growing. We focus on mitochondrial replacement in order to discuss the challenges and successes of what it takes to make the cutting edge of science translate from research to patients. Mitochondria – bacteria sized cellular organelles --convert fuel from food into the body's most biologically useful form of energy or ATP. Large numbers of mitochondria DNA (mtDNA) deletions in brain and muscle, become fatal or in young adulthood with epilepsy, while a maternally inherited point mutation in patients with Leber's hereditary optic neuropathy, a cause of blindness in young adults. Currently, mitochondria diseases are refractory or incurable; however, nuclear genome transfer between patients' and healthy eggs to replace mutant mtDNAs holds promises. Considering that a polar body contains few mitochondria and shares the same genomic material as an oocyte, we perform polar body transfer to prevent the transmission of mtDNA variants. We compare the effects of different types of germline genome transfer, including spindle-chromosome transfer, pronuclear transfer, and polar body transfer, in mice. Genetic analysis confirms that the F1 generation from polar body transfer possesses minimal donor mtDNA carryover. Moreover, the mtDNA genotype remains stable in F2 progeny after polar body transfer. Our investigation demonstrates that mitochondrial replacement has great potential to prevent inherited mitochondrial diseases.

Funding Source: This study was supported by grants (2012CB966300, 2010CB945500, 81271003) from the National Nature Science Foundation and Ministry of Science and Technology of China

DEVELOPMENT OF THE HUMAN GERMLINE

Surani, Azim

Wellcome Trust/Cancer Research UK Gurdon Institute/ University of Cambridge, U.K.

Specification of primordial germ cells (PGCs) in mammals occurs during development of postimplantation epiblast cells, which is followed by dynamic epigenetic changes and comprehensive DNA demethylation. Specification of human PGCs (hPGCs) occurs during ~Wk2 of gestation. We recently developed an in vitro model with hESCs and iPSC, to examine the mechanism of hPGC specification. The in vitro derived PGCs showed conserved characteristics with authentic hPGCs isolated from Wk5-Wk7 human embryos, and a human seminoma cell line. This unexpectedly revealed SOX17 as the key regulator hPGC fate, which is not the case in mice. SOX17 gene dosage is apparently critical for hPGC fate, and requires BLIMP1 for the repression of mesendodermal fate. BLIMP1-SOX17 also contributes to the initiation of epigenome resetting in the early human germ cell lineage. Differences in the mechanisms of PGC specification between mouse and human are likely to be due to the evolutionary divergence in their post-implantation development, including the mechanisms that confer competence for germ cell fate. These observations provide insights on early human development at gastrulation. Advances in human germ cell biology will be important for an exploration of the transmission of genetic and epigenetic information to subsequent generations, and their consequences for human diseases.

FRIDAY 24 JUNE, 13:15 – 15:15

CONCURRENT III: STEM CELL AGING

Level 2, Room 2004

DIMINISHED APOPTOTIC PRIMING UNDERLIES INCREASED SURVIVAL OF AGED HEMATOPOIETIC STEM CELLS IN RESPONSE TO DNA DAMAGE

Rossi, Derrick J.[1,2], Gutierrez-Martinez, Paula[2], Hogdal, Leah[3], Nagai, Manavi[2] and Letai, Anthony[3]

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Aging in the hematopoietic system is characterized by reduced regenerative response, diminished immune competence, and elevated disease incidence; phenotypes that are attributable to a large extent to the hematopoietic stem cell (HSC) compartment. The mechanistic basis for age-associated HSC decline is complex with evidence indicating the involvement of a number of factors including DNA damage accumulation. How HSCs respond to DNA damage and whether this response changes during aging are poorly understood. Herein, we exposed HSCs purified from young and old mice to multiple different types of DNA damaging agents, and show that aged HSCs have increased survival at the clonal level. Whereas young HSCs exposed to DNA damaging agents have diminished in vivo potential compared to untreated HSCs, the potential of old HSCs was unchanged by DNA damage induction. Using BH3 profiling we determined that HSCs are the least apoptotically primed population in the primitive compartment, and further, that the differential survival of old HSCs is attributable to attenuated apoptotic priming in old HSCs. Young HSCs exhibited greater dependence on the anti-apoptotic protein BCL-2 than aged HSCs. We further show that lineage-biased HSCs exhibit

differential apoptotic priming. Taken together these data demonstrate that old HSCs are intrinsically resistant to DNA damage induced apoptosis due to diminished BAD-BCL-2 dependent apoptotic priming, and that this likely underlies the oligoclonal expansion, and mutation accrual observed in the HSC compartment during aging.

REMODELING OF THE MULTIPOTENT PROGENITOR (MPP) POOL DIRECTLY CONTRIBUTES TO BLOOD AGING IN MICE

Verovskaya, Evgenia, Reynaud, Damien, Bakker, Sietske T., Zhang, Si Yi, Ho, Theodore T., Pietras, Eric M. and Passegué, Emmanuelle

Department of Medicine, Division of Hematology/ Oncology, The Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco, CA, U.S.

Blood production declines with age, resulting in anemia, lymphocytopenia and myeloid cell expansion, which predispose the elderly to a whole range of bone marrow (BM) failures and myeloid malignancies. Blood production is normally controlled by hematopoietic stem cells (HSC), through the regulated production of distinct multipotent progenitor (MPP) populations with specific myeloid or lymphoid lineage biases. While the mechanisms driving HSC aging are starting to be elucidated**,** it remains largely unknown how aging is affecting the MPP pool. Analyses of the BM of young (~6-12 week-old) and aged (~20-30 month-old) mice revealed decreased numbers of lymphoid-biased MPP4 and elevated production of myeloid-biased MPP2/3, suggesting changes in early lineages specification pathways from old HSCs. Old MPP2/3 also showed reduced clonogenic potential in methylcellulose assays, implying age-associated functional decline similar to old HSCs. In contrast, old MPP4 had elevated myeloid colony-forming activity and were unable to produce $CD19^{+}$ B cells when forced to differentiate in OP9/IL-7 conditions, demonstrating a strong myeloid bias. Young and old HSC, MPP2, MPP3 and MPP4 cells were also transplanted into sub-lethally irradiated congenic recipient mice and followed for blood reconstitution over time. Chimerism analyses showed a clear myeloid-bias in all old MPP populations, and confirmed reduced reconstitution activity from old MPP2/3. Genome-wide microarray and targeted Fluidigm gene expression analyses highlighted cell cycle genes as the most differentially regulated pathways in old MPP3 and MPP4, and suggested the constitutive activation of normally transient myeloid regeneration pathways from old HSCs. We are now exploring the mechanisms driving the old HSC activation and the functional impairment of old MPP2/3, focusing on the role of the aged BM niche microenvironment. Our results indicate that the remodeling of the MPP pool is an important contributor to blood aging, and suggest that the "reprogramming" of all old MPPs towards preferential production of myeloid cells directly contributes to lineage skewing and impaired blood production. Altogether, they open new directions for translational approaches aimed at rebalancing lineage production and rejuvenating blood production in the elderly.

Funding Source: Rubicon Grant from Netherlands Organization for Scientific Research; Stem Cell Grant from BD Biosciences

MECHANISMS UNDERLYING LOSS OF INTESTINAL HOMEOSTASIS WITH AGE IN DROSOPHILA MELANOGASTER

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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. In Drosophila melanogaster, advanced age leads to changes in the intestine, including an increase in intestinal stem cell (ISC) proliferation, accumulation of mis-differentiated cells, an increase in bacterial load, activation of inflammatory pathways, increases in ROS levels, and loss of intestinal barrier function. However, the relationship between these phenotypes remains unclear. We have investigated the links between age-related changes in the behavior of Drosophila ISCs and the loss of intestinal barrier function. Aging results in the mis-localization of occluding junction proteins in the posterior midgut, with the strongest alterations observed at the Tricellular Junction (TCJ) – a specialized structure located where three cells converge. Acute loss of the TCJ protein Gliotactin (Gli) in differentiated cells results in premature emergence of ISC aging phenotypes, including increased ISC proliferation and a block in differentiation in intestines from young flies, demonstrating that compromised TCJ function is sufficient to alter ISC behavior in a non-autonomous manner. Thus, occluding junctions are an integral component of the ISC niche. Blocking the Jun N-terminal kinase (JNK) signaling pathway is sufficient to suppress changes in ISC behavior but has no effect on loss of intestinal barrier function, as a consequence of Gli depletion. Our work provides a pivotal link between TCJ, stem cell behavior, and intestinal homeostasis and provides new insights into causes of age-onset and gastrointestinal diseases.

HO-1 DEFICIENCY IN THE NICHE TRIGGERS PREMATURE EXHAUSTION OF MOUSE HEMATOPOIETIC STEM CELLS

Szade, Krzysztof[1], Zukowska, Monika[1], Bukowska-Strakova, Karolina[1], Nowak, Witold Norbert[1], Szade, Agata Anna[1], Kachamakova-Trojanowska, Neli[1], Jozkowicz, Alicja[1] and Dulak, Jozef[2]

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The niche is critical for maintenance of hematopoietic stem cells (HSC), however the niche-derived factors that may regulate aging of HSC remain undiscovered. Here we report that heme oxygenase-1 (HO-1) in the niche protects HSC from premature exhaustion. HO-1 is an enzyme degrading heme to carbon monoxide, iron ions and biliverdin. While the expression of HO-1 in hematopoietic stem and progenitor cells ($Lin^-c\text{-}Kit^+Sca\text{-}1^+$, LKS) was low, we detected a high HO-1 expression in macrophages (6.8 fold higher vs. LKS), mesenchymal precursors (PaS, 13.2 fold higher), CXCL12-abudant reticular cells (CAR, 18.7 fold higher) and in the subset of $Sca\text{-}1^+$ endothelial cells (EC, 17.1 fold higher). Notably, HO-1 expression in CAR and EC decreased in old animals. We found that HSC ($LSK\ CD48^-CD150^+CD34^-$) from young HO-1 deficient ($HO\text{-}1^{-/-}$) mice extensively proliferated, lost quiescence and showed symptoms of premature aging. Young $HO\text{-}1^{-/-}$ mice possessed expanded HSC pool with more DNA damage. Next generation sequencing (NGS) revealed that transcriptome of young $HO\text{-}1^{-/-}$ HSC resembled transcriptome of old $HO\text{-}1^{+/+}$ HSC with dysregulated cell cycle, DNA repair process and altered metabolism. To verify the HSC-extrinsic role of HO-1 in regulation of HSC, we transplanted HSC from $HO\text{-}1^{+/+}$ donor mice into $HO\text{-}1^{+/+}$ or $HO\text{-}1^{-/-}$ recipients. After 32 weeks blood chimerism in $HO\text{-}1^{-/-}$ recipients was lower. When the same number of donor-derived bone marrow (BM) cells from $HO\text{-}1^{+/+}$ or $HO\text{-}1^{-/-}$ primary recipients was transplanted to the secondary $HO\text{-}1^{+/+}$ recipients, only the cells from $HO\text{-}1^{+/+}$ reconstituted primary recipients. Next, young $HO\text{-}1^{-/-}$ HSC reconstituted primary $HO\text{-}1^{+/+}$ recipients worse than $HO\text{-}1^{+/+}$ HSC. However, when the same number of donor derived cells from the primary recipients were transplanted to secondary recipients, $HO\text{-}1^{-/-}$ cells were as efficient as $HO\text{-}1^{+/+}$ cells in blood reconstitution. Comparison of transcriptomes of CAR and EC from $HO\text{-}1^{+/+}$ and $HO\text{-}1^{-/-}$ mice revealed that HO-1 deficiency caused decreased expression of SDF-1 and SCF, as well as altered expression of TGFß1. Lack of HO-1 was also linked with downregulation of angiopoietin-like 4. Concluding, HO-1 deficiency in the BM niche accelerates exhaustion of HSC stemness potential. This can be linked to decreased expression of SDF-1, SCF, and Angpl-4.

Funding Source: The research was supported by National Science Center in Poland within Preludium program (2013/11/N/NZ3/00956).

ESC-SPECIFIC FILIA/FLOPED/BLM COMPLEX REGULATES REPLICATION STRESS RESPONSE AND SAFEGUARDS GENOMIC STABILITY

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Replication stress is a complex phenomenon that has serious implications for genomic stability. Embryonic stem cells (ESCs) have an unusual cell cycle distribution that S phase represent 75% of the total cell cycle. Hence ESCs face with greater replication stresses than somatic cells. Understanding of the factors that regulate replication stress response could address the unique mechanisms of genomic stability in ESCs. With DNA fiber assay, we found that ESCs have greater capacities than somatic cells in response to replication stress, including fork stability, recovery, restart and new initiation of dormant origin. With iPOND (isolate proteins on nascent DNA) technology and immunoprecipitation (IP), we identified Filia (official symbol khdc3) and Floped (official symbol Ooep), both of which are ESC-specific proteins, located at replication forks, and interact with helicase BLM. Filia and Floped promote fork velocity, stability, recovery and restart under replication stress, and deletion cause genomic instability. Furthermore, ectopic expressions of Filia and/or Floped in somatic cells enhance response capacity to replication stress. Phosphorylation of serine 151 is responsible for the functions of Filia in a double strand breaks (DSBs) repair independent manner. BLM localize at stalled replication forks in an ubiquitin-dependent manner. Filia and Floped promote ubiquitylation of BLM, thus trigger BLM recruitment to sites of replication fork stalling and prevent genomic instability. Taking together, these data highlight an important ESC-specific protein complex responsible for replication stress response and genomic maintenance.

EPIGENETIC REGULATION OF AGING NEURAL STEM CELLS

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Aging is accompanied by a decline in tissue regeneration in mammals. In the nervous system, neural stem cells are thought to be critical for learning and memory. During aging, both the pool of neural stem cells and their ability to give rise to new neurons decline. Thus, neural stem cell decline may underlie age-dependent cognitive deterioration. However, the mechanisms that promote a youthful neural stem cell pool are largely unknown. Epigenetic changes in chromatin states may be particularly important in aging neural stem cells. We have previously shown that conserved chromatin modifiers of the COMPASS family, which is responsible for trimethylation of lysine 4 on histone H3 (H3K4me3), regulate longevity in the worm C. elegans. We are currently characterizing epigenetic chang-

es, specifically changes in H3K4me3, in neural stem cells in aging mouse cohorts. We used next-generation sequencing to identify the genome-wide distribution of H3K4me3 in young and old adult neural stem cells. By directly purifying young and old neural stem cells, we have also examined coding and non-coding RNAs in aging neural stem cells. This global analysis has provided key insights into how this chromatin mark may promote youthful neural stem cell function. The knowledge of the epigenetic network controlling adult neural stem cell homeostasis might help counter brain aging in long-lived species, including humans.

FRIDAY 24 JUNE, 13:15 – 15:15

CONCURRENT III: DIRECT CELLULAR REPROGRAMMING

Level 2, Rooms 2009/2011

THE MECHANISMS UNDERLYING CELLULAR PLASTICITY: LICENSERS AND DRIVERS OF A NATURAL REPROGRAMMING EVENT

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Whereas postmitotic somatic cellular identity is generally a stable feature of multicellular organisms, natural interconversions between functionally distinct somatic cell types (aka transdifferentiation or Td) have been reported in species as diverse as jellyfish and mice. In some cases, Td events occur with remarkable precision and efficiency. For example, our laboratory has shown that a rectal cell suddenly looses its differentiated identity and is reprogrammed into a motoneuron with invariant precision, in 100% of the wild type Caenorhabditis elegans animals. We have further shown that this fascinating Td event proceeds through discrete steps in absence of cell division: dedifferentiation and then re-differentiation into the new cell type, similarly to vertebrate examples of Td, such as newt lens regeneration. Direct reprogramming can also be induced experimentally, however at a very low frequency, and remains rare in vivo. Why do some cells but not their neighbours, change their identity? We have used the rectal Y cell into the PDA motor neuron conversion, a defined, single cell, natural transdifferentiation event to investigate the mechanisms that ensure invariance and how extrinsic cues and the intrinsic context impact on the ability of a cell to change its identity. Our results support a model where both the microenvironment and the intrinsic cellular context combine to empower a cell with the competence to transdifferentiate. In addition, our findings emphasise the importance of the temporality and dynamics of the underlying molecular events preceding the initiation of natural cell fate conversion, as the same signals necessary to set up a competence to Td can, when provided out-of-time, block Td.

MODELING ACQUIRED AND GENETIC HEARING LOSS USING INDUCED SENSORY HAIR CELLS THROUGH DIRECT CELLULAR REPROGRAMMING OF HUMAN FIBROBLASTS

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Hearing loss affects 360 million people worldwide. Loss of cochlear hair cells is the primary cause of deafness. The mechanisms by which hair cells degenerate in response to sustained noise, exposure to certain FDA-approved drugs, or genetic mutations are poorly understood. For research purposes, it is difficult to obtain these specialized cells for mechanistic and therapeutic studies because they are fragile and very few in number. To overcome these limitations, we identified a cocktail of transcription factors that converts mouse and human fibroblasts into functional hair cells. Induced hair cells (iHCs) express key hair cell markers including Atoh1, Parvalbumin, and Myo6, possess a genome wide transcriptional signature highly similar to primary hair cells, express functional mechanotransduction channels, and display electrophysiological properties characteristic of hair cells. To determine if iHCs are capable of modeling the selective degeneration of hair cells in response to exposure to ototoxic drugs, we measured iHC survival after treatment with aminoglycoside antibiotics, which cause hair cell loss and deafness in patients. We found that similarly to primary hair cells, mouse and human iHCs rapidly degenerate in a dose-dependent manner when treated with gentamicin. In contrast, induced neurons generated from the same fibroblasts did not degenerate when exposed to gentamicin. These results indicate that iHCs are selectively and appropriately sensitive to known ototoxins. To determine if iHCs recapitulate pathogenic aspects of hereditary hearing loss, we used CRISPR/Cas9 genome editing in iPSCs to engineer point mutations into KCNQ4, which encodes a voltage-gated potassium channel that is essential for hair cell function and is one of the most commonly mutated genes in patients with genetic hearing loss. An inactivating G321S mutation in KCNQ4 reduced the potassium current in iHCs by 75%, indicating that the KCNQ4 channel is responsible for a portion of the outward current that is appropriate for hair cells and that iHCs accurately model key aspects of KCNQ4 mutations in hair cells. Together, our results indicate that iHCs provide a new model for identifying mechanisms and treatments for acquired and genetic hearing loss.

Funding Source: NIH T32 Training Grant in Hearing and Communications Neuroscience

DIRECT REPROGRAMMING OF HUMAN AND RODENT ASTROCYTES INTO FUNCTIONAL INDUCED DOPAMINERGIC NEURONS IN VITRO AND IN VIVO

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Cell replacement therapies for neurodegenerative diseases such as Parkinson's disease currently focus on cell transplantation. An alternative strategy would be to directly reprogram host brain cells in situ. While rodent astrocytes have been reprogrammed into neurons, a dopaminergic phenotype has not yet been obtained from either human astrocytes in vitro or mouse astrocytes in vivo. Our results show that a combination of four transcription factors and microRNAs (4F) are capable of reprogramming human astrocytes. The efficiency of human astrocyte reprogramming was further improved by the addition of small molecules promoting chromatin remodeling and by modulating relevant developmental pathways, such as TGFb, Shh and Wnt signaling. This combined protocol gives rise to human astrocyte-derived iDA neurons with appropriate midbrain markers and excitability in vitro. Moreover, 4F alone are sufficient for direct in vivo reprogramming of striatal mouse astrocytes in a unilateral 6-hydroxydopamine (6-OHDA) model of Parkinson's disease. In vivo reprogrammed iDAs showed action potentials and the ability to cycle synaptic vesicles, while gait analysis revealed that the animals recovered gait symmetry and synchrony. Thus, our results show that human astrocytes can be directly reprogrammed and that direct in vivo reprogramming of mouse astrocytes into iDAs is possible. These findings provide the basis for the development of an alternative cell replacement therapy for Parkinson's disease without the need of transplantation and immunosuppression, via in vivo direct iDA reprogramming of human astrocytes in the brain.

Funding Source: This work was mainly funded by the Swedish Foundation for Strategic Research (SRL program) and the European Commission (NeuroStemcellRepair) funds.

ACTIVE LINEAGE-SPECIFIC TRANSCRIPTIONAL REPRESSION IS REQUIRED FOR PROPER CELL FATE TRANSITIONS

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Cells can be converted to unrelated lineages with transcription factors specific to the target cell type. Typically the same combinations of factors accomplish reprogramming from many different donor cell types. Use of target cell-specific factors explains induction of the target cell program, but it is unclear how the same factors can silence multiple different donor programs. Studying the conversion of fibroblasts to neurons we found that the neuronal reprogramming factor Myt1l can access most of its physiologic targets in fibroblasts and acts predominantly as repressor through recruitment of the Sin3/HDAC complex to silence many non-neuronal programs including the fibroblast-specific transcriptome. One of the repressed pathways is Notch by silencing of several members**,** explaining how newborn neurons can escape Notch activation during normal development. Based on our findings, we propose that active and sequence-specific repression mechanisms exist to generally suppress many unrelated lineage programs enabling cell fate choice and stability involved in development and disease.

MOLECULAR MECHANISMS UNDERLYING DIRECT CARDIAC REPROGRAMMING OF NEONATAL MOUSE CARDIAC FIBROBLASTS

Stone, Nicole, Mohamed, Tamer M A, Ivey, Kathryn N., Srivastava, Deepak, Pratt, Karishma, Radzinsky, Ethan, Yu, Pengzhi (Palmer) and Gifford, Casey

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Direct cardiac reprogramming offers a promising approach to restore heart function and repair damaged myocardium resulting from disease or developmental anomalies. Exogenous expression of the cardiac transcription factors Gata4, Mef2c, and Tbx5 (GMT) can convert cardiac fibroblasts to beating, cardiomyocyte-like cells in vitro and in vivo, resulting in functional improvement in mice after injury, though with limited efficiency. Here, we have employed genome-wide analyses of the temporal epigenetic and transcriptional landscape changes induced by GMT with or without chemical enhancement to unravel the mechanism by which cells transition from fibroblast to induced cardiomyocyte-like cells (iCMs). We purified Thy1+ neonatal mouse cardiac fibroblasts, induced cardi-

ac reprogramming with GMT retroviruses, with or without timed addition of a reprogramming-enhancing chemical cocktail (GMTc). We collected iCMs based on αMHC-driven GFP expression at various time points post-transduction and investigated transcriptional changes that occur progressively over six weeks. RNA-seq revealed dynamic regulation of pathways including Wnt and TGF-ß, accompanied by a decrease in expression of DNA and histone methyltransferases and induction of cardiac developmental and contractile genes over time. We found evidence of co-occupancy between reprogramming factors and Smad2/3/4, providing a potential mechanism by which TGF-b signaling modulates direct reprogramming. Dynamic changes in open chromatin defined by ATAC-Seq revealed significant alterations in transcription factor motif enrichment that suggested pioneer activity of the reprogramming factors. At regions of dynamic chromatin state, we found enrichment for known motifs of multiple cardiac-related transcription factors, suggesting establishment of the endogenous cardiomyocyte gene network. Chemical enhancement resulted in specific enrichment of Mef2 motifs in open chromatin and appeared to result in more rapid and complete closure of chromatin at fibroblast loci. These results begin to reveal the step-wise molecular events that are induced by GMT across the genome, leading to the rapid epigenetic changes during the cell fate transition from fibroblasts to iCMs.

Funding Source: NIH and CIRM

EPIGENETIC BARRIERS TO DIRECT CARDIAC REPROGRAMMING

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Direct reprogramming of fibroblasts to induced cardiomyocytes (iCMs) involves epigenetic re-patterning, yet the underlying mechanism is largely unknown. We took advantage of our recently generated polycistronic system and determined the dynamics of two critical histone marks, H3K27me3 and H3K4me3, and DNA methylation states of representative loci during iCM reprogramming. Our data suggest early rapid activation of the cardiac program and later progressive suppression of fibroblast fate at both epigenetic and transcriptional levels. In addition, we performed a shRNA-based loss-of-function screen to explore the role of epigenetic factors in iCM reprogramming. Among the identified epigenetic regulators of iCM reprogramming, the polycomb ring finger oncogene Bmi1 acted as a major epigenetic barrier during the early phase of iCM reprogramming. Genetic and epistasis analyses suggested that the inhibitory effect of Bmi1 on iCM reprogramming was not completely mediated by its downstream effectors involved in cell proliferation. Instead, we discovered a novel role of Bmi1 in directly binding the regulatory regions of cardiogenic genes. Knockdown of Bmi1 resulted in a marked decrease in repressive histone mark H2AK119ub and an increase in active histone mark H3K4me3 at these loci, and de-repressed these cardiogenic genes during iCM reprogramming. We further demonstrated that Bmi1 depletion substituted for Gata4 in reprogramming fibroblasts into beating iCMs. Thus, our findings implicate Bmi1 as a critical epigenetic barrier to cardiac reprogramming. Furthermore, our studies reveal a previously uncharacterized function of Bmi1 in repressing cardiogenic factors, and demonstrate that removing a specific epigenetic barrier could facilitate the generation of functional iCMs with fewer transcription factors.

FRIDAY 24 JUNE, 13:15 – 15:15

CONCURRENT III: SKELETAL STEM CELLS

Level 2, Room 2024

SKELETAL STEM CELLS: HISTORY, ORIGINS AND FUNCTIONS IN HEALTH AND DISEASE

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Based on the pioneering work of Alexander Friedenstein and Maureen Owen, it is well known that bone marrow (BM) contains a non-hematopoietic, rapidly adherent fibroblastic cell population. Their studies, and those that followed, determined that these cells originate from BM stroma (BM stromal cells, BMSCs), and that a subset of BMSCs are clonogenic and multipotent. By rigorous assays, these cells form bone, hematopoiesis-supportive stroma (a defining feature), and marrow adipocytes upon in vivo transplantation, and cartilage in an in vitro pellet culture. These tissue-specific "skeletal stem cells (SSCs)," a term coined by Paolo Bianco, arise from multiple embryonic specifications during development, dispelling the widely held view of a single common post-natal "mesenchymal stem cell" dispersed throughout the body. Paolo Bianco and coworkers went on to determine that SSCs are BM sinusoidal pericytes (cells on the abluminal surface), are a part of the hematopoietic stem cell niche, and have the ability to self-renew in serial transplantation assays. Although pericytes are found on the surface of blood vessels in all tissues, they are not a lineage that emanates from a common progenitor. In bone, they are formed during the developmental process of vascular invasion, whereby endothelial cells hijack committed osteogenic cells to become pericytes. Their inherent osteogenic potential is revealed during tissue turnover and injury repair. Ex vivo expanded SSCs/BMSCs have shown that they are capable of extensive bone regeneration in numerous pre-clinical studies. However, more work is needed to develop appropriate, weight-bearing scaffolds that support SSC/BMSC-mediated bone formation, along with

methods to encourage rapid vascularization. In addition to their central function in controlling skeletal homeostasis, SSCs/BMSCs were found to play a major role not only in skeletal diseases (e.g., fibrous dysplasia of bone), but also in certain hematological diseases and disorders (e.g., dyskeratosis congenita). In summary, SSCs are bona fide post-natal stem cells that can be utilized to not only to recreate a bone/marrow organoid, but also to model disease, and as such, they are value tools for devising new stem cell-based therapies.

A PERIOSTEAL SUBSET OF SKELETAL STEM/PROGENITOR CELLS CONSTITUTES A MAJOR SOURCE OF NEW OSTEOBLASTS DURING FRACTURE REPAIR IN VIVO

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The life-long regenerative process of the mammalian skeleton is dependent on the presence of skeletal stem cells (SSCs). However, little is known about the in vivo identity and function of endogenous SSCs in fracture repair. Due to the wide tissue distribution and the technical difficulty in detecting rare SSCs in vivo, which SSCs are responsible for fracture healing and how these cells respond to fracture injury have not been elucidated. We have previously shown that transient activation of the myxovirus resistance-1 (Mx1) promoter genetically marks endogenous SSCs in vivo. Here, using a series of dual SSC reporter models in combination with sequential in vivo imaging technology, we discovered that Mx1 and alpha smooth muscle actin (αSMA) combination specify endogenous periosteal SSCs and that these cells are major contributors to bone repair. Gene expression analysis and sequential in vivo imaging of a Mx1 and Nestin (a perivascular mesenchymal cell marker) double reporter model revealed that $Mx1^+$ SSCs are present in both perivascular and periosteal locations of calvarial and long bones and $Mx1^+Nestin^-$ periosteal cells, rather than Nestin+ perivascular cells, express the highest levels of SSC markers and respond to fracture injury in vivo. These $Mx1^+$ periosteal cells are αSMA positive and $Mx1^+αSMA^+$ periosteal cells rapidly migrate toward the injury site, proliferate, and provide the majority of new osteoblasts during fracture healing, as shown by a Mx1 and αSMA double reporter model. In addition, we identified inflammatory cytokines and factors that stimulate the migration of $Mx1^+$ SSCs. Our findings further define the in vivo identity of skeletal stem cells by delineating their physiological roles in bone remodeling and repair. These data indicate that a subset of periosteal cells with Mx1 and αSMA expression represents a dynamic and injury-responsive SSC population, which is not only a major source of new osteoblasts for fracture healing but is also functionally distinct from other mesenchymal populations in bone marrow.

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CLEC11A IS AN OSTEOGENIC FACTOR THAT IS NECESSARY AND SUFFICIENT FOR THE MAINTENANCE OF THE ADULT SKELETON

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Skeletal stem cells (SSCs) in adult bone marrow maintain the skeleton by giving rise to osteoblasts throughout life that regenerate bone and repair fractures. We have discovered that these cells, as well as osteoblasts, synthesize a secreted C-type lectin domain superfamily member, Clec11a, which promotes osteogenesis. Clec11a-deficient mice were born in normal numbers, appeared developmentally normal, and had normal hematopoiesis but exhibited significantly reduced limb and vertebral bone. Adult Clec11a-deficient mice exhibited significantly reduced trabecular bone formation, reduced bone strength, and delayed fracture healing. Bone marrow stromal cells from Clec11a-deficient mice showed decreased osteogenic differentiation, but normal adipogenic and chondrogenic differentiation, in culture. Recombinant Clec11a promoted osteogenesis by bone marrow stromal cells in culture and increased bone formation in vivo. Administration of recombinant Clec11a to osteoporotic mice restored normal bone mass. Recombinant human Clec11a promoted osteogenesis by human bone marrow stromal cells in culture and in vivo. Clec11a maintains the adult skeleton by promoting the differentiation of mesenchymal progenitors into mature osteoblasts.

Funding Source: Damon Runyon Cancer Research Foundation

HETEROGENEITY AND PLASTICITY OF MOUSE PERICYTES REVEALED BY IN VIVO FATE MAPPING

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Pericytes are small cells that line most blood vessels. Cell culture studies have demonstrated that isolated pericytes can in vitro give rise to diverse cell types of the mesodermal lineage (striated and smooth muscle, adipose, bone and chondrogenic cells). Yet, lack of pericyte-specific marker genes has prevented establishing the fate of pericytes in vivo and showing whether they possess similar plasticity in tissue context. We found that pericytes can

be identified in most mouse tissues and organs by simultaneous expression of two genes (Cspg4+Mcam+). We designed a novel transgenic fate mapping strategy that involves sequential activation of Cre and Flippase recombinases and is applicable to cell types without a unique molecular marker. By generating a new mouse model we have tracked pericyte differentiation from early embryonic development to adults. We have characterized the expression of stemness and lineage markers in pericytes across mouse organs. Pericytes are restricted to vascular fate in embryonic development. A subset of perivascular cells give rise to the vascular smooth muscle of the aorta early in development and their progeny constitutes the majority of the aortic wall in the adults. Pericytes differentiate into bone cells, but show no or little contribution to other mesodermal tissues of the limbs (skeletal muscle, cartilage). In internal organs their counterparts show greater functional divergence and plasticity.

Funding Source: This research was supported by BBSRC fellowship (BB/M013170/1) to U.R.

NOVEL SMALL MOLECULE AGONIST OF GP130 ACTIVATES PROGENITOR PROGRAM IN DIFFERENTIATED ARTICULAR CHONDROCYTES AND PROMOTES ARTICULAR CARTILAGE REPAIR IN RAT MODELS OF ARTHRITIS

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Human adult articular cartilage is one of several static tissues that has little capacity for repair; joint surface injuries create irreversible damage and often result in osteoarthritis (OA). Here we show that Leukemia Inhibitory Factor (LIF) signaling regulates articular chondrocyte development and unveil a novel small molecule partial agonist of this pathway. RNA-sequencing and functional assays demonstrated that fetal chondrocytes are significantly more proliferative, migratory and metabolically active than adult cells, and that this difference is largely controlled by a LIF-STAT3-MYC circuit. High throughput screening identified a partial agonist of LIF signaling, Regulator of Cartilage Growth and Differentiation 423 (RCGD 423), that elicited robust but transient increases in MYC and active STAT3 proteins in human adult chondrocytes, driving increased proliferation, migration and metabolism. LIF activated a similar program in adult articular chondrocytes, but also significantly stimulated catabolism, while RCGD 423 showed no catabolic activity. Furthermore, treatment of porcine articular cartilage explants bearing focal defects with RCGD 423 resulted in substantial defect closure in five weeks. Injection of RCGD 423 into rat joints increased active Stat3 and Myc in articular chondrocytes and reduced articular cartilage damage caused by focal defects and medial meniscus destabilization. Current studies are focused on determining if RCGD 423 and its derivatives have disease-modifying activity in clinically relevant models of OA. In parallel, mechanistic studies of RCGD 423 revealed that it activates gp130 (IL6ST), the co-receptor for LIF, with a proposed binding site in the ligand-binding domain; drug-mediated inhibition of gp130 abolished all effects of RCGD 423. Combined, these results identify a family of small molecule gp130 agonists that could be used to regenerate tissues including cartilage and potentially other senescent tissues that respond to STAT3/MYC activation. In addition, our data show that RCGD 423 can be used in vitro for propagation of mouse pluripotent stem cells and potentially other stem cell applications.

Funding Source: This work is supported by CIRM RBV-07230 to DE

SKELETAL STEM CELLS

Longaker, Michael

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Stem cell regulation in the skeletal system remains relatively unexplored. While contemporary efforts have begun to identify bone, cartilage, and stromal progenitors for rigorous functional characterization, little is known about how individual progenitors relate to one another from a stem cell lineage perspective. We have now succeeded in mapping bone and cartilage development from a population of highly pure, post-natal skeletal stem cells (mouse Skeletal Stem Cell, mSSC) and its downstream distinct progenitors of bone, cartilage and stromal tissue. We then determined the mSSC lineage relationships to its progeny. By conducting single cell transcriptomic comparison of purified mSSC and downstream lineage-restricted progenitors of bone and cartilage, we have identified unique genetic regulatory mechanisms guiding mSSC expansion and lineage commitment. We have also identified specific mSSC niche factors upstream of mSSC regulatory pathways that are potent inducers of skeletal regeneration. Specific combinations of recombinant mSSC niche factors can even activate mSSC genetic programs in situ, even in non-skeletal tissues, resulting in de-novo formation of cartilage or bone and bone marrow stroma. Skeletal stem cells are also critically important to regeneration of damaged skeletal tissues. To determine if skeletal disorders could arise from defects in the activity of skeletal stem cells or its downstream lineages, we have examined poor fracture healing associated with Diabetes Mellitus. Through the stem cells lens, we identified specific SSC niche-related abnormalities that could impair skeletal repair in diabetic rodent models including repressed expression of IHH. These deficiencies also correspond to molecular changes observed in skeletal progenitors

isolated from diabetic human patients undergoing joining replacement procedures. We further show that these deficiencies could be reversed, however, by precise delivery of purified IHH to the fracture site using a specially formulated slow-release hydrogel. We anticipate that further refinement of the skeletal stem cell lineage map in mice and humans will facilitate exploration of new areas of inquiry on the basic mechanism of skeletal genesis during embryonic development and into the maintenance of skeletal structures in adulthood.

FRIDAY 24 JUNE, 13:15 – 15:15

CONCURRENT III: HEMATOPOIESIS

Level 2, Rooms 2014/2016/2018

ROLE OF NON-CANONICAL POLYCOMB REPRESSIVE COMPLEX 1 IN FATE DECISION OF HEMATOPOIETIC STEM CELLS

Iwama, Atsushi

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Polycomb group (PcG) proteins function in transcriptional repression through histone modifications. Among PcG proteins, Bmi1/Pcgf4, a component of canonical Polycomb Repressive Complex 1 (PRC1), has been well characterized as a critical regulator of self-renewal and multipotency of hematopoietic stem cells (HSCs). Recently, several non-canonical PRC1 complexes have been identified. However, their role in hematopoiesis remains uncharacterized. PRC1.1 consists of Ring1b, Pcgf1, Kdm2b/Fbxl10 and Bcl6 corepressor (Bcor). We found that deletion of Pcgf1 in mice did not compromise self-renewal capacity of HSCs, but induced accumulation of granulocyte-macrophage progenitors (GMP) and mature myeloid cells, eventually leading to the development of a myeloproliferative neoplasm (MPN)-like disease in mice. Detailed analysis of HSC and multipotent progenitor (MPP) fractions revealed marked skewing to myeloid lineages in MPP fractions at the expense of B lymphocyte commitment, suggesting that Pcgf1 is a crucial regulator of myeloid vs. B lymphocyte lineage commitment of HSCs. Pcgf1-deficient hematopoietic cells showed a clear reduction in global H2AK119ub1 levels, but exogenous Bmi1 could not complement Pcgf1 loss in HSPCs. I would like to discuss the role of PRC1.1 in hematopoiesis.

CLONAL FATE MAPPING QUANTIFIES THE NUMBER OF HEMATOPOIETIC STEM CELLS BORN IN THE DEVELOPING AORTA

Henninger, Jonathan[1], Santoso, Buyung[2], Hans, Stefan[3], Durand, Ellen[1], Moore, Jessica[1], Mosimann, Christian[4], Brand, Michael[3], Traver, David[2] and Zon, Leonard[1]

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Experimental approaches to assess the absolute number of HSCs formed in development have remained challenging. We applied two approaches of single-cell and clonal analysis with fate mapping in zebrafish to quantify developing HSCs. Activating a creER^{T2}-dependent reporter in cd41:eGFP^{+} HSCs by laser induction enabled long-term assessment of their blood contribution. Targeting 10 cd41:eGFP^{+} cells in the aorta and analyzing reporter expression in granulocytes of the marrow 6-9 months later revealed that on average 30 (25-36) HSC clones exist during peak production from the aorta. We also applied the Brainbow-based multicolor Zebrabow system to induce heritable color barcoding unique to each HSC and its progeny. The Zebrabow transgene consists of three fluorescent proteins (dTomato, CFP, YFP) driven by a ubiquitous promoter in a cassette, and are flanked by lox site variants. Different expression levels of the three fluorophores give unique colors to each stem cell clone. For clonal labeling of HSCs, we crossed transgenic Tg(ubi:-Zebrabow) to Tg(draculin (drl):creER^{T2}) zebrafish. The drl regulatory elements are active during all stages of hematopoietic development. Tg(ubi:Zebrabow; drl:creER^{T2}) embryos were treated with tamoxifen at various stages of embryogenesis and grown to adulthood. We observed up to 20 unique colors in the granulocyte population. Our findings reveal that on average 21 HSC clones (19-24, 95% CI) exist prior to HSC emergence and 30 clones (23-34) are present during peak production from the aorta, which strongly agrees with our cd41:eGFP fate mapping results. Longitudinal analysis revealed stable contribution of embryonic HSCs to adult hematopoiesis over 11 months. We sublethally irradiated Zebrabow adults and found reduced clonal diversity in the granulocytes of the marrow at 6 weeks (average cluster size 16.2% vs. 8.5% in controls, $p<0.05$) and 20 weeks (21.0% vs. 6.1% in controls, $p<0.05$) post-irradiation. In some cases, a single clone constituted over 80% of granulocytes in the marrow. Transplant of labeled marrow into lethally irradiated recipients yielded polyclonal engraftment with reduced clonal diversity. Our findings provide the first quantitative insights into early

clonal events that regulate blood development and provide a novel system to examine the genetics of clonality.

Funding Source: This work was supported by NIH F31HL126338 (JH), NIH R01-DK074482 (DT), NIH F32DK752433 (B.S.), the Deutsche Forschungsgemeinschaft(SFB655), the TU Dresden and the European Union (Zf Health), NIH R01-HL04880, NIH P01-HL032262, NIH 5P30-DK49216, NIH 5

REVEALING HETEROGENEITY IN MOUSE HEMATOPOIETIC STEM CELL COMPARTMENT

Miyanishi, Masanori[1], Chen, James[2], Wang, Sean[2], Yamazaki, Satoshi[3], Sinha, Rahul[1], Cao, Kevin[2], Seita, Jun[1], Sahoo, Debashis[4], Nakauchi, Hiromitsu[3,5] and Weissman, Irving L.[1]

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Hematopoietic stem cells (HSCs) are by definition the cells that have the ability to give rise to all the differentiated mature blood cells throughout life, endowed with the properties of self-renewal and multipotency. The first reported purification of mouse HSCs, performed by Weissman et al in 1988, used the surface markers Thy-1, Lineage, and Sca-1. Currently, the Lineage$^-$c-Kit$^+$Sca-1$^+$Flk2$^-$CD34$^{-/lo}$CD150$^+$ definition, arguably represents the most stringent marker profile for mouse immunophenotypic HSCs (pHSCs). While these additional surface markers have improved the prospective isolation of this exceedingly rare population (less than 0.01% of total nucleated cells in bone marrow), many of aspects on HSC biology including diversity, niche, ageing, and others, remains controversial, potentially, due in part to our inability to robustly isolate the long-term (LT)-HSCs from within the heterogeneity of the pHSC compartment. To address this issue, we sought to identify candidate genes capable of labeling heterogeneous populations among pHSCs. Through unbiased multi-step screenings utilizing microarray based gene expression analysis of 28 hematopoietic and 8 stromal fractions, RNA sequencing of highly purified stem and progenitors, and single cell qPCR, we found that homeobox B5 (Hoxb5) is expressed only in a subset of the pHSCs and not in any other hematopoietic or non-hematopoietic compartment of mouse bone marrow. A novel mouse reporter driven by the endogenous regulation of Hoxb5 showed that approximately 20% of the pHSC, 2% of the MPPa, and none of the other bone marrow compartments including the CD45-negative compartment. By transplantation, only the Hoxb5-positive pHSCs exhibit long-term reconstitution capacity in primary transplants, and importantly, in secondary transplants, suggesting that Hoxb5 marks specifically the LT-HSC. Based on these findings, we investigated the HSC anatomic niche with CUBIC (clear, unobstructed brain imaging cocktails and computational analysis) mediated in situ imaging, revealing direct attachment of >94% of LT-HCS to VE-cadherin+ cells in the bone marrow, implicating a near homogenous location of LT-HSC.

MUSASHI-2 POST-TRANSCRIPTIONALLY ATTENUATES ARYL HYDROCARBON RECEPTOR SIGNALING TO EXPAND HUMAN HEMATOPOIETIC STEM CELLS

Hope, Kristin[1], Rentas, Stefan[1], Holzapfel, Nicholas[1], Belew, Muluken[1], Pratt, Gabriel[2], Voisin, Veronique[3], Wilhelm, Brian[4], Bader, Gary[3] and Yeo, Gene[5]

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Although umbilical cord blood (CB)-derived hematopoietic stem cells (HSCs) are essential in many life saving regenerative therapies, their limiting number in each CB unit has significantly restricted their clinical use and the subsequent advantages they provide during transplantation. Hampering the development of targeted and efficient strategies that expand these critical cell types for regenerative therapies is a profound lack of understanding of the molecular pathways that underpin the unique human HSC self-renewal program. Whereas transcription factor networks have been explored in the regulation of self-renewal and lineage decisions of human HSCs, the post-transcriptional mechanisms guiding HSC fate have not been closely investigated. Here we show that the RNA-binding protein (RBP) Musashi-2 (MSI2) exhibits preferential expression in the most primitive cells of the human hematopoietic hierarchy and that when depleted through lentiviral RNAi, is critical for human HSC self-renewal and in vivo repopulating capacity in NSG mice. Conversely when overexpressed, MSI2 induces multiple pro-self-renewal phenotypes, including a 17-fold increase in short-term repopulating cells and a net 23-fold ex vivo expansion of long-term in vivo repopulating HSCs. By performing a global UV cross-linking immunoprecipitation sequencing (CLIP-seq) analysis of MSI2-RNA interactions combined with detailed biochemical validations of key target mRNA associations, we determined that MSI2 directly attenuates flux through the aryl hydrocarbon receptor (AHR) signaling pathway via coordinate post-transcriptional downregulation of canonical AHR pathway components in CB HSPCs. Finally, we show that restoration of AHR activity abolishes the MSI2-induced expansion of primitive hematopoietic cell types providing evidence that MSI2's enforcement of AHR pathway silencing is the mechanism

through which it enhances HSPC expansion. Our study provides new mechanistic insight into RBP-controlled RNA networks that underlie the self-renewal process and gives evidence that manipulating such networks ex vivo provides a novel and powerful means to enhance the regenerative potential of human HSCs.

Funding Source: This work was supported by an OICR New Investigator Award, OICR Cancer Stem Cell Program Grant and CIHR Operating Grant to K.H. and partially supported by grants from the NIH and CIRM to G.W.Y. G.W.Y is an Alfred P. Sloan Research Fellow. S.R. i

PRESENTATION FROM LATE BREAKING ABSTRACTS

ENDOCARDIAL PROGENITOR CELLS CONTRIBUTE TO BLOOD VESSELS IN HEART AND LIVER

Zhang, Hui, Tian, Xueying and **Zhou, Bin**

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

Coronary blood vessels and liver vasculature are essential for development, maintenance and regeneration of heart and liver. There is uncertainty regarding the developmental origins of coronary vessels with two principal sources suggested; sinus venosus or ventricular endocardium. By genetic lineage tracing we found that sinus venosus, but not ventricular endocardium, contributes to the majority of coronary vascular endothelial cells in the embryonic ventricular free walls. In the neonatal heart a significant portion of coronary vessels are not derived from pre-existing vessels in the inner ventricular free wall. These vessels arise de novo from ventricular endocardium at a perinatal stage. We also found that sinus venosus endocardium gives rises to liver vasculature during embryonic development. Inhibition of endocardial angiogenesis results in reduced endocardial contribution to the liver vasculature, and defects in liver organogenesis. These endocardium-derived liver endothelial cells respond to injury and give rise to new blood vessels during liver regeneration. Altogether, these studies show that coronary and liver vasculature share a common developmental origin, and that endocardial progenitors are a source of vascular endothelial cells during development.

FATE MAPPING AND ENDOGENOUS BARCODING OF UNPERTURBED HEMATOPOIESIS

Rodewald, Hans-Reimer[1], Pei, Weike[1], Busch, Katrin[1], Rode, Immanuel[1], Roessler, Jens[1], Wang, Xi[2], Chen, Wei[2], Feyerabend, Thorsten[1] and Hoefer, Thomas[1]

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The structure of the hematopoietic tree, from which blood and immune cells emerge, has been studied in detail, yielding a high resolution map of stem and progenitors cell populations down to the single cell level. In contrast, functional descriptions of the system (e.g. developmental potential, rates of differentiation, regulation of output under steady state and challenge) remain more ill-defined. In particular, the operation of normal hematopoiesis is only poorly understood. A major limitation in this area has been the difficulty to gain information on HSC in the bone marrow under non-perturbed conditions. In vivo hematopoiesis research has mostly relied on the transplantation of donor hematopoietic stem cells (HSC) or progenitors into myeloablated recipients. After transplantation and engraftment, very few (in the order of tens) of HSC contribute to the maintenance of hematopoiesis. Yet, it remains unclear whether post transplantation and normal hematopoiesis are similar or not. We have developed an in vivo fate mapping system that allows us to track the output of HSC under steady state conditions. Measurements of the hematopoietic flow emerging from HSC led us to estimate that large numbers of HSC (in the order of at least 5000 per mouse) contribute to steady state hematopoiesis in adult mice. However, the quantitative contribution of each HSC is low, and the day-to-day blood and immune cell production is largely, and for long periods provided by downstream short-term stem cells and multipotent progenitors (which each posses extended self-renewal capacities). Flux measurement also showed that the myeloid bias, often attributed to aged HSC, is an inherent feature of hematopoiesis that is only marginally enhanced with age. In parallel with these fate mapping experiments, we are developing an endogenous Cre recombinase-dependent barcoding system for non-invasive, permanent tagging of cells. We are in the process of characterizing the properties of this new genetic tool to study hematopoietic lineage relationships, and the potential that HSC 'realize' during normal hematopoiesis.

FRIDAY 24 JUNE, 13:15 – 15:15

CONCURRENT III: EPITHELIAL CELL DEVELOPMENT AND REGENERATION

Level 2, Room 2002

ADULT STEM CELLS UNDERGO DIET-DEPENDENT CIRCADIAN REPROGRAMMING DURING AGEING

Aznar Benitah, Salvador

ICREA, Institute for Research in Biomedicine (IRB), Barcelona, Spain

Tissue maintenance depends on the correct functioning of adult stem cells. Our work and that of others has previously shown that adult stem cell function is tightly regulated temporally by circadian rhythms. This might be paramount for tissue homeostasis, since the main consequence of knocking out certain components of the core clock machinery in adult stem cells is progeria, and a very shortened lifespan in mice. The prevailing model is that circadian rhythms are progressively lost with age, and that in fact, this might be an important factor contributing to ageing in mammals. However, to date there is no formal proof for this. We have now studied the consequences of physiological ageing on the temporal control of stem cell function in different tissues in a large cohort of mice. Contrary to what we expected, the core clock machinery remains robustly rhythmic in old stem cells in all tissues tested. However, unexpectedly, the circadian output becomes almost completely reprogrammed during ageing. That is, the circadian transcriptome of young stem cells related to tissue homeostasis becomes substituted in old stem cells by a new circadian program related to stress traits. Circadian reprogramming is common to all adult stem cells studied, however, its nature reflects the functionality of the tissue (i.e. tissue with a high-turnover rate, metabolic center, detoxifying organ, etc). Interestingly, circadian reprogramming in stem cells can be almost completely reverted by long-term caloric restriction, but cannot be recapitulated by a high-fat diet in young mice. Altogether, our results indicate that adult stem cells undergo circadian reprogramming, rather than circadian arrhythmia, and that circadian rhythms are essential mediators of the effects of metabolism on physiological ageing.

BALANCING STEM CELL PROLIFERATION, DIFFERENTIATION AND MIGRATION DURING WOUND HEALING

Aragona, Mariaceleste, Dekoninck, Sophie, Lenglez, Sandrine, Mascré, Guilhem and Blanpain, Cedric

Universite Libre De Bruxelles, Belgium

Wound healing is essential to repair the skin epidermis after injuries. Spatially distinct stem cells (SCs) located in discrete regions of the epidermis contribute to wound healing including bulge, infundibulum and interfollicular epidermis (IFE) SCs. However, how do these different SCs balance proliferation, migration and differentiation to repair the wound is poorly understood. Here, we used a combination of lineage tracing, clonal analysis, proliferation kinetic experiments on whole mount skin epidermis, coupled with molecular profiling of different regions surrounding the wound, to dissect the cellular and molecular mechanisms that regulate wound healing in mice. Interestingly, we identified a proliferative hub located from 0.5 to 1.5 mm of the wound and a non-proliferative migrating leading edge. Clonal analysis of IFE and Infundibulum SCs revealed that, although IFE were first recruited, both SCs produce a progeny forming streaks of cells of similar size from the proliferative region toward the centre of wound, suggesting these two SCs present similar clonal dynamics during wounding. This analysis also revealed that activated SCs produce sheath of differentiating cells that migrated suprabasally on the top of basal cells toward the wound centre. Molecular profiling of cells isolated from different skin regions surrounding the wound edge identified molecules associated with proliferation, differentiation and migration in the different proliferative and migratory zones. Altogether this study demonstrates the existence and molecularly characterized two distinct cellular compartments during wound healing, a migrating zone and a proliferative hub producing sheath of basal progenitors and suprabasal cells that migrated on the top of each other to close the wound. These results have important implications for acute and chronic wound disorders.

MATURE ADIPOCYTES LOSE ADIPOCYTE-SPECIFIC CHARACTERISTICS AND CONTRIBUTE TO MULTIPLE ASPECTS OF EPITHELIAL TISSUE REGENERATION

Shook, Brett, Xiao, Eric and Horsley, Valerie

Yale University, New Haven, CT, U.S.

Multiple stromal cell populations support the homeostasis and tissue regeneration of epithelial tissues such as the lung, skin and mammary gland, including lipid-filled fibroblasts or adipocytes. Yet the function of lipid-filled mesenchymal cells in epithelial tissues is not well understood. Here, we examined the contribution of mature adipocytes to the regeneration of epithelial tissues using the skin as a model system. Using genetic lineage tracing, transcriptional profiling, and diphtheria-mediate ablation of mature adipocytes in mice, we find that mature adipocytes control multiple aspects of epithelial tissue regeneration after injury. First, we find that immediately upon injury, post-mitotic mature adipocytes lose their adipogenic potential, migrate into wound beds, proliferate and con-

tribute long-term to stromal regeneration. Second, we find that adipocytes are required for multiple aspects of regeneration of skin wounds including inflammation and stromal regeneration. Transcriptional profiling and functional studies reveals multiple adipocyte-derived cytokines by which adipocytes function to control epithelial tissue repair. Adipocytes through cell fate plasticity and paracrine signaling create are necessary for epithelial tissue regeneration and stromal repair.

Funding Source: Brett Shook is a New York Stem Cell Foundtion - Druckenmiller Fellow. This work was supported by the New York Stem Cell Foundation.

HEDGEHOG SIGNALING IN TASTE CELL MAINTENANCE AND REGENERATION

Lu, Wan Jin, and Beachy, Philip

Stanford University, Stanford, CA, U.S.

The sensation of taste contributes centrally to discrimination of substances whose ingestion sustains us and others that are detrimental to our well-being. Even in modern times, with safe and abundant sources of nutrients all around us, taste sensation becomes a significant clinical issue when its loss, often associated with neuronal damage or the cytotoxic treatments and radiation employed in cancer therapy, causes unwanted weight reduction and a significant decrement in quality of life. A particularly acute manifestation of this problem occurs in cancer patients treated with a Hedgehog (Hh) pathway antagonist who are forced or choose to discontinue therapy due to loss of taste sensation, a specific biological effect caused by this class of mechanism-based cancer therapeutic agent. Alluded by these clinical observations, we established a pharmacological blockade of Hh signaling in mice, and found that Hh antagonism leads to dramatic loss of taste receptor cells (TRCs), indicating a central role of Hh signaling in TRC maintenance. We determined that there are two distinct cellular sources of Sonic hedgehog (Shh) available in the vicinity of TRCs: by innervating neurons and by cells within basal portion of the taste bud. In the presence of Hh blockade, we found that Shh-expressing basal cells of the taste buds are lost but the neuronal sources of Shh are unaffected. Upon release of Hh blockade, we observed that TRCs are capable of regenerating, in a Hh-dependent manner. Since the only remaining Hh source in regenerating TRCs emanates from the innervating neurons, this suggest that neuronal derived Shh represents a cellular memory that specifies a regenerative program within the lingual epithelium. We are deploying both genetic and pharmacological tools to further characterize the role of neuronal Shh to TRC regeneration. Our study highlights the involvement of non-renewing neurons as a static source of patterning information to specify the location of TRC in the lingual epithelium during homeostatic cell turnover and more importantly, during regeneration when local signals are not available.

Funding Source: HHMI, DRG 2102-11, CIRM TG2-01159 and NIH 1R21NS093556-01

MEDIATOR 1 DEFICIENCY ENHANCES EPIDERMAL CELL FATE AND ACCELERATES INJURY INDUCED EPIDERMAL REGENERATION IN MURINE SKIN

Oda, Yuko[1], Hu, Lizhi[1,2], Nguyen, Thai1, Fong, Chak[1] and Bikle, Daniel D[1]

[1]VA Medical Center/University of California, San Francisco, CA, U.S., [2]Tianjin Medical University, Tianjin, China

Cell fates are defined by specific transcriptional program. Previously, we developed a unique stem cell regeneration mouse model, in which transcriptional program for ectoderm organs such as tooth and skin is switched. Genomic deletion of one subunit of Mediator complex, Med1, resulted in defective enamel regeneration, in which dental stem cells were inhibited from undergoing transcriptional program for dental fate. Instead, they exerted skin program for both hair and epidermis, and post-natally regenerate ectopic hairs in the incisors. Here, we report that Med1 also modulates epidermal and hair cell fates in the skin. Med1 ablation further enhanced epidermal lineage and consistently accelerated injury induced epidermal regeneration during adult ages. However, it blunted hair lineage resulting in hair loss in the skin. Ablation of Med1 increased the number of Lrig1 expressing isthmus stem cells and basal cells containing potential interfollicular epidermal stem cells, which regenerate epidermis during cutaneous wound healing process. Med1 deficiency also constitutively activated these stem cells and increased their proliferation. Microarray profiling indicated that Med1 deletion causes activation of b-catenin and suppression of TGFb signaling. Med1 deficiency induced the expression of b-catenin target genes to control cell fate and proliferation. It also decreased TGFb expression in interfollicular epidermis. Med1 removal increased the proliferation and migration of epidermal cells, and induced nuclear translocation of b-catenin, and decreased TGFb1 expression in vitro. In contrast, Med1 deficiency blunted hair lineage by defects in CD34 hair follicle stem cells and aberrant hair cycle regulation. Our finding together with previous observations demonstrated that Med1 governs ectoderm cell fate in both tooth and skin. Med1 ablation blunts hair lineage but induces epidermal cell fate to accelerated injury induced epidermal regeneration in the skin. Accelerated regeneration is derived from constitutive activation of epidermal stem cells, and increased proliferation and migration of their progeny by balancing of

b-catenin induced growth promoting and TGFb mediated growth inhibitory activities in the skin.

Funding Source: This work was supported by the National Institutes of Health grant R01 AR050023 (DDB), DOD grant CA110338 (DDB), a VA Merit Review (DDB).

STEM CELL FUNCTION AND SENSITIVITY TO CYTOTOXIC STRESS ARE CONTROLLED BY PROTEIN TRANSLATION RATES

Frye, Michaela

University of Cambridge, U.K.

Whether protein synthesis and cellular stress response pathways interact to control stem cell functions is currently unknown. Here, we show that skin stem cells synthesise less protein than their immediate progenitors in vivo, even when forced to proliferate in a tumour model. Our analyses reveal that activation of stress response pathways drives both a global reduction of protein synthesis and altered translation of specific mRNAs that together promote stem cell functions and tumourigenesis. Mechanistically we show that inhibition of post-transcriptional cytosine-5 methylation locks stem cells in this distinct translational inhibition program. Paradoxically, this stress-induced translation inhibition renders stem cells hypersensitive to cytotoxic stress, as tumour regeneration after treatment with 5-fluorouracil is blocked. Thus, stem cells must revoke translation inhibition pathways to regenerate a tissue or tumour.

FRIDAY 24 JUNE, 9:00 – 11:15

PLENARY V: GENE THERAPY AND STEM CELLS

CAR THERAPY, BEYOND THE CD19 PARADIGM

Sadelain, Michel

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

T cell engineering provides a means to rapidly generate therapeutic T cells of any specificity. This approach is now being used in oncology to generate potent immune responses that eradicate tumor cells and overcome immune barriers in the tumor microenvironment. Chimeric antigen receptors (CARs) are synthetic receptors that mediate antigen recognition, T cell activation, and, in the case of second generation CARs, costimulation. We demonstrated over a decade ago that human T cells engineered with a CAR specific for CD19 eradicated B cell malignancies in mice. We subsequently reported remarkable complete remission rates in adults with chemorefractory, relapsed acute lymphoblastic leukemia, induced by the infusion of autologous T cells expressing the CD19-specific CAR 19-28z. T cell engineering, combining gene transfer and gene editing technologies, may further enable the use of alternative, ie, non-autologous, cell sources. We hypothesize that T cell-derived induced pluripotent stem cells (TiPSCs) may provide an unlimited source for such therapeutic T cells. We previously reported that TiPSCs engineered to express a CD19-specific CAR could be effectively differentiated into CD19-specific T cells (CAR-TiPSC-T) that displayed therapeutic activity in vivo in a xenogeneic lymphoma model. Remarkably, despite expression of their endogenous αß TCR, these CAR TiPSC-T cells possessed an innate-like phenotype and function, resembling that of γð T cells rather than ab T cells. We are currently studying the molecular underpinnings of this lineage diversion. Using genetic means to control TCR and CAR expression, we can now restore differentiation to the CD4+/CD8+ T cell development pathway. In addition to serving as a valuable system for the study of human T cell differentiation, TiPSCs engineered with TCRs or CARs may be useful for the generation of therapeutic “off-the-shelf”, antigen specific T cells.

CHIMERIC ANTIGEN RECEPTOR T CELLS FOR THE TREATMENT OF CANCER: FROM BLOOD TO BRAIN

Brown, Christine E.

Beckman Research Institute, City of Hope, Duarte, CA, U.S.

Chimeric antigen receptors (CARs) are synthetic immunoreceptors that can redirect T cell killing to eliminate malignant cells. As ‘living drugs’ CAR T cells have the potential to self-renew and generate long-term antitumor immunity. Given the clinical successes of CAR T cells for the treatment of refractory B-cell malignancies, there is a strong push toward advancing this immunotherapy to solid tumors. This presentation will focus on the lessons learned from CAR T cell immunotherapy against blood cancers for achieving success against solid tumors. We will discuss the application of CAR T cells for the treatment of glioblastoma (GBM), the most therapeutically challenging and lethal of solid tumors. We have developed a CAR T cell therapy for GBM targeting IL-13 receptor α2 (IL13Rα2), a cell surface receptor over-expressed by the majority of high-grade gliomas. Using preclinical models and translational studies, we have optimized second-generation IL13Rαα2-targeted CAR T cells, incorporating enhancements in CAR design, T cell manufacturing and optimal route of delivery. We have recently initiated an FDA-authorized phase I clinical trial evaluating the safety of intracranial adoptive transfer of IL13Rα2-targeted CAR T cells in patients with GBM. Early clinical findings suggest that intracranial delivery of second-generation

IL13Rα2-targeted CAR T cells is safe and well-tolerated, and that after adoptive transfer, CAR T cells survive and maintain activity, capable of eliciting potent antitumor responses against GBM. These findings provide encouraging evidence for the potential of CAR T cell therapy for the treatment of solid tumors.

HEMATOPOIETIC STEM CELL BASED GENE THERAPY FOR THE TREATMENT OF LYSOSOMAL STORAGE DISORDERS

Biffi, Alessandra

Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, U.S.

In most Lysosomal Storage Disorders (LSDs) hematopoietic stem and progenitor cell (HSPC) transplantation is not or poorly effective. HSPC gene therapy could ameliorate the outcome of allogeneic transplant and provide an expectation of efficacious treatment for these LSD. Autologous HSPCs, which are immediately available and can significantly reduce transplant-related morbidity and mortality, can be genetically modified to express supra-normal levels of the therapeutic enzyme, and become a quantitatively more effective source of functional enzyme than normal donor's cells. We have thus implemented an approach based on the transplantation of autologous, gene corrected HSPCs for the treatment of severe LSDs lacking efficacious and safe therapeutic opportunities. To this goal we exploited lentiviral vectors (LV) for HSPC gene correction. We proved the therapeutic potential of HSPC gene therapy in the murine model of different LSDs and in patients affected by metachromatic leukodystrophy (MLD), a severe dysmyelinating LSD. Clinical experience has demonstrated that timing of enzyme delivery to the affected tissues is a critical variable impacting on the long-term prognosis of the treated patients also in the gene therapy setting. We are thus experimentally addressing the critical need of enhancing brain microglia turnover with donor cells following HSPC transplantation in order to anticipate the time of clinical benefit and improve the efficacy of the transplant procedure. This work thus far provided hints for designing novel and more efficacious approaches for treating LSDs having a severe CNS involvement.

THE JOHN MCNEISH MEMORIAL LECTURE

PRECLINICAL AND CLINICAL DEVELOPMENT OF GENOME-EDITED CELLS

Urnov, Fyodor

Sangamo BioSciences, Inc., Richmond, CA, U.S.

Genome editing uses a targetable nuclease – a zinc finger nuclease (ZFN), a meganuclease, a TAL effector nuclease (TALEN), or an RNA-guided enzyme such as Cas9 – to give the investigator facile control over the genome sequence of a cell. This ability to drive targeted genetic change at endogenous loci is now in its second decade of development, accelerated by a toolbox for native gene correction, disruption, and integration established with ZFNs. The notion of using genome editing in the clinic has been reduced to practice via the application of ZFNs to disrupt the CCR5 gene and create HIV resistant CD4 T cells in a cohort of HIV-positive human subjects. Expanding on this approach, we have established clinical scale conditions for ex vivo ZFN-driven targeted multi-locus knockout in human T cells. For example, use of ZFNs directed against the T-cell receptor alpha constant (TRAC) and beta-2-microglobulin (B2M) loci in purified T-cells eliminates expression of CD3 and HLA-A/B/C in ~90% of treated cells, highlighting the potential of ZFN-mediated genome editing for production of universal T cells from allogeneic donors. We are also developing a treatment for the beta-hemoglobinopathies that aims to attain therapeutically relevant levels of fetal hemoglobin via ZFN-driven targeted disruption of the erythroid enhancer of the BCL11A gene in human hematopoietic stem and progenitor cells (HSPCs); in the context of this effort, we achieve >80% single-step targeted editing of the enhancer at clinical-scale. Aiming to expand the range of HSPC genome editing approaches that can be used in the clinic, we have developed a method which combines AAV6-based delivery of a corrective donor with mRNA delivery of ZFNs yielding >40% targeted gene correction or transgene integration in HSPCs. This ability to engineer the genome of primary human cells with such efficiency, precision, and scale, combined with a growing regulatory and clinical track record of ZFN use, has reduced to practice a fundamentally new approach to the challenge of disease treatment.

SATURDAY 25 JUNE, 9:00 – 11:15

PLENARY VI: DISEASE MODELING USING STEM CELLS

HUMAN PLURIPOTENT STEM CELL-DERIVED TISSUES AS NEW MODELS TO STUDY DEVELOPMENT AND DISEASE OF THE DIGESTIVE TRACT

McCracken, Kyle William[1], McGrath, Patrick[1], Workman, Michael[1], Munera, Jose[1], Sinagoga, Katie[1], Martin, Baptiste[1], Mayhew, Christopher N.[1], Watson, Carey[1], Shroyer, Noah F.[1], Helmrath, Michael[1], Aihara, Eitaro[2], Montrose, Marshall[2], Shumaker, Michael[2], Zavros, Yana[2] and **Wells, James M.**[1]

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Successful efforts to direct the differentiation of human embryonic and induced pluripotent stem cells (PSCs) into specific organ cell types in vitro have largely been guided by studies in embryonic development. We have used signaling pathways that control early endoderm organ specification and morphogenesis in vivo to generate complex, three-dimensional organ tissues with improved functionality from human PSCs in vitro. We identified that by modulating FGF, Wnt and BMP signaling pathways, we were able to control anterior-posterior patterning PSC-derived definitive endoderm as well as gut tube morphogenesis in vitro. The resulting three-dimensional gut tube tissues resembled either foregut or mid/hindgut. These gut tube tissues could be further directed into specific organ tissue types by additional manipulation of embryonic signaling pathways. For example we have been able to use a temporal series of growth factor manipulations that mimic embryonic intestinal development to generate three-dimensional human small and large intestinal organoids (HIOs). We have also generated foregut-derived organoids including fundic and antral gastric organoids. Organoids contain epithelial structures diverse cell types that are unique to their representative organ. Moreover, we are able to manipulate specific cell lineages using genetic gain- and loss-of-function approaches. We have also engineered additional complexity into organoids, for example we have incorporated a functional enteric nervous system into HIOs and generated intestinal tissue that is capable of peristaltic-like motility. Lastly, we are using organoids to model diseases caused by genetic or infectious agents. For example we have modeled epithelial repair induced by infection with Helicobacter pylori and established a new human model for neonatal diabetes and congenital malabsorption.

DEVELOPMENT OF AN IN VITRO PARADIGM MODELING TISSUE REPAIR IN INFLAMMATORY BOWEL DISEASE

Jensen, Kim B.

BRIC - Biotech Research & Innovation Centre, Copenhagen, Denmark

Inflammatory bowel disease (IBD) is an umbrella term for a number of distinct disorders characterised by uncontrolled inflammation in the gastrointestinal tract with increasing prevalence world-wide. Compromised barrier function of the epithelium in the GI tract represents one risk factor, as this causes direct exposure to commensal microbiota. Current treatment of patients targets aberrant intestinal inflammation in order to allow the GI tract to achieve mucosal healing. We have developed an in vitro paradigm for studying intestinal epithelial repair, which recapitulates the important aspects of tissue repair in vivo. At the molecular level tissue repair requires extensive and dynamic cellular reprograming via a novel mechanism both in vitro and in vivo. Our increased understanding of the process of normal epithelial tissue repair will provide new insights into disease development and help us to identify novel therapeutic strategies for a more tailored approach to target the disease in the future.

APPLICATIONS OF PATIENT IPSCS TO UNDERSTANDING CAUSES AND FINDING TREATMENTS FOR NEURODEGENERATIVE DISEASE

Finkbeiner, Steven

Gladstone Institutes, San Francisco, CA, U.S.

With populations aging in the US, Europe and Asia, the prevalence of Alzheimer's disease (AD), Parkinson's disease (PD), and other adult-onset neurodegenerative diseases is rapidly increasing. Despite the enormous societal demand, no significant disease-modifying therapies exist for any of these disorders. Pre-clinical models of these diseases have shown low reliability in predicting the results of human clinical trials, and this failure has discouraged efforts to find new treatments. In this talk, we will describe our efforts to develop preclinical models of AD, PD, amyotrophic lateral sclerosis (ALS)/frontotemporal dementia (FTD), and Huntington's disease from patient-derived iPSCs. We developed an automated imaging platform, known as robotic microscopy, which makes it possible to follow individual differentiated iPSCs longitudinally and in a high-throughput fashion. Despite their exciting promise, phenotypic analysis of differentiated iPSC cultures is challenging in part because the cultures are heterogeneous and contain fully differentiated cells as well as immature dividing cells. With longitudinal single-cell analysis, we can track subpopulations of differentiated cells, increasing the sensitivity of the analysis by 2–3 orders of magnitude. With this approach, we can observe signifi-

cant and robust disease-associated phenotypes in differentiated patient cells than in healthy controls without the need to add exogenous stressors. In turn, these phenotypic differences have facilitated mechanistic studies to elucidate the basis for these differences and to identify strategies to mitigate them including the development of small molecule inducers of autophagy. While more work is needed to establish whether disease models based on patient iPSCs will be useful for patient stratification and predict results of clinical trials, the observation that these models exhibit disease-associated phenotypes provides a platform to understand the molecular basis of these phenotypic differences and identify interventions to mitigate them.

GENE EDITING: LESSONS FROM STEM CELL TOURISM

Charo, R. Alta

University of Wisconsin, Madison, WI, U.S.

Stem cell tourism is a persistent problem, with patients tempted by simplistic newspaper headlines and misleading web-based advertisements. With the advent of gene editing comes another technology ripe for similarly futile, expensive and sometimes dangerous interventions being advertised to desperate people. Complicating matters are the varying, often confusing rules governing cell-based therapies in the US and abroad, as well as a national mood of general impatience with the pace of careful pre-market research. What can we learn from the experience with stem cell clinics, and how can we do a better job bringing the promise of gene-editing to patients?

THE ERNEST MCCULLOCH MEMORIAL LECTURE

CHEMO GENOMIC DISSECTION OF HSC SELF RENEWAL

Sauvageau, Guy and Fares, Iman

Institute for Research in Immunology & Cancer, Montreal, QC, Canada

In this session we will present results from our chemogenomic screens designed to identify small molecule agonists of human hematopoietic stem cells, from normal and leukemic tissues. We will then demonstrate the utility of these new tool compounds to dissect the self-renewal machinery of adult stem cells and to identify new cell surface markers for human adult stem cells.

Funding Source: Grants from Genome Canada and the CIHR, Canadian Institute of Health Research.

SATURDAY 25 JUNE, 13:15 – 15:15

CONCURRENT IV: ROAD TO THE CLINIC

Level 2, Rooms 2001/2003/2005/2007

CELL THERAPY FOR GUT MOTILITY DISORDERS

Young, Heather, Stamp, Lincon, Gwynne, Rachel and Bornstein, Joel

University of Melbourne, Parkville, Australia

The enteric nervous system (ENS) plays an essential role in gut motility. Diseases of the ENS result in bowel motility disorders that are some of the most challenging clinical conditions to manage. Cell therapy offers the potential to treat gastrointestinal motility disorders caused by enteric neuropathies. We have previously shown that following transplantation into the colon of recipient mice, enteric neural progenitors isolated from the fetal and postnatal mouse bowel proliferate, migrate and differentiate into glia and a variety of neurochemical types of neurons. However, it was unclear whether graft-derived neurons integrate into the circuitry of the recipient and directly regulate gut motility. We have used optogenetic and electrophysiological approaches to examine whether transplanted enteric neural progenitors generate neurons that functionally innervate the colon. Neural progenitors expressing the light-sensitive ion channel, channelrhodopsin, were isolated from the fetal or postnatal bowel and transplanted into the colon of postnatal mice. The responses of recipient colonic smooth muscle cells to selective (light) stimulation of graft-derived neurons were examined. Light stimulation of graft-derived cells resulted in excitatory and inhibitory junction potentials, the electrical events underlying contraction and relaxation respectively, in colonic circular muscle cells. The pharmacological properties of the junction potentials evoked by stimulation of graft-derived cells were similar to those elicited by stimulation of endogenous excitatory and inhibitory motor neurons. Interneurons were also generated from graft-derived cells, but their pharmacological properties varied with the age of the donors from which enteric neural progenitors were obtained. Our data demonstrate that transplanted progenitors generate different functional classes of enteric neurons involved in the control of gut motility.

TRANSPLANTATION OF HUMAN EMBRYONIC STEM CELL (HESC)-DERIVED GABAERGIC NEURONS AMELIORATES NEUROGENIC BLADDER DYSFUNCTION AND CENTRAL NEUROPATHIC PAIN

Nicholas, Cory[1], Fandel, Thomas M[2], Trivedi, Alpa A[2], Zhang, Haoqian[2], Chen, Jiadong[2], Martinez, Aida F[2], Noble-Haeusslein, Linda J[2] and Kriegstein, Arnold R[2]

[1]Neurona Therapeutics, South San Francisco, CA, U.S., [2]University of California, San Francisco, CA, U.S.

Inhibitory (GABAergic) interneuron cell-based therapy may represent a novel treatment modality for patients with intractable neurological disorders associated with loss of neuronal inhibition and concomitant focal hyper-excitability, including: epilepsy, neuropathic pain, neurodegenerative and neuropsychiatric disease. Seminal studies from the past decade demonstrate that rodent interneuron precursor cells, dissected from the medial ganglionic eminence (MGE), can enhance GABAergic inhibition and rescue behavioral impairments following transplantation into relevant animal models. In this study, we examine whether human MGE-like cells derived from hESCs can mitigate neuropathic pain and bladder spasticity in a mouse model of sub-acute spinal cord injury. Chronic pain and incontinence are among the most severe consequences of spinal cord injury and are without effective treatment options. Both conditions are associated with loss of GABAergic tone in the spinal cord and neuronal hyper-excitability. Here, we find that hESC-MGE cells differentiate into GABAergic interneuron subtypes six months post-transplantation into the injured cord and receive synaptic inputs, suggesting functional integration with host neuronal circuitry. Disease-modifying activity of hESC-MGE cells is demonstrated by improved bladder function and mitigation of hyperalgesia and allodynia. Therefore, hESC-MGE cell transplantation may represent an effective therapeutic strategy for augmenting GABAergic tone and reducing key disabling consequences of spinal cord injury.

Funding Source: National Institute of Health Challenge Grant RC1 NS068200 (A.R.K., L.J.N.), the California Institute of Regenerative Medicine Early Translational Research Grant TR3-05606 (A.R.K.), and philanthropic support from Mr. Robert Sieker.

A CELL THERAPY FOR PARKINSON'S DISEASE

Irion, Stefan[1], Tomishima, Mark[1], Riviere, Isabelle[1], Zabierowski, Susan[1], Kordower, Jeffrey H.[2], Wakeman, Dustin R.[2], Henchcliffe, Claire[3], Tabar, Viviane[1] and Studer, Lorenz[1]

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In 2011, we demonstrated the generation of functional midbrain dopaminergic neurons (mDA) from human embryonic stem cells (hESCs). Based on this study, we are now developing a cell therapy for Parkinson's Disease (PD). This treatment, if available at scale, manufactured in defined conditions and at high purities could potentially bring life-long relief from the devastating symptoms of PD. Indeed, fetal cell transplantation studies provided fundamental proof-of-concept data and restored function in some patients for 18 years or more. However, the biology and ethics of fetal cell grafts are not suitable as an off-the-shelf product. Despite these problems, cell therapy for PD remains attractive due to the possibility of restoring actual dopamine (DA) neurons capable of integration into the host circuitry. With an award from New York State (NYSTEM), we began to develop hESC-derived mDA neurons as a cellular therapy for PD. Today, we have established robust and scalable manufacturing protocols and moved the cell production from the academic lab into MSKCC's cGMP production facility. The cell product can be cryopreserved and thawed at high viability. In addition, we now produce 1-2 billion cells in a single production run, theoretically treating several hundred patients. Further, this production scale allows us to run ALL safety and efficacy testing on the same batch of cells that will eventually serve for the first-in-human clinical trial. Currently, we are finalizing our release criteria and production runs and are planning a pre-IND meeting with the FDA to discuss our planned IND-enabling studies. These will begin in the summer of 2016 and if completed successfully, will allow us to seek FDA approval for a clinical trial in 2017 (IND). In this presentation, we will show details of our differentiation and quality control protocols and present some of the challenges we faced to date during the move from bench to bedside. These include scientific, financial, legal and logistical issues. We will further describe our efforts in defining the best patient population for this trial and the global effort of the GForce-PD group to harmonize and control cell therapy for PD. Sharing our experience with the stem cell community will be of great value to all attendees and will have broad applicability to stem cell therapies in general.

Funding Source: NYSTEM C028503

GENERATION OF HLA CLASS I-ENGINEERED PLURIPOTENT STEM CELLS THAT ARE NOT RECOGNIZED AS ALLOGENEIC OR LYSED BY NK CELLS

Gornalusse, German[1], Hirata, Roli K [1], Funk, Sarah[1], Manske, Gabriel[1], Prunkard, Donna[1], Colunga, Aric[1], Riolobos, Laura[1], Hanafi, Laila[2], Turtle, Cameron[2] and Russell, David W.[1]

[1]University of Washington, Seattle, WA, U.S., [2]Fred Hutchinson Cancer Research Center, Seattle, WA, U.S.

Long-term engraftment of cellular products derived from human pluripotent stem cells is limited by the rejection of cells with polymorphisms in the human leukocyte antigen (HLA) genes, especially the HLA class I genes. Previously, we created class I-negative ESCs by knocking out the ß2-Microglobulin (B2M) gene, which encodes the common subunit of all HLA class I heterodimers. Even though the B2M-/- cells lacked class I surface expression and did not trigger allogeneic CD8+ T cell responses, they could be lysed by Natural Killer (NK) cells through the "missing self" response. This NK cell-dependent lysis is normally inhibited through interactions with class I molecules, including the minimally polymorphic HLA-E protein. We surmised that B2M-/- cells could be engineered by recombinant adeno-associated virus (rAAV)-mediated gene editing to express HLA-E as a single chain protein fused to B2M. We introduced HLA-E constructs at the B2M locus, such that an HLA-E single chain dimer (SCD) or trimer (SCT) would be expressed under the control of the B2M promoter. Human Elf-1 embryonic stem cells (ESCs) were serially infected with these rAAV vectors, and 7 to 43% of selected clones were accurately edited based on screening by PCR and Southern blots. We report that these edited, undifferentiated ESCs and ESC-derived hematopoietic cells expressed HLA-E SCD or SCT and no other HLA molecules on their cell surface, even upon IFN-γ treatment. In a typical NK donor containing 85% NKG2A+ cells, we showed that the expression of either SCD or SCT was able to prevent NK-mediated lysis and reverse the missing self-phenomenon observed in class I negative cells. Blocking antibodies against HLA-E or NKG2A confirmed that the HLA-E/NKG2A interaction was responsible. In vitro cytotoxicity assays showed that allogeneic CD8+ T cells failed to elicit a cytotoxic response to HLA-E expressing cells, unlike their B2M+/+ counterparts. We demonstrated the lack of reactivity of these engineered cells to B-cell mediated responses by a complement-dependent cytotoxicity (CDC) assay with human anti-HLA antibodies. We will also present our results of in vivo allogeneic responses to ESC-derived teratomas containing B2M+/+ or SCT cells in NSG mice. These HLA-engineered ESCs could be developed as universal donor cells in regenerative medicine applications.

Funding Source: National Institute of Health.

CLINICAL ASSESSMENT OF HESC-DERIVED OLIGODENDROCYTE PROGENITOR CELLS (AST-OPC1) IN PATIENTS WITH SENSORIMOTOR-COMPLETE THORACIC AND CERVICAL SPINAL CORD INJURIES.

Lebkowski, Jane S.[1], Fessler, Richard[2], Chen, David[3], Steinberg, Gary[4], McKenna, Stephen[5], Apple, David[6], Peck Leslie, Donald[6], Schaefer, Maria[7], Jones, Linda[8] and Wirth III, Edward[1]

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Spinal cord injury (SCI) produces numerous devastating and life-changing effects including loss of limb function, impaired cardiovascular control, neurogenic pain, increased infections, and other clinical sequelae. The complex pathology in the injured spinal cord including severed axons, parenchymal cavitation, demyelination, inflammation, and scarring restricts repair of the lesion by classic pharmacological drugs. AST-OPC1 are oligodendrocyte progenitors differentiated from human embryonic stem cells (hESCs) which have been shown to promote remyelination of axons, produce neurotrophic factors and stimulate vascularization of the injury site. A phase 1 clinical trial assessing the safety of AST-OPC1 has been completed in 5 subjects with neurologically-complete T3-T11 thoracic spinal cord injury. All subjects were administered a low dose of 2 x 10^6 AST-OPC1 5mm caudal of the lesion epicenter within 14 days of injury using a syringe positioning device to facilitate controlled dose delivery. Subjects received a low dose of tacrolimus for 46 days which was tapered and eventually discontinued at day 60. To date, all 5 patients have been followed for over 4 years. There have been no serious adverse events related to AST-OPC1, tacrolimus, or the injection procedure. There were no reports of abnormal cyst formation or enlarging masses at the injection sites on MRI scans. There were no unexpected changes in neurological function. A second Phase 1/2 clinical trial is now underway in patients with sensorimotor complete C5-C7 cervical spinal cord injury patients. In this trial, 3 cohorts of patients are receiving escalating doses of 2-20 x 10^6 AST-OPC1 14-30 days post-injury. The trial is designed to examine safety of AST-OPC1 and the potential effects on upper extremity motor function including improvements in neurological level of motor function. Improvements in 2 or more levels of neurological function in the patient population would translate into clinically significant improvements in ability for self-care, independence and quality of life. After enrollment of 13 patients, it is intended to expand enrollment

in the trial to 40 patients to provide further safety and activity data regarding AST-OPC1. Data to date from this trial in cervical spinal cord injury will be presented.

Funding Source: Asterias Biotherapeutics and the California Institute of Regnerative Medicine

HEMATOPOIETIC STEM CELL GENE THERAPY FOR ADENOSINE DEAMINASE-DEFICIENT SEVERE COMBINED IMMUNE DEFICIENCY (ADA-SCID)

Kohn, Donald B.[1], Shaw, Kit[1], Carbonaro-Sarracino, Denise[1], Davila, Alejandra[1], Barman, Provabati[1], Terrazas, Dayna[1], Yu, Allen[1], Campo, Beatriz[1], Candotti, Fabio[1], Thrasher, Adrian[2] and Gaspar, Bobby[2]

[1]University of California, Los Angeles, Los Angeles, CA, U.S., [2]UCL Institute of Child Health, London, U.K.

Hematopoietic stem cell transplantation (HSCT) has been clinically applied successfully for the treatment of human severe combined immune deficiency (SCID) for more than four decades. However, outcomes for SCID patients lacking an HLA-identical sibling donors, using either unrelated donor HSC or haplo-identical T cell-depleted grafts, have had lower rates of success, with immunological complications increasing risks of morbidity and mortality. Autologous HSCT using HSC that have been genetically-corrected (gene therapy) may have similar benefits to allogeneic HSCT, with the advantages that each patient can be their own perfectly-matched donor and immunologic complications are avoided. ADA-SCID was the first human disease for which gene therapy was applied, although initial efforts did not lead to benefit. Subsequent improvements in ADA gene deliver vectors, the methods for isolating and manipulating human HSC and the use of reduced intensity myeloreductive conditioning did lead to clinical benefits in the majority of treated patients at multiple centers. While initial results using murine gamma-retrovirus-based vectors for ADA-SCID have shown efficacy and safety, other clinical trials using this type of vector have been complicated by the development of leukoproliferative disorders as a result of vector-mediated insertional oncogenesis. More recently, lentiviral vectors have been developed in which the enhancer elements of the long terminal repeats, which are the primary cause of insertional oncogenesis, are eliminated in self-inactive or "SIN" vectors. Ongoing clinical trials in the US and the UK using a SIN lentiviral vector (EFS-ADA) are leading to robust immune reconstitution in the enrolled ADA-SCID subjects, with persistent expression of ADA, reconstitution of lymphocyte numbers and function and 100% survival to date. This progression to clinical efficacy and safety has taken more than 25 years to achieve and demonstrates that the iterative "bench-to-bedside" process can lead to effective stem cell-based therapies.

SATURDAY 25 JUNE, 13:15 – 15:15

CONCURRENT IV: TISSUE ENGINEERING

Level 2, Rooms 2020/2022

PLATFORM TECHNOLOGY FOR MATURATION OF HUMAN STEM CELL DERIVED CARDIOMYOCYTES AND DRUG DISCOVERY

Radisic, Milica[1], Zhao, Yimu[1], Feric, Nicole[1], Zhang, Boyang[1], Aschar-Sobbi, Roozbeh[1], Conant, Genna[1], Ronaldson, Kacey[2], Pahnke, Aric[1], Vunjak-Novakovic, Gordana[2] and Backx, Peter[1]

[1]University of Toronto, Toronto, ON, Canada, [2]Columbia University, New York, NY, U.S.

The current drug development process is both very slow (15 year average) and costly ($1.5B/drug average). Despite this hefty investment, drugs are routinely withdrawn from the market due to serious toxicities and adverse cardiovascular effects. To address the limitations of drug screening with animal cells and tissues, we have developed Biowire II platform, a human cardiac tissue array using cardiomyocytes (CMs) derived from human induced pluripotent stem cells (hiPSCs) that: 1) captures the physiological hallmarks of the adult human myocardium, 2) is situated in an inert plastic platform compatible with current drug screening equipment and practices and 3) enables on-line non-destructive readouts of contractile force and Ca^{2+} transients, and the collective behaviour of ion channels. In the Biowire II platform, immature human CMs and support cells in a hydrogel matrix were seeded into inert polystyrene microwells fitted with a pair of flexible polymer wires for tissue alignment. Upon compaction, the human cardiac tissues were electrically field stimulated over the course of weeks and were demonstrated to have highly organized myofibril ultrastructure, improved electrical properties (ET, MCR), a positive force-frequency relationship (1-4Hz), post-rest potentiation, a recorded conduction velocity of 35.7 cm/s and an action potential profile with human adult-like characteristics (I_{to1} notch, plateau, a rapid upstroke velocity and resting membrane potential of -70mV). The Biowire II platform was also amenable to various cell sources (CDI iCell CMs and CMs^2; human embryonic stem cell derived Hes2 and Hes3 CMs; hiPSC BJ1D and C2A CMs). The engineered human cardiac tissues obtained using the Biowire II platform were both physically and functionally reproducible. Using non-destructive force readouts, the chronotropic and inotropic effects of isoproterenol, nifidipine and thapsigargin were captured. Whole cell patch clamp recordings from the intact Biowire II tissues demonstrated the appropriate effects of dofetilide, flecainide and 4-Aminopyridine on action potential. Taken together, the inert plastic platform generates high fidelity human engineered cardiac tissues

with structural and functional maturation hallmarks that can be used as an in vitro drug testing platform.

Funding Source: Supported by the Society for Biomaterials

REGULATING MESODERM REGIONALIZATION GENERATES KIDNEY ORGANOIDS FROM HUMAN PLURIPOTENT STEM CELLS

Takasato, Minoru[1], Er, Pei X.[1], Chiu, Han S.[2], Maier, Barbara[2], Baillie, Gregory J.[2], Ferguson, Charles[2], Parton, Robert G.[2], Wolvetang, Ernst J.[2], Roost, Matthias S.[3], Chuva de Sousa Lopes, Susana M.[3] and Little, Melissa H.[1,4]

[1]Murdoch Children's Research Institute, Melbourne, Australia, [2]The University of Queensland, Brisbane, Australia, [3]Leiden University Medical Center, Leiden, Netherlands, [4]The University of Melbourne, Melbourne, Australia

Human kidney has no postnatal progenitor cell, hence nephrons are never renewed spontaneously once they are lost or severely damaged. This irreversible progression of kidney damage causes the continuous 6.3% rising of the end-stage renal disease per annum globally. Therefore, there is an urgent need for renal regenerative strategies generating kidney tissues artificially. One approach is employing directed differentiation of human pluripotent stem cells (hPSCs). Directing differentiation of hPSCs into kidney is challenging as the adult kidney comprises >25 distinct cell types, derived from 4 progenitors, including ureteric, nephron, vascular and stromal progenitors. Here we identified the developmental mechanism regulating mesoderm regionalization, in which primitive streak cells longer influenced by canonical WNT signaling differentiate into the posterior intermediate mesoderm whereas shorter period of WNT followed by FGF9 promotes the anterior intermediate mesoderm development. By utilizing this knowledge for hPSCs directed differentiation, we successfully performed a preferential induction of collecting duct versus kidney mesenchyme progenitors. When these 2D cultures were aggregated and grown in 3D, kidney organoids were formed with containing nephrons associated with a collecting duct network surrounded by renal interstitium and endothelial network. Nephrons patterned and segmented into distal tubule, proximal tubule and glomerulus. When transcription profiles of kidney organoids were compared to human fetal tissues, they showed highest congruence with first trimester human kidney. Furthermore, Dextran uptake experiment showed reabsorption functionality of proximal tubules, and proximal tubules differentially apoptose in response to cisplatin, a nephrotoxicant. Here, we also performed RNA-seq to investigate transcriptional variability of kidney organoids between experimental and clonal replicates, which will help the generation of homogeneous kidney organoids from various hPSC lines. In summary, kidney organoids represent powerful models of the human organ for future applications, including nephrotoxicity screening, disease modelling and as a source of cells for therapy.

ENGINEERING THE HEMOGENIC NICHE TO ENHANCE DEFINITIVE BLOOD PROGENITOR CELL GENERATION FROM HUMAN PLURIPOTENT STEM CELLS

Rahman, Nafees[1], Brauer, Patrick M.[1,2], Usenko, Tatiana[1], Tewary, Mukul[1], Zuniga-Pflucker, Juan Carlos[1,2] and Zandstra, Peter W.[1]

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Human pluripotent stem cells (hPSCs) provide an exciting source for cellular therapy because they can be expanded while maintaining the potential to differentiate towards specialized tissues. However, in vitro generation of hPSC-derived cells, such as definitive hematopoietic cells, remains challenging and typically only generate primitive blood cells. In the developing embryo, blood cell emergence is controlled by spatial and temporal cues that include cytokines, shear force, oxygen tension and local cell density. We hypothesize that engineering aspects of the native definitive blood niche in vitro will enable more robust generation of adult-like blood progenitor cells. To this end, we have investigated whether hPSC-derived hemogenic endothelial (HE) cells seeded into engineered niches of controlled size and distribution could be optimized to promote differentiation towards phenotypical CD45+ blood cells, including definitive blood precursors. First, we used engineered microwells to initiate hPSC differentiation as size-controlled cell aggregates which are then cultured in serum-free conditions to promote HE induction. This optimized protocol consistently yielded 0.32 ± 0.015 $CD34^+VECAD^+$ HE cells per input hPSC. These cells were demonstrated to be capable of giving rise to definitive blood cells as assessed by pro-T lymphoid progenitor generation (30% $CD5^+CD7^+$) and short-term (10 wks) reconstitution of NSG irradiated mice. These HE cells served as our starting population to study the effects of lithography-based micropatterned (MP) controlled parameters such as colony size, spacing and clustering on the endothelial-to-hematopoietic transition. We found that MP treatments with smaller area coverage yielded five times more CD45+ blood cells than MP treatments with larger area coverage or unpatterned controls ($p \leq 0.05$). Ongoing studies have revealed endogenously secreted inhibitory factors within larger coverage areas thereby elucidating key molecular signals that can be perturbed to enhance hPSC-derived blood cell production. Collectively, we showed that control of cell coverage can be used to manipulate production of CD45+ blood cells. This demonstrates that in vitro niche engineering, to mimic in

vivo embryonic development, may be used as a model to investigate blood cell emergence.

Funding Source: Canadian Institute of Health Research Ontario Research Fund

DE NOVO GENERATION OF DIVERSE ORGAN BUDS FROM iPSCs TOWARDS THERAPY

Takebe, Takanori[1,2] and Taniguchi, Hideki[2]

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In vitro organogenesis is now becoming a realistic goal of stem cell biology, as one can obtain an unlimited number of pluripotent stem cells through reprogramming technology. One practical challenge is to develop a four-dimensional (4-D) stem cell culture system whereby multiple progenitors communicate in a spatiotemporal manner, as observed in organogenesis. During early hepatogenesis, the multicellular communication that occurs among mesenchymal stem cells, undifferentiated vascular endothelial cells and anterior visceral endodermal cells are required to initiate the budding of the rudimentary liver in the foregut (known as the liver bud). To recapitulate early organogenesis, we recently showed that specified hepatic cells (immature endodermal cells destined to follow the hepatic cell fate) self-organized into 3-D iPSC-derived liver buds when co-cultivated on solidified Matrigel with stromal cell populations, including human endothelial and mesenchymal progenitors. By transplanting in vitro grown organ bud, we have demonstrated the vascularized and functional liver tissues in an immunodeficient animal with therapeutic potential**.** Furthermore, we also demonstrated the applicability of this approach to other systems by delineating the extracellular mechanisms guiding organ bud formation. Specifically, mesenchymal progenitors initiated organ bud formation within these heterotypic cell mixtures, which was dependent upon substrate matrix stiffness. Defining optimal mechanical properties of the substrate promoted formation of 3D, transplantable organ buds from tissues including kidney, pancreas, intestine, heart, lung, brain, cartilage and tumors**.** Transplanted pancreatic and renal buds were rapidly vascularized and self-organized into functional, tissue-specific structures. Considering a critical shortage of donor organs for treating end-stage organ failure, our proposed principle, i.e. organ-bud transplantation, offers an alternative approach to the generation of a three-dimensional, vascularized organ. This will highlight the enormous therapeutic potential using in vitro-grown organ-bud transplantation for treating organ failure.

Funding Source: Research Center Network for Realization of Regenerative Medicine, A-MED. PRESTO, JST.

DIFFERENTIATION OF V2A INTERNEURONS FROM HUMAN PLURIPOTENT STEM CELLS

Butts, Jessica C.[1, 2], Mendoza-Camacho, Federico N.[1], McCreedy, Dylan[1], Taneja, Praveen[3], Noble-Haeusslein, Linda[4] and McDevitt, Todd [4,5]

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The spinal cord contains many neural cell types, including motor neurons (MNs) and many classes of spinal interneurons (INs), which play critical roles in motor and sensory function. Following spinal cord injury (SCI), loss of IN populations disrupts the transduction of important motor signals and typically results in paralysis. V2a INs, which are excitatory (glutamatergic) neurons that span several spinal cord segments, have therapeutic promise to restore diminished motor function following SCI, however sources of human V2a INs for transplantation studies have yet to be described. Directed differentiation of human pluripotent stem cells (hPSCs) into V2a INs may address this critical need, thus the objective of this work was to differentiate putative V2a INs (Chx10+) from hPSCs using developmentally relevant signaling cues. Initially the concentration and timing of retinoic acid (RA), Purmorphamine (Pur, a Shh agonist), and DAPT (a Notch inhibitor) were systematically varied until a population of ~30% Chx10+ cells was obtained after 17 days of differentiation using 100nM RA, 100nM Pur, and 1μM DAPT in human ESCs (H7) and iPSCs (WTC11). Compared to a similar MN protocol, the gene expression of V2a IN lineage markers Chx10 and Lhx3 was increased >90-fold for both markers. After prolonged culture (>50 days) of V2a IN populations, Chx10 expression was maintained while ß-III-tubulin expression decreased. Concurrently, neurofilament and vesicular glutamate transporter 2 (VGlut2) expression increased over time, consistent with neuronal maturation into a glutamatergic phenotype. Spontaneous electrical activity, demonstrated by calcium flux, was observed as early as day 20 and persisted throughout maturation of V2a INs. After 60 days, V2a IN cultures produced sustained action potential firing in response to step-wise current injections in whole cell patch clamp recordings. Populations of V2a INs (~4 x 10^5 cells) transplanted into the naïve spinal cord (T9) of SCID mice survived two weeks post-transplantation, expressed VGlut2, and extended axonal projections over 2mm caudal to the transplantation site. Altogether, these results provide the first report of V2a IN differentiation from hPSCs and should enable further investigation of the phenotype and function of V2a INs in vitro and in vivo.

USING TISSUE ENGINEERING APPROACHES TO BETTER UNDERSTAND NEURAL DEVELOPMENT AND INJURY

Sakiyama-Elbert, Shelly E.

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Spinal cord injury (SCI) is a debilitating condition that results in significant loss of motor function and reduction in quality of life for the approximately 265,000 Americans affected. For many years, a dogma held by those studying SCI was that long-range regeneration of descending tracts was the key to regaining function. However, more recent research has shown that functional recovery is due to local rewiring of these tracts to propriospinal neurons and plasticity of spared neural tissue within the spinal cord. To better understand how this regeneration occurs, we need to identify which neuronal populations are involved in these local rewiring events after SCI. Our lab has developed novel tools to generate high purity populations of ventral spinal motoneurons and interneurons from pluripotent stem cell lines, using CRISPR/Cas9-based genome engineering. These tools allow us to characterize the synapse formation requirements, to study connectivity between interneurons, motoneurons, and cortical neurons in a model in vitro system, and to define cues that promote functional connectivity of these networks. They also provide a potential population for transplantation to better understand the roles of specific interneuron populations in functional recovery after SCI and can be used in combination with biomaterial scaffolds to enhance cell survival and differentiation in vivo.

SATURDAY 25 JUNE, 13:15 – 15:15

CONCURRENT IV: STEM CELL METABOLISM

Level 2, Rooms 2009/2011

AMPK MAINTAINS METABOLIC HOMEOSTASIS IN LEUKEMIA-INITIATING CELLS

Nakada, Daisuke

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How cancer cells adapt to metabolically adverse conditions in patients and strive to proliferate is a fundamental question in cancer biology. Here we show that AMP-activated protein kinase (AMPK), a metabolic checkpoint kinase, confers metabolic stress resistance to leukemia-initiating cells (LICs) and promotes leukemogenesis. Upon dietary restriction, MLL-AF9-induced murine AML activated AMPK and maintained leukemogenic potential. AMPK deletion significantly delayed leukemogenesis and depleted LICs by reducing the expression of glucose transporter 1 (Glut1), compromising glucose flux, and increasing oxidative stress and DNA damage. LICs were particularly dependent on AMPK to suppress oxidative stress in the hypoglycemic bone marrow environment. Strikingly, AMPK inhibition synergized with physiological metabolic stress caused by dietary restriction and profoundly suppressed leukemogenesis. Our results indicate that AMPK protects LICs from metabolic stress, and that combining AMPK inhibition with physiological metabolic stress potently suppresses AML by inducing oxidative stress and DNA damage.

METABOLIC REGULATION OF MUSCLE STEM CELL EPIGENETIC STATE DURING REGENERATION

Yucel, Nora D., Porpiglia, Ermelinda, Mai, Thach and Blau, Helen M.

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

Metabolism has recently emerged as an important regulator of epigenetic state, in particular during stem cell fate transitions. Though skeletal muscle is a highly metabolically active tissue, whose metabolic function declines in both age and disease, little is yet known about the role of metabolism in the muscle stem cell (MuSC) niche. Here we use Mass Cytometry (CyTOF) to capture changes in metabolism and histone acetylation at the single cell level in vivo following injury. We demonstrate that during activation by injury, skeletal muscle stem cells transiently increase histone acetylation, followed by a striking drop upon commitment to differentiation. In vitro, we used flow cytometry and chromatin immunoprecipitation to show that commitment in fact entails the selective preservation of histone acetylation on myogenic differentiation genes amidst on a background of global loss. We show that this loss of histone acetylation is required for commitment, and is regulated at the substrate level by the glycolytic enzyme pyruvate dehydrogenase (PDH). Pharmacological or genetic activation of PDH activity results in increased histone acetylation during proliferation and, subsequently, loss of myogenic differentiation in an acetylation-dependent manner. Moreover, mice lacking PDH inhibitory kinases, PDK2 and PDK4, accumulate uncommitted satellite cells upon injury and exhibit impaired muscle regeneration. Finally, we show that short-term high fat diet, which increases expression of PDK4 in skeletal muscle, results in aberrantly decreased acetylation of MuSCs at homeostasis. These studies identify PDH as a previously unrecognized metabolic mediator of histone acetylation state critical for muscle stem cell fate during regeneration and metabolic imbalance.

Funding Source: National Science Foundation Graduate Research Fellowship (NSF GRFP)

GLUTAMINE METABOLISM REGULATES THE PLURIPOTENCY TRANSCRIPTION FACTOR OCT4 IN HUMAN EMBRYONIC STEM CELLS VIA A POST-TRANSLATIONAL REDOX-SENSITIVE MECHANISM

Marsboom, Glenn[1], Zhang, Guo-Fang[2], Pohl-Avila, Nicole[1], Zhang, Yanmin[1], Kang, Hojin[1], Yuan, Yang[1], Brunengraber, Henri[3], Malik, Asrar B.[1] and Rehman, Jalees[1]

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Recent studies suggest that cellular metabolism can regulate pluripotency in human embryonic stem cells (hESCs) but the underlying mechanisms are not fully understood. Using stable isotope-assisted metabolomics, we found that glutamine metabolism is highly active in undifferentiated hESCs when compared to differentiating hESCs and that proteins involved in glutamine uptake (SLC1A5) and metabolism (GLS2) also exhibit higher expression levels. We also found that glutamine withdrawal led to a rapid and selective degradation of OCT4 protein (50% reduction in 4 days) while the levels of the pluripotency transcription factor NANOG were unaffected. Glutamine-derived glutathione levels decreased 10-fold in response to glutamine withdrawal and resupplying cell-permeable glutathione rescued OCT4 levels during glutamine deprivation, suggesting a post-translational redox regulation of OCT4. Indeed, treatment with the intracellular superoxide generator DMNQ at a non-toxic dose of 100μM resulted in a rapid degradation of OCT4 (<50% of OCT4 remaining after just 5 hours). We were able to directly demonstrate that OCT4 is oxidized on its cysteine residues in response to glutamine withdrawal using a maleimide-mediated pulldown. OCT4 has 9 cysteines, which are all completely conserved across mammal species. Site-directed mutagenesis identified cysteines 185, 198, 221, and 252 in the DNA binding domains of OCT4 as being necessary for DNA binding. We next used the redox regulation of OCT4 to enhance hESC differentiation. Endothelial differentiation was enhanced 2-fold in the absence of glutamine and the ESC-derived endothelial cells exhibited greater angiogenic capacity in vitro and in vivo. In conclusion, these findings demonstrate that the pluripotency transcription factor OCT4 can serve as a metabolic sensor in hESCs and that metabolic cues act in concert with growth factor signaling to orchestrate stem cell differentiation.

Funding Source: This work was supported by a Parker B. Francis fellowship and an American Heart Scientist Development grant 15SDG23250002 (GM), R01-GM094220 (JR), R01-HL118068 (JR and ABM), Roadmap Grant R33-DK070291 (HB), and R01-HL090152 (ABM).

LIN28 REGULATES MOUSE NAIVE/ PRIMED PLURIPOTENCY AND STEM CELL METABOLISM

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The RNA binding proteins LIN28A and LIN28B play critical roles in embryonic development, tumorigenesis, and pluripotency. Somatic cells can be reprogrammed to induced pluripotent stem (iPS) cells by overexpression of OCT4 and SOX2 together with NANOG and LIN28A (OSNA), but the exact roles of LIN28A and its closely related paralog LIN28B are still poorly understood. Here we show that LIN28B likewise promotes reprogramming through both let-7-dependent and independent mechanisms, and that reactivation of both endogenous LIN28A and B loci are required for maximal reprogramming efficiency. The LIN28B locus has open chromatin and is activated early during reprogramming, whereas LIN28A is activated at later stages by OCT4, marking the transition to bona fide iPS cells. Though both paralogs are dispensable for pluripotency maintenance, they facilitate conversion from naïve to primed state pluripotency. By proteomic and metabolomic analysis, we demonstrate roles of LIN28 in maintaining low mitochondrial function associated with primed pluripotent stem cells, and in regulating one-carbon metabolism, nucleotide metabolism and histone methylation. LIN28 binds mRNAs of proteins important for oxidative phosphorylation, and is associated with their reduced mRNA stability and protein abundance. Thus, LIN28A and LIN28B play cooperative roles in regulating reprogramming, naïve/primed pluripotency and stem cell metabolism.

THE APICOSOME: A NOVEL CALCIUM-HARNESSING ORGANELLE THAT ENHANCES SURVIVAL OF DISSOCIATED HUMAN EMBRYONIC STEM CELLS

Taniguchi, Kenichiro[1], Shao, Yue[1], Townshend, Ryan F[2], Lopez, Shawn A[2], Freddo, Andrew M[2], Chue, Deming[2], Spence, Jason R[2], Fu, PhD, Jianping[1], Margolis, MD, Benjamin[2], O'Shea, K Sue[2] and Gumucio, PhD, Deborah L[2]

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Dissociation-induced apoptosis in hESC is inhibited by small molecule inhibitors of Rho-associated kinase (ROCK) and myosin-II. However, the biological link be-

tween ROCK-myosin-II signaling and the apoptotic cascade is missing. Here, we show that a novel organelle that forms de novo in dissociated hESC bridges this missing link. While analyzing lumen formation in dissociated hESC following our recent work, we unexpectedly found that single hESCs form a previously unrecognized organelle that is enriched in apical polarity markers (filamentous actin, the actin binding protein EZRIN and apical protein atypical PKCζ) and is thus called an "apicosome". By transmission electron microscopy, the apicosome is decorated with microvilli. Importantly, apicosome formation is suppressed as the concentration of ROCK or myosin-II inhibitors is decreased, suggesting that apicosome formation is inhibited by pro-apoptotic ROCK-myosin-II activation. Furthermore, actin polymerization via formins promotes apicosome formation; hESCs expressing a wild-type or constitutively active (ΔN3) formin mammalian diaphanous homolog 1 (mDia1) transgene show increased cell survival in the presence of pro-apoptotic ROCK-myosin II-signaling (cultured in the absence of ROCK or myosin-II inhibitors). These data suggest that formin-induced apicosome formation promotes survival of dissociated hESC. Since cytoplasmic Ca^{2+} is an important apoptotic signal, we examined the localization of Ca^{2+} using Fluo-3, a cell permeant ratiometric fluorescent calcium indicator. Strikingly, Ca^{2+} is enriched in the apicosome, clearly showing that the apicosome functions as an intracellular Ca^{2+} reservoir in dissociated hESC, potentially suppressing Ca^{2+}-mediated apoptosis. Overall, we establish that the apicosome is a previously unrecognized organelle that is critical for cell survival and functions in intracellular Ca^{2+} storage in dissociated hESC.

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THE ACTIVATION OF THE UPR^{ER} IS AN ESSENTIAL STEP IN THE ACQUISITION OF PLURIPOTENCY DURING REPROGRAMMING

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Somatic cells can be reprogrammed into a pluripotent stem cells state. Cellular reprogramming is achieved by the forced expression of 4 transcription factors: OCT4, SOX2, KLF4 and cMYC. This process theoretically requires a global remodeling of the organelles and a drastic change in metabolism. We therefore hypothesized that the early steps of reprogramming would result in the activation of a variety of stress pathways in the cell, which might in turn impact the efficiency of reprogramming. We focused in particular on the endoplasmic reticulum unfolded protein response (UPR^{ER}). Here we show that the UPR^{ER} is activated during reprogramming and that its activation can increase the efficiency of this process and possibly the quality of the pluripotent stem cells. These results suggest that the low efficiency of cellular reprogramming is partly the result of the cell's inability to initiate a proper stress response to cope with the newly expressed load of protein that will eventually change the fate of this cell.

SATURDAY 25 JUNE, 13:15 – 15:15

CONCURRENT IV: REGULATORY NETWORKS IN DIFFERENTIATION AND DISEASE

Level 2, Room 2002

NON-CODING REGULATORY GENOME IN BLOOD STEM CELL DEVELOPMENT AND MALIGNANCIES

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Transcriptional enhancers determine cellular identity and influence a variety of cellular processes, but the molecular processes controlling enhancer activation and deactivation during stem cell development remain largely unknown. By comparing enhancer landscape, transcriptional factor occupancy and transcriptomic changes in human hematopoietic stem/progenitor cells and lineage committed erythroid progenitors, we uncovered driver transcription factors and their combinatorial patterns in enhancer turnover during hematopoietic lineage specification. Despite indistinguishable chromatin features, we revealed through genome editing the functional hierarchy and diversity of enhancer clusters (so-called 'super-enhancers). These studies provide initial insights into enhancer dynamics and gene expression programs directing lineage and developmental stage-specific transcription during hematopoiesis. To facilitate the molecular characterization of enhancers within their native environment, we recently developed methods to isolate enhancer-associated molecular interactions in situ by repurposing the CRISPR/Cas9 system. These approaches allow to selectively and significantly enrich molecular interactions required for enhancer activities, and to unbiasedly identify enhancer-regulating protein, RNA complexes and long-range DNA interactions during hematopoiesis. Our studies will not only uncover underlying principles regulating lineage-defining enhancer elements, but also establish a

new approach for investigation of non-coding regulatory elements which can be extended to many different cell types and human diseases.

MAPPING THE REGULATORY LANDSCAPE OF HUMAN MESODERM DEVELOPMENT

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Stem-cell differentiation to desired lineages requires navigating alternating developmental paths often leading to unwanted cell-types. This task necessitates comprehensive developmental roadmaps. Here we map bifurcating lineage choices leading from pluripotency to twelve human mesodermal lineages, including bone, muscle and heart. We defined the extrinsic signals controlling each binary lineage decision, enabling us to logically block differentiation towards unwanted fates and rapidly steer pluripotent stem cells towards 76-99% pure human mesodermal lineages at most branchpoints. These included sclerotome that could form an ectopic human bone in vivo and cardiomyocytes that could engraft human fetal heart in vivo. Comprehensively cataloging mesoderm cell-states through single-cell transcriptomics uncovered somite segmentation, a previously-unobservable human embryonic event transiently marked by HOPX expression. Chromatin-state analysis revealed how extrinsic signals imprint mesodermal chromatin. Collectively this roadmap of lineage choices and dynamic molecular transitions enables navigation of mesodermal development to uncover developmental processes and produce engraftable human progenitors.

Funding Source: California Institute for Regenerative Medicine

FUNCTIONAL CRISPR/CAS9 SCREENS IN MOUSE ESCS UNVEIL CRITICAL ENHANCERS FOR EXITING PLURIPOTENCY

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Embryonic development involves a plethora of processes that need to be tightly controlled in order to ensure the proper generation, from a single cell, of all the specialised tissues in an organism. One of the key mechanisms to maintain cellular identity is through differential enhancer regulation. Specific enhancer activation is accompanied by the recruitment of chromatin remodellers and transcriptional modulators, allowing the shaping of cell-specific 3D chromatin conformations and transcriptomes. It has been recently described that some pluripotency-associated transcription factors such as Nanog and Oct4 undergo widespread genomic relocalization in cells transiting from naïve to primed pluripotent states. This supports specific enhancer landscape configurations during programmed cell identity changes. Genome-wide, functional enhancer screens can be performed using gRNAs targeted to transcription factor binding sites; however, this approach becomes limited for larger DNA domains such as super enhancers. It has been shown that co-expression of two gRNAs targeting collinear genomic regions results in NHEJ-mediated deletion of the flanked locus. By using cell surface markers we show high efficiency of NHEJ for up to 20Kb DNA stretches. Furthermore, we have developed a novel strategy to construct dual gRNA expression vector libraries with pooled pre-designed gRNA pairs, which allows large scale functional enhancer screens. By analysing ESC-associated super enhancers and Oct4, p300 and H3K27Ac ChIP-Seq data, we identified ~2000 potential regulatory regions in naïve and primed ESCs with potential relevance for regulating the exit from pluripotency. With a custom-made gRNA finder, we have generated a list of paired gRNAs flanking the identified enhancers and constructed a dual gRNA library. Then, we perform a large scale functional enhancer screening for the identification of regulatory elements critical for ESC differentiation. Our work provides new strategies to systematically explore non coding regions in the genome, especially those spanning large sequences such as super-enhancers, lncRNAs or repetitive elements.

Funding Source: MF is funded through EMBO-LT (ALTF 836-2014) and Marie Sklodowska-Curie IEF (DUALgrENP) KK is funded through ERC (ROADtoIPS), MRC and BBSRC.

DE NOVO MAPPING OF GENE REGULATORY NETWORKS AND THEIR DYNAMICS DURING PLURIPOTENT STEM CELL DIFFERENTIATION VIA COMBINATORIAL CRISPR-CAS9 SCREENS

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Our ability to unravel developmental processes and improve human pluripotent stem cell (hPSC) differentiation to mature organotypic tissues will entail a deeper understanding of the underlying driver gene regulatory networks, the temporal and spatial contexts in which they operate, and an ability to directly modulate their activity. In this regard considerable effort has been invested in unraveling the complex genetic mechanisms underlying cell fate determination, and recent advances in loss-of-function screening techniques have become increasingly powerful at identifying individual members of pathways. Unfortunately, these single-gene screens are often unable to provide information on the interactions between pathways and the co-dependencies of genes that ultimate-

ly drive organogenesis. To gain insights into the gene networks underlying these complex processes we have thus developed a new class of high throughput reverse genetic screening approaches that enable combinatorial deciphering of the role of both single and interacting genes via a single high throughput experiment. Here we apply this approach to hepatic differentiation of hPSCs for modeling liver organogenesis. Specifically, we optimized a four stage induction protocol whereby hPSCs are first directed to definitive endoderm, then into a stage resembling the primitive gut tube, followed by induction to hepatoblasts and finally mature hepatocytes (in which over 50% of cells are positive for the mature hepatic surface marker ASGPR). Utilizing a novel dual-gRNA CRISPR-Cas9 screening format, we exhaustively computed the dynamics of ~12000 genetic interactions during the course of this multi-step process by assaying cells via fluorescence activated cell sorting at each stage. Our foundational study confirmed known regulators of liver specification as well as unraveled novel interactions. Depletion of certain dual-gRNAs in hepatic cells were found at each defined stage of differentiation, suggesting that genetic regulatory circuits are essential for lineage specification. Our results demonstrate that combinatorial CRISPR-Cas9 screening in cell fate commitment can construct cell-type specific genetic interaction networks that underpin organogenesis.

Funding Source: Burroughs Wellcome Fund, March of Dimes Foundation, University of California San Diego.

SYSTEMATIC IDENTIFICATION OF GENE FAMILY REGULATORS IN MOUSE AND HUMAN EMBRYONIC STEM CELLS

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Pluripotent self-renewing embryonic stem cells (ESCs) have been the focus of a growing number of high-throughput experiments, revealing the genome-wide locations of hundreds of transcription factors and histone modifications. While most of these datasets were used in a specific context, all datasets combined offer a comprehensive view of chromatin characteristics and regulatory elements that govern cell states. We recently assembled all published genome-wide ChIP experiments in mouse and human ESCs into a searchable database and webtool allowing epigenomic analysis (Livyatan et al., Cell Stem Cell, 2015). Here, using hundreds of datasets in ESCs, we generated colocalization maps of chromatin proteins and modifications, and built a discovery pipeline for regulatory proteins of gene families. We define alternative promoters of pluripotency factors, provide an expanded epigenetic profile for lincRNA genes beyond the basal "K4–K36" and detect subclasses of lincRNAs that may be indicative of their potential function, and offer an Enhancer Finder function which scans the upstream region of any given gene for potential regulatory elements. By comparing genome-wide binding data with over-expression and knockdown analysis of hundreds of genes, we discovered that the pluripotency-related factor Nr5a2 separates mitochondrial from cytosolic ribosomal genes, regulating their expression. We further show that genes with a common chromatin profile are enriched for distinct Gene Ontology (GO) categories. Finally, by combining these data with single cell RNA-sequencing (scRNA-seq) data, we were able to assign an epigenomic signature for heterogeneous and stable genes in ESCs. Our approach can be generalized to reveal common regulators of any gene group; discover novel gene families, and identify common genomic elements based on shared chromatin features.

Funding Source: European Research Council (ERC)

REGULATORY NETWORK CONTROL OF BLOOD CELL DEVELOPMENT

Göttgens, Berthold

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The Göttgens group uses a combination of experimental and computational approaches to study how transcription factor networks control the function of blood stem cells and how mutations that perturb such networks cause leukaemia. This integrated approach has resulted in the discovery of new combinatorial interactions between key blood stem cell regulators, as well as experimentally validated computational models for blood stem cells. I will present results from our current research, which focuses on single cell genomics of early blood development and the development of computer models to chart the transcriptional landscape of blood stem and progenitor cell differentiation.

SATURDAY 25 JUNE, 13:15 – 15:15

CONCURRENT IV: DISEASE MODELING II

Level 2, Rooms 2014/2016/2018

DISEASE MODELING OF COLORECTAL CANCER USING ORGANOIDS

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The biological understanding of colorectal cancer requires faithful disease modeling recapitulating the disease diversity in patient populations. We optimized stem cell niche factor medium for colorectal tumor organoids and

established 55 organoid lines from various histological subtypes and clinical stages, including some rare, previously uncultured subtypes. We also generated four pairs of primary and metastatic colorectal cancer organoids. Tumor organoids reproduce the histopathological grade and differentiation capacity of parental tumors in vitro and upon xenografting. Integrated molecular analyses of tumor organoids identify gene expression signatures specifying tumor subtype. Niche-independent growth is predominantly gained through genetic aberrations that occur during the adenoma-carcinoma transition. Metastasis-derived organoids exhibit higher metastatic capacity than their primary site-derived organoids despite similar niche factor requirements and genetic profiles. These observations collectively underscore the importance of genotype-phenotype analyses at single-patient level to provide insights into colorectal tumorigenesis.

CAPTURING THE BIOLOGY OF MILD VERSUS SEVERE DISEASE IN A PLURIPOTENT STEM CELL-BASED MODEL OF FAMILIAL DYSAUTONOMIA

Zeltner, Nadja[1], Fattahi, Faranak[1], Dubois, Nicole[2], Lafaille, Fabien[3], Saurat, Nathalie[1], Zimmer, Bastian[1], Tchieu, Jason[1], Lee, Gabsang[4], Studer, Lorenz[1] and Casanova, Jean-Laurent[3]

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Molecular and functional aspects of human genetic disease can be recapitulated in vitro using patient-specific pluripotent stem cells (PSCs). Familial Dysautonomia (FD) is a debilitating disorder that primarily affects derivatives of the neural crest (NC). For unknown reasons, FD patients present with mild or severe disease despite carrying the identical, homozygous point mutation in IKBKAP. Here, we present in vitro phenotypes that capture severe and mild FD in human PSC-derived cellular lineages. Patient-specific cells only from severe but not mild FD display an impaired capacity of developing into NC derivatives including autonomic and sensory neurons, thus they have neurodevelopmental defects. However, both severe and mild FD cells show defects in peripheral neuron survival, indicating neurodegeneration as the primary culprit in mild FD. Importantly, neuronal degeneration in mild FD can be halted by treatment with candidate therapeutic compounds kinetin and SKF-86466. Genetic reversal of the FD mutation in severe FD iPSCs reversed NC, but not sensory neuron lineage phenotypes, implicating that the known FD mutation does not account for all symptoms. Whole-exome sequencing provided candidate mutations only found in severe but not mild FD patients, providing insight into the mechanistic reason FD presents in mild and severe forms. Our study demonstrates that human PSC-based disease modeling is sensitive in recapitulating disease severity and paves the road for applications in personalized medicine.

CHROMOSOMAL INSTABILITY AND MOLECULAR DEFECTS IN INDUCED PLURIPOTENT STEM CELLS WITH NIJMEGEN BREAKAGE SYNDROME

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Hebrew University, Nahariyya, Israel

Nijmegen breakage syndrome (NBS) results from the absence of the NBS1 protein, responsible for detection of DNA double-strand breaks (DSBs). NBS is characterized by microcephaly, growth retardation, immunodeficiency, and cancer predisposition. Here we show successful reprogramming of NBS fibroblasts into induced pluripotent stem cells (NBS-iPSCs). Our data suggest a strong selection for karyotypically normal fibroblasts to go through the reprogramming process. NBS-iPSCs then acquire numerous chromosomal aberrations and show a delayed response to DSB induction. Furthermore, NBS-iPSCs display slower growth, mitotic inhibition, a reduced apoptotic response to stress and abnormal cell cycle-related gene expression. Importantly, NBS neural progenitor cells (NBS-NPCs) show down-regulation of neural developmental genes, which seems to be mediated by p53. Our results demonstrate the importance of NBS1 in early human development, shed new light on the molecular mechanisms underlying this severe syndrome and further expand our knowledge of the genomic stress cells experience during the reprogramming process.

GENETIC CORRECTION OF A HIPSC MODEL FOR MITOCHONDRIAL DISEASE

Wong, Raymond Ching-Bong[1], Hung, Sandy Alice[1,2], van Bergen, Nicole[1,2], Lim, Shiang Y[3], Hernandez, Damien[3], Mackey, David[4], Liang, Helena[1], Kearns, Lisa[1], Hewitt, Alex[1], Trounce, Ian[1,2] and Pebay, Alice[1,2]

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In recent years, the field of human induced pluripotent stem cell (hiPSC) disease modeling has focused on the use of isogenic control, i.e. by correcting the genetic defects to verify the disease phenotypes observed in the hiPSC model. However, the difficulty of genetically manipulating mitochondrial DNA (mtDNA) is an obstacle for using hiPSC isogenic controls to model homoplasmic mtDNA diseases. Here we report the use of cybrid tech-

nology to correct mtDNA mutations and generate hiPSC isogenic controls for modeling Leber's Hereditary Optic neuropathies (LHON). LHON is the most common mitochondrial disease and is caused by homoplasmic mtDNA mutations. It is a blinding disease that is characterised by damaged retinal ganglion cells (RGCs), specialised neurons that relay visual information obtained by the retina for processing in the brain. Using an episomal reprogramming method, we generated patient-specific iPSCs from control and LHON patients. In addition, we depleted the mutated mitochondria in LHON cells and replaced it with healthy mitochondria by cellular fusion, generating cybrid isogenic controls with corrected mtDNA mutations. We performed genotypic analysis to confirm the correction of mtDNA mutation in cybrid hiPSCs and microsatellite analysis to confirm the cell origin. Characterisation of these iPSCs demonstrates that the cells are positive for pluripotent markers TRA-160 and OCT4 and retain abilities to differentiate in vitro into cells representative of the three germ layers. Following RGC differentiation, we showed that LHON-specific RGCs exhibit disease phenotypes that recapitulate those observed in LHON patients. Notably, these phenotypes are alleviated in the cybrid hiPSCs, suggesting that the correction of mtDNA mutations by cybrid technology can reverse the diseased phenotypes observed in this hiPSC model. Our study represents the first proof-of-concept that hiPSCs can be utilised to model LHON. In addition, this is the first study to describe the use of cybrid technology for generating hiPSC isogenic controls with a corrected mtDNA mutation, which can be applied to hiPSC modeling of various homoplasmic mitochondrial diseases.

IDENTIFICATION OF A NOVEL RISK FACTOR FOR INTRACRANIAL ANEURYSMS IN ADPKD USING IPSC MODELS

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Autosomal dominant polycystic kidney disease (ADPKD) is the most prevalent, potentially lethal, monogenic disorder, and is characterized by the development of multiple renal cysts and various extrarenal manifestations. Cardiovascular complications are the main cause of death in ADPKD patients and intracranial aneurysms (ICAs), causing subarachnoid hemorrhage (SAH), are the most serious problem. The diagnostic and therapeutic strategies for ICAs in ADPKD have not been fully established. Here we report the derivation of induced pluripotent stem cells (iPSCs) from skin fibroblasts from seven ADPKD patients, among whom four had ICAs. The vascular cells differentiated from ADPKD-iPSCs show altered Ca^{2+} entry and gene expression profiles compared with those from control-iPSCs. By microarray analyses, we have also identified several molecules whose expression levels are specifically altered in the iPSC-derived vascular cells from ADPKD patients with ICAs. Among the molecules, both mRNA and protein expression of a metalloenzyme gene, matrix metalloproteinase (MMP) 1 and its secretion into culture media show statistically significant elevations in the iPSC-derived endothelia from ADPKD patients with ICAs as compared to the patients without. Furthermore, we confirmed the correlation between the serum MMP1 levels and the development of ICAs in 354 ADPKD patients, indicating that high serum MMP1 levels may be a novel risk factor and become more beneficial when combined with other risk factors, such as a family history of ICAs or SAH. These results suggest that vascular cells differentiated from patient-specific iPSCs can be used for studying the mechanisms of vascular complications in

ADPKD and for identifying novel disease-related molecules that may be used in clinical practice.

Funding Source: This work was partially supported by Otsuka Pharmaceutical Co., Ltd., by a Grant-in-Aid for Progressive Renal Diseases Research from the Ministry of Health, Labour and Welfare of Japan, by the Japan Society for the Promotion of Science (JSPS) throug

MODELLING GENETIC KIDNEY DISEASE USING PATIENT-DERIVED IPSC

Little, Melissa H.[1,2], Er, Pei[1], Takasato, Minoru[1], Maier, Barbara[1,3], Hale, Lorna[1], Howden, Sara Emily[1], Phipson, Belinda[1], Oshlack, Alicia[1], Simons, Cas[2], Wolvetang, Ernst[4], Sun, Jane[4], Mallett, Andrew[5], Bennetts, Bruce[6] and Alexander, Stephen[6]

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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. This is likely to be an underestimate due to de novo mutations and a lack of detection of a definitive mutation. Advances in Next Generation sequencing have facilitated increased access for such families to the prospect of a diagnosis, however we estimate that a causative gene is identified in only 40% of cases. Research genomics has recently been increasingly applied to identify novel potential causative gene associations, however such variants of unknown significance require functional validation in order to be of diagnostic value. The use of induced pluripotent stem cells (iPSC), derived from patients with identified known or novel gene mutations, is one approach that has the potential to determine the functional significance of previously un-described gene variants. The capacity to direct the differentiation of iPSC to cell types of biological significance for the disease in question is increasing. We have developed a protocol for the successful differentiation of human pluripotent stem cells, including hESC and iPSC, to a kidney organoid. This involves the stepwise induction of appropriate patterning events known to result in kidney development, and 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 investigate genetic kidney disease using organoids containing mutations in known and novel genes associated with kidney disease. This presentation will discuss progress on the derivation of patient and corrected patient iPSC together with the derivation of iPSC from unaffected family members. It will also discuss the development of characterisation approaches tailored for the study of distinct kidney disease types, including nephronophthisis, proximal tubulopathies and glomerulopathies.

SATURDAY 25 JUNE, 13:15 – 15:15

CONCURRENT IV: LEUKEMIA AND STEM CELLS

Level 2, Room 2024

SINGLE CELL BIOLOGY IDENTIFIES STEM CELL FATE REGULATORS IN HEMATOLOGICAL MALIGNANCIES

Kent, David

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The discovery of significant heterogeneity in normal and malignant hematopietic stem cells (HSCs) has challenged our understanding of how single cells are subverted to drive leukemia. To design therapies for diseases of stem cell origin and to better provide cell populations for clinical applications, it is critical to understand this diversity and its impact on disease pathogenesis. Our lab's research focuses on understanding the complex biology of human myeloid malignancies and the impact that individual mutations have on the clonal evolution of disease. Recently, we developed single cell approaches to study malignant mouse HSCs using JAK2V617F mutant myeloproliferative neoplasms as a model. Using mathematical modeling, in vivo imaging, single cell gene expression and single cell functional assays, we have identified a subset of JAK2V617F mutant HSCs that drive a stem cell defect that can be rescued by crossing to loss of function TET2 mice. In vitro and in vivo functional assays demonstrate that JAK2V617F increases the proliferation and differentiation capacity but reduces the self-renewal capacity of single HSCs, and mathematical modelling localised this effect to the apex of the hierarchy. Single cell gene expression in $EPCR^{+}CD150^{+}CD48^{-}CD45^{+}$ long term HSCs revealed that JAK2 single mutant HSCs lack a distinct subset of HSC regulator genes (including Bmi1, Pbx1, and Meis1), only some of which were specifically restored to normal levels in TET2/JAK2 double mutant single HSCs. This allows refinement of the molecular network involved in perpetuating disease and together these data illustrate the power of single cell biological approaches to uncovering novel molecular networks in heterogenous cell populations.

THE CONSERVED METHYLATION-SENSITIVE ENHANCER DERARE MAINTAINS HEMATOPOIETIC STEM CELLS THROUGH REGULATION OF HOXB CLUSTER

Qian, Pengxu[1], Ahn, Youngwook[1], De Kumar, Bony[1], Nolte, Christof[1], Paulson, Ariel[1], Li, Zhenrui[1], Zhao, Meng[1], Tao, Fang[2], Perry, John M.[1], He, Xi. C.[1], Krumlauf, Robb[1] and Li, Linheng[1]

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The Hox genes have been well documented as key regulators and contributors in both normal hematopoiesis and leukemogenesis, yet it is largely unknown whether and how multiple Hox genes in a cluster are regulated and function in hematopoiesis. Our transcriptome analysis in 17 murine hematopoietic cell types, including hematopoietic stem cells (HSCs), progenitor and lineage cells, showed that most of HoxB cluster genes were predominantly enriched in the permanently reconstituting long-term (LT) HSCs. Interestingly, one differentially methylated region in HoxB cluster, identified by genome-wide DNA methylation analysis, gradually gained methylation during HSC differentiation and shared the same sequence as the retinoic acid responsive element DERARE, which was recently reported to regulate multiple HoxB gene expression in the central nervous system. To test whether DERARE is required for normal hematopoiesis, we utilized the DERARE knockout mouse and found that homozygous deletion of DERARE led to 2-fold reduction in both the frequency and absolute number of LT-HSCs. Functionally, limiting dilution, competitive repopulating unit assays showed a 2.5-fold decrease in functional HSCs of DERARE$^{\Delta}$ mice compared to wildtype control. We further performed serial transplantation and observed a 4.3-fold reduction of repopulation rate after secondary transplantation of DERARE$^{\Delta}$ HSCs, indicating long-term reconstitution capacity was impaired. Mechanistically, DERARE in LT-HSCs enriched with enhancer markers, and deletion of DERARE reduced expression of most of HoxB genes. Finally, the clinical data analysis from 200 acute myeloid leukemia patients in the Cancer Genome Atlas project revealed that lowly methylated DERARE was significantly correlated with overexpression of HoxB genes, high cytogenetic risk, and poor prognosis, suggesting DERARE contributes to leukemogenesis. Collectively, our study demonstrates the essential roles of the methylation-sensitive enhancer DERARE in both maintenance of LT-HSCs and contribution to leukemogenesis through regulation of HoxB cluster genes.

MYELOID-BIASED MULTIPOTENT PROGENITOR EXPANSION BY DEREGULATED NOTCH AND WNT SIGNALING DRIVES MYELOID MALIGNANCY

Kang, Yoon-A, Reynaud, Damien, Pietras, Eric and Passegué, Emmanuelle

Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, Department of Medicine, Division of Hematology/Oncology, University of California, San Francisco, CA, U.S.

Myeloproliferative neoplasms (MPN) are characterized by the deregulated production of myeloid cells. Despite clinical successes with tyrosine kinase inhibitors (TKI), much remains to be learned about the mechanisms driving aberrant myeloid cell output in MPNs to develop better treatment options, especially for patients with TKI resistances. Myeloid cell production is entirely controlled by the differentiation rates of the self-renewing hematopoietic stem cells (HSC). HSCs give rise to non self-renewing multipotent progenitors (MPP), which differentiate into either myeloid- or lymphoid-committed progenitors. We recently identified MPP3 as a novel myeloid-biased MPP subset that is functionally distinct from the lymphoid-primed MPP4, and is specialized in producing myeloid cells with low contribution to the lymphoid lineage. We also demonstrated that MPP3 is part of an inducible myeloid regeneration pathway that is activated in HSCs, and leads to both the transient overproduction of MPP3 and the myeloid reprogramming of MPP4 to rebuild the myeloid lineage in various regenerative settings. Here, we show that transient myeloid regeneration pathways are constitutively activated in myeloid malignancies, and directly contribute to the deregulated output of myeloid cells observed in a variety of MPN mouse models. Strikingly, we find that transformed HSCs with leukemia-initiating stem cell (LSC) activity have consistently decreased Notch and increased Wnt signaling activity. Using both pharmacological and genetic approaches, we demonstrate that a combination of high Wnt and low Notch activities directly activates myeloid regeneration pathways from normal HSCs, with overproduction of MPP3 and myeloid-reprogramming of MPP4. Moreover, we show that re-balancing Wnt and Notch activities in LSCs can block the aberrant activation of myeloid regeneration pathways, and extend survival by restoring proper lineage output in MPN mice. Our results illuminate new features of myeloid malignancies linking deregulated signaling activities in LSCs to the aberrant production of multipotent progenitors that drive myeloid cell output. They also suggest that targeting the abnormal Notch and Wnt activities could be used to develop new HSC-based anti-differentiation therapies for the treatment of a broad range of MPNs.

Funding Source: NIH/NHLBI R01HL092471 UCSF Program for Breakthrough Biomedical Research (PBBR)

INHIBITION OF THE VASCULAR NICHE PROTEIN, PLEIOTROPHIN, ABROGATES CHRONIC MYELOID LEUKEMIA PATHOGENESIS

Himburg, Heather, Zhao, Liman and Chute, MD, John

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

Tyrosine kinase inhibitor (TKI) revolutionized the treatment of patients with chronic myeloid leukemia (CML), but TKI therapy alone is not curative. Leukemic stem cells (LSCs) are thought to confer resistance to TKI therapy in CML. The mechanisms underlying LSC resistance to TKI therapy are poorly understood but LSC-niche interactions have been postulated. Our laboratory discovered a paracrine factor, pleiotrophin (PTN), which is secreted by bone marrow endothelial cells (BM ECs) in the hematopoietic stem cell (HSC) vascular niche and is necessary for maintenance of HSCs in vivo. Since PTN functions as a niche-mediated regulator of normal HSC fate in vivo, we hypothesized that LSCs in CML might hijack the PTN signaling axis for the purpose of propagating leukemia at the expense of normal hematopoiesis. In order to test our hypothesis, we crossed SCL-tTA/BCR-ABL mice, which develop CML over time under the control of doxycycline-treatment, with either PTN-/- or PTN+/+ mice, and evaluated CML propagation in vivo. SCLtTA/BCR-ABL;PTN+/+ mice displayed the expected evolution of chronic phase CML (splenomegaly, increased WBCs, left-shifted myelopoiesis, decreased survival). In contrast, SCLtTA/BCR-ABL;PTN-/- mice displayed normal range WBCs, decreased splenomegaly and significantly increased survival. At 300 days post-induction of BCR-ABL, 33% percent of SCLtTA/BCR-ABL;PTN-/- mice remain alive compared to only 7% of SCLtTA/BCR-ABL;PTN+/+ mice ($p<0.0001$). To determine if PTN signaling also affects the progression of human CML, we tested whether inhibiting PTN with a neutralizing antibody decreased leukemic colony growth in a methylcellulose colony forming assay. At the dose tested, anti-PTN treatment significantly reduced leukemic colony formation from CD34+ CML cells ($p=0.02$) but did not affect healthy donor colony growth. Thus, targeted inhibition of PTN may be a viable method of eradicating the CML stem cell without damaging the normal HSC compartment.

RNA EDITASE ADAR1 REGULATES CELL CYCLE OF HEMATOPOIETIC STEM CELL

Jiang, Qingfei[1], Zipeto, Maria Anna[1], Leu, Heather[2], Delos Santos, Nathan[2], Atien, Etienne[2], Morris, Sheldon[2] and Jamieson, Catriona H.M.[2]

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Compelling murine studies demonstrate that adenosine-to-inosine (A-to-I) RNA editing mediated by adenosine deaminase associated with RNA1 (ADAR1) is vital for both fetal and adult hematopoiesis. While genetic ablation of ADAR1 editase leads to murine embryonic lethality due to severe defects in erythropoiesis, conditional deletion in the hematopoietic system impairs maintenance indicative of cell type and context specific roles for ADAR1 in cell fate specification and self-renewal. We have previously shown that inflammation-responsive ADAR1 plays important roles in both stem cell differentiation and self-renewal in CML (chronic myeloid leukemia) disease progression. Though we have established ADAR1-mediated RNA editing as a novel therapeutic target for treating CML, we do not yet understand the underlying mechanism of RNA editase's involvement in normal hematopoiesis. In our new study, we describe ADAR1's role in cell cycle regulation of normal hematopoietic stem cell (HSC) and its molecular editing targets. Our results demonstrated that ADAR1 induces G_0 to G_1 phase transition in normal hematopoietic stem cells, as demonstrated by elevated expression of Ki67, reduced DiR signal, and in vivo cord blood engraftment. Cell cycle qRT-qPCR microarray and whole transcriptome RNA-sequencing analysis indicates that CDKN1a expression level is reduced by >80% in normal cord blood $CD34^+$ cells over-expressing ADAR1. However, there are no direct A-to-I editing observed in CDKN1a transcript by whole transcriptome sequencing. We found that miR-26a-5p, a miRNA frequently down-regulated in leukemia, is inhibited by ADAR1-mediated RNA editing in normal cord blood $CD34^+$ cells. Lentiviral expression of mature miR26-5p enhances CDKN1a expression, inhibits cord blood proliferation in vivo, as well as reduces HSC self-renewal in colony-formation assay. Importantly, ADAR1 directly binds and edits the DROSHA cleavage site of pri-miR26a, thereby prevent proper miR26a-5p biogenesis. Our finding suggests carefully regulated A-to-I editing by ADAR1 is essential for the maintenance of proper cell proliferation in HSC. For future study, we will investigate if the elevated expression of ADAR1 in CML BC LSC contributes to false regulation of cell cycle that leads to the expansion of malignant leukemia stem cells.

Funding Source: NIH NCI 1 R21 CA189705-01A1

MED12 REGULATES HEMATOPOIETIC STEM CELL SUPER-ENHANCER DYNAMICS

Aifantis, Iannis

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

Stem cells rely on the finely coordinated activity of cell intrinsic and extrinsic cues to self-renew and differentiate. Cell-specific gene expression programs rely on the orchestrated function of transcription factors, co-activators and transcriptional machinery at enhancers and promoters. Mediator is a large co-activator complex that bridges promoters with transcription factors bound to cell-specific

enhancers. We found that Med12, a member of the Mediator kinase module, is an essential regulator of hematopoietic stem cell (HSC) function as in-vivo deletion of Med12 rapidly exhausts adult HSCs leading to mouse lethality. Deletion of other members of the Mediator kinase module is dispensable for HSC self-renewal and differentiation. Med12 and essential hematopoietic transcription factors co-occupy HSC-specific enhancers and super-enhancers. Med12 loss destabilizes p300 binding at enhancers and results in prompt de-activation of HSC super-enhancers and loss of "stemness" gene signatures. Our data describe a novel kinase-independent function for Med12 in the regulation of HSC enhancers and the maintenance of stem cell function. We believe that alterations in Med12-dependent regulation of enhancers may contribute to malignant transformation, especially as MED12 mutations have been found in both solid and blood tumors.

SATURDAY 25 JUNE, 13:15 – 15:15

CONCURRENT IV: TECHNOLOGY FRONTIERS

Level 2, Room 2004

APPLICATION OF REPROGAMMING AND IPSC APPROACHES TO DRUG DISCOVERY

Labow, Mark[1], Bidinosti, Michael[2], Galimberti, Ivan[2], Guglielmo, Roma[2], Luthi, Andreas[3], Meisner-Kober, Nicole[2], Daniela, Gabriel[2], Groot-Kormelink, Paul[2], Latario, Brian[1], Baryza, Jeremy[1], Hild, Marc[1], Mapa, Filipa[1], Nash, Mark[2] and Mueller, Matthias[2]

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Reprogramming technologies offer the potential for building cell models of disease that are of high physiologic relevance and scalable for high throughput approaches. Further, reprogramming of patient cells may be of particular utility in creating disease models which are caused by complex mutations that would be difficult to engineer in naïve cells. We have created a number of iPSC models for neurodevelopmental and neuromuscular disease from patients carrying large deletion and nucleotide expansion mutations. To date, the models have been remarkable in exhibiting key molecular markers related to their disease-causing mutations. In this talk, we will discuss our experience in testing differentiated derivatives of these cells for disease related phenotypes, target validation, and high throughput compound screening. Finally, we also discuss phenotypic differences observed between differentiated cells derived from iPSCs and adult fibroblasts.

HIGHLY MULTIPLEXED SIMULTANEOUS DETECTION OF PROTEINS AND RNA IN SINGLE CELLS

Gherardini, Pier Federico[1], Frei, Andreas[1], Bava, Felice Alessio[1], Zunder, Eli R[2], Hsieh, Elena W Y[3] and Chen, Shih-Yu[1]

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Measurements of gene expression are a fundamental tool to understand how genetic networks coordinately function in normal cells and tissues and how they malfunction in disease. The most commonly used methods (e.g. qPCR, microarrays or RNA-seq) are bulk assays that only measure the average expression in a sample. As such they cannot detect expression differences between different cellular populations in a complex sample. To enable detection of expression signatures specific to individual cells we developed PLAYR (Proximity Ligation Assay for RNA), a technology for highly multiplexed quantification of transcripts in single cells by flow- and mass-cytometry. PLAYR is compatible with standard antibody staining of proteins, thus allowing simultaneous quantification of up to 40 different mRNAs and proteins. Given the multiplexing capabilities of the CyTOF mass cytometer, we consider this technology to be complementary to single-cell RNAseq in providing information on a selected panel of genes, but with a throughput of hundreds or thousands of cells per second and a very low cost per sample. Moreover, cells are fixed at the beginning of the protocol and no reverse transcription is required, thus minimizing experimental variability due to sample processing or PCR amplification bias. PLAYR was validated in multiple biological systems and showed a range of detection from highly abundant down to transcripts that are expressed at ~10 copies per cell. Moreover we compared our technology with RT-qPCR, thus confirming that PLAYR can be used to reliably quantify relative changes in transcript abundance across different biological conditions. In conclusion PLAYR expands high-throughput deep phenotyping of cells beyond protein epitopes to include RNA expression. We believe that such an approach will help to define new cell populations that share patterns of temporally or spatially regulated gene expression. The elevated sample throughout makes PLAYR particularly useful when studying rare cell populations. Moreover protein co-detection enables the study of post-transcriptional regulation and the relationship between signaling and gene expression with single cell resolution.

AMPLIFICATION OF OCCULT MTDNA MUTATIONS DURING NUCLEAR REPROGRAMMING CAUSES INTRA-PERSON HIPSCS VARIABILITY

Perales Clemente, Ester[1], Cook, Alexandra[1], Evans, Jared[1], Roellinger, Samantha[1], Secreto, Frank J[1], Oglesbee, Devin[1], Mootha, Vamsi[2], Hirano, Michio[3], Schon, Eric[3], Terzic, Andre[1] and Nelson, Timothy J.[1]

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Nuclear reprogramming technology has ushered a new era of research, but functional variability among human induced pluripotent stem cells (hiPSCs) clones remains a limitation, especially assembling high-quality hiPSCs biorepositories. Beyond the inter-person variability, the root cause of intra-person variability remains unknown. Mitochondria, the powerhouses of the cell, play a major role in energy production, but also have an important role during nuclear reprogramming, guiding the transition from somatic oxidative metabolism to pluripotent glycolytic bioenergetics. Human mitochondria have their own genome called mitochondrial DNA (mtDNA), the coexistence of multiple variants of mtDNA in a cell or tissue is referred to as heteroplasmy. Mutations in both nuclear and mitochondrial DNA may lead to mitochondrial disease, with a reduced bioenergetic output in the affected tissue. Herein, we performed mtDNA next gen sequencing (NGS) on 84 hiPSC clones derived from a cohort of 19 individuals consisting of mitochondrial and non-mitochondrial disease patients. The analysis of mtDNA variants showed that probable damaging mutations are amplified from the original fibroblasts, generating mutant hiPSCs with a detrimental effect in their differentiated progeny, in both healthy and diseased individuals. Specifically, hiPSC-derived cardiomyocytes with mtDNA amplified mutations, showed impaired mitochondrial respiration compared with their wild-type counterparts. We propose mtDNA NGS as a new selection criteria to ensure hiPSCs quality for disease modelling, drug discovery and regenerative medicine.

Funding Source: This work was supported by the Marriott Mitochondrial Disorders Clinical Research Network (E.P.C., D.O., V.K.M., M.H., E.A.S. and T.J.N.), the Leducq Foundation (E.P.C., T.J.N., and A.T.), the Todd and Karen Wanek Family Program for Hypoplastic Left

CIRM'S HUMAN INDUCED PLURIPOTENT STEM CELL BANK AT THE CORIELL INSTITUTE: THE WORLD'S LARGEST PUBLIC COLLECTION OF PLURIPOTENT STEM CELLS FOR THE UNDERSTANDING AND TREATMENT OF COMPLEX GENETIC DISEASES

Perez, Cristian A[1], Huber, Daniel[1], Hand, Julia[1], Tenorio, Matthew[1], Lin, Stephen[2], Novak, Thomas[3] and MacKnight, Andrew[1]

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Induced pluripotent stem cells (iPSCs) reprogrammed from patient-derived skin or blood cells have become a key resource for human disease modeling and therapy discovery and development. The California Institute for Regenerative Medicine (CIRM) recognized the value and need for these resources and created the CIRM Human Induced Pluripotent Stem Cell Bank. To ensure the proper storage, handling, and distribution of these samples CIRM partnered with the Coriell Institute for Medical Research, a leader in biobanking management. With a satellite location in Novato, California, Coriell provides clinical data management, data hosting, and biospecimen storage and distribution services. The CIRM hiPSC Bank includes a range of genetically complex diseases: Alzheimer's disease, Blinding Eye Diseases, Cardiomyopathies, Fatty Liver Disease, Hepatitis C, IPF, Autism Spectrum, Cerebral Palsy, Epilepsy, and also normal controls. These iPSCs are produced by Cellular Dynamics International (CDI), which is funded to derive iPSC lines from 3,000 donors using a proprietary non-integrating episomal vector system. To ensure the quality of the lines, each one undergoes a rigorous quality control (Chromosomal Integrity, Pluripotency, Identity Confirmation, Loss of Reprograming, Mycoplasma, and Sterility) prior to being banked by the Coriell Institute. A majority of donors are also screened and negative for HIV, HBV, and HCV. The resource it is currently comprised of hundreds of iPSC lines with extensive clinical data. The specimens are presented to users via Coriell's online CIRM hiPSC Bank catalog (catalog.coriell.org/CIRM) where users have the ability to perform detailed clinical data searches, browse dedicated disease and sample pages and place orders. Importantly, each of these iPSCs are fully licensed to ensure Freedom to Operate for commercial entities. The overall quality of these lines, Freedom to Operate, available clinical data, and accessible catalog experience makes this an unmatched resource for researchers. The CIRM hiPSC Bank at Coriell contributes to fulfill CIRM's mission of accelerate stem cell treatments to patients with unmet medical needs by

making high quality iPSCs publicly available worldwide to investigators from academia, non-profits and industry.

Funding Source: Grant IR1-06600 from the California Institute for Regenerative Medicine (CIRM)

PRESENTATION FROM LATE BREAKING ABSTRACTS

IDENTIFICATION OF GENOME-EDITING CONDITIONS THAT FAVOR HDR IN HUMAN IPS CELLS BY SYSTEMATIC QUANTIFICATION OF HDR AND NHEJ

Miyaoka, Yuichiro[1], Berman, Jennifer R.[2], Cooper, Samantha B.[2], Mayerl, Steven J.[3], Chan, Amanda H.[3], Zhang, Bin[2], Karlin-Neumann, George A.[2] and Conklin, Bruce R.[3,4]

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Genome-editing in human induced pluripotent stem (iPS) cells holds great promise in experimental biology and therapies. Precise genome-editing that relies on the repair of sequence-specific nuclease-induced DNA nicking or double-strand breaks (DSBs) by homology-directed repair (HDR) is critical for these applications. However, nonhomologous end-joining (NHEJ), an error-prone repair process, acts concurrently, reducing the rate of high-fidelity edits. The identification of genome-editing conditions that favor HDR over NHEJ has been hindered by the lack of a simple method to measure HDR and NHEJ directly and simultaneously at endogenous loci. To overcome this challenge, we developed a novel, rapid, digital PCR-based assay that can simultaneously detect one HDR or NHEJ event out of 1,000 copies of the genome. Using this assay, we systematically monitored genome-editing outcomes of CRISPR-associated protein 9 (Cas9), Cas9 nickases, catalytically dead Cas9 fused to FokI, and transcription activator-like effector nuclease at three disease-associated endogenous gene loci in human iPS cells as well as HEK293T cells and HeLa cells. Although it is widely thought that NHEJ generally occurs more often than HDR, we found that more HDR than NHEJ was induced under multiple conditions. Surprisingly, the HDR/NHEJ ratios were highly dependent on gene locus, nuclease platform, and cell type. The new assay system, and our findings based on it, will enable mechanistic studies of genome-editing and help improve accuracy of genome-editing in human iPS cells.

MIRNA SWITCHES THAT IDENTIFY AND ISOLATE TARGET CELLS IN HIGH-RESOLUTION

Saito, Hirohide

Kyoto University, Kyoto, Japan

Activities of microRNAs (miRNAs) are dynamically changed during cell reprogramming or differentiation. We have recently developed a new method, "miRNA switch", for high-resolution identification and purification of target live-cells by precisely detecting endogenous miRNA activities that function as a cell signature. Our miRNA switches are composed of synthetic mRNAs encoding a protein of interest tagged with complementary sequences of target miRNAs. Using flow cytometry, we found that a set of miRNA switches identify a specific cell population as a sharp peak and clearly separate different cell types based on less than two-fold differences in miRNA activities. The corresponding miRNA-responsive switches purified variety of target cells differentiated from human pluripotent stem cells with high efficiency, accuracy, and safety. Moreover, the designed switches automatically enriched or eliminated the target cells without cell sorting. Our miRNA switches have a potential to purify desired cell types and uncover heterogeneity of the cell populations.

SATURDAY 25 JUNE, 16:00 – 18:20

PLENARY VII: CELL THERAPY IN CLINICAL TRIALS

WHERE ARE WE CLINICALLY WITH CELL BASED THERAPIES FOR PARKINSON'S DISEASE IN 2016?

Barker, Roger A.

University of Cambridge, U.K.

Parkinson's disease (PD) is a common neurodegenerative condition that is diagnosed clinically with a core pathology that involves alpha-synuclein Lewy body formation and the loss of the dopaminergic nigral neurons. While the disease has been recognised to have pathology that extends out of this site with clinical features to match, it can nevertheless be successfully treated with dopaminergic drugs. These therapies, although improving patients for many years, are not without complications and side effects due to the fact that they release dopamine in a non physiological way and at sites where it is not needed. Thus a better approach would be to put back the dopamine in a physiological way at the site where it is needed- the striatum- through dopaminergic neuronal transplants. Of the many different cell therapies have been tried in

PD, the one that has proven most successful involves allografted human fetal ventral mesencephalic (fVM) tissue which contains the developing nigral dopaminergic neurons. Although the results to date using this approach have been inconsistent, it is now become clearer as to the reasons for this, and this has led us to a new FP7-EU funded trial (TRANSEURO) that grafted its first patients in 2015 and which is still ongoing. This study has paved the way for the next generation of trials using stem cell based therapies for PD given the ethical and logistical problems inherent with human fVM tissue. This has now evolved to the point where authentic midbrain dopamine cells can be reliably made from human ES cell sources with evidence of long term functional efficacy in animal models of PD. As such several groups are now entering the final stages of pre clinical testing of this new dopaminergic cell product with the aim of undertaking the first in human trials in PD in the next 2-3 years – assuming all the regulatory issues associated with this type of therapy (which are different in different continents) can be properly addressed and answered.

Funding Source: Supported by Burroughs Wellcome Fund

HOW SHOULD WE GENERATE 300B PLATELETS FROM IPS CELLS?

Eto, Koji

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

Two million platelet transfusions are performed annually in the US. Limitations of current platelet supply system based on donated blood include bacterial/viral contamination and imbalance between demand and supply. Owing to its short 5 day shelf life, 20% of platelet products are discarded. In addition, immune-mediated platelet transfusion refractoriness is a critical issue, most frequently caused by alloantibodies against class I human leukocyte antigen (HLA) on platelets. iPS cell technology must provide strategies for overcoming these issues. Yet our primary question is how can standard transfusion dose of 300 billion platelets be practically generated from iPS cells. The production process consists of the following 3 parts: (1) large scale expansion of platelet precursors, the megakaryocytes (MKs), (2) efficient release of functional and healthy platelets from MKs, and (3) concentration and purification of platelets with minimal damages. For (1) large scale expansion, we have already established iPS cell derived immortalized MK cell line (imMKCL), which showed continuous growth and platelet release. Our recent issue to be addressed was (2) the process for facilitating "functional" platelet yield. To solve this issue, we sought for key mechanistic points through in vivo observations. The obtained findings contributed to the development of a new bioreactor-based device instead of inefficient classical 'culture dish' method. The testing of the final platelet product from this new method proved to have an adequate competence, with shortened bleeding time in animal models post transfusion. In addition, just one universal type platelets which lack class I HLA molecule shall become commercializable by combining our technologies. This HLA null platelet product shall evade anti-HLA alloimmunity, and be an ideal commercial product showing universal effectiveness with lowered production cost. The symposium will cover the total strategy of future platelet product.

PATIENT-DERIVED INDUCED PLURIPOTENT STEM CELLS FOR MODELING AND TREATMENT OF INHERITED RETINAL DISEASE

Stone, Edwin M.

University of Iowa Carver College of Medicine, Iowa City, IA, U.S.

Inherited retinal degenerative disorders such as retinitis pigmentosa are characterized by death of the light sensing photoreceptive neurons of the outer retina. Like the rest of the CNS, the retina has little capacity for endogenous regeneration, and as a result, photoreceptor cell death causes debilitating irreversible blindness. Gene augmentation has the potential to prevent photoreceptor cell death, while cell replacement could actually repopulate the retina with new functioning photoreceptor cells and restore vision. In this talk I will show how we are using patient-specific iPSCs to evaluate disease pathophysiology, test novel gene-based therapeutics and develop autologous photoreceptor cell replacement for the treatment of retinal degenerative blindness.

KEYNOTE ADDRESS

PROBING TRANSCRIPTION REGULATION IN ES CELLS AND DISEASE MODELS BY SINGLE MOLECULE IMAGING

Tjian, Robert[1,2], Liu, Zhe[3], Li, Li[3] and Zhang, Zhengjian[3]

[1]Howard Hughes Medical Institute, Chevy Chase, MD, U.S., [2]University of California, Berkeley, CA, U.S., [3]Janelia Farm, Ashburn, VA, U.S.

Combinatorial cis-regulatory networks encoded in animal genomes represents the foundational gene expression mechanism for directing cell-fate commitment and maintenance of cell identity by transcription factors (TFs). However, the temporal dynamics and 3D spatial organization of cis-elements and how such sub-nuclear structures influence TF activity remains poorly understood. Here, we combine in vivo and in vitro single-molecule imaging, transcription factor (TF) mutagenesis and ChIP-exo mapping to determine how TFs dynamically search for and assemble on their cognate DNA target sites. We used super resolution lattice light-sheet microscopy to localize and functionally probe TF-bound enhancer organization in living

ES cells. Our results suggest an integrated model linking cis-element 3D spatial distribution to local versus global target search modalities essential for regulating eukaryotic gene transcription. We have also begun to study the behavior of TFs and their interaction with proteins implicated in disease. In particular, we have used single molecule imaging to track the movement of Sp1 in cells bearing the mutant mHtt protein with expanded Gln repeats. Our preliminary findings suggest that mHtt aggregates may influence the availability of Sp1 to regulate transcription of its target genes.

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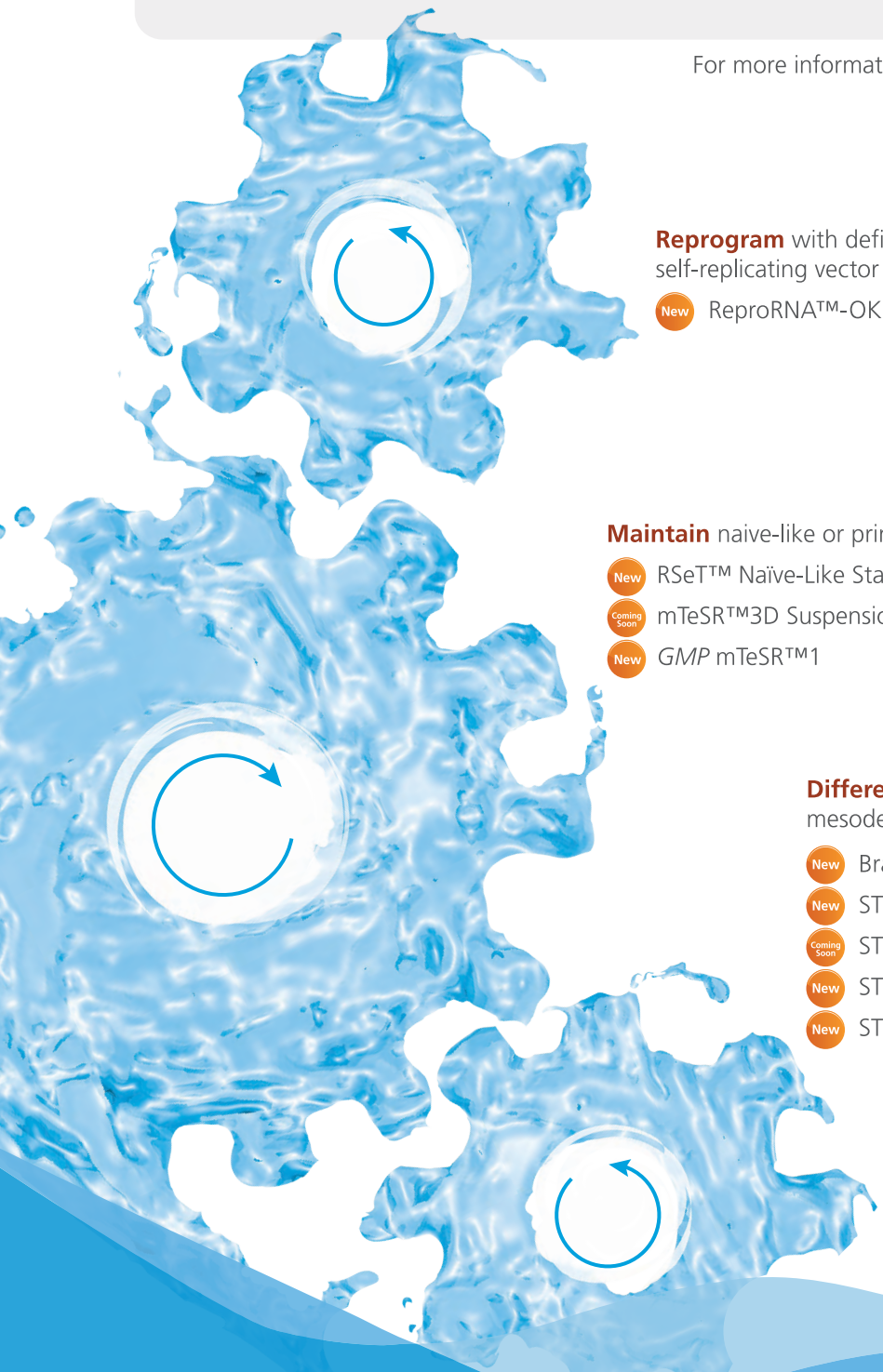

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