ISSCR

Program Guide

Brilliant together.

ISSCR 2019 Annual Meeting

26–29 June
Los Angeles, USA

The global stem cell event

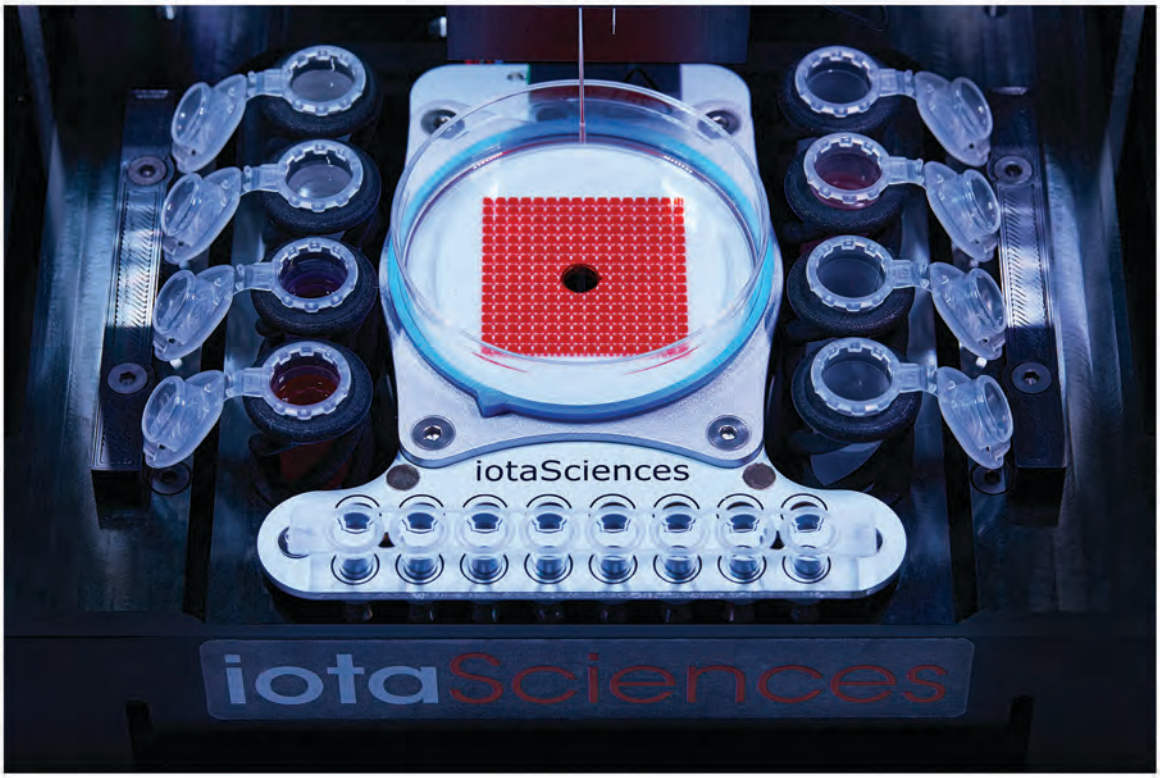
www.isscr2019.org

Co-sponsored by:
USC Stem Cell

iotaSciences

shaping fluids

Single-cell cloning made easy



Automated and consistent workflow with <1 µl volume

Visit us at the startup pavilion booth SUP10 for live demo

iotasciences.com/isocell

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Dear Colleagues,

On behalf of the International Society for Stem Cell Research (ISSCR), we warmly welcome you to the 2019 Annual Meeting in beautiful Los Angeles, California, U.S., a hub of culture and entertainment and a center of innovation and technology, with many world class research institutions, biotech companies, and a vibrant stem cell community. We are pleased that Los Angeles will be hosting the world's largest gathering of stem cell researchers.

Our scientific program highlights the latest advances in stem cell research and its potential to transform human health. This year you will see several new approaches to meeting presentations, including the plenary sessions, which will highlight the continuum of stem cell science from basic research to clinical trials. Each plenary will focus on a specific tissue type and feature speakers using diverse approaches and tools to dissect the underpinnings of stem cells in the development and disease of that tissue type.

This year we will also focus on the next generation of stem cell researchers; for the first time 16 plenary talks will be delivered by abstract-selected speakers. This innovation was inspired by one of our keynote speakers, John Gurdon, whose landmark experiments on nuclear transplantation began when he was a graduate student, illustrating that transformative science can be done at any career stage.

We are excited about two new programs this year that provide opportunities for networking and skills-building: the Women in Science Luncheon will bring together female leaders in STEM to share insights and provide tips on communication challenges and the Science Advocacy and Communications Seminar will feature discussions about how to communicate research to policy makers, media, and the public. We will have many sessions on clinical advances throughout the meeting, as well as a pre-meeting workshop on Advancing Clinical Trials with Stem Cells, and Focus Sessions and Innovation Showcases highlighting new companies and products.

We hope you will seek out the many opportunities at ISSCR 2019 to learn about new research approaches and expand your network of colleagues and friends. Each year this meeting inspires us with new ideas and showcases the many advances taking place across the breadth of stem cell science. Enjoy the meeting and explore the vibrant offerings while you are in Los Angeles!

Sincerely,

Douglas Melton
ISSCR President

Marius Wernig
Program Chair

USC Stem Cell

26 June 2019

Dear Stem Cell Researchers,

As co-host of this year's ISSCR meeting, USC Stem Cell and the Choi family welcomes you to the 2019 Annual Meeting of the International Society for Stem Cell Research (ISSCR).

We are delighted the City of Los Angeles is hosting its first ISSCR. Los Angeles is a leading hub for the biosciences. The University of Southern California (USC) and other local institutions are spearheading stem cell-based clinical trials to treat everything from macular degeneration (USC/City of Hope) to "bubble baby disease" (University of California, Los Angeles), from HIV/AIDS (City of Hope) to chronic viral infections (Children's Hospital of Los Angeles) to ALS (Cedars-Sinai). These programs in research centers in the City of Los Angeles, and many more throughout the State of California, have been supported by the voter-initiated California Institute for Regenerative Medicine.

Our city has much to offer—from its lively cultural scene, to the beauty of its mountains and beaches, entertainment provided by movie studios and theme parks, and outstanding international cuisine. Within 5 miles of the LA Convention Center, you can check out the Broad Museum (worth a wait if no reservation), catch a game at the Staples Center, visit the Music Center to see a show at the Dorothy Chandler Pavilion or symphony at the Walt Disney Concert Hall, take a hike to Griffith Park Observatory, eat at Grand Central Market, ride the Angels Flight Railway, visit El Pueblo de Los Angeles Historical Monument at Olvera Street, or browse titles at the Last Bookstore and vinyl records at Amoeba Music.

Come meet our researchers at USC Stem Cell exhibitor booth (#805) and enjoy the 2019 ISSCR.

Andy McMahon
Director, Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC

CO-SPONSOR

USC Stem Cell

GOLD SPONSORS

Americans for Cures

BlueRock Therapeutics

CEDARS-SINAI

Cell Stem Cell

CIRM

Fate Therapeutics

maxwell BIOSYSTEMS

semma THERAPEUTICS

STEMCELL TECHNOLOGIES

SILVER SPONSORS

Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA

Novo Nordisk

Takeda

UC San Diego Health Sanford Stem Cell Clinical Center

UC San Diego Stem Cell Program

WiCell

BRONZE SPONSORS

Allen Institute for Cell Science

Boston Children's Hospital Stem Cell Program

Caribou Biosciences

EMBO Molecular Medicine

Harvard Stem Cell Institute

The Jackson Laboratory

Massachusetts General Hospital Center for Regenerative Medicine

Miltenyi Biotec

The New York Stem Cell Foundation

CONTRIBUTORS

Cell Research

DDNews

Drug Target Review

Karger Publishers

ISSCR 2020

THE GLOBAL STEM CELL EVENT

ABSTRACT SUBMISSION AND EARLY REGISTRATION OPEN 4 DECEMBER 2019.

ISSCR

CO-SPONSORED BY:
HSCI Harvard Stem Cell Institute

www.isscr2020.org

TABLE OF CONTENTS

Click on the Table of Contents to jump to the section.

REGISTRATION AND BADGE PICKUP

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

TUESDAY, 25 JUNE 14:00 – 18:00
WEDNESDAY, 26 JUNE 7:00 – 20:30
THURSDAY, 27 JUNE 7:30 – 18:30
FRIDAY, 28 JUNE 7:30 – 18:30
SATURDAY, 29 JUNE 8:00 – 18:00

For hotel matters, please visit the housing assistance desk in the registration area:

WEDNESDAY, 26 JUNE 13:00 - 18:00
THURSDAY, 27 JUNE 9:00 - 16:00
FRIDAY, 28 JUNE 9:00 - 12:00

ATTENDEE ORIENTATION

Curious to find out how to best navigate through ISSCR 2019? Join us at the LACC, West Hall Lobby for our Attendee Orientation where ISSCR staff and experienced ISSCR members will explain the annual meeting's highlights and facilitate attendee introductions before the meeting kicks off. There will be two scheduled Attendee Orientations:

TUESDAY, 25 JUNE 15:00 – 16:30
WEDNESDAY, 26 JUNE 7:45 – 8:45

INTERNET ACCESS

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

To connect to the Wi-Fi:

Network/SSID: ISSCR2019

Password: STEMCELLS1

MOBILE APP

Have the ISSCR 2019 schedule in the palm of your hand. Download the free ISSCR 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
- Connect with fellow attendees onsite using the Make Connections feature
- Check the locations of sessions using the maps.
- Receive important real-time communications from ISSCR under messages
- Favorite multiple sessions to build a personalized schedule
- View exhibitors and sponsors and locate them on the interactive floor plan
- Stay in-the-know and join in on social media with #ISSCR2019

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

or go to https://goo.gl/NbQxaa

PC users can go to www.eventscribe.com/2019/ISSCR

RECORDINGS PROHIBITED

Still photography, video and/or audio taping of the sessions, presentations and posters at the ISSCR 2019 Annual Meeting is strictly prohibited. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

WHERE CAN I FIND....?

Speaker Ready Room

Speakers are welcome to review their uploaded presentations in the Speaker Ready Room (Room 501, Level Two) during the following times:

TUESDAY, 25 JUNE 16:00 – 18:00
WEDNESDAY, 26 JUNE 8:00 – 18:00
THURSDAY, 27 JUNE 7:30 – 18:00
FRIDAY, 28 JUNE 7:30 – 18:00
SATURDAY, 29 JUNE 8:00 – 16:30

Plenary speakers are welcome to upload presentations to the Plenary (West Hall B, Level One) during Technical Rehearsals. Rehearsal times:

TUESDAY, 25 JUNE 16:00 – 18:00
WEDNESDAY, 26 JUNE 10:00 – 12:00
THURSDAY, 27 JUNE 7:30 – 8:30
FRIDAY, 28 JUNE 7:30 – 8:30
SATURDAY, 29 JUNE 7:30 – 8:30

Media Office

Credentialed members of the media may use work stations, wireless internet, and a printer during posted hours in the Media Office (Room 514, Level Two). Please visit the Media Office for media panel details.

WEDNESDAY, 26 JUNE 13:00 – 16:00
THURSDAY, 27 JUNE 9:00 – 16:00
FRIDAY, 28 JUNE 7:00 – 16:00

Coat and Baggage Check

Conveniently located in West Hall Pre-Function (next to the Plenary, West Hall B).

WEDNESDAY, 26 JUNE 7:00 – 20:45
THURSDAY, 27 JUNE 7:30 – 20:30
FRIDAY, 28 JUNE 7:30 – 20:30
SATURDAY, 29 JUNE 8:00 – 19:00

Please be sure to collect your items at the end of the day; items cannot be left overnight.

Business Center – Image Quest Plus, LLC

Located in the Concourse Corridor on Level One. Any fees associated with printing, copies or general office needs will be at the cost of the individual.

WEDNESDAY, 26 JUNE 8:00 – 19:00
THURSDAY, 27 JUNE 8:00 – 19:00
FRIDAY, 28 JUNE 8:00 – 19:00
SATURDAY, 29 JUNE 8:00 – 19:00

Mothers' Room

Located around the corner from ISSCR Registration and connected with the First Aid Room.

WEDNESDAY, 26 JUNE 8:00 – 19:00
THURSDAY, 27 JUNE 8:00 – 19:00
FRIDAY, 28 JUNE 8:00 – 19:00
SATURDAY, 29 JUNE 8:00 – 19:00

Discover Los Angeles Desk

Please be sure to stop by the Discover Los Angeles desk for information about the city, places to visit and dine. The desk is located across from ISSCR Registration in the West Hall Pre-Function of the Los Angeles Convention Center. Hours:

TUESDAY, 25 JUNE 14:00 – 18:00
WEDNESDAY, 26 JUNE 9:00 – 17:00
THURSDAY, 27 JUNE 9:00 – 17:00
FRIDAY, 28 JUNE 9:00 – 17:00
SATURDAY, 29 JUNE 9:00 – 16:00

THINGS YOU SHOULD KNOW

Café Options

A coffee cart will be available in the mornings in the ISSCR Registration Area.
Hours of operation:

WEDNESDAY, 26 JUNE 7:00 – 11:00
THURSDAY, 27 JUNE 7:30 – 11:30
FRIDAY, 28 JUNE 7:30 – 11:30
SATURDAY, 29 JUNE 8:00 – 12:00

Lunch and beverage options will be available at the Galaxy Court (located across from ISSCR Registration). Hours of operation:

WEDNESDAY, 26 JUNE 11:00 – 16:00
THURSDAY, 27 JUNE 11:00 – 16:00
FRIDAY, 28 JUNE 11:00 – 16:00
SATURDAY, 29 JUNE 11:00 – 15:00

Show Your Badge Program

Attendees can present the name badges at various locations in Los Angeles in order to obtain special discounts. For a list of participating restaurants and outlets, please go to the following link:

https://www.discoverlosangeles.com/show-your-badge-offers

Smoking

Smoking is prohibited in the LACC.

Lost and Found

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

ATM Machines

There are 3 ATM machines, located in the LACC, West Building:

- One in the West Hall Lobby, Level One
- One in the West Hall Pre-Function space (outside of the Exhibit Hall)
- One located in the Concourse corridor, next to the Image Quest Plus, LLC (business center)

Parking and Valet

Self-parking is available in the West Hall Garage from 5:30 to 21:00.

Daily parking rate ranges $15-$30 USD. Prices are subject to change.

Acceptable methods of payment include cash and all major credit cards (Visa, MasterCard, American Express and Discover). They do not accept checks. Please note attendees are responsible for paying their own parking garage fees. Valet service is not available.

Message Center

The most effective way to reach out to fellow attendees is through the ISSCR mobile app. Read more on page 8.

Job Opportunities

Post resumes and employment opportunities in the ISSCR Job Match. Meet with any connections at the ISSCR Job Match Lounge located in the Exhibit Hall. Find out more about ISSCR Job Match on page 30.

ISSCR STAFF:

Nancy Witty, Chief Executive Officer

Keith Alm, Chief Operating Officer

Eric Anthony, Director of Policy

Anne Nicholas, Director of Communications

Glori Rosenson, Director of Outreach

Cathy Vijeh, Director of Global Events

Bethany Almon, Senior Manager of Integrated Marketing

Chris Barry, Scientific Communications & Education Manager

Lynnea Brand, Committees Manager

Merrill Drew, Membership Outreach Manager

Dodie Dwyer, Administrative Coordinator

Yvonne Fischer, Managing Editor, *Stem Cell Reports*

Erika Kowalczyk, Meetings Manager

Ray McDonald, Registration Manager

Jack Mosher, Scientific Affairs Senior Manager

Jennifer Moore, Administrative Coordinator

David Perez, Exhibits & Sponsorship Sales Manager

Julie Perlin, Scientific Communications & Education Manager

Liz Weislogel, Meeting Program Manager

BOARD OF DIRECTORS

OFFICERS

PRESIDENT
Douglas A. Melton
Harvard University and Harvard Stem Cell Institute, USA

PAST PRESIDENT
Hans C. Clevers
Hubrecht Institute, Netherlands

PRESIDENT ELECT
Deepak Srivastava
Gladstone Institutes, USA

CLERK
Amander T. Clark
University of California, Los Angeles, USA

VICE PRESIDENT
Christine L. Mummery
Leiden University Medical Center, Netherlands

TREASURER
Arnold R. Kriegstein
University of California San Francisco, USA

DIRECTORS

Roger A. Barker
University of Cambridge, UK

Marianne E. Bronner
California Institute of Technology, USA

Fiona Doetsch
Biozentrum at the University of Basel, Switzerland

Valentina Greco
Yale Medical School, USA

Konrad Hochedlinger
Massachusetts General Hospital and Harvard University, USA

Jane S. Lebkowski
Patch Technologies, USA

Ruth Lehmann
NYU School of Medicine, USA

Urban Lendahl
Karolinska Institute, Sweden

Haifan Lin
Yale University School of Medicine, USA

Melissa H. Little
Murdoch Children's Research Institute and University of Melbourne, Australia

Charles E. Murry
Institute for Stem Cell and Regenerative Medicine, University of Washington, USA

Martin F. Pera
The Jackson Laboratory, USA

Hans R. Schöler
Max Planck Institute for Molecular Biomedicine, Germany

Takanori Takebe
Cincinnati Children's Hospital Medical Center, USA/Tokyo Medical and Dental University and Yokohama City University, Japan

Joanna Wysocka
Stanford University, USA

EX OFFICIO MEMBERS

Sally Temple
Neural Stem Cell Institute, USA

Leonard I. Zon
Boston Children's Hospital, USA

ANNUAL MEETING PROGRAM COMMITTEE

Marius Wernig, Chair
Stanford University, USA

Helen M. Blau
Stanford University School of Medicine Baxter Lab for Stem Cell Biology, USA

Joseph V. Bonventre
Brigham & Women's Hospital, USA

Cord Dohrmann
Evotec, Germany

Willem E. Fibbe
Leiden University Medical Center, Netherlands

Anne Grapin-Botton
DanStem, University of Copenhagen, Denmark

Linda Griffith
Massachusetts Institute of Technology, USA

Brigid L. Hogan
Duke University Medical Center, USA

Hardy Kagimoto
Healios K.K., Japan

Dong-Wook Kim
Yonsei University College of Medicine, Korea

Juergen A. Knoblich
IMBA-Institute of Molecular Biotechnology, Austria

Chris Lengner
University of Pennsylvania, USA

Andrew P. McMahon
University of Southern California, USA

Maria T. Millan
California Institute for Regenerative Medicine (CIRM), USA

Christine L. Mummery
Leiden University Medical Center, Netherlands

Toshiro Sato
Keio University, Japan

Judith Shizuru
Stanford School of Medicine, USA

Benjamin David Simons
University of Cambridge, UK

Molly M. Stevens
Imperial College London, UK

Masayo Takahashi
RIKEN Center for Developmental Biology, Japan

Kenneth S. Zaret
University of Pennsylvania School of Medicine, USA

Yi Arial Zeng
Institute of Biochemistry and Cell Biology, SIBS, CAS, China

Douglas A. Melton, Ex Officio Member
Harvard University, USA

COMMITTEES

AUDIT
Connie J. Eaves, Chair
Hongkui Deng
Katarina Le Blanc
Ruth Lehmann
Glyn Stacey
Paul Tesar

AWARDS
Janet Rossant, Chair
Amander T. Clark
Hans C. Clevers
Urban Lendahl
Douglas A. Melton
Amy Wagers

CLINICAL TRANSLATION
Roger A. Barker, Chair
Melissa K. Carpenter
Stuart Forbes
Steven A. Goldman
Catriona H.M. Jamieson
Charles E. Murry
Jun Takahashi
Gordon C. Weir

EDUCATION COMMITTEE
Esteban Orlando Mazzoni, Chair
William J. Anderson
Sina Bartfeld
Anna Couturier
Yvanka de Soysa
Scott Hawley
Yuin Han Jonathan Loh
Alysson R. Muotri
Jose Polo

ETHICS
Megan Munsie, Chair
Annelien L. Bredenoord
R. Alta Charo
Misao Fujita
Insoo Hyun
Rosario Isasi
Kazuto Kato
Krishanu Saha
Douglas Sipp
Jeremy Sugarman

FINANCE
Arnold R. Kriegstein, Chair
Gregory A. Bonfiglio
Marianne E. Bronner
Haifan Lin
Daniel R. Marshak
Lee Rubin

INDUSTRY
Nils Pfaff, Chair
Kristian Tryggvason, Chair
Robert Deans
Brad Hamilton
Setsuko Hashimoto
Steven Kattman
Felicia Pagliuca
Lee Rubin
Bob Valamehr
Claudia Zylberberg

INTERNATIONAL
Andrew George Elefanty, Chair
Malin Parmar, Chair
Nissim Benvenisty
Robert H. Blelloch
Susan Lim
Yuin Han Jonathan Loh
Il-Hoan Oh
Lygia Pereira
Eugenia Piddini
Ole Pless
Shahragim Tajbakhsh
Takanori Takebe

JUNIOR INVESTIGATORS
Andrea Ditadi, Chair
Lucy Erin O'Brien, Chair
Ting Chen
Joshua D. Currie
Yvanka de Soysa
Elisa Laurenti
Yo Mabuchi
Esteban Orlando Mazzoni
Thao M. Nguyen
Roger Emanuel Rönn
Arial Yi Zeng

MEMBERSHIP
Linheng Li, Chair
Nissim Benvenisty
Amander T. Clark
Ira J. Fox
Akitsu Hotta
Stephen Huhn
Dan S. Kaufman
Cristina Lo Celso
Meritxell Huch Ortega
Douglas Sipp
Omer Yilmaz
Qi Zhou

NOMINATING
Hans C. Clevers, Chair
Fred H. Gage
Rudolf Jaenisch
Gordon M. Keller
Christine L. Mummery
Sally Temple
Fiona M. Watt
Shinya Yamanaka

PUBLIC POLICY
Sean J. Morrison, Chair
Oliver Brüstle
R. Alta Charo
George Q. Daley
Lawrence S.B. Goldstein
Robin Lovell-Badge
Duanqing Pei
Fernando Pitossi
Douglas Sipp
Jeremy Sugarman
Alan O. Trounson

PUBLICATIONS
Kathrin Plath, Chair
Marianne E. Bronner
Eran Meshorer
Christine L. Mummery
Emmanuelle Passegue
Hans Robert Schöler
Yasuhiro Yamada
Martin F. Pera, Ex Officio

STRATEGIC OVERSIGHT
Amander T. Clark, Chair
Ruth Lehmann
Urban Lendahl
Martin F. Pera
Elly Tanaka
Sally Temple

STEM CELL REPORTS

EDITORS

EDITORIAL BOARD

ISSCR ABSTRACT REVIEWERS

Helen Abud
Henrik Ahlenius
Cantas Alev
Robin Ali
Timothy Allsopp
Christopher Antos
Ernest Arenas
Katie Ayers
Hossein Baharvand
Anne Bang
Allison Bardin
Nick Barker
Roger Barker
Luis Batista
Eduard Batlle
Aurelie Baudet
Isabel Beerman
Milena Bellin
Uri Ben-David
Nissim Benvenisty
Benedikt Berninger
Luca Biasco
Tim Blenkinsop
Marnie Blewitt
Barak Blum
Dario Bonanomi
Paola Bonfanti
Dominique Bonnet
Richard Boyd
Catharina Brandsten
Kristen Brennand
Josh Brickman
Vania Broccoli
Marianne Bronner
Benoit Bruneau
Massimiliano Caiazzo
Jingli Cao
Rafael Carazo Salas
Grant Challen
Ian Chambers
Charles Chan
Ting Chen
Christine Cheung
Ken Chien
Susana Chuva de Sousa Lopes
Dennis Clegg
Hans Clevers
Andrew Cohen
April Craft
Leslie Crews
Richard Davis
Francesco Dazzi
Frederick de Sauvage
Hongkui Deng
Bruno Di Stefano
Sheng Ding
Andrea Ditadi
Fiona Doetsch
Sergei Doulatov
Micha Drukker
Nicole Dubois
Sirio Dupont
Connie Eaves
Rachel Eiges
Yechiel Elkabetz
Ulrich Elling
Anna Falk
Isabel Fariñas
Jian Feng
Lesley Forrester
Valentina Fossati
Benjamin Freedman
Michaela Frye
Paul Gadue
Jacques Galipeau
Shaorong Gao
Caroline Gargett
Anthony Gavalas
Bernhard Gentner
Casey Gifford
Jeffery Gimble
Wolfram Goessling
Elisa Gomez Perdiguero
Magdalena Götz
Marie Jose Goumans
Mina Gouti
Shane Grealish
May Griffith
Stan Gronthos
Carolina Guibentif
David Hay
Eva Hedlund
Claire Henchcliffe
Julian Heng
Tracy Heng
Alex Hewitt
Kunihiko Hinohara
Robin Hobbs
Konrad Hochedlinger
Akitsu Hotta
Sara Howden
Guang Hu
Ping Hu
Alice Huang
Penyu Huang
Meri Huch
James Hudson
Lijian Hui
Samer Hussein
Justin Ichida
Haruhisa Inoue
Rosario Isasi
Tetsuya Ishii
Keisuke Ito
Mayumi Ito
Atsushi Iwama
Rudolf Jaenisch
Johan Jakobsson
Young Jang
Sebastian Jessberger
Dhanisha Jhaveri
Jianwei Jiao
Ying Jin
Robert Johnston
Keisuke Kaji
Hayato Kaneda
Yonehiro Kanemura
Dan Kaufman
Kiarash Khosrotehrani
Carla Kim
Daniel Kim
Agnete Kirkeby
Bon-Kyoung Koo
Haruhiko Koseki
Chulan Kwon
Nico Lachmann
Julia Ladewig
Michael Laflamme
Madeline Lancaster
Christophe Lancrin
Fredrik Lanner
Louise Laurent
Katarina Le Blanc
Jane Lebkowski
Gabsang Lee
Sang-Hun Lee
Martin Leeb
Urban Lendahl
Wan-ju Li
Xiajun John Li

ISSCR ABSTRACT REVIEWERS

Heiko Lickert
Rebecca Lim
Melissa Little
Hongjun Liu
Yuin Han Loh
Angelo Lombardo
Sally Lowell
William Lowry
Tenneille Ludwig
Zhen-Ge Luo
Mattias Lutolf
Stephanie Ma
Maria Carolina Marchetto
Graziano Martello
Zubin Master
Sandro Matosevic
Fulvio Mavilio
Esteban Mazzoni
Todd McDevitt
Edwina McGlinn
Shannon McKinney-Freeman
Alexander Meissner
Philippe Menasché
Simon Mendez-Ferrer
Brad Merrill
Tobias Merson
Eran Meshorer
Sarah Millar
Gabriella Minchiotti
Guo-li Ming
Samantha Morris
Klaas Mulder
Megan Munsie
Alysson Muotri
Takashi Nagasawa
Andras Nagy
Luigi Naldini
Stephane Nedelec
Christian Nefzger
Elizabeth Ng
Thao Nguyen
Carien Niessen
Susie Nilsson
Trista North
Maria Cristina Nostro
Sara Nunes Vasconcelos
Michael O'Connor
Il-Hoan Oh
Steve Oh
Yohei Okada
Hideyuki Okano
Valeria Orlova
Pierre Osteil
Dmitry Ovchinnikov
Nathan Palpant
Athanasia Panopoulos
Eirini Papapetrou
In-Hyun Park
Malin Parmar
Simona Parrinello
Sergiu Pasca
Robert Passier
Alice Pebay
Martin Pera
Stuart Pitson
Kathrin Plath
Jose Polo
Alessandro Prigione
Stephanie Protze
Louise Purton
April Pyle
Li Qian
Jing Qu
Shahin Rafii
Emma Rawlins
Jeremy Rich
Anne Rios
Isabelle Riviere
Nicolas Rivron
Pamela Robey
Roger Rönn
Janet Rossant
Filip Roudnicky
Holger Russ
Alessandra Sacco
Michel Sadelain
Krishanu Saha
Mitinori Saitou
Max Salick
Maike Sander
Tomo Saric
Kazunobu Sawamoto
Thorsten Schlaeger
Markus Schober
Hans Scholer
Vittorio Sebastiano
Michael Shen
Qin Shen
Molly Shoichet
Robert Signer
Jose Silva
Douglas Sipp
Austin Smith
Julie Sneddon
Lukas Sommer
Hongjun Song
Lincon Stamp
Ed Stanley
Christopher Sturgeon
Shahragim Tajbakhsh
Kazutoshi Takahashi
Claire Tanner
Michael Teitell
Derk ten Berge
Adrian Kee Keong Teo
Paul Tesar
Guiseppe Testa
Thorold Theunissen
Mark Tomishima
Leigh Turner
Achia Urbach
Ludovic Vallier
Louis Vermeulen
Jane Visvader
Richard Wade-Martins
Amy Wagers
Darcy Wagner
Haoyi Wang
Jianlong Wang
Xiaoqun Wang
Christine Wells
Sara Wickstrom
Ernst Wolvetang
Joseph Wu
Wei Xie
Yasuhiro Yamada
Nan Yang
Omer Yilmaz
Qilong Ying
Shosei Yoshida
Nadja Zeltner
Hao Zhu
Leonard Zon
Thomas Zwaka
Robert Zweigerdt

JOIN US ON WEDNESDAY, 26 JUNE DURING PLENARY I FOR THE 2019 ISSCR AWARDS PRESENTATIONS

LAWRENCE GOLDSTEIN SPECIAL RECOGNITION

Lawrence Goldstein, PhD, of the University of California, San Diego, USA, will be recognized for his extraordinary contributions to science, policy and the ISSCR. Dr. Goldstein's service to the field has been critically important in highlighting the role science plays in public life and society. He has promoted understanding of the field of regenerative medicine and effective stem cell policy. In recognition of Dr. Goldstein's leadership, the ISSCR will be establishing the Lawrence Goldstein Science Policy Fellowship Program to train the next generation of stem cell policy and regulatory advocates.

ISSCR PUBLIC SERVICE AWARD

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

The 2019 recipients, Eli and Edythe Broad, have made significant contributions to the field of stem cell research, with investments that underscore their belief that it has the potential to treat some of the most devastating diseases and conditions and significantly improve human health. The Broad Foundation has supported the California Institute for Regenerative Medicine (CIRM) and pledged $113 million in stem cell center grants to create and sustain three stem cell centers in California, and support 375 scientists doing transformational work. The Broad Center of Regenerative Medicine and Stem Cell Research at UCLA, the Broad Center of Regeneration Medicine and Stem Cell Research at UCSF, and the Broad Center for Regenerative Medicine and Stem Cell Research at USC all operate extensive research programs with funding through The Broad Foundation.

ISSCR AWARD FOR INNOVATION

The ISSCR Award for Innovation 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.

The 2019 ISSCR Award for Innovation will be presented to John E. Dick, PhD, FRS, Senior Scientist, Princess Margaret Cancer Centre, University Health Network, and Professor, University of Toronto, Canada during the Presidential Symposium on Wednesday, 26 June. John E. Dick's research into leukemia led to the discovery of leukemia stem cells in acute myeloid leukemia (AML), an aggressive and often fatal blood cancer. He has tracked how leukemia stem cells arise from normal stem cells, findings that have led to new methods of predicting which individuals in the general population are at risk of developing AML.

Dr. Dick will present his research in Plenary IV, Stem Cells and Regeneration of Endodermal Organs on Friday, 28 June, at 10:50.

ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR

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

The ISSCR Dr. Susan Lim Award for Outstanding Young Investigator will be presented to Barbara Treutlein, PhD, ETH Zurich, Department of Biosystems Science and Engineering, Basel, Switzerland in recognition of her transformational work in single-cell transcriptomics, a technology used to study gene expression in single cells within organisms. Treutlein was one of the first to reconstruct the development of a complex mammalian tissue, and to provide a molecular description of individual cell regeneration in the axolotl limb.

Dr. Treutlein will present her research in Plenary VI, From Bench to Bedside: Surface Ectoderm and Endocrine Organs, on Saturday, 29 June, at 10:50.

ISSCR TOBIAS AWARD LECTURE

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

The ISSCR Tobias Award Lecture will be presented to Scott Armstrong, MD, PhD, Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Harvard Medical School, Boston, USA. Dr. Armstrong's work has focused on discovery of developmental pathways that drive childhood cancers and developing new treatment approaches. He directs a rigorous research program to develop treatments that target epigenetic mechanisms using new small molecule approaches.

Dr. Armstrong will deliver the ISSCR Tobias Award Lecture in Plenary VII, Basics and Translation: Neural Ectoderm, on Saturday, 29 June, at 16:05.

CONGRATULATIONS TO THE 2019 TRAVEL AWARD WINNERS

2019 ISSCR ZHONGMEI CHEN YONG TRAVEL AWARDS FOR SCIENTIFIC EXCELLENCE

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

Christopher Ahuja
Juan Alvarez-Dominguez
Madeline Andrews
Yishai Avior
Shiran Bar
Michela Bartoccetti
Aparna Bhaduri
Romeo Blanc
Kayleigh Bozon
Freya Bruveris
Claudia Carabana Garcia
Marine Charrier
Di Chen
Hao Chen
Wei-Ju Chen
Elisa Clark
Malkiel Cohen
Amanda Collier
Samuel Collombet
Mahmoud Dabbah
Wahiba Dhahri
Marlon Dias
Susan Eliazer
Ramy Elsaid
Elena Enzo
Vinutha Eshwara Swamy
Ugomma Eze
Ali Fathi
Hananeh Fonoudi
Mukul Girotra
Janin Grajcarek
David Grommisch
Mingxia Gu
Wenting Guo
Jiangping He
Franklin Herbert
Mirabelle Ho
Miriel Ho
Chun Ho Chan
Wenxiang Hu
Wei Huang
Jin Hui Hor
Tsuyoshi Iida
Satoshi Ikeo
Ammar Jabali
Jin Jea Sung
Marie Jonsson
Rukhsana Kausar
Cody Kime
Azuma Kimura
Siddharth Kishore
Olivia Krefft
Cynthia Lau
Andrew Lee
Choon-Soo Lee
Elyad Lezmi
Ang Li
Bo Li
Lu Li
Xiaolin Lin
Katrin Linda
Nils Lindstrom
Kadi Lohmussaar
Wan-Jin Lu
Leo Machado
Bushra Memon
Michela Milani
Aditya Mithal
Masashi Miyauchi
Taiki Nakajima
Yoko Nishinaka-Arai
Sara Nolbrant
Daniel Ortmann
Anna Osnato
Pierre Osteil
Ralitsa Petrova
Antonella Pinto
Jens Puschhof
Francesca Rapino
Erin Sanders
Aditya Sankar
Munirah Santosa
Denise Serra
Arun Sharma
Elad Sintov
Enrique Sosa
Berna Sozen
Junichi Tanaka
Fang Tao
Dan Vershkov
Daniel Wagner
Magdalena Wagner
Zhenghao Yang
Atilgan Yilmaz
Linfeng Zhang
Valentina Zinna
Jan Zylicz

Receipients of the Caribou Bioscience Travel Awards

Mariaceleste Aragona
Thomas Ambrosi
Joel Blanchard
Bruno Di Stefano
Alicia Mayeuf-Louchart
Edwin Rosado-Olivieri
Bo Shen
Jian Shu
Bing Zhang
Jiasheng Zhong

ISSCR MERIT ABSTRACT AWARDS

The ISSCR recognizes outstanding abstracts with the ISSCR Merit Abstract Awards. These awards are given to ISSCR trainee members who have submitted distinguished abstracts as judged by the ISSCR 2019 abstract reviewers.

Juan Alvarez-Dominguez
Thomas Ambrosi
Madeline Andrews
Mariaceleste Aragona
Aparna Bhaduri
Romeo Blanc
Joel Blanchard
Kayleigh Bozon
Freya Bruveris
Vincenzo Calvanese
Hao Chen
Di Chen
Elisa Clark
Malkiel Cohen
Samuel Collombet
Bruno Di
Marlon Dias
Susan Eliazer
Elena Enzo
Ugomma Eze
Ali Fathi
Hananeh Fonoudi
Mukul Girotra
Ernesto Goulart
David Grommisch
Mingxia Gu
Franklin Herbert
Mirabelle Ho
Wenxiang Hu
Wei Huang
Tsuyoshi Iida
Satoshi Ikeo
Ammar Jabali
Marie Jonsson
Cody Kime
Azuma Kimura
Siddharth Kishore
Choon-Soo Lee
Andrew Lee
Lu Li
Ang Li
Nils Lindstrom
Cambrian Liu
Kadi Lohmussaar
Wan-Jin Lu
Hiroyuki Matsumura
Alicia Mayeuf-Louchart
Bushra Memon
Aditya Mithal
Masashi Miyauchi
Taiki Nakajima
Yoko Nishinaka-Arai
Sangbum Park
Ralitsa Petrova
Antonella Pinto
Jens Puschhof
Edwin Rosado-Olivieri
Alexander Ross
Erin Sanders
Aditya Sankar
Munirah Santosa
Arun Sharma
Bo Shen
Takahiro Shiga
Jian Shu
Joanna Smeeton
Enrique Sosa
Junichi Tanaka
Fang Tao
Kei-ichi Tsukiboshi
Magdalena Wagner
Daniel Wagner
Zhenghao Yang
Qi Yao
Atilgan Yilmaz
Linfeng Zhang
Bing Zhang
Jiasheng Zhong
Jan Zylicz

WEDNESDAY, 26 JUNE, PLENARY I

JOHN B. GURDON, *FRS, WELLCOME TRUST/CANCER RESEARCH UK GURDON INSTITUTE, UNIVERSITY OF CAMBRIDGE, UK*

Dr. Gurdon was a Zoology undergraduate at Oxford University. In 1971 he joined the MRC molecular biology lab in Cambridge. In 1983 he co-founded a research Institute of developmental and cancer biology (now named the Gurdon Institute) with Professor Laskey, acting as Chairman until 2002. His career has concentrated on nuclear transplantation in the frog and experiments to discover the value of mRNA microinjection, mechanisms of response to morphogen gradients, and recently, mechanisms of nuclear reprogramming by *Xenopus* oocytes and eggs. He was Master of Magdalene College Cambridge, UK from 1995-2002 and has received various recognitions for his work.

PAOLA ARLOTTA, *PHD, HARVARD UNIVERSITY, USA*

Dr. Arlotta is the Golub Family Professor and Chair of the Department of Stem Cell and Regenerative Biology at Harvard University. She is interested in understanding the mechanistic principles that govern brain development during embryogenesis. Her work integrates developmental, evolutionary and stem cell biology knowledge to inform novel strategies for modeling human brain development and neuropsychiatric disease in vitro, using brain organoids. Arlotta is the recipient of many awards, including the 2017 George Ledlie Prize from Harvard, The 2018 Fannie Cox Prize for excellence in science teaching, and the 2018 Friedrich Wilhelm Bessel Research Award from the Humboldt Foundation.

HANS CLEVERS, *MD, PHD, HUBRECHT INSTITUTE, NETHERLANDS*

Dr. Clevers obtained his MD degree in 1984 and his PhD degree in 1985 from the University Utrecht, the Netherlands. His postdoctoral work (1986-1989) was done with Cox Terhorst at the Dana-Farber Cancer Institute of the Harvard University, Boston, USA. From 1991-2002 Hans Clevers was Professor in Immunology at the University Utrecht and, since 2002, Professor in Molecular Genetics. From 2002-2012 he was director of the Hubrecht Institute in Utrecht. From 2012-2015 he was President of the Royal Netherlands Academy of Arts and Sciences (KNAW). Since June 1, 2015 he is director Research of the Princess Máxima Center for pediatric oncology.

KARL KOEHLER, *PHD, INDIANA UNIVERSITY SCHOOL OF MEDICINE, USA*

Karl Koehler is Assistant Professor of Otolaryngology-Head and Neck Surgery at Indiana University School of Medicine. He became a tenure-tracked faculty member shortly after completing his PhD in Neuroscience in 2014 under the mentorship of Eri Hashino. Karl's early work led to a novel culture system for growing mouse and human inner ear organoids, which his lab now uses to model congenital ear disorders and test gene therapies for hearing restoration. In addition, his group has shown how this unique organoid model can be used to generate hair-bearing skin tissue. Karl was recently named the Philip F. Holton Scholar of Otology at IU School of Medicine. His work is funded by the US National Institute of Health and Department of Defense.

ANNE MCLAREN MEMORIAL LECTURE

Wednesday, 26 June, Plenary II

ALLAN SPRADLING, *PHD, CARNEGIE INSTITUTION FOR SCIENCE, USA*

Allan Spradling heads a research group and is Director Emeritus at the Department of Embryology, Carnegie Institution for Science in Baltimore. He is a Howard Hughes Medical Institute Investigator and Adjunct Professor at Johns Hopkins University. Using both Drosophila and mice, Spradling's group studies how oocytes are constructed and the underlying biology that makes oogenesis possible. Like meiosis itself, they find that many aspects of female gametogenesis are conserved across species. These similarities provide insight into understanding how chromatin organization changes during germ cell development, and how completed oocytes achieve and maintain a quiescent state prior to fertilization. Mature, unfertilized oocytes lack transcription and fully depend on translational regulation of mRNAs that are stored in conserved RNP particles like those located at neural synapses.

PATIENT ADVOCATE

Friday, 28 June, Plenary V

NANCI RYDER

Nanci Ryder, a renowned Hollywood publicist and co-founder of BWR Public Relations, was diagnosed with ALS in 2014. Since then, she has worked tirelessly to raise public awareness about ALS, and to advance the search for effective treatments and cures for ALS along with the help of her many friends and supporters. Along with her family and friends, like Renée Zellweger and Courteney Cox, she has participated in the Los Angeles County Walk to Defeat ALS as "Team Nanci", raising over $690,000 in support of the ALS community. She has received many awards for her awareness and fundraising efforts, including from the Publicists Guild, The ALS Association, and The ALS Association Golden West Chapter.

JOHN MCNEISH MEMORIAL LECTURE

Friday, 28 June, Plenary V

ANDREW PLUMP, *MD, PHD, TAKEDA PHARMACEUTICAL COMPANY, USA*

Andrew Plump is the President of Research and Development of Takeda Pharmaceutical Company and serves as a member of the company's Board of Directors. His career spans nearly 30 years in the pharmaceutical industry and academia and his experience encompasses early research through regulatory approval and patient access. Dr. Plump's approach toward drug research and development is reflected in a virtuous cycle of "bench to bedside to bench" learning. He is a true translational physician-scientist, with deep knowledge in biomedical research, experimental medicine, early development, genomics and biomarkers and a history of scientific contributions in neuroscience, cardiovascular and metabolic diseases.

ERNEST MCCULLOCH MEMORIAL LECTURE

Saturday, 29 June, Plenary VII

LORENZ P. STUDER, *MD, MEMORIAL SLOAN KETTERING CANCER CENTER, USA*

Lorenz P. Studer is the Director of the Center for Stem Cell Biology and a Member of the Developmental Biology Program at the Memorial Sloan Kettering Cancer Center. His lab has established techniques for turning human pluripotent stem cells into the diverse cell types of the nervous system. He has been among the first to realize the potential of patient-specific stem cell in modeling human disease and developed strategies to manipulate cellular age in pluripotent-derived lineages. Finally, he currently leads a multidisciplinary consortium to pursue the clinical application of human stem cell-derived dopamine neurons for the treatment of Parkinson's disease. Recent awards related to those studies include a Macarthur Fellowship, the Ogawa-Yamanaka Prize and the Jacob Heskel Gabbay award in Biotechnology and Medicine.

KEYNOTE ADDRESS

Saturday, 29 June, Plenary VII

SHINYA YAMANAKA, *MD, PHD, GLADSTONE INSTITUTES, USA AND CENTER FOR IPS CELL RESEARCH & APPLICATION, KYOTO UNIVERSITY, JAPAN*

Shinya Yamanaka is most recognized for his discovery of induced pluripotent stem cells (iPSC), which are differentiated cells that have been reprogrammed to the pluripotent state. He is Director of the Center for iPS Cell Research and Application (CiRA), which was founded in 2008 in response to his discovery, at Kyoto University, Japan, and Senior Investigator at the Gladstone Institutes in the United States. He earned his MD in 1987 from Kobe University and PhD. in 1993 from Osaka City University. Upon graduation, he went to the Gladstone Institutes as a scientist, where he first learned genetics and the use of embryonic stem cells. In 1996, he returned to Japan and has since continuously researched pluripotency. He has been a professor at Kyoto University since 2004. The awards he has received include the ISSCR McEwen Award for Innovation in 2011 and the Nobel Prize in 2012.

SCHEDULE AT A GLANCE

Tuesday, 25 June	
9:00 - 17:30	Pre-Meeting Education: Workshop on Clinical Translation: Cedars-Sinai Medical Center, Harvey Morse Auditorium
15:00 - 16:30	Attendee Orientation

Wednesday, 26 June	
7:45 - 8:45	Attendee Orientation
9:00 - 12:00	Focus Sessions
9:30 - 12:00	Science Advocacy and Communications Seminar
11:30 - 12:45	Early Career Group Leader Luncheon
13:00 - 15:15	Plenary I: Presidential Symposium
15:15 - 16:00	Refreshment Break
15:15 - 20:30	Exhibit Hall Open
15:15 - 18:30	Poster Set Up
16:00 - 18:00	Plenary II: Pluripotency and Germ Cells
18:00 - 20:30	Opening Reception
18:30 - 20:30	Poster Session I
21:00 - 24:00	Junior Investigator Social Night – The Reserve

Thursday, 27 June	
8:00 - 8:30	Innovation Showcases
8:30 - 9:00	Morning Coffee
9:00 - 11:15	Plenary III: Mechanisms and Applications of Mesodermal Tissues I
11:00 - 20:00	Exhibit Hall Open
11:00 - 13:15	Poster Set Up
11:15 - 13:00	Lunch Break
11:30 - 12:30	Innovation Showcases
11:30 - 13:00	Junior Investigator Meet the Experts Luncheon
12:15 - 13:00	Meet-up Hubs
13:15 - 15:15	Concurrent Sessions IA - E

15:15 - 16:00	Meet-up Hubs
15:15 - 16:00	Refreshment Break
16:00 - 18:00	Concurrent Sessions IIA - E
18:00 - 20:00	Poster Session II and Reception

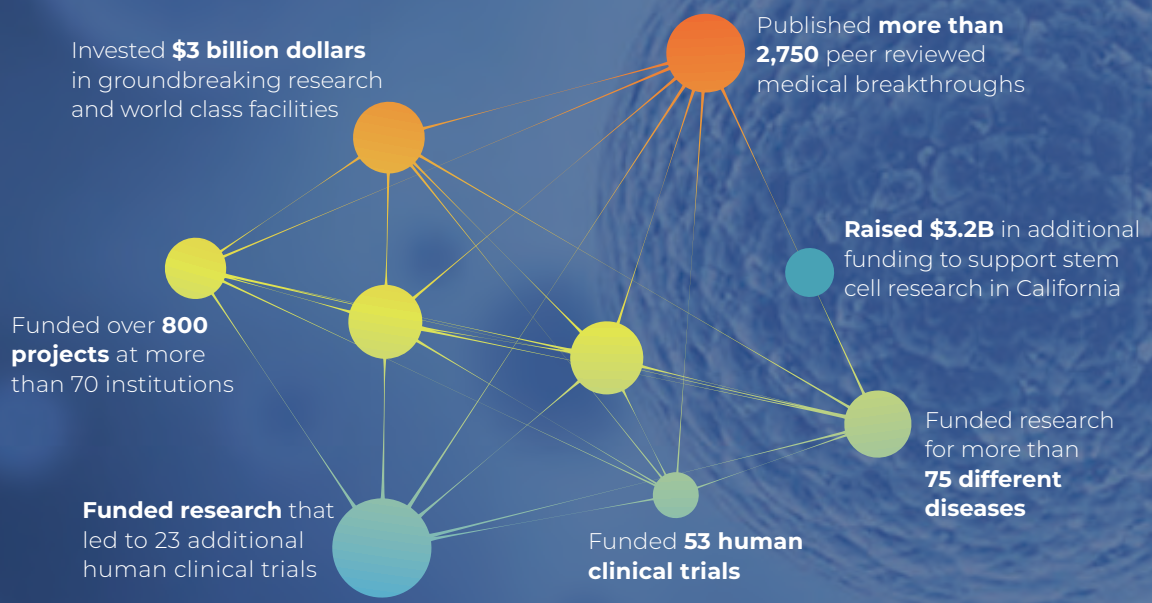
Friday, 28 June	
8:00 - 8:30	Innovation Showcases
8:30 - 9:00	Morning Coffee
9:00 - 11:20	Plenary IV: Stem Cells and Regeneration of Endodermal Organs
11:00 - 20:00	Exhibit Hall Open
11:00 - 13:15	Poster Set Up
11:20 - 13:00	Lunch Break
11:30 - 12:30	Innovation Showcases
11:30 - 13:00	Women in Science Luncheon
12:15 - 13:00	Meet-up Hubs
13:15 - 15:15	Concurrent Sessions IIIA - E
15:15 - 16:00	Meet-up Hubs
15:15 - 16:00	Refreshment Break
16:00 - 18:00	Plenary V: Mechanisms and Applications of Mesodermal Tissues II
18:00 - 20:00	Poster Session III and Reception

Saturday, 29 June	
8:30 - 9:00	Morning Coffee
9:00 - 11:20	Plenary VI: From Bench to Bedside: Surface Ectoderm and Endocrine Organs
11:20 - 13:15	Lunch Break
11:30 - 13:00	Junior Investigator Career Panel Luncheon
12:15 - 13:00	Meet-up Hubs
13:15 - 15:15	Concurrent Sessions IVA - E
15:15 - 16:00	Meet-up Hubs
15:15 - 16:00	Refreshment Break
16:00 - 18:45	Plenary VII: Basics and Translation: Neural Ectoderm

In 2004, California became the FIRST in the world to provide dedicated, long-term funding for cutting-edge medical research at the ballot.

With the support of 7 million voters, the 2004 ballot initiative Proposition 71 secured $3 billion to turbocharge new therapy development and medical research in California.

In the past 15 years, the California stem cell program has:



Most recently, CIRM funded research has **saved the lives** of at least 42 children, cured bubble baby disease, and is helping develop life changing treatments for **diabetes**, **HIV/AIDS**, **leukemia**, **blindness**, **spinal cord injury**, **cancer**, and many other chronic diseases.

Dedicated, guaranteed, long-term funding for stem cell research is critical in our collective fight against chronic disease. The success of the California Institute of Regenerative Medicine is proof of how much we can do when advocates, scientists and government take action together.

"Thank you for giving me my life back."

–KRIS BOESEN, 23, Bakersfield, former quadriplegic, current patient CIRM-funded spinal cord injury clinical trial

Americans *for* Cures
www.americansforcures.org


Ready for your next career move?
• Quickly find opportunities in stem cell science
• Customize job alerts for newly-posted positions
• Upload your resume so employers can find you
Looking for your next hire?
• Reach more than 20,000 potential applicants using ISSCR's monthly newsletter
• Save time by tracking your applicants through our career center
• Member pricing starts at just $200.00 per listing
ISSCR
JOB BOARD
jobbank.isscr.org

MOBILE APP GUIDE

Take the first step to a successful networking strategy by reaching out to researchers attending ISSCR 2019 via our free mobile app. To learn how to download the ISSCR 2019 mobile app, refer to page 6. 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 2019 mobile app and expand your professional network during the annual meeting.

NETWORKING AT A GLANCE

What better way to nurture your research and career than networking? ISSCR 2019 provides many opportunities for scientists in all stages of their careers to exchange insightful and relevant advice that helps advance their research and lab work. ISSCR understands our members' needs and offers various avenues to help scientists foster and strengthen their professional networks. Here is a quick glance at what ISSCR 2019 has to offer.

TUESDAY, 25 JUNE

15:00 – 16:30
Attendee Orientation
LACC, Level One, West Hall 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 2019 experience and work with other attendees to solve a fun challenge. You may even walk away with a prize.

WEDNESDAY, 26 JUNE

7:45 – 8:45
Attendee Orientation
LACC, Level One, West Hall Lobby

A second chance to learn how to navigate ISSCR 2019.

9:30 – 12:00
Science Advocacy and Communications Seminar
Sponsored by UC San Diego Health Sanford Stem Cell Clinical Center & UC San Diego Stem Cell Program

LACC, Level Two, Room 411

To learn more, see page 32.

11:30 – 12:45
Early-Career Group Leader Luncheon – It's About Time! Managing Priorities in Research and Mentoring
LACC, Level One, Petree Hall

This is a ticketed event that requires pre-registration. To learn more, see page 30.

15:15 – 20:30
Exhibit Hall
LACC, Level One, West Hall A

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 29. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Job Match Lounge.

18:00 – 20:30
Poster Session I and Opening Reception
Sponsored by WiCell

LACC, Level One, West Hall A

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 – 24:00
Junior Investigator Social Night
In Memory of Jordan Klein; Sponsored by Americans for Cures

The Reserve, 650 South Spring Street, Los Angeles

ISSCR annual meeting badge and photo ID required for entry. Must be age 21 or older to attend. To learn more, see page 30.

THURSDAY, 27 JUNE

11:00 – 20:00
Exhibit Hall
LACC, Level One, West Hall A

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 29. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Job Match Lounge.

11:30 – 13:00
Junior Investigator Meet the Experts Luncheon
Sponsored by Boston Children's Hospital Stem Cell Program, Harvard Stem Cell Institute and Massachusetts General Hospital Center for Regenerative Medicine.

LACC, Level One, Petree Hall

This is a ticketed event that requires pre-registration. To learn more, see page 30.

12:15 – 13:00
Guangzhou Regenerative Medicine and Health Guangdong Provincial Laboratory Introduction
Exhibit Hall – Meet-up Hub #1

Guangzhou Regenerative Medicine and Health Guangdong Provincial Laboratory (GRMH-GDL) was established by Guangdong province on December 22, 2017 to enhance research ability. At present, a number of international high level scientists have joined GRMH-GDL. And it have published more than 50 articles in Cell, Nature and other internationally journals, making important contribution to scientific research.

How EBiSC Helps Researchers to Access and Share High-Quality Research-Grade IPSC Lines
Exhibit Hall – Meet-up Hub #2

The European Bank of induced Pluripotent Stem Cells (EBiSC) enables academic and commercial researchers to access high-quality hiPSC lines across >36 disease backgrounds including healthy 'disease-free' individuals, along with associated datasets. Depositing hiPSC lines generated in your research project (such as StemBANCC and HipSci) assures secure storage, ease of distribution to other researchers and sustainability of research assets at project end.

Meet with representatives of the second project phase of the European Bank for induced Pluripotent Stem Cells (EBiSC2) (https://cells.ebisc.org) and discuss how EBiSC can help you with:

- Ordering lines from the EBiSC catalogue
- Depositing your hiPSC lines into EBiSC
- Planning your iPSC research project to simplify hiPSC line deposition
- Progressing your research through use of EBiSC services, including:
- hiPSC reprogramming
- Gene-editing
- Banking
- Quality Control

Learn more about ongoing developments within EBiSC2 to improve hiPSC banking, differentiation and Quality Control using high-throughput and automated technologies, including supply of differentiated cell populations direct to users.

15:15 – 16:00
Industry Scientists Networking
Exhibit Hall – Meet-up Hub #1

The ISSCR Industry Committee invites interested attendees to stop by the Meet-up Hub to exchange and discuss about various industry-related topics. These may include potential entry opportunities, potential career paths and developments in the industry.

15:15 – 16:00
German Stem Cell Network
Exhibit Hall – Meet-up Hub #2

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

18:00 – 20:00
Poster Session II and Reception
LACC, Level One, West Hall A

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, 28 JUNE

11:00 – 20:00
Exhibit Hall
LACC, Level One, West Hall A

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 29. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Job Match Lounge.

11:30 – 13:00
Women in Science Luncheon
LACC, Level One, Petree Hall

This is a ticketed event that requires pre-registration. To learn more, see page 31.

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

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

15:15 – 16:00
Policy, Ethics, and Regulatory Issues
Exhibit Hall – Meet-up Hub #2

Are policy, ethics, or regulatory issues impacting your research? Stop by the Meet-up Hub to discuss these issues with ISSCR leaders and find out about opportunities to get involved in the ISSCR's advocacy program.

18:00 – 20:00
Poster Session III and Reception
LACC, Level One, West Hall A

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, 29 JUNE

11:00 – 16:00
Exhibit Hall
LACC, Level One, West Hall A

Network with industry professionals with over 140 exhibiting companies. Explore the possibilities on page 29. Take advantage of casual networking and meeting spaces at ISSCR Central and ISSCR Job Match Lounge.

11:30 – 13:00
Junior Investigator Career Panel Luncheon – Embracing Change: Recipes for a Successful Scientific Career Path
LACC, Level One, Petree Hall

This is a ticketed event that requires pre-registration. To learn more, see page 31.

15:15 – 16:00
Volunteer Opportunities at the ISSCR
Exhibit Hall – Meet-up Hub #1

Interested in learning more about volunteer opportunities? ISSCR outreach and communications staff will be available to answer your questions.

15:15 – 16:00
Diversity, Inclusion, and Equity in Stem Cell Biology
Exhibit Hall – Meet-up Hub #2

Please join us to learn from each other about inclusive practices to build better research communities that support representation and participation of scientists from diverse backgrounds. This meet-up is for individuals from all career stages and institutional profiles to openly discuss barriers to inclusion in stem cell biology and strategies to mitigate them.

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 Timeline
- Discover all of your Member Benefits
- *Stem Cell Report's* commemorative issue

DAILY ATTENDEE SURVEYS ARE OPEN AT ISSCR CENTRAL!

We want to hear from you! Each day of the meeting, a new, short survey will be available in ISSCR Central. Answer the questions for a chance to win a complimentary registration to ISSCR 2020 in Boston, USA. Each survey answered gives you another chance to win! The random drawing will take place on Saturday after the Exhibit Hall closes, and winners will be contacted by email.

MEET-UP HUBS

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

JOB MATCH

This innovative opportunity connects academic and industry employers with scientists looking for their next position.

Annual meeting attendees can opt in to Job Match at any time, at no additional fee. Browse the online Job Match Directory for job match profiles that meet your interests. Employers can view details of potential candidates and view CVs and poster information. Job seekers can view open position details.

Contact your favorites to make appointments to meet in person during the annual meeting. The ISSCR Job Match Lounge and ISSCR Central will be open in the Exhibit Hall during Exhibit Hall hours, or you can meet at a job seeker's poster.

EARLY-CAREER GROUP LEADER LUNCHEON

IT'S ABOUT TIME! MANAGING PRIORITIES IN RESEARCH AND MENTORING

WEDNESDAY, 26 JUNE 11:30 – 12:45
LACC, Level One, Petree Hall

Gone are the carefree days of your postdoc days, where you could commit your time solely to research. Group Leaders experience a constant barrage of tasks, both large and small, that must be balanced correctly in order to achieve success. Engage with other early-career group leaders, the ISSCR Board of Directors, and the ISSCR Junior Investigators Committee to discuss strategies and experiences on time management to maximize your mentorship, research, and well-being.

This is a ticketed event that requires pre-registration. The event is for ISSCR members who are early-career research group leaders (principal investigators or junior faculty for 8 or fewer years). A nominal fee applies.

JUNIOR INVESTIGATOR SOCIAL NIGHT

WEDNESDAY, 26 JUNE 21:00 – 00:00
In Memory of Jordan Klein; Sponsored by Americans for Cures

Start your ISSCR 2019 experience by meeting, mingling, dancing and socializing with fellow young investigators from around the world during the meeting's first night. Light snacks will be provided.

Venue: The Reserve

Address: 650 South Spring Street, Los Angeles, CA 90014

What to Expect:

The night will begin with time to meet and mingle. Light snacks will be provided. When the DJ starts spinning, JIs can dance the night away.

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

This event is for trainee members (postdoctoral fellows and students.)

JUNIOR INVESTIGATOR MEET THE EXPERTS LUNCHEON

THURSDAY, 27 JUNE, 11:30 – 13:00
LACC, Level One, Petree Hall

Sponsored by Boston Children's Hospital Stem Cell Program, Harvard Stem Cell Institute and Massachusetts General Hospital Center for Regenerative Medicine.

Junior Investigators are invited to meet with leaders over lunch to examine research techniques and topics, career paths and more. This relaxed networking luncheon allows 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. A nominal fee applies. This event is for trainee members (postdoctoral fellows and students.)

WOMEN IN SCIENCE LUNCHEON

A SEAT AT THE TABLE: WOMEN AT THE LEADING EDGE OF SCIENCE

FRIDAY, 28 JUNE, 11:30 – 13:00
LACC, Level One, Petree Hall

Women in STEM fields face some unique challenges and are often acutely aware of the role their gender plays as they advance both personally and professionally throughout their careers. For the first time, the ISSCR will host a panel of esteemed women in science to discuss how women scientists communicate in fields still largely dominated by men, how they make their voices heard in exchanges with colleagues and the public, and what experiences have shaped their current thinking about gender roles and balance in science.

After a seated luncheon and time for networking with leaders in stem cell science, the panel will share their thoughts and insights about their own experiences with science communications, and how they've learned to navigate headwinds and avoid pitfalls as they move ahead.

Registration is required. A nominal fee applies.

MODERATOR
Christine Mummery
Professor of Developmental Biology, Leiden University Medical Center, The Netherlands

PANELISTS
Rachel Haurwitz
President and Chief Executive Officer, Caribou Biosciences, USA

Kelsey Martin
Dean, David Geffen School of Medicine, University of California Los Angeles, USA

Laura Mosqueda
Dean, Keck School of Medicine, University of Southern California, USA

JUNIOR INVESTIGATOR CAREER PANEL LUNCHEON

EMBRACING CHANGE: RECIPES FOR A SUCCESSFUL SCIENTIFIC CAREER PATH

SATURDAY, 29 JUNE, 11:30 – 13:00
LACC, Level One, Petree Hall

Junior Investigators are invited to join the ISSCR Junior Investigators Committee and a panel of experts for an in-depth discussion in a casual lunch setting.

What is your career vision? Do you have a desire to work in science, but are unsure exactly with the right future job looks like? No matter if you need to decide what to do after completing your master, your PhD, or your post-doc, making the decisions that set the course of your career can be daunting. *Should I continue along the academic path to attempt starting my own group or should I seek my fortune in industry? Should I study a new field or should I stick with what I already know? Am I sure that the current plan is really what would be fulfilling and right for me later down the road? Are there other career avenues that I haven't yet considered? And what if I find out that the path I chose is not the right one for me? How difficult will it be to change?* If these are questions keeping you up at night, then this is the luncheon for you! Come listen to our panelists tell the stories of their "not-so-linear" careers, and of the turns they took that allowed them to successfully reach their goals. Find inspiration in how to change and shape your journey in science, and have your questions answered on how you may move your own career forward.

This is a ticketed event that requires pre-registration. A nominal fee applies. This event is for trainee members (postdoctoral fellows and students.)

MODERATOR
Yvanka de Soysa
J. David Gladstone Institutes and UCSF, USA
Member, ISSCR Junior Investigators Committee

PANELISTS
Kenny Gibbs
National Institute of General Medical Sciences, USA

Megan Munsie
University of Melbourne, Australia

Felicia Pagliuca
Semma Therapeutics, USA

Nikolaus Rajewsky
Max Delbrück Center for Molecular Medicine, Germany

SCIENCE ADVOCACY AND COMMUNICATIONS SEMINAR

Sponsored by UC San Diego Stem Cell Program and UC San Diego Health Sanford Stem Cell Clinical Center

WEDNESDAY, 26 JUNE 9:30 – 12:00
LACC, Level Two, Room 411

Ethical and regulatory issues continue to confront the field of stem cell research and affect the development of new regenerative medicine products. Rogue clinics marketing unproven treatments as stem cell-based therapies are increasing despite the efforts of regulators to rein them in while speeding the development of products proven to be safe and effective. Last year's shocking announcement of the first CRISPR babies is a failure of scientific self-regulation and poses a new threat to the field. This pre-meeting Ethics and Regulatory Forum will feature two sessions with perspectives from leading scientists, ethicists, and regulators on how the field can address these challenges. The first session will focus on germline genome editing include talks on the ethical, regulatory, scientific, and societal considerations of this technology. The second session will focus on the current regulatory environment for stem cell-based interventions and the challenges posed by unproven clinics.

AGENDA:

9:30 – 9:35 WELCOME AND INTRODUCTION
Lawrence Goldstein, *University of California, San Diego, USA*

9:35 – 10:15 WHY IS IT IMPORTANT TO COMMUNICATE WITH POLICYMAKERS, THE MEDIA, AND THE PUBLIC?
Sean Morrison, *UT Southwestern, USA*
Sally Temple, *Neural Stem Cell Institute, USA*
Alan Trounson, *Hudson Institute of Medical Research, USA*

10:15 – 10:45 WHAT DO SCIENCE JOURNALISTS WANT TO LEARN FROM SCIENTISTS?
Bradley J. Fikes, *San Diego Union Tribune, USA*
Meghana Keshavan, *STAT, USA*

10:45 – 11:00 HOW DO YOU COMMUNICATE THE IMPORTANCE OF SCIENCE TO THE PUBLIC, PRESS, AND POLICYMAKERS?
Steven Peckman, *University of California, Los Angeles, USA*

11:00 – 11:30 WHAT IS THE CURRENT PUBLIC PERCEPTION OF STEM CELL SCIENCE? HOW CAN THAT GUIDE COMMUNICATION STRATEGIES WITH THE PUBLIC?
Paul Mandabach, *Winner & Mandabach Campaigns, USA*
Jason Stewart, *Americans for Cures, USA*

11:30 – NOON MODERATED DISCUSSION WITH SPEAKERS AND AUDIENCE QUESTIONS
Moderator: Lawrence Goldstein, *University of California, San Diego, USA*

FOCUS SESSIONS

WEDNESDAY, 26 JUNE 9:00 – 12:00

Focus Session: Clincial Development and Commercialization of iPSC-Based Therapies

Organized by: Allele Biotechnology & Pharmaceuticals

With an increasing number of iPSC-based cell therapy programs around the globe heading to clinical phase, this session will be a timely discussion from the pioneers on their experiences from planning and execution of clinical trials using iPSC-derived products. The attendees will have an opportunity to listen to experts speaking on their first-hand experience from conducting a first-in-human clinical trial using iPSC-derived cells, cGMP manufacturing challenges, regulatory aspects-in particular on the need for harmonization/convergence of rules across jurisdictions, value assessment and reimbursement strategies, and other challenges and path to commercialization of an iPSC-based product. The speakers will present their views first followed by a panel discussion.

Room 403B, Level Two

9:00 – 9:05 Welcome & Introductory Remarks
Rajesh Ambasudhan, PhD, *Chief Strategist, Allele Biotechnology & Pharmaceuticals, USA*

9:05 – 9:30 Clinical Development of an iPSC-derived Therapeutic MSC Product
Ross Macdonald, PhD, *CEO, Cynata Therapeutics, Australia*

9:30 – 9:55 Off-the-Shelf Cell-based Cancer Immunotherapy: An iPSC Product Platform for Mass Production of Universal Cell Products
Bob Valamehr, MBA, PhD, *Chief Development Officer, Fate Therapeutics, USA*

9:55 – 10:20 Regenerative Therapy for Heart Failure Patients
Yoshiki Sawa, MD, *Professor, Osaka University, Japan*

10:20 – 10:45 Developing iPSC-based Autologous Cell Therapy for Macular Degeneration: from Bench to Bedside
Kapil Bharti, PhD, *Earl Stadtmawn Investigator, National Eye Institute, NIH, USA*

10:45 – 11:00 cGMP Manufacturing and Banking of iPSCs and Derived Products for Clinical Trials and Commercialization
Jiwu Wang, PhD, *CEO, Allele Biotechnology & Pharmaceuticals, USA*

11:00 – 11:15 Strategies for Obtaining Approval for iPSC-based Therapies
Mahendra Rao, MD, PhD, *Chief Strategy Officer, Q-Therapeutics, USA*

11:15 – 11:30 Value Assessment, Affordability, and Reimbursement Strategies for iPSC-based Cell Therapies
Gorba Thorsten PhD, *Translating Center Director, IQVIA, USA*

11:30 – 12:00 Panel Discussion

Focus Session: Cutting Edge Regenerative Medicine Using Stem Cells

Organized by: Fujita Health University and The Japan Agency for Medical Research and Development (AMED)

After Professor Shinya Yamanaka in Japan was awarded the Nobel Prize for the induction of iPS cells support has been given to make the clinical application of regeneration in Japan a reality by the All Japan. As a result, the world's first clinical application of iPS was carried out. Clinical study and trial on retinal diseases (age-related macular degeneration) and Parkinson's diseases have been started, in addition plans for research on spinal cord injuries and heart failure etc are scheduled. Studies using somatic stem cells are also being driven. In this session we will introduce Japan's support system and announce the progress on regenerative medicine research in the clinical application stage, safety, and ethics, etc. There will also be talks about trends and efforts in regenerative medicine research in the UK and the US. At the end a discussion with the audience will be held regarding the future direction of research. In this session we will introduce Japan's support system and announce the progress on regenerative medicine research in the clinical application stage, safety, and ethics, etc. There will also be talks about trends and efforts in regenerative medicine research in the UK and the US. At the end a discussion with the audience will be held regarding the future direction of research.

Room 502, Level Two

9:00 – 9:05 Opening Remarks
Shinya Yamanaka MD, PhD, *Center for iPS Cell Research and Application, Kyoto University, Japan*

9:05 – 9:15 Accelerating Regenerative Medicine R & D in Japan
Yuka Suzuki, MSc, MPP, *Japan Agency for Medical Research and Development, Japan*

9:15 – 9:33 R&D of a Cell-based Therapy for Parkinson's Disease
Jun Takahashi MD, PhD, *Center for IPS Cell Research and Application, Kyoto University, Japan*

9:33 – 9:51 Regenerative Medicine for Spinal Cord Injuries Using IPS Cells
Masaya Nakamura, MD, PhD, *Keio University, Japan*

9:51 – 10:09 Intestinal Epithelial Stem Cell Organoid and IBD
Ryuichi Okanoto, MD, PhD*, Tokyo Medical and Dental University, Japan*

10:09 – 10:27 iPSCs-based Regenerative Medicine and Drug Development for CNS disorders
Hideyuki Okano, MD, PhD, *Keio University, Japan*

10:27 – 10:45 Genetic Instability Should Be Checked in Clinical Application for Pluripotent Stem Cell-Derived Cinal Products?
Akifumi Matsuyama, MD, PhD, *Fujita Health University, Japan*

10:45 – 10:55 Patient and Public Involvement in Stem Cell Research
Kaori Muto, PhD, *The University of Tokyo, Japan*

10:55 – 11:10 The Current Situation of the National Consortium for Regenerative Medicine and National Regenerative Medicine Database
Kiyoshi Okada MD, PhD, *The Japanese Society for Regenerative Medicine, Japan*

11:10 – 11:28 Leveraging the Clinical Translation of iPS Cells
Ilyas Singec, MD, PhD, *National Center for Advancing Translational Sciences, NIH, USA*

11:28 – 12:00 Q&A Session

Focus Session: From Fundamental to Therapeutic Applications of Pluripotent Stem Cells

Organized by: The French Society for Stem Cell Research and The Belgian Society for Stem Cell Research

The French and Belgian societies for stem cell research are pleased to invite you to their joint focused session highlighting stem cell research in France and in Belgium. Both societies have been recently created to foster exchanges with the international community, to disseminate information to scientists and the public, and to promote young scientists working in the field of stem cell biology. In this context, the objective of this focused session is to present the diverse themes of research involving stem cells that are developed in both societies. Invited speakers from selected institutions of excellence in France and Belgium will present their recent research highlights. Short selected talks will also be presented by PhD students and post-doctoral fellows. This session will also include open discussions around research opportunities in France and Belgium and modalities to integrate into existing academic structures. Young scientists who have gone through this process will share their experiences.

Room 408A, Level Two

9:00 – 9:10 Welcome and Introduction
Cécile Martinat, PhD, *I-Stem, France*

9:10 – 9:30 Foxe1 is a Gatekeeper of NKX2.1+ Progenitors' Differentiation into Thyroid Follicular Cells
Sabine Costagliola, PhD, *Université Libre de Bruxelles, Belgium*

9:30 – 9:45 Gains of Chromosome 12p13.31 Inhibit Exit of Pluripotency During Hepatic Differentiation of Human Pluripotent Stem Cells
Alexander Keller, MSc, *Vrije, Universiteit Brussel, Belgium*

9:45 – 10:05 « Axon-ing » Naive Pluripotency: Control of Self-Renewal and Lineage Commitment by the Axon Guidance Cue Netrin-1
Fabrice Lavial, PhD, *Cancerology Research Center of Lyon, France*

10:05 – 10:20 Manipulating Cell Fate to Improve Tissue Regeneration During Aging
Quentin Alle, MSc, *Institute for Regenerative Medicine and Biotherapy, France*

10:20 – 10:40 The Reprogramming Dynamics of X Chromosome Reactivation
Vincent Pasque, PhD, *KU Leuven, Belgium*

10:40 – 10:55 Pooled Kinome Wide CRISPR/Cas9 Screen in Human Stem Cell-Derived Neurons to Identify Pharmacological Targets for ALS/FTD
Wenting Guo, PhD, *KU Leuven, Belgium*

10:55 – 11:15 Preclinical Validation of a Tissue Engineered Product Consisting in RPE Derived From Human Embryonic Stem Cells Disposed on Human Amniotic Membrane Animal Models
Christelle Monville, PhD, *I-Stem, France*

11:15 – 11:30 The Mouse Fetal Liver Stroma: Signals For HSC Expansion
Francisca Soares da Silva, MSc, *Institut Pasteur, France*

11:30 – 12:00 Panel Discussion: Research Opportunities in France and in Belgium
Shahragim Tajbakhsh, PhD, *Institut Pasteur, France*

Focus Session: From Innovation to Product: Developing an Investigational New Drug (IND) Application

Organized by: The ISSCR Industry Committee

With stem cell science rapidly moving from the laboratory towards the patient, there is a growing interest in the translational pathway and the processes involved. This

is especially true for academics who are increasingly looking to capitalize on discoveries. Drawing on experts from industry and academics, this program focuses on the critical aspects of the Investigational New Drug application including the preclinical data, manufacturing information and the clinical protocols necessary for a cell-based clinical trial. This material is relevant to similar documents required for clinical trials in other regulatory regions.

Concourse E, Level One

9:00 – 9:05 Welcome and Opening Remarks
Lee Rubin, PhD, *Harvard Deparment of Stem Cell & Developmental Biology, USA*

9:05 – 9:20 Introduction to the IND Application
Deborah Hursh, PhD, *US Food and Drug Administration, USA*

9:20 – 9:35 Introduction to the IND Application
Melissa Carpenter, PhD, *Carpenter Group Consulting, USA*

9:35 – 9:40 Q&A Session I
Lee Rubin, PhD, *Harvard Deparment of Stem Cell & Developmental Biology, USA*

9:40 – 9:55 CMC
Derrick Hei, PhD, *BlueRock Therapeutics, USA*

9:55 – 10:10 CMC
Joseph Gold, PhD, *City of Hope, USA*

10:10 – 10:15 Q&A Session II
Lee Rubin, PhD, *Harvard Deparment of Stem Cell & Developmental Biology, USA*

10:15 – 10:30 Pre-clinical Testing (1 of 2)
Catherine Priest, PhD, *Neurona Therapeutics, USA*

10:30 – 10:45 Pre-clinical Testing (2 of 2)
Dorthe Bach Toft, *Novo Nordisk, Denmark*

10:45 – 10:50 Q&A Session III
Felicia Pagliuca, PhD, *Semma Therapeutics, USA*

10:50 – 11:05 Clinical Testing (1 of 2)
Roger Barker, MBBS, PhD, *Unviersity of Cambridge, UK*

11:05 – 11:20 Clinical Testing (2 of 2)
Sunil Agarwal, MD, *Sana Biotechnology, USA*

11:20 – 11:25 Q&A Session IV
Felicia Pagliuca, PhD, *Semma Therapeutics, USA*

11:25 – 11:55 Panel Discussion

11:55 – 12:00 Closing Remarks
Felicia Pagliuca, PhD, *Semma Therapeutics, USA*

Focus Session: New Insights Into Early Human Development: Scientific, Policy And Ethical Considerations

Organized by: The ISSCR Ethics Committee

In this focus session, panelists will discuss scientific, ethical and policy issues raised by the use of human pluripotent stem cells or extended embryo culture to model various stages of early human development. The session will include presentations describing how researchers are using stem cells to better understand implantation, gastrulation and organogenesis, and discussions of technical and other challenges in such research. The session will also feature a review of current policies pertaining to research involving early human embryos and analyze whether they are fit-for-purpose and adequately address ethical issues raised by such research. How to inform and engage the broader community and the public at large on these advances, specifically around the need to develop an appropriate and consistent nomenclature, will also be discussed.

Concourse F, Level One

9:00 – 9:05 Welcome and Introduction of Session and Speakers
Megan Munsie, PhD, *University of Melbourne, Australia*

9:05 – 9:25 The History and Current Status of Research Understanding Early Development and the Justification for Current Approaches
Janet Rossant, PhD, FRS, *Gairdner Foundation, Canada*

9:25 – 9:40 From Blastocyst Development to the Window of Implantation: What Stem Cell-Based Model Can Teach Us
Nicolas Rivron, PhD, *Austrian Academy of Science, Austria*

9:40 – 9:55 Why Research on Early Human Development Using Stem Cell-Derived Models is Important
Jianping Fu, PhD, *University of Michigan, USA*

9:55 – 10:15 Ethical Considerations Related to Research Into Early Human Development
Insoo Hyun, PhD, *Case Western Reserve University School of Medicine, USA*

10:15 – 10:25 Break

10:25 – 10:45 Current Policy Frameworks Across the Globe, Including the ISSCR Guidelines for Stem Cell Research and Clinical Translation, and Discussion Around Fit for Purpose
Geoff Lomax, PhD, *California Institute for Regenerative Medicine, USA*

10:45 – 11:05 Stakeholder Views – How Scientists and Various Publics View Human Embryo Research and Who Should be Making Decisions on its Regulation
Kirstin Matthews, PhD, *Rice University, USA*

11:05 – 11:55 Panel Discussion and Questions from the Audience
Megan Munsie, PhD, *University of Melbourne, Australia*

11:55 – 12:00 Summary
Megan Munsie, PhD, *University of Melbourne, Australia*

Focus Session: Stem Cell Engineering for Therapeutic Applications

Organized by: Center for Gene Therapy, City of Hope; Presented by City of Hope

Stem cell-derived therapeutics are at the forefront of regenerative medicine and, with technological advances, provide new approaches to unmet medical needs. This Focus Session reviews several of the latest stem cell engineering technologies and selected disease-specific developments. Experts will first cover three key areas: novel nuclease-based genome editing of human stem cells, epigenomic editing of embryonic stem cells using targeted methylation, and engineering of safeguards into pluripotent stem cell-based therapies to remove the rise of teratoma formation. In the second part of the Focus Session, experts will discuss applications of stem cell technology to three important disease areas: an IPSC-derived approach to neurological diseases, hematopoietic stem cell (HSC) graft engineering to optimize HSC transplantation outcomes, and use of neural stem cells for delivery of cancer therapy to the brain. This focus on stem cell technologies will expose the attendees to the latest laboratory and clinical strategies for application of stem cells to a broad range of novel therapeutics.

Room 403A, Level Two

9:00 – 9:10 Welcome and Overview
John Zaia, MD, *City of Hope, USA*

9:10 – 9:30 Novel Approaches for Targeted Stem Cell Genome Editing
Kevin Morris, PhD, *Beckman Research Institute, City of Hope, USA*

9:35 – 9:55 Targeted Methylation for Epigenomic Editing of ESCs
Joshua Tompkins, PhD, *Beckman Research Institute, City of Hope, USA*

10:00 – 10:20 Gene Editing to Establish a Safeguard System for Pluripotent Stem Cell-based Therapy
Jiing-Kuan Yee, PhD, *Beckman Research Institute, City of Hope, USA*

10:25 – 10:45 Coffee Break

10:45 – 11:05 iPSC Approach to Neurological Diseases
Yanhong Shi, PhD, *Beckman Research Institute, City of Hope, USA*

11:10 – 11:30 Engineering of the Graft for Improved Blood Stem Cell Transplantation
Angelo Cardoso, MD, PhD, *Beckman Research Institute, City of Hope, USA*

11:35 – 11:55 Neural Stem Cells for Cancer Therapy
Karen Aboody, MD, *Beckman Research Institute, City of Hope, USA*

Focus Session: Tools For Basic And Applied Research

Organized by: Stem Cell COREdinates
Supported by: Thermo Fisher Scientific and Stem Cell Technologies

Stem Cell COREdinates (www.COREdinates.org) is a consortium of human pluripotent stem cell-focused core facilities that have joined forces to share experiences, expertise with protocols and reagents, and to establish "best practices." In the first part of our Focus session we will have selected presentations from Stem Cell COREdinate

members. These presentations will cover different aspects of our activities including cell culture optimization, gene editing and 3D Bioprinting. The second part of the session will focus on Parkinson's disease. Speakers from the MJ Fox Foundation, from the California Parkinson's Registry and from the GForce (A Global Effort to Bring Cell Based Therapies to PD Patients) will participate.

Room 408B, Level Two

9:00 – 09:05 Welcome and Overview of COREdinates
Laurence Daheron, PhD, *Harvard University, USA*

9:05 – 9:20 Fast and Robust Approach for Stem Cell Engineering
Andriana Beltran, PhD, *UNC School of Medicine, USA*

9:20 – 9:35 Optimization of hPSC Maintenance Conditions for True Culture Versatility
Andrew Gaffney, PhD, *Stem Cell Technologies, Canada*

9:35 – 9:50 In Vitro Models and Tissue Fabrication via 3D Bioprinting
Brigitte Arduini, PhD, *Rensselaer Polytechnic Institute, USA*

9:50 – 10:05 Optimized Genome Editing Using CRISPR MIX
Sebastian Diecke, PhD, *MDC, Germany*

10:05 – 10:20 Reducing Genome Engineering of iPSCs to a Practice for Disease Model Construction
David Piper, PhD, *Thermo Fisher, USA*

10:20 – 10:35 Comparative Analysis of Different Media Condition for Growth & Maintenance of Pluripotent Stem Cells
Mehrnaz Ghazvini, PhD, *University of Rotterdam, Netherlands*

10:35 – 10:50 Highly Efficient CRISPR-Cas9 Mediated Genome Editing in Human Pluripotent Stem Cells
Jean Ann Maguire, PhD, *ChOP Philadelphia, USA*

10:50 - 11:05 The Evolution of Stem Cell Genetics: a Decade of Data
Erik McIntire, PhD, *WiCell, USA*

11:15 – 11:30 The Impact of Population Based Studies on Promoting Stem Cell Research
Neptune Mizrahi, PhD, *Public Policy Advocate, MJ Fox Foundation, USA*

11:30 – 11:45 Developing Stem Cell-based Therapies for Parkinson's Disease
Deirdre Hoban, PhD, *Lund University, Sweden*

11:45 – 12:00 Cell Therapy for Parkinson's Disease
Stefan Irion, MD, *BlueRock Therapeutics, USA*

ISSCR Code of Conduct

The ISSCR is committed to providing a safe and productive meeting environment that fosters open dialogue and discussion and the exchange of scientific ideas, while promoting respect and equal treatment for all participants, free of harassment and discrimination. All participants are expected to treat others with respect and consideration, follow venue rules, and alert staff or security of any dangerous situations or anyone in distress. Attendees are expected to uphold standards of scientific integrity and professional ethics. These policies apply to all attendees, speakers, exhibitors, staff, contractors, volunteers, and guests at the meeting and related events.

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

California is leaving its mark **on stem cell research.**

CIRM
CALIFORNIA'S STEM CELL AGENCY
FUNDED

Take a look at some of the scientists we are funding who are talking at ISSCR

Plenary Session Speakers:

Irv Weissman – *Stanford*

Hanna Mikkola – *UCLA*

Hiromitsu Nakauchi – *Stanford & Univ. of Tokyo*

Anthony Oro – *Stanford*

Kristin Baldwin – *Scripps Research Institute*

They, and other speakers – look for the CIRM Funded logo in this brochure – are helping advance the field and transforming how we think about medicine, developing promising new therapies for patients with unmet medical needs.

At every stage of research we are making our mark:

- ***5*** *CIRM-supported therapies expedited by the FDA*
- ***6*** *Alpha Stem Cell Clinics to deliver therapies to patients*
- ***33*** *new treatment candidates now in development*
- ***53*** *clinical trials funded*
- ***1,000*** *stem cell projects funded*
- ***2,000*** *patients enrolled in CIRM-supported clinical trials*

CIRM Offers Something Better Than Hope.

For more information visit, **www.cirm.ca.gov**

CIRM
CALIFORNIA'S STEM CELL AGENCY

Accelerating stem cell treatments to patients with unmet medical needs.

Click here for Program Changes and Errata

TUESDAY, 25 JUNE

9:00 – 17:30	**ADVANCING CLINICAL TRIALS WITH STEM CELLS** *Sponsored by Cedars-Sinai Board of Governors Regenerative Medicine Institute*	OFFSITE: Cedars-Sinai Medical Center, Harvey Morse Auditorium
14:00 – 18:00	**REGISTRATION OPEN**	West Hall Pre-Function, Level One
15:00 – 16:30	**ATTENDEE ORIENTATION**	West Hall Lobby, Level One

WEDNESDAY, 26 JUNE

7:00 – 20:30	**REGISTRATION OPEN**	West Hall Pre-Function, Level One
7:45 – 8:45	**ATTENDEE ORIENTATION**	West Hall Lobby, Level One
8:30 – 9:00	**MORNING COFFEE** *Sponsored by The Jackson Laboratory*	West Hall Pre-Function, Level One
	FOCUS SESSIONS (See page 32 for details)	
9:00 – 12:00	**CLINICAL DEVELOPMENT AND COMMERCIALIZATION OF IPSC-BASED THERAPIES** *Organized by Allele Biotechnology and Pharmaceuticals*	Room 403B, Level Two
9:00 – 12:00	**CUTTING EDGE REGENERATIVE MEDICINE USING STEM CELLS** *Organized by Fujita Health University and The Japan Agency for Medical Research and Development (AMED)*	Room 502, Level Two
9:00 – 12:00	**FROM FUNDAMENTAL TO THERAPEUTIC APPLICATIONS OF PLURIPOTENT STEM CELLS** *Organized by The French Society for Stem Cell Research and The Belgian Society for Stem Cell Research*	Room 408A, Level Two
9:00 – 12:00	**FROM INNOVATION TO PRODUCT: DEVELOPING AN INVESTIGATIONAL NEW DRUG (IND) APPLICATION** *Presented by the ISSCR Industry Committee*	Concourse E, Level One
9:00 – 12:00	**NEW INSIGHTS INTO EARLY HUMAN DEVELOPMENT: SCIENTIFIC, POLICY AND ETHICAL CONSIDERATIONS** *Presented by the ISSCR Ethics Committee*	Concourse F, Level One
9:00 – 12:00	**STEM CELL ENGINEERING FOR THERAPEUTIC APPLICATIONS** *Organized by Center for Gene Therapy, City of Hope* *Presented by City of Hope*	Room 403A, Level Two

WEDNESDAY, 26 JUNE *(continued)*

9:00 – 12:00	**TOOLS FOR BASIC AND APPLIED RESEARCH** *Presented by the Stem Cell COREdinates* *Supported by Thermo Fisher Scientific and STEMCELL Technologies*	Room 408B, Level Two
9:30 – 12:00	**SCIENCE ADVOCACY AND COMMUNICATIONS SEMINAR** *Sponsored by UC San Diego Health Sanford Stem Cell Clinical Center and UC San Diego Stem Cell Program*	Room 411, Level Two
11:30 – 12:45	**EARLY-CAREER GROUP LEADER LUNCHEON** *Advance registration required*	Petree Hall, Level One
13:00 – 15:15	**PLENARY I: PRESIDENTIAL SYMPOSIUM** *Sponsored by Fate Therapeutics* **Chair: Douglas Melton** *Harvard University, USA*	West Hall B, Level One
13:00 – 13:05	**WELCOME REMARKS**	
13:05 – 13:10	**PRESIDENT'S ADDRESS: DOUGLAS MELTON**	
13:10 – 13:15	**PRESENTATION OF ISSCR PUBLIC SERVICE AWARD TO ELI AND EDYTHE BROAD**	
13:15 – 13:20	**SPECIAL RECOGNITION OF LAWRENCE GOLDSTEIN**	
13:20 – 13:25	**RECOGNITION OF ISSCR ZHONGMEI CHEN YONG TRAVEL AWARDS**	
13:25 – 13:30	**PRESENTATION OF ISSCR DR. SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR TO BARBARA TREUTLEIN**	
13:30 – 13:35	**PRESENTATION OF ISSCR INNOVATION AWARD TO JOHN DICK**	
13:35 – 13:40	**PRESENTATION OF ISSCR TOBIAS AWARD TO SCOTT ARMSTRONG**	
13:40 – 14:00	**John B. Gurdon** *University of Cambridge, UK* IS IT WORTH A RISK IN CHOOSING A PROJECT AT THE START OF YOUR CAREER?	
14:00 – 14:20	**Paola Arlotta** *Harvard University, USA* UNDERSTANDING HUMAN BRAIN DEVELOPMENT AND DISEASE: FROM EMBRYOS TO BRAIN ORGANOIDS	
14:20 – 14:40	**Karl Koehler** *Indiana University School of Medicine, USA* FROM HAIR CELLS TO HAIR FOLLICLES: GENERATION OF SENSORY ORGANOIDS FROM PLURIPOTENCY	

WEDNESDAY, 26 JUNE *(continued)*

14:40 – 15:00	**Hans C. Clevers** *Hubrecht Institute, Netherlands* STEM CELL-BASED ORGANOIDS AS AVATARS IN HUMAN DISEASE	
15:15 – 16:00	**REFRESHMENT BREAK**	West Hall A, Level One (Exhibit Hall)
15:15 – 20:30	**EXHIBIT HALL OPEN**	West Hall A, Level One
16:00 – 18:00	**PLENARY II: PLURIPOTENCY AND GERM CELLS** *Sponsored by Takeda Pharmaceutical Co. LTD* **Chair: Amander T. Clark** *University of California, Los Angeles, USA*	West Hall B, Level One
16:00 – 16:20	**Austin Smith** *University of Cambridge, UK* FORMATIVE PLURIPOTENCY	
16:20 – 16:40	**Anna-Katerina Hadjantonakis** *Memorial Sloan Kettering Cancer Center, USA* EMERGENCE OF PLURIPOTENCY AND CONTROL OF TISSUE SIZE: A DYNAMIC BALANCING ACT PLAYED OUT IN THE MAMMALIAN BLASTOCYST	
16:40 – 17:00	**Clodagh O'Shea** *The Salk Institute, USA* Title not available at time of printing	
17:00 – 17:11	**Bruno Di Stefano** *Massachusetts General Hospital, Harvard University, USA* DDX6 CONTROLS HUMAN STEM CELL FATE BY MODULATING CHROMATIN PLASTICITY THROUGH P-BODY HOMEOSTASIS	
17:11 – 17:22	**Linfeng Zhang** *Tongji University, China* HISTONE H3 ACETYLATION PLAYS IMPORTANT ROLES IN BOTH WIDE-TYPE AND SCNT PRE-IMPLANTATION EMBRYO DEVELOPMENT	
17:22 – 17:33	**Fang Tao** *Stowers Institute for Medical Research, USA* BETA-CATENIN ASSOCIATED PROTEIN COMPLEX MAINTAINS GROUND STATE MOUSE EMBRYONIC STEM CELL BY RESTRICTING LINEAGE DIFFERENTIATION	
17:33 – 17:53	**Allan Spradling** *Carnegie Institution for Science, USA* ANNE MCLAREN MEMORIAL LECTURE: OOCYTES: THE ULTIMATE STEM CELLS	

WEDNESDAY, 26 JUNE *(continued)*

18:00 – 20:30	**OPENING RECEPTION** *Sponsored by WiCell*	West Hall A, Level One (Exhibit Hall)
18:30 – 20:30	**POSTER SESSION I** ODD numbered posters present from 18:30 to 19:30 EVEN numbered posters present from 19:30 to 20:30 *Sponsored by WiCell*	West Hall A, Level One (Exhibit Hall)
21:00 – 24:00	**JUNIOR INVESTIGATOR SOCIAL NIGHT** *Advance registration required* *In Memory of Jordan Klein; Sponsored by Americans for Cures*	The Reserve 650 South Spring Street

THURSDAY, 27 JUNE

7:30 – 18:30	**REGISTRATION OPEN**	West Hall Pre-Function, Level One
	INNOVATION SHOWCASES (Details on page 113)	
8:00 – 8:30	**CELL GUIDANCE SYSTEMS** A NOVEL SUSTAINED RELEASE GROWTH FACTOR TECHNOLOGY FOR IMPROVED QUALITY IN STEM CELL DIFFERENTIATION AND ORGANOID CULTURE **Christian Pernstick** *Cell Guidance Systems, UK*	Room 408B, Level Two
8:00 – 8:30	**UNION BIOMETRICA** AUTOMATION FOR ANALYSIS, IMAGING, AND HANDLING OF CELL CLUSTERS, SPHEROIDS, AND ORGANOIDS IN STEM CELL RESEARCH **Rock Pulak** *Union Biometrica, Inc., USA*	Room 502, Level Two
8:00 – 8:30	**AJINOMOTO** DEVELOPING THE NEXT GENERATION OF IPSC CELL-BASED ADOPTIVE CELL THERAPY **Raul Vizcardo** *Surgery Branch, National Cancer Institute, NIH Center for Cell-Based Therapy, USA* **Hajime Ohnuki** *Ajinomoto Co., Inc., Japan*	Room 403A, Level One
8:00 – 8:30	**MOLECULAR DEVICES** FUNCTIONAL AND MECHANISTIC NEUROTOXICITY PROFILING USING HUMAN IPSC-DERIVED NEURAL 3D CULTURES **Cassiano Carromeau** *StemoniX, USA*	Room 403B, Level Two
8:00 – 8:30	**EPPENDORF** SMART STEM CELL CULTIVATION- A SYNTHETIC READY-TO-USE SURFACE FOR HUMAN IPS CELLS **Nadine Mellies** *Eppendorf AG, Germany*	Room 408A, Level Two

THURSDAY, 27 JUNE *(continued)*

8:00 – 8:30	**NOVO NORDISK** STEM CELL R&D AT NOVO NORDISK A/S **Jacob Sten Peterson** *Novo Nordisk A/S, Denmark*	Concourse E, Level One
8:00 – 8:30	**ROKIT HEALTHCARE**	Concourse F, Level One
8:30 – 9:00	**MORNING COFFEE** *Sponsored by Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA*	West Hall Pre-Function, Level One
9:00 – 11:15	**PLENARY III: MECHANISMS AND APPLICATIONS OF MESODERMAL TISSUES I** **Chair: Paula Cannon** *University of Southern California, USA*	West Hall B, Level One
9:00 – 9:15	**ISSCR BUSINESS MEETING**	
9:15 – 9:35	**Ryuichi Nishinakamura** *Kumamoto University, Japan* BUILDING THE KIDNEY IN VITRO FROM PLURIPOTENT STEM CELLS	
9:35 – 9:55	**Golnaz Vahedi** *Perelman School of Medicine, University of Pennsylvania, USA* LINEAGE-DETERMINING TRANSCRIPTION FACTOR TCF-1 INITIATES THE EPIGENETIC IDENTITY OF T CELLS	
9:55 – 10:06	**Nils Lindstrom** *University of Southern California, USA* A SPATIAL, TRANSCRIPTOMIC, MOLECULAR, AND GENE NETWORK BLUE-PRINT FOR THE HUMAN NEPHROGENIC PROGRAM	
10:06 – 10:17	**Tobias Deuse** *University of California, San Francisco, USA* IMMUNE REJECTION OF ALLOGENEIC MOUSE AND HUMAN CELL TRANSPLANTS DERIVED FROM IPSCS IS PREVENTED BY GENETIC ENGINEERING	
10:17 – 10:28	**Christine Wells** *University of Melbourne, Australia* AN INTEGRATED MYELOID ATLAS REVEALS CULTURE CONDITIONING IS A MAJOR PHENOTYPE THAT DISCRIMINATES IN VIVO FROM PLURIPOTENT-DERIVED MACROPHAGES	
10:28 – 10:48	**Hanna Mikkola** *University of California, Los Angeles, USA* DECODING HUMAN HEMATOPOIETIC STEM CELL SELF-RENEWAL	CIRM FUNDED

THURSDAY, 27 JUNE *(continued)*

10:48 – 11:08	**Irving Weissman** *Stanford University, USA* NORMAL AND NEOPLASTIC STEM CELLS	CIRM FUNDED
11:00 – 20:00	**EXHIBIT HALL OPEN**	West Hall A, Level One
	INNOVATION SHOWCASES (Details on page 113)	
11:30 – 12:30	**MILTENYI BIOTEC GMBH** A THERAPY FOR PARKINSON'S DISEASE: LATEST CLINICAL RESEARCH HIGHLIGHTS AND CONCEPTS FOR MANUFACTURING OF ATMPs **Daisuke Doi** *Center for iPS Cell Research and Application (CiRA), Japan* **Sebastian Knoebel** *Miltenyi Biotec GmbH, Germany*	Room 408A, Level Two
11:30 – 12:30	**BIOLAMINA** BIOLOGICALLY RELEVANT CELL CULTURE - ADVANCES IN TRANSLATIONAL RESEARCH FOR ALS, PARKINSON'S AND CARDIOVASCULAR DISEASES **Michal Izrael** *Kadimastem Ltd, Israel* **Malte Tiburcy** *University Medical Center Göttingen, Germany* **Alessandro Fiorenzano** *Lund University, Sweden*	Room 403B, Level Two
11:30 – 12:30	**MAXWELL BIOSYSTEMS** HUMAN IPSCS FOR CNS DRUG DISCOVERY - FUNCTIONAL PHENOTYPE CHARACTERIZATION AND NOVEL BIOMARKERS BY HIGH-RESOLUTION MICROELECTRODE ARRAY (MEA) TECHNOLOGY **Marie Obien** *MaxWell Biosystems, Switzerland* **Michele Fiscella** *MaxWell Biosystems, Switzerland*	Room 408B, Level Two

THURSDAY, 27 JUNE *(continued)*

11:30 – 12:30	**STEMCELL TECHNOLOGIES** ORGANOID CULTURE EVOLUTION: ADVANCED CULTURE SYSTEMS ENABLING THE NEXT GENERATION OF ORGANOID APPLICATIONS **Ryan Condor** *STEMCELL Technologies Inc., Canada*	Concourse E, Level One
11:30 – 12:30	**BIO-TECHNE** PIONEERING SOLUTIONS FOR CELL AND GENE THERAPY MANUFACTURING - FROM GMP ANCILLARY MATERIAL TO PRODUCT ANALYSIS **Scott Schachtele** *Bio-Techne, USA*	Concourse F, Level One
11:30 – 12:30	**FUJIFILM IRVINE SCIENTIFIC** UNDERSTANDING THE USE OF CANCER STEM CELLS IN CELL THERAPY **Vanda Lopes** *FUJIFILM Irvine Scientific, USA*	Room 403A, Level Two
11:30 – 12:30	**THERMO FISHER SCIENTIFIC** IMPROVING HPSC-DERIVED MODELS: OPTIMAZATION OF CULTURE METHODS FOR GENE EDITING AND DISEASE MODELING USING ORGANOIDS **Madel Durens** *Hussman Institute for Autism, USA* **Yi-Hsien Chen** *Washington University School of Medicine, USA*	Room 502, Level Two
11:30 – 13:00	**JUNIOR INVESTIGATOR MEET THE EXPERTS LUNCHEON** *Junior Investigator event; advance registration required* *Sponsored by The Stem Cell Program at Boston Children's Hospital, Harvard Stem Cell Institute, and Massachusetts General Hospital Center for Regenerative Medicine*	Petree Hall, Level One
12:15 – 13:00	**MEET-UP HUBS** (see page 30 for details)	West Hall A, Level One (Exhibit Hall)
	GUANGZHOU REGENERATIVE MEDICINE AND HEALTH GUANGDONG PROVINCIAL LABORATORY INTRODUCTION	Meet-up Hub #1
	HOW EBISC HELPS RESEARCHERS TO ACCESS AND SHARE HIGH-QUALITY RESEARCH-GRADE IPSC LINES	Meet-up Hub #2

THURSDAY, 27 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IA: ENGINEERING TISSUES AND ORGANS** Concourse E, Level One

Chair: Deepak Srivastava
Gladstone Institutes, USA

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

13:20 – 13:40 **Takanori Takebe**
Cincinnati Children's Hospital Medical Center, USA and Tokyo Medical and Dental University, Japan
NEXT-GEN ORGANOIDS FROM PLURIPOTENCY: NARRATIVE ENGINEERING

13:40 – 13:51 **Fred Etoc**
The Rockefeller University and Rumi Scientific, USA
SELF-ORGANIZATION OF SPATIAL PATTERNS IN ARTIFICIAL HUMAN EMBRYOS AND ORGANOIDS

13:51 – 14:02 **Antonella Pinto**
Sanford Burnham Prebys Medical Discovery Institute, USA
DERIVATION OF FOLLICULOGENIC DERMAL PAPILLA CELLS FROM HUMAN IPSC

14:02 – 14:13 **Jianyong Han**
State Key Laboratory for Agrobiotechnology, China Agricultural University, China
SELF-ASSEMBLED EMBRYO-LIKE STRUCTURES COMPRISING THREE TYPES OF BLASTOCYST-DERIVED STEM CELLS

14:13 – 14:24 **Andrew Lee**
Carnegie Mellon University, USA
3D BIOPRINTING A CONTRACTILE VENTRICLE USING HUMAN STEM CELL-DERIVED CARDIOMYOCYTES

14:24 – 14:35 **Leonardo Morsut**
University of Southern California, USA
SYNTHETIC GENETIC CIRCUITS TO CONTROL STEM CELL PROGRAMS IN TISSUE ASSEMBLY

14:35 – 14:46 **Leslie Crews**
University of California, San Diego, USA
LONG-TERM PERFORMANCE OF IMPLANTED BIOPRINTED HUMAN LIVER TISSUE IN A REGENERATIVE MOUSE MODEL OF LIVER FAILURE

14:46 – 15:06 **Valerie Weaver**
University of California, San Francisco, USA
Forcing Tumor Initiation and Progression

THURSDAY, 27 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IB: STEM CELL-BASED DISEASE MODELING** Concourse F, Level One

Chair: Fred Gage
Salk Institute for Biological Studies, USA

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

13:20 – 13:40 **Sandra Engle**
Biogen, USA
MODELING DISEASE BIOLOGY WITH HUMAN STEM CELL-DERIVED CELLS TO ENABLE DRUG DISCOVERY

13:40 – 13:51 **Vanessa Langness**
University of California, San Diego, USA
MODELING THE EFFECTS OF CHOLESTEROL ON ALZHEIMERS DISEASE PATHOGENESIS IN IPSC DERIVED NEURONS

13:51 – 14:02 **Anna Falk**
Karolinska Institutet, Sweden
SKEWED FATE CHOICE AND DELAYED NEURONAL MATURATION OF NEURAL STEM CELLS FROM AN AUTISM PATIENT WITH BI-ALLELIC NRXN1 MUTATION REVEALED BY SINGLE CELL RNA-SEQ

14:02 – 14:13 **Alessandro Prigione**
Max Delbrueck Center for Molecular Medicine, Germany
SURF1 MUTATIONS CAUSATIVE OF LEIGH SYNDROME IMPAIR HUMAN NEUROGENESIS

14:13 – 14:24 **Irfan Kathiriya**
J. David Gladstone Institutes, USA
GENE REGULATION BY TRANSCRIPTION FACTOR DOSAGE IN A HUMAN CELLULAR MODEL OF CONGENITAL HEART DISEASE

14:24 – 14:35 **Malkiel Cohen**
Whitehead Institute for Biomedical Research, USA
IN VIVO TUMOR FORMATION OF HUMAN NEUROBLASTOMA IN INTERSPECIES CHIMERAS

14:35 – 14:46 **Ali Fathi**
University of Wisconsin, Madison, USA
CHEMICAL INDUCTION OF AGING PHENOTYPES IN STEM CELL-DERIVED NEURONS FOR MODELING NEURODEGENERATIVE DISEASES

14:46 – 15:06 **Arnold Kriegstein**
University of California, San Francisco, USA
CHALLENGES FOR IN VITRO MODELING OF HUMAN BRAIN DISEASE

THURSDAY, 27 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IC: STEM CELL AGING** Room 502, Level Two

Chair: Catriona Jamieson
University of California, San Diego School of Medicine, USA

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

13:20 – 13:40 **Salvador Aznar Benitah**
Institute for Research in Biomedicine (IRB Barcelona), Spain
ADULT STEM CELL CLOCKS IN HOMEOSTASIS AND AGING

13:40 – 13:51 **Weiqi Zhang**
Institute of Biophysics, CAS, China
A SINGLE-CELL TRANSCRIPTOMIC ATLAS OF ARTERIAL AGING OF CYNOMOLGUS MONKEY

13:51 – 14:02 **Bo Shen**
University of Texas Southwestern Medical Center, USA
THE IDENTIFICATION OF A NOVEL PERI-ARTERIAL SKELETAL STEM/PROGENITOR CELL IN ADULT BONE MARROW

14:02 – 14:13 **Kodanda Nalapa Reddy**
Cincinnati Children's Hospital and Medical Center, USA
SUPPRESSION OF THE ACTIVITY OF SMALL RHO GTPASE CDC42 AMELIORATES INTESTINAL STEM CELL AGING

14:13 – 14:24 **Romeo S. Blanc**
University of Rochester Medical Center, USA
AGED MACROPHAGES DRIVE PERSISTENT INFLAMMATION ALTERING STEM CELL FATE DURING MOUSE MUSCLE REGENERATION

14:24 – 14:35 **Adelaida Palla**
Stanford University, USA
OVERCOMING THE AGED NICHE TO IMPROVE SKELETAL MUSCLE REGENERATION

14:35 – 14:46 **Hiroyuki Matsumura**
Tokyo Medical and Dental University, Japan
STEM CELL COMPETITION AND DIVISION GOVERN SKIN HOMEOSTASIS AND AGEING

14:46 – 15:06 **Pura Muñoz-Cánoves**
Pompeu Fabra University, ICREA and CNIC, Barcelona, Spain
UNDERSTANDING MUSCLE STEM CELL REGENERATIVE DECLINE WITH AGING

THURSDAY, 27 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT ID: STEM CELL HETEROGENEITY** Room 408A, Level Two

Chair: Leanne Jones
University of California, Los Angeles, USA

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

13:20 – 13:40 **Kathrin Plath**
University of California, Los Angeles School of Medicine, USA
A NEW MECHANISM UNDERLYING HETEROCHROMATIN FORMATION DURING EMBRYONIC STEM CELL DIFFERENTIATION

13:40 – 13:51 **Rebecca Ihrie**
Vanderbilt University, USA
LOCATION-DEPENDENT MAINTENANCE OF AN INTRINSIC, DIFFERENTIAL SUSCEPTIBILITY TO MTORC1-DRIVEN TUMOR GROWTH IN A PERSISTENT STEM CELL NICHE

13:51 – 14:02 **Gianni Carraro**
Cedars-Sinai Medical Center, USA
HUMAN BASAL PROGENITOR CELL DIVERSITY AND INVOLVEMENT IN LUNG REMODELLING

14:02 – 14:13 **David Grommisch**
Karolinska Institutet, Sweden
FUNCTIONAL PROGENITOR CELL HETEROGENEITY IN THE MOUSE ESOPHAGEAL EPITHELIUM

14:13 – 14:24 **Thomas Ambrosi**
Stanford University, USA
EVIDENCE FOR TWO DEVELOPMENTALLY DISTINCT SKELETAL STEM CELL POPULATIONS

14:24 – 14:35 **Helen Zhu**
Shanghai Jiao Tong University, China
IDENTIFICATION OF A NOVEL BASAL STEM CELL SUB-POPULATION IN THE PROSTATE

14:35 – 14:46 **Hui Shu**
Shanghai Institute of Biochemistry and Cell Biology (SIBCB), China
TRACING THE HETEROGENEITY OF MOUSE SKELETAL STEM CELLS

14:46 – 15:06 **Nikolaus Rajewsky**
Max Delbrück Center for Molecular Medicine, Germany
Title not available at time of printing

THURSDAY, 27 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IE: NON-MAMMALIAN MODEL ORGANISMS FOR STEM CELL BIOLOGY** Room 408B, Level Two

Chair: Ruth Lehmann
HHMI/Skirball Institute, USA

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

13:20 – 13:40 **Jenna Galloway**
Harvard Medical School and Massachusetts General Hospital, USA
HARNESSING THE REGENERATIVE ABILITY OF ZEBRAFISH TO TRANSFORM ORTHOPEDIC MEDICINE

13:40 – 13:51 **Christopher Antos**
ShanghaiTech University, China
CALCINEURIN SCALES REGENERATING ZEBRAFISH FINS BY REGULATING THE BIOELECTRICAL PROPERTIES OF THEIR CELLS

13:51 – 14:02 **Daniel Wagner**
Harvard Medical School, USA
SINGLE-CELL DECOMPOSITION OF VERTEBRATE CELL FATE HIERARCHIES, DEVELOPMENTAL PLASTICITY, AND CONTROL LOGIC

14:02 – 14:13 **Alyson Ramirez**
Harvard University, USA
INVESTIGATING THE MECHANISM OF ANTERIOR-POSTERIOR AXIS FORMATION DURING REGENERATION IN THE ACOEL WORM HOFSTENIA MIAMIA

14:13 – 14:24 **Mark Kowarsky**
Stanford University, USA
MOLECULAR SIGNATURES OF CHORDATE DEVELOPMENT: TWO DISPARATE PATHWAYS, ONE CHORDATE

14:24 – 14:35 **Lucy Erin O'Brien**
Stanford School of Medicine, USA
OCCLUDING JUNCTIONS COORDINATE EPITHELIAL INTEGRATION WITH GROWTH OF STEM CELL PROGENY DURING INTESTINAL TURNOVER IN DROSOPHILA

14:35 – 14:46 **D'Juan Farmer**
University of Southern California, USA
DECIPHERING THE EMBRYONIC ORIGINS AND THE GENETIC REGULATION OF SKELETAL STEM CELLS IN THE ZEBRAFISH SKULL

14:46 – 15:06 **Jessica Whited**
Harvard University, USA
MAINTENANCE OF GENOMIC INTEGRITY IN PROLIFERATING BLASTEMA CELLS OF REGENERATING AXOLOTL LIMBS

THURSDAY, 27 JUNE *(continued)*

15:15 – 16:00	**MEET-UP HUBS** (see page 30 for details)	West Hall A, Level One (Exhibit Hall)
	GERMAN STEM CELL NETWORK	Meet-up Hub #1
	INDUSTRY SCIENTISTS NETWORKING	Meet-up Hub #2
15:15 – 16:00	**REFRESHMENT BREAK** *Sponsored by Eli and Edythe Broad Center of Regenerative Medicine and Stem Cell Research at UCLA*	West Hall A, Level One (Exhibit Hall)
16:00 – 18:00	**CONCURRENT IIA: MECHANISMS OF PLURIPOTENCY AND IPS CELL REPROGRAMMING**	Concourse E, Level One
	Chair: Hans R. Schöler *Max Planck Institute for Molecular Biomedicine, Germany*	
16:00 – 16:05	**TOPIC OVERVIEW BY CHAIR**	
16:05 – 16:25	**Sally Lowell** *MRC Centre for Regenerative Medicine, University of Edinburgh, UK* THINK GLOBAL ACT LOCAL: DO LOCAL MORPHOLOGICAL CHANGES INFLUENCE DIFFERENTIATION OF PLURIPOTENT CELLS?	
16:25 – 16:36	**Peter Rugg-Gunn** *The Babraham Institute, UK* DEFINING ESSENTIAL REGULATORS OF HUMAN NAÏVE PLURIPOTENT STEM CELL REPROGRAMMING USING GENOME-WIDE CRISPR-CAS9 SCREENING	
16:36 – 16:47	**Xi Chen** *University of Southern California, USA* DISSECTING THE MOLECULAR MECHANISM UNDERLYING THE DISTINCT FUNCTIONS OF GSK3A AND GSK3B USING MOUSE EMBRYONIC STEM CELLS	
16:47 – 16:58	**Xiaodong Liu** *Monash University, Australia* DISTINCT EARLY EMBRYONIC PREIMPLANTATION DEVELOPMENTAL PROGRAMS DRIVE REPROGRAMMING INTO PRIMED AND NAIVE INDUCED PLURIPOTENCY	
16:58 – 17:09	**Sara-Jane Dunn** *Microsoft Research, UK* A COMMON MOLECULAR LOGIC DETERMINES EMBRYONIC STEM CELL SELF-RENEWAL AND REPROGRAMMING	
17:09 – 17:20	**Grace Hancock** *University of California, Los Angeles, USA* KLF4 AND TFCP2L1 IN HUMAN PRIMORDIAL GERM CELL DEVELOPMENT	

THURSDAY, 27 JUNE *(continued)*

17:20 – 17:31 **Rupa Sridharan**
University of Wisconsin, Madison, USA
DEFINING EPIGENETIC CONTROL OF PLURIPOTENCY WITH SINGLE CELL ANALYSIS

17:31 – 17:51 **Hitoshi Niwa**
Kumamoto University, Japan
OVERLAPPING FUNCTION OF KLF FAMILY MEMBERS AND TBX3 PREVENTS SELF-DESTRUCTION OF MOUSE ES CELLS BY ACTIVATION OF FOXD3

16:00 – 18:00 **CONCURRENT IIB: MOLECULAR AND CELLULAR DYNAMICS** Concourse F, Level One

Chair: Urban Lendahl
Karolinska Institute, Sweden

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

16:05 – 16:25 **Sebastian Jessberger**
University of Zurich, Switzerland
CELLULAR AND MOLECULAR DYNAMICS OF INDIVIDUAL STEM CELLS IN THE BRAIN

16:25 – 16:36 **Cody Kime**
RIKEN, Japan
INDUCED 2C EXPRESSION AND IMPLANTATION-COMPETENT BLASTOCYST-LIKE CYSTS FROM PRIMED PLURIPOTENT STEM CELLS

16:36 – 16:47 **Mariana Justino De Almeida**
Columbia University, USA
REGULATION OF HSC FUNCTION BY MITOCHONDRIAL DYNAMICS

16:47 – 16:58 **Samuel Collombet**
EMBL, Germany
EARLY MOUSE EMBRYOGENESIS INVOLVES A SWITCH IN CHROMATIN ORGANIZATION FROM PREFORMED ASYMMETRIC COMPARTMENTS TO DE NOVO DOMAINS

16:58 – 17:09 **Ang Li**
University of Texas, USA
CALCIUM OSCILLATIONS COORDINATE CHICKEN FEATHER MESENCHYMAL CELL MOVEMENT BY SHH/WNT DEPENDENT MODULATION OF GAP JUNCTION NETWORKS

17:09 – 17:20 **Erin Sanders**
Stanford University, USA
REAL-TIME KINETICS OF NOTCH-MEDIATED FATE DECISIONS IN THE DROSOPHILA ADULT INTESTINE

THURSDAY, 27 JUNE *(continued)*

17:20 – 17:31 **Abderhman Abuhashem**
Sloan-Kettering Institute for Cancer Research, USA
RNA POLYMERASE II PAUSING REGULATES FGF4 SIGNALING IN THE MOUSE PRE-IMPLANTATION EMBRYO

17:31 – 17:51 **Cristina Lo Celso**
Imperial College London, UK
HEALTHY AND MALIGNANT HAEMATOPOIESIS IN THE BONE MARROW: DYNAMIC CELLS IN AN EVOLVING ENVIRONMENT

16:00 – 18:00 **CONCURRENT IIC: STEM CELL NICHES** Room 502, Level Two

Chair: Fiona Doetsch
Biozentrum, University of Basel, Switzerland

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

16:05 – 16:25 **Paul Frenette**
Albert Einstein College of Medicine, USA
REVITALIZATION OF HSC NICHE ACTIVITY BY REPROGRAMMING MSC FUNCTION

16:25 – 16:36 **Magdalena Wagner**
Karolinska Institutet, Sweden
CHARACTERIZATION OF “OOGONIAL STEM CELLS” ISOLATED BY DDX4 ANTIBODY BASED FACS IN THE HUMAN OVARY

16:36 – 16:47 **Bing Zhang**
Harvard University, USA
PSYCHOLOGICAL STRESS DRIVES MELANOCYTE STEM CELL EXHAUSTION THROUGH ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM

16:47 – 16:58 **Helen Abud**
Monash University, Australia
NEUREGULIN1 PROMOTES INTESTINAL STEM CELL PROLIFERATION AND EPITHELIAL REGENERATION FOLLOWING INJURY

16:58 – 17:09 **Heather Himburg**
University of California, Los Angeles, USA
INHIBITION OF SEMAPHORIN 3A PROMOTES VASCULAR AND HEMATOPOIETIC STEM CELL REGENERATION

17:09 – 17:20 **Liming Zhao**
Stanford University, USA
RESCUE OF OSTEONECROSIS BY TRANSPLANTATION OF INTACT BLOOD VESSEL STEM CELL NICHES

THURSDAY, 27 JUNE *(continued)*

17:20 – 17:31 **Susan Eliazer**
University of California, San Francisco, USA
WNT4 FROM THE NICHE CONTROLS THE MECHANO-PROPERTIES AND QUIESCENCE OF MOUSE MUSCLE STEM CELLS

17:31 – 17:51 **Kim Jensen**
BRIC - Biotech Research and Innovation Centre, Denmark
TRACING THE ORIGIN OF ADULT STEM CELLS

16:00 – 18:00 **CONCURRENT IID: TISSUE REGENERATION AND HOMEOSTASIS** Room 408A, Level Two

Chair: Lucy Erin O'Brien
Stanford School of Medicine, USA

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

16:05 – 16:25 **Fabio Rossi**
University of British Columbia, Canada
MESENCHYMAL PROGENITORS AS ORGANIZERS OF THE REGENERATIVE PROCESS

16:25 – 16:36 **Edwin Rosado-Olivieri**
Harvard Stem Cell Institute, USA
IDENTIFICATION OF A LIF-RESPONSIVE REPLICATION-COMPETENT SUBPOPULATION OF HUMAN BETA CELLS

16:36 – 16:47 **Wan-Jin Lu**
Stanford University School of Medicine, USA
NEURONAL COORDINATION OF TASTE RECEPTOR CELL REGENERATION

16:47 – 16:58 **Yaron Fuchs**
Technion-Israel Institute of Technology, Israel
THY1.2 MARKS A DISTINCT STEM CELL POPULATION THAT CONTRIBUTES TO EPIDERMAL HOMEOSTASIS AND REPAIR

16:58 – 17:09 **Xiaomin Bao**
Northwestern University, USA
HIGH CPSF EXPRESSION IN HUMAN EPIDERMAL PROGENITORS SUPPRESSES TERMINAL DIFFERENTIATION THROUGH ALTERNATIVE POLYADENYLATION

17:09 – 17:20 **Joshua Currie**
University of Toronto, Canada
THE PRRX1 LIMB ENHANCER MARKS AN ADULT POPULATION OF INJURY-RESPONSIVE, MULTIPOTENT DERMAL FIBROBLASTS

THURSDAY, 27 JUNE *(continued)*

17:20 – 17:31 **Joanna Smeeton**
University of Southern California, USA
ROBUST REGENERATION OF LIGAMENTS AND ARTICULAR CARTILAGE IN THE ADULT ZEBRAFISH JAW JOINT

17:31 – 17:51 **Michal Shoshkes Carmel**
Hebrew University of Jerusalem, Israel
SUBEPITHELIAL TELOCYTES CONSTITUTE THE INTESTINAL STEM CELL NICHE

16:00 – 18:00 **CONCURRENT IIE: LINEAGE CHOICE AND ASYMMETRIC CELL DIVISION** Room 408B, Level Two

Chair: Marianne E. Bronner
California Institute of Technology, USA

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

16:05 – 16:25 **Haifan Lin**
ShanghaiTech University, China and Yale University School of Medicine, USA
PUMILIO PROTEINS ARE KEY POST-TRANSCRIPTIONAL REGULATORS OF EMBRYONIC STEM CELL PLURIPOTENCY AND EARLY EMBRYOGENESIS

16:25 – 16:36 **Shahragim Tajbakhsh**
Pasteur Institute, France
REGULATION OF THE MOUSE SKELETAL MUSCLE STEM CELL NICHE DURING HOMEOSTASIS AND REGENERATION

16:36 – 16:47 **Atilgan Yilmaz**
The Hebrew University of Jerusalem, Israel
DEFINING ESSENTIAL GENES FOR NEUROECTODERM

16:47 – 16:58 **Martin Leeb**
University of Vienna, Austria
DISSECTING THE REGULATORY PRINCIPLES OF ES CELL DIFFERENTIATION

16:58 – 17:09 **Pierre Osteil**
Children's Medical Research Institute, Australia
MIXL1 ORCHESTRATES CELL FATE DECISIONS DURING MOUSE AND HUMAN GASTRULATION: A MULTIOMIC STUDY

17:09 – 17:20 **Aslam Akhtar**
George Washington University, USA
THE ROLE OF FEZF2 IN REGULATING NEURAL STEM CELL FATE IN THE POSTNATAL VENTRICULAR ZONE

THURSDAY, 27 JUNE *(continued)*

17:20 – 17:31	**Angela Wu** *Hong Kong University of Science and Technology, Hong Kong* SINGLE-CELL TRANSCRIPTOMIC DISSECTION OF CELL FATE DETERMINING MOLECULAR SWITCHES IN MOUSE PAX7-EXPRESSING SOMITIC MESODERM	
17:31 – 17:51	**Yukiko Yamashita** *University of Michigan, USA* RIBOSOMAL DNA AND THE RDNA-BINDING PROTEIN INDRA MEDIATE NON-RANDOM SISTER CHROMATID SEGREGATION IN DROSOPHILA MALE GERMLINE STEM CELLS	
18:00 – 20:00	**POSTER SESSION II AND RECEPTION** ODD numbered posters present from 18:00 to 19:00 EVEN numbered posters present from 19:00 to 20:00	West Hall A, Level One (Exhibit Hall)

FRIDAY, 28 JUNE

7:30 – 18:30	**REGISTRATION OPEN**	West Hall Pre-Function, Level One
	INNOVATION SHOWCASES (Details on page 113)	
8:00 – 8:30	**CELL MICROSYSTEMS, INC.** HIGH VIABILITY CLONAL COLONY PROPAGATION OF STEM CELLS USING THE CELLRAFT AIR SYSTEM **Nick Trotta** *Cell Microsystems, Inc., USA*	Room 403A, Level Two
8:00 – 8:30	**STEMBIOSYS, INC.** DEVELOPMENT AND APPLICATION OF CELL DERIVED MATRICES FOR BIOLOGICALLY RELEVANT CELL CULTURE **Travis Block** *StemBioSys, Inc., USA* **Sy Griffey** *StemBioSys, Inc., USA*	Room 502, Level Two
8:00 – 8:30	**10X GENOMICS** THE EMERGENT LANDSCAPE OF THE MOUSE GUT ENDODERM AT SINGLE-CELL RESOLUTION **Jens Durruthy** *10X Genomics, USA* **Anna-Katerina Hadjantonakis** *Sloan-Kettering Institute for Cancer Research, USA*	Room 408B, Level Two
8:00 – 8:30	**XYLYX BIO, INC.** TISSUE-SPECIFIC ECM SUBSTRATES FOR STEM CELL AND ORGANOID CULTURES **John O'Neill** *Xylyx Bio, Inc., USA*	Room 408A, Level Two

FRIDAY, 28 JUNE *(continued)*

9:00 – 11:20 **PLENARY IV: STEM CELLS AND REGENERATION OF ENDODERMAL ORGANS** — West Hall B, Level One
Sponsored by Semma Therapeutics

Chair: Christine L. Mummery
Leiden University Medical Center, Netherlands

9:00 – 9:20 **Nan Tang**
National Institute of Biological Sciences, China
THE DRIVING FORCE OF ALVEOLAR DEVELOPMENT AND REGENERATION

9:20 – 9:40 **Markus Grompe**
Oregon Health and Science University, USA
A UNIVERSAL SYSTEM FOR PHARMACOLOGICAL SELECTION OF GENE EDITED HEPATOCYTES

9:40 – 10:00 **Sangeeta Bhatia**
Massachusetts Institute of Technology, USA
REGENERATION ON A CHIP: MICROFLUIDIC VASCULARIZED HUMAN HEPATIC ENSEMBLES

10:00 – 10:11 **Alexander Ross**
University of Cambridge, UK
DEVELOPING A HUMAN HEPATOBLAST ORGANOID MODEL TO STUDY DEVELOPMENT, SCREEN MEDICAL COMPOUNDS, AND DEVELOP POTENTIAL CELL BASED THERAPIES

10:11 – 10:22 **Vivian Li**
The Francis Crick Institute, UK
CO-REPRESSORS MTG8 AND MTG16 REGULATE NICHE EXIT AND EARLY FATE DECISION OF MOUSE INTESTINAL STEM CELLS

10:22 – 10:33 **Omer Yilmaz**
Massachusetts Institute of Technology, USA
ENDOGENOUS METABOLITES HELP INSTRUCT INTESTINAL STEM CELL FATE

10:33 – 10:53 **James Wells**
Cincinnati Children's Hospital, USA
PLURIPOTENT STEM CELL-DERIVED GASTROINTESTINAL ORGANOIDS AS NEW MODELS TO STUDY HUMAN DEVELOPMENT AND DISEASE

10:53 – 11:13 **John Dick**
University Health Network, Canada
THE ISSCR AWARD FOR ONNOVATION LECTURE: STEM CELLS PLAY A ROLE IN HUMAN LEUKEMIA FROM THE BEGINNING TO THE END

11:00 – 20:00 **EXHIBIT HALL OPEN** — West Hall A, Level One

FRIDAY, 28 JUNE *(continued)*

INNOVATION SHOWCASES
(Details on page 113)

11:30 – 12:30 **BIOLOGICAL INDUSTRIES** — Room 502, Level Two
CELEBRATING 10-YEARS OF INNOVATION WITH NUTRISTEM MEDIA: 3D CULTURE, MINIBRAIN, AND NATURAL KILLER CELLS

Sebastien Mosser
Neurix SA, Switzerland

Allen Feng
HebeCell Corp, USA

11:30 – 12:30 **CORNING LIFE SCIENCES** — Room 403B, Level Two
WHAT'S NEW AND NEXT FOR STEM CELL RESEARCH: DISSOLVABLE MICROCARRIERS FOR SCALE-UP AND ORGANOIDS FOR DISEASE MODELING AND HIGH THROUGHPUT SCREENING

Chris Saurez
Corning Life Sciences, USA

11:30 – 12:30 **STEMCELL TECHNOLOGIES** — Concourse E, Level One
DEVELOPMENT, COMPATIBILITY, AND APPLICATIONS OF mTeSR™ PLUS; AN ENHANCED MEDIUM FOR THE MAINTENANCE OF HUMAN PLURIPOTENT STEM CELLS

Melanie Kardel
STEMCELL Technologies Inc., Canada

Loren Ornelas
Cedars-Sinai Medical Center, USA

Dhruv Sareen
Cedars-Sinai Medical Center, USA

11:30 – 12:30 **LONZA PHARMA AND BIOTECH** — Room 408B, Level Two
PLURIPOTENT STEM CELL BASED THERAPIES: FROM BENCH TO COMMERCIALIZATION

Pupsa Pandey
Lonza Pharma and Biotech, USA

FRIDAY, 28 JUNE *(continued)*

11:30 – 12:30	**MATRIXOME, INC.** LAMININ E8 TECHNOLOGY FOR STEM CELL PROLIFERATION AND DIFFERENTIATION: FROM MOLECULAR MECHANISM TO CLINICAL APPLICATION **Takuji Yamamoto** *Matrixome, Inc., Japan* **Yuhei Hayashi** *Osaka University, Japan* **Yukimasa Taniguchi** *Institute for Protein Research, Osaka University, Japan*	Concourse F, Level One
11:30 – 12:30	**HEALIOS K.K.** THE FOREFRONT OF ORGANOID MEDICINE **Takanori Takebe** *Cincinnati Children's Hospital, Tokyo Medical and Dental University, Yokohama City University, Japan*	Room 403A, Level Two
11:30 – 12:30	**THERMO FISHER SCIENTIFIC** A NEW HSC EXPANSION MEDIUM FOR SUPERIOR CD34+ CELL EXPANSION AND ENGRAFTMENT USED IN COMBINATION WITH A NOVEL GENE TAGGING SYSTEM FOR EFFICIENT GENE EDITING CONFIRMATION AND LINEAGE TRACKING **Curt Civin** *University of Maryland School of Medicine, USA* **Jonathan Chestnut** *Thermo Fisher Scientific, USA*	Room 408A, Level Two
11:30 – 13:00	**WOMEN IN SCIENCE LUNCHEON** A SEAT AT THE TABLE: WOMEN AT THE LEADING EDGE OF SCIENCE *Advance registration required*	Petree Hall, Level One
12:15 – 13:00	**MEET-UP HUBS** (see mobile app for details)	West Hall A, Level One (Exhibit Hall)

FRIDAY, 28 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIA: ORGANOID MODELS** Concourse E, Level One

Chair: Sandra Engel
Biogen, USA

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

13:20 – 13:40 **Frederic de Sauvage**
Genentech, Inc, USA
MODELING COLORECTAL CANCER PROGRESSION THROUGH ORTHOTOPIC IMPLANTATION OF ENGINEERED ORGANOIDS

13:40 – 13:51 **Elisa Giacomelli**
Leiden University Medical Centre, Netherlands
CARDIAC- BUT NOT DERMAL FIBROBLASTS INDUCE STRUCTURAL AND FUNCTIONAL MATURATION OF HIPSC-DERIVED CARDIOMYOCYTES IN 3D MICROTISSUES

13:51 – 14:02 **Trinh Khiet (Tracy) Tran**
University of Southern California, USA
HUMAN STEM CELL-DERIVED PODOCYTES IN DEVELOPMENTAL BIOLOGY AND DISEASE MODELING

14:02 – 14:13 **Denise Serra**
Friedrich Miescher Institute, Switzerland
SELF-ORGANIZATION AND SYMMETRY BREAKING IN MOUSE INTESTINAL ORGANOID DEVELOPMENT

14:13 – 14:24 **Nur Yucer**
Cedars-Sinai Health System, USA
MODELING OVARIAN CANCER USING BRCA1 MUTANT IPSC-DERIVED 3D HUMAN FALLOPIAN TUBE

14:24 – 14:35 **Jens Puschhof**
Hubrecht Institute, Netherlands
SNAKE VENOM GLAND ORGANOIDS

14:35 – 14:46 **Momoko Watanabe**
University of California, Los Angeles, USA
TFAP2C IS A CRITICAL INDICATOR AND REGULATOR OF RELIABLE AND EFFICIENT FOREBRAIN ORGANOID DIFFERENTIATION FROM HUMAN PLURIPOTENT STEM CELLS

14:46 – 15:06 **Emma Rawlins**
Gurdon Institute, University of Cambridge, UK
CELL-CELL INTERACTIONS IN NORMAL HUMAN EMBRYONIC LUNG DEVELOPMENT

FRIDAY, 28 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIB: EPIGENETIC REGULATION OF CELL IDENTITY** Concourse F, Level One

Chair: Joanna Wysocka
Stanford University, USA

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

13:20 – 13:40 **Wei Xie**
Tsinghua University, China
EPIGENETIC INHERITANCE AND REPROGRAMMING DURING EARLY MAMMALIAN DEVELOPMENT

13:40 – 13:51 **Uma Sangumathi Kamaraj**
Duke NUS Medical School, Singapore
EPIMOGRIFY: A SYSTEMATIC APPROACH TO IDENTIFYING CELL MAINTENANCE FACTORS AND CELL CONVERSION FACTORS BY MODELLING THE CELL'S EPIGENETIC LANDSCAPE

13:51 – 14:02 **Marie Jonsson**
Lund University, Sweden
GLOBAL DNA DEMETHYLATION OF HUMAN NEURAL PROGENITOR CELLS LEADS TO ACTIVATION OF NEURONAL GENES VIA EVOLUTIONARILY YOUNG LINE-1 ELEMENTS

14:02 – 14:13 **Thomas Zwaka**
Icahn School of Medicine at Mount Sinai, USA
RONIN MEDIATES PROMOTER-PROMOTER INTERACTIONS THAT INFLUENCE GENE REGULATION IN PLURIPOTENCY

14:13 – 14:24 **Ping Hu**
Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, China
AN MICRORNA PROCESSING MECHANISM TARGETING CRYPTOCHROME CIRCADIAN REGULATOR 2 MODULATES MYOGENESIS

14:24 – 14:35 **Juan Alvarez-Dominguez**
Harvard University, USA
EPIGENOME DYNAMICS REVEAL NEW INSIGHTS INTO HUMAN ISLET DIFFERENTIATION AND MATURATION

14:35 – 14:46 **Sihem Cheloufi**
University of California, Riverside, USA
EPIGENETIC CONTROL OF CELLULAR PLASTICITY BY MANIPULATING CHROMATIN ORGANIZATION PATHWAYS

14:46 – 15:06 **Ibrahim Cissé**
Massachusetts Institute of Technology, USA
SUPER-RESOLUTION IMAGING OF TRANSCRIPTION IN LIVE MAMMALIAN CELLS

FRIDAY, 28 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIC: STEM CELLS AND CANCER** Room 502, Level Two
Sponsored by EMBO Molecular Medicine

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

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

13:20 – 13:40 **Eduard Batlle**
Institute for Research in Biomedicine, (IRB Barcelona), Spain
CANCER STEM CELLS, RIBOSOMAL BIOGENESIS AND PROTEIN SYNTHESIS

13:40 – 13:51 **Viviane Tabar**
Memorial Sloan Kettering Cancer Center, USA
RADIAL GLIA CONTRIBUTE TO TUMORIGENESIS IN ADULT GLIOBLASTOMA

13:51 – 14:02 **William Stanford**
Ottawa Hospital Research Institute, Canada
TARGETING THE MTF2-MDM2 AXIS SENSITIZES REFRACTORY ACUTE MYELOID LEUKEMIA TO CHEMOTHERAPY

14:02 – 14:13 **SuEllen Pommier**
Oregon Health and Science University, USA
IDENTIFICATION OF HUMAN CIRCULATING BREAST CANCER STEM/PROGENITOR CELLS THAT SURVIVE CHEMOTHERAPY, INITIATE EX VIVO TUMOR GROWTH AND SHOW ELEVATED METASTATIC GENE EXPRESSION

14:13 – 14:24 **Ann-Sofie Thorsen**
University of Cambridge, UK
CHARACTERISING STEM CELL BEHAVIOUR IN KRASG12D PRO-ONCOGENIC FIELDS OF THE MOUSE INTESTINE CHARACTERISING STEM CELL BEHAVIOUR IN KRASG12D PRO-ONCOGENIC FIELDS OF THE MOUSE INTESTINE

14:24 – 14:35 **Yu-Hsuan Lin**
University of Texas Southwestern Medical Center, USA
THE ROLES OF POLYPLOIDY IN MOUSE LIVER CANCER AND REGENERATION

14:35 – 14:46 **Wei-Qiang Gao**
Shanghai Jiao Tong University, China
TRIM32 SUPPRESSES PROLIFERATION OF CEREBELLAR GRANULE CELL PROGENITORS AND MEDULLOBLASTOMA FORMATION IN THE MOUSE BY DEGRADING GLI1/SONIC HEDGEHOG SIGNALING

14:46 – 15:06 **Dominique Bonnet**
The Francis Crick Institute, UK
INTERDEPENDENCE OF MALIGNANT MYELOID CELLS AND THEIR NICHE: "IT TAKES TWO TO TANGO"

FRIDAY, 28 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIID: INFLAMMATION AND MICROBIOME** Room 408A, Level Two

Chair: Tracy Grikscheit
Saban Research Institute, Children's Hospital Los Angeles, USA

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

13:20 – 13:40 **Frederic Geissmann**
Memorial Sloan Kettering Cancer Center, USA
Title not available at time of printing

13:40 – 13:51 **Asuka Morizane**
Kyoto University, Japan
CONTROL OF IMMUNE RESPONSE IN THE CELL THERAPY FOR PARKINSON'S DISEASE

13:51 – 14:02 **Akitsu Hotta**
CiRA, Kyoto University, Japan
CUSTOM DISRUPTION OF HLA GENES IN HUMAN IPS CELLS BY CRISPR-CAS9 GENOME EDITING TO SUPPRESS T AND NK CELL ALLO-REACTIVITY

14:02 – 14:13 **Andreas Ritter**
University Hospital Frankfurt, Germany
LOW DOSE KINASE INHIBITOR TREATMENT RESCUES THE PRIMARY CILIUM AND ITS FUNCTION IN OBESE ADIPOSE-DERIVED MESENCHYMAL STEM CELLS

14:13 – 14:24 **Kyle Loh**
Stanford University School of Medicine, USA
EFFICIENTLY RECONSTITUTING THE STEPWISE DEVELOPMENT OF DEFINITIVE BLOOD PROGENITORS FROM HUMAN PLURIPOTENT CELLS VIA AN ARTERY-LIKE INTERMEDIATE

14:24 – 14:35 **Ramy Elsaid**
Institut Pasteur, France
THYMOPOIESIS IN TIME AND SPACE - DECIPHERING THE IMPACT OF DEVELOPMENTAL TIMING ON LYMPHOCYTE OUTPUT IN THE EMBRYONIC MOUSE THYMUS

14:35 – 14:46 **Elad Sintov**
Harvard University, USA
A HUMAN INDUCED PLURIPOTENT STEM CELL BASED IN VITRO MODEL FOR AUTOIMMUNE TYPE-1 DIABETES

14:46 – 15:06 **Shruti Naik**
NYU School of Medicine, USA
INFLAMMATORY TUNING OF EPITHELIAL STEM CELLS

FRIDAY, 28 JUNE *(continued)*

13:15 – 15:15 **CONCURRENT IIIE: STEM CELL ETHICS** Room 408B, Level Two

Chair: Megan Munsie
University of Melbourne, Australia

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

13:20 – 13:40 **Marianne Hamilton Lopez**
Duke-Robert J. Margolis, MD, Center for Health Policy, USA
STRATEGIES FOR PAYMENT REFORM IN AN ERA OF TRANSFORMATIVE THERAPIES: MOVING FROM VOLUME TO VALUE

13:40 – 13:51 **Zubin Master**
Mayo Clinic, USA
EDUCATING PATIENTS ABOUT UNAPPROVED STEM CELL TREATMENTS: EVALUATING A REGENERATIVE MEDICINE CONSULTATION SERVICE

13:51 – 14:02 **Haley Nadone**
Arizona State University, USA
WEIGHING UP THE EVIDENCE USED BY DIRECT-TO-CONSUMER STEM CELL CLINICS IN THE SOUTHWEST US

14:02 – 14:13 **Aaron Levine**
Georgia Institute of Technology,, USA
ETHICAL TRADEOFFS IN THE MANUFACTURING OF AUTOLOGOUS CELL THERAPIES

14:13 – 14:24 **Saranya Wyles**
Mayo Clinic, USA
MIND THE GAP: TRAINING NEXT-GENERATION PHYSICIANS IN REGENERATIVE MEDICINE AND SURGERY

14:26 – 14:46 **Douglas Sipp**
RIKEN Center for Biosystems Dynamics Research and Keio University School of Medicine, Japan
THE ETHICS AND ECONOMICS OF PRICE-SETTING FOR STEM CELL PRODUCTS

14:46 – 15:06 **Speaker to be named**

15:15 – 16:00 **MEET-UP HUBS** (see page 30 for details) West Hall A, Level One (Exhibit Hall)

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

POLICY, ETHICS, AND REGULATORY ISSUES Meet-up Hub #2

15:15 – 16:00 **REFRESHMENT BREAK**

FRIDAY, 28 JUNE *(continued)*

16:00 – 18:00 **PLENARY V: MECHANISMS AND APPLICATIONS OF MESODERMAL TISSUES II** — West Hall B, Level One

Chair: Melissa H. Little
Murdoch Children's Research Institute, Australia

16:00 – 16:10 **Nanci Ryder, Patient Advocate**

16:10 – 16:30 **Andrew Plump**
Takeda Pharmaceutical Co., USA
JOHN MCNEISH MEMORIAL LECTURE: USHERING IN A NEW ERA OF MEDICINE: THE PROMISE OF CELL THERAPIES

16:30 – 16:50 **Peter Carmeliet**
VIB-KU Leuven Center for Cancer Biology, Belgium
ANGIOGENESIS REVISITED: ROLE AND (THERAPEUTIC) IMPLICATIONS OF ENDOTHELIAL METABOLISM

16:50 – 17:10 **Denis Duboule**
Ecole Polytechnique Fédérale, Switzerland
ES CELLS BASED GASTRULOIDS AS A PLATFORM TO STUDY DEVELOPMENTAL GENE REGULATION

17:10 – 17:21 **Alicia Mayuef-Louchart**
Université de Lille-Egid, France
DIFFERENTIATION OF BROWN ADIPOCYTE PROGENITORS OF MOUSE IN VIVO: NEW CONCEPTUAL ADVANCES IN STEM CELL METABOLISM

17:21 – 17:32 **Lu Yue**
Hong Kong University of Science and Technology, Hong Kong
DEK-MEDIATED INTRON RETENTION REGULATES MOUSE MUSCLE STEM CELL QUIESCENCE TO ACTIVATION TRANSITION

17:32 – 17:52 **Charles Murry**
University of Washington, USA
ASSESSING GENOMIC INTEGRITY FOR STEM CELL CLINICAL TRIALS

18:00 – 20:00 **POSTER SESSION III AND RECEPTION** — West Hall A, Level One (Exhibit Hall)
ODD numbered posters present from 18:00 to 19:00
EVEN numbered posters present from 19:00 to 20:00

SATURDAY, 29 JUNE

8:00 – 18:00 **REGISTRATION OPEN** — West Hall Pre-Function, Level One

8:30 – 9:00 **MORNING COFFEE** — West Hall Pre-Function, Level One

9:00 – 11:20 **PLENARY VI: FROM BENCH TO BEDSIDE: SURFACE ECTODERM AND ENDOCRINE ORGANS** — West Hall B, Level One

Sponsored by Semma Therapeutics

Chair: Valentina Greco
Yale Medical School, USA

9:00 – 9:20 **Ting Chen**
National Institute of Biological Sciences, China
MESENCHYMAL NICHE HETEROGENEITY GOVERNS REGIONAL EPITHELIAL REGENERATION AND DISEASE INITIATION

9:20 – 9:40 **Hiromitsu Nakauchi** CIRM FUNDED
University of Tokyo, Japan
GENERATION OF FUNCTIONAL ORGANS VIA INTERSPECIES BLASTOCYST COMPLEMENTATION

9:40 – 10:00 **Anthony Oro** CIRM FUNDED
Stanford University School of Medicine, USA
CHROMATIN DYNAMIC STRATEGIES DURING SURFACE ECTODERM COMMITMENT

10:00 – 10:11 **Sangbum Park**
Yale University, USA
CAPTURING EPITHELIAL-IMMUNE INTERACTIONS TO MAINTAIN TISSUE HOMEOSTASIS

10:11 – 10:22 **Mariaceleste Aragona**
Université Libre de Bruxelles, Belgium
STEM CELLS DYNAMICS AND SIGNALLING CONTROLLING MECHANICAL FORCE-MEDIATED MOUSE SKIN EPIDERMAL EXPANSION

10:22 – 10:33 **Wenxiang Hu**
University of Pennsylvania, USA
PATIENT ADIPOSE STEM CELL-DERIVED ADIPOCYTES REVEAL GENETIC VARIATION THAT PREDICTS ANTI-DIABETIC DRUG RESPONSE

10:33 – 10:53 **Felicia Pagliuca**
Semma Therapeutics, USA
DEVELOPMENT OF A STEM CELL DERIVED ISLET CELL THERAPY FOR THE TREATMENT OF DIABETES

SATURDAY, 29 JUNE *(continued)*

10:53 – 11:13	**Barbara Treutlein** *ETH Zurich, Switzerland* ISSCR DR SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE: RECONSTRUCTING DEVELOPMENT AND REGENERATION USING SINGLE-CELL GENOMICS	
11:00 – 16:00	**Exhibit Hall Open**	West Hall A, Level One
11:30 – 13:00	**JUNIOR INVESTIGATOR CAREER PANEL LUNCHEON** *Junior Investigator event; advance registration required*	Petree Hall, Level One
12:15 – 13:00	**MEET-UP HUBS** (see mobile app for details)	West Hall A, Level One (Exhibit Hall)
13:15 – 15:15	**CONCURRENT IVA: ROAD TO THE CLINIC** *Sponsored by The New York Stem Cell Foundation* **Chair: Roger A. Barker** *University of Cambridge, UK*	Concourse E, Level One
13:15 – 13:20	**TOPIC OVERVIEW BY CHAIR**	
13:20 – 13:40	**Koji Eto** *Center for IPS Cell Research and Application (CIRA), Kyoto University, Japan* DEVELOPMENT OF TURBULENCE-BASED PRODUCTION OF IPSC-DERIVED PLATELETS TOWARDS CLINICAL APPLICATION AND BEYOND	
13:40 – 13:51	**Sandra Petrus-Reurer** *Karolinska Institutet, Sweden* GENERATION, CHARACTERIZATION AND TRANSPLANTATION IN A PRECLINICAL MODEL OF HUMAN EMBRYONIC STEM CELL-DERIVED RETINAL PIGMENT EPITHELIAL CELLS LACKING HUMAN LEUKOCYTE ANTIGEN-1 AND -2	
13:51 – 14:02	**Clive Svendsen** *Cedars-Sinai, USA* PRECISION BRAIN HEALTH: ANSWER ALS IS A POPULATION BASED MULTI-OMICS PROGRAM TO IDENTIFY ALS SUBGROUPS, BIOMARKERS AND DRUGGABLE PATHWAYS USING IPSC TECHNOLOGY	
14:02 – 14:13	**Meghan Good** *National Institutes of Health (NIH), USA* PATIENT-DERIVED TUMOR INFILTRATING LYMPHOCYTES CAN BE REPROGRAMMED AND DIFFERENTIATED TO CANCER ANTIGEN SPECIFIC T CELLS	
14:13 – 14:24	**Lucas Chase** *Opsis Therapeutics / Fujifilm-Cellular Dynamics, Inc., USA* DEVELOPMENT OF A HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED PHOTORECEPTOR REPLACEMENT THERAPY FOR INHERITED RETINAL DEGENERATIVE DISEASES	

SATURDAY, 29 JUNE *(continued)*

14:24 – 14:35 **David Alagpulinsa**
Massachusetts General Hospital, USA
LONG-TERM IMMUNOPROTECTION AND FUNCTIONAL SURVIVAL OF HUMAN STEM CELL-DERIVED BETA CELLS MICROENCAPSULATED IN ALGINATE WITH CXCL12 IN A HEALTHY NON-HUMAN PRIMATE WITHOUT SYSTEMIC IMMUNOSUPPRESSION

14:35 – 14:46 **Cory Nicholas**
Neurona Therapeutics, USA
DEVELOPMENT OF A HUMAN ESC-DERIVED INHIBITORY INTERNEURON CELLULAR THERAPEUTIC TO TREAT REFRACTORY EPILEPSY AND NEUROPATHIC PAIN

14:46 – 15:06 **Mark Humayun** CIRM FUNDED
Keck Medicine of University of Southern California, USA
BIO-ENGINEERED HESC-DERIVED RETINAL PIGMENTED EPITHELIAL CELL IMPLANT FOR AGE-RELATED MACULAR DEGENERATION

13:15 – 15:15 **CONCURRENT IVB: DEVELOPMENTAL PRINCIPLES FOR STEM CELLS** Concourse F, Level One

Chair: Martin F. Pera
The Jackson Laboratory, USA

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

13:20 – 13:40 **Shaorong Gao**
Tongji University, China
EPIGENETIC REGULATION IN EARLY EMBRYO DEVELOPMENT AND SOMATIC CELL REPROGRAMMING

13:40 – 13:51 **Aparna Bhaduri**
University of California, San Francisco, USA
UNDERSTANDING AREA SPECIFIC CELL TYPES IN THE DEVELOPING HUMAN CORTEX

13:51 – 14:02 **Freya Bruveris**
Murdoch Childrens Research Institute, Australia
DISTINCT STAGE DEPENDENT REQUIREMENTS FOR RUNX1 AND GROUP F SOX GENES DURING HUMAN HAEMATOPOIESIS

14:02 – 14:13 **Julie Sneddon**
University of California, San Francisco, CA, USA
CELL FATE DETERMINATION OF ENDOCRINE PROGENITORS IN MURINE AND HUMAN PANCREATIC DEVELOPMENT

14:13 – 14:24 **Tsotne Chitiashvili**
University of California, Los Angeles, USA
X CHROMOSOME DYNAMICS FROM PREIMPLANTATION HUMAN EMBRYOS TO DEVELOPING PRIMORDIAL GERM CELLS

SATURDAY, 29 JUNE *(continued)*

14:24 – 14:35 **Wei Huang**
University of California, San Francisco, USA
PROPERTY OF EMBRYONIC HUMAN OLIGODENDROCYTE PRECURSOR CELLS AND MECHANISM OF HUMAN WHITE MATTER EXPANSION

14:35 – 14:46 **Ksenia Gnedeva**
Keck School of Medicine of University of Southern California, USA
THE YAP/TEAD TRANSCRIPTION FACTOR COMPLEX CONTROLS A SELF-RENEWAL PROGRAM IN THE SENSORY PROGENITORS OF THE MOUSE ORGAN OF CORTI

14:46 – 15:06 **Olivier Pourquié**
Harvard University/Brigham and Women's Hospital, USA
BUILDING MUSCLES: FROM SOMITES TO MUSCULAR DYSTROPHIES

13:15 – 15:15 **CONCURRENT IVC: STEM CELL METABOLISM** Room 502, Level Two

Chair: Heather Christofk
University of California, Los Angeles, School of Medicine, USA

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

13:20 – 13:40 **Joshua Brickman**
University of Copenhagen, Denmark
METABOLIC UNDERPINNINGS OF TOTIPOTENCY

13:40 – 13:51 **Daniela Cornacchia**
Sloan Kettering Institute for Cancer Research, USA
LIPID DEPRIVATION INDUCES A STABLE NAÏVE-TO-PRIMED INTERMEDIATE STATE OF PLURIPOTENCY IN HUMAN PSC

13:51 – 14:02 **Jose Rivera-Feliciano**
Harvard University, USA
A NOVEL INSULIN-INDEPENDENT GLUCOSE LOWERING ACTIVITY

14:02 – 14:13 **Aaron Ambrus**
University of California, Los Angeles, USA
ISOCITRATE DEHYDROGENASE 1 MAINTAINS QUIESCENCE OF MURINE HAIR FOLLICLE STEM CELLS

14:13 – 14:24 **Manmeet Raval**
University of Southern California, USA
MAPPING AND PHARMACOLOGIC TARGETING OF METABOLIC PATHWAYS TO REJUVENATE AGED MUSCLE STEM CELLS

14:24 – 14:35 **Wen Gu**
University of Texas Southwestern Medical Center, USA
NON-OXIDATIVE BRANCH OF PENTOSE PHOSPHATE PATHWAY IS IMPORTANT FOR NEURAL DIFFERENTIATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS

SATURDAY, 29 JUNE *(continued)*

14:35 – 14:46 **Mukul Girotra**
University of Lausanne, Switzerland
REPROGRAMMING HEMATOPOIETIC STEM CELL FUNCTION VIA MODULATION OF MITOCHONDRIAL ACTIVITY

14:46 – 15:06 **Weiping Han**
Singapore Bioimaging Consortium, Singapore
ADAPTIVE METABOLIC PROGRAMMING PROMOTES LIVER CANCER CELL PROLIFERATION

13:15 – 15:15 **CONCURRENT IVD: MECHANISMS OF TRANSDIFFERENTIATION** Room 408A, Level Two

Chair: Marius Wernig
Stanford University, USA

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

13:20 – 13:40 **Thomas Graf**
Center for Genomic Regulation, Barcelona, Spain
DISSECTING CELL PLASTICITY, ONE CELL AT A TIME

13:40 – 13:51 **Antonio del Sol**
University of Luxembourg, Luxembourg
SINGLE-CELL BASED COMPUTATIONAL APPROACH TO IDENTIFY CELL SUBPOPULATION IDENTITY TRANSCRIPTIONAL CORE: APPLICATIONS TO CELLULAR CONVERSION

13:51 – 14:02 **Da-Hyun Kim**
Seoul National University, Korea
CAMP/EPAC1/RAP1 AXIS PLAYS AN ESSENTIAL ROLE IN ETV2-INDUCED ENDOTHELIAL REPROGRAMMING

14:02 – 14:13 **Cheen Euong Ang**
Stanford University, USA
THE NOVEL LNCRNA LNC-NR2F1 IS PRO-NEUROGENIC AND MUTATED IN HUMAN NEURODEVELOPMENTAL DISORDERS

14:13 – 14:24 **Keisuke Kaji**
University of Edinburgh, UK
UNVEILING REPROGRAMMING ROADBLOCK AND ESSENTIAL GENES VIA A CRISPR/CAS9-MEDIATED GENOME-WIDE KNOCKOUT SCREEN

14:24 – 14:35 **Samantha Morris**
Washington University School of Medicine, USA
SINGLE-CELL MAPPING OF LINEAGE AND IDENTITY IN DIRECT REPROGRAMMING

SATURDAY, 29 JUNE *(continued)*

14:35 – 14:46 **Lu Li**
Shanghai Institute of Biochemistry and Cell Biology (SIBCB), China
INNATE IMMUNE SIGNALLING AND WNT SIGNALLING FUNCTION SEQUENTIALLY IN HEPATOCYTE REPROGRAMMING

14:46 – 15:06 **Jongpil Kim**
Dongguk University, Korea
DIRECT LINEAGE REPROGRAMMING FOR CELL THERAPY AND MODELING DISEASE

13:15 – 15:15 **CONCURRENT IVE: TOOLS TO INTERROGATE STEM CELLS** Room 408B, Level Two

Chair: Barbara Treutlein
ETH Zurich, Switzerland

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

13:20 – 13:40 **Long Cai**
California Institute of Technology, USA
SPATIAL GENOMICS: TRANSCRIPTOME PROFILING IN SITU BY RNA SEQFISH+

13:40 – 13:51 **Christa Haase**
Massachusetts General Hospital, USA
SPATIALLY-RESOLVED SINGLE CELL ANALYSIS OF BONE MARROW MICRO-DOMAINS IN STEADY STATE AND DISEASE

13:51 – 14:02 **Jian Shu**
Broad Institute of MIT and Harvard/Whitehead Institute, USA
RECONSTRUCTION OF DEVELOPMENTAL LANDSCAPES AND TRAJECTORIES FROM INTEGRATIVE ANALYSIS OF LARGE-SCALE SINGLE-CELL DATA

14:02 – 14:13 **Michael Bonaguidi**
University of Southern California, USA
NEW SINGLE CELL TOOLS TO ADVANCE REGENERATIVE MEDICINE

14:13 – 14:24 **Kenichiro Kamei**
Kyoto University, Japan
TRANSPLANTABLE NANO CELLULAR MATRICES FOR SCALED-UP CULTURE OF HUMAN ES/IPS CELLS

14:24 – 14:35 **Yuqi Tan**
Johns Hopkins School of Medicine, USA
SINGLECELLNET: A COMPUTATIONAL TOOL TO ASSESS THE FIDELITY OF CELL FATE ENGINEERING AND TO AID CELL ATLASES

SATURDAY, 29 JUNE *(continued)*

14:35 – 14:46	**Michela Milani** *San Raffaele Telethon Institute for Gene Therapy (SR-TIGET), Italy* TARGETING OF HEPATOCYTE SUBPOPULATION CONTRIBUTING TO POST-NATAL LIVER GROWTH IS CRUCIAL FOR MAINTENANCE OF TRANSGENE EXPRESSION IN LIVER-DIRECTED GENE THERAPY	
14:46 – 15:06	**Melike Lakadamyali** *University of Pennsylvania, Perelman School of Medicine, USA* SUPER-RESOLUTION IMAGING OF CHROMATIN IN REPROGRAMMING AND DIFFERENTIATION	
15:15 – 16:00	**MEET-UP HUBS** (see page 30 for details)	West Hall A, Level One (Exhibit Hall)
	DIVERSITY, INCLUSION, AND EQUITY IN STEM CELL BIOLOGY	Meet-up Hub #1
	VOLUNTEER OPPORTUNITIES AT THE ISSCR	Meet-up Hub #2
15:15 – 16:00	**REFRESHMENT BREAK**	West Hall A, Level One (Exhibit Hall)
16:00 – 18:45	**PLENARY VII: BASICS AND TRANSLATION: NEURAL ECTODERM** *Sponsored by BlueRock Therapeutics* **Chair: Jane S. Lebkowski** *Regenerative Patch Technologies, USA*	West Hall B, Level One
16:00 – 16:05	**PRESIDENT-ELECT REMARKS: DEEPAK SRIVASTAVA**	
16:05 – 16:25	**Scott Armstrong** *Dana-Farber Cancer Institute, and Division of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School/The Broad Institute of MIT and Harvard, USA* ISSCR TOBIAS AWARD LECTURE:TARGETING CHROMATIN TO REVERSE LEUKEMIA STEM CELL GENE EXPRESSION	
16:25 – 16:45	**Lorenz Studer** *Memorial Sloan Kettering Cancer Center, USA* ERNEST MCCULLOCH MEMORIAL LECTURE: BUILDING AND REPAIRING THE HUMAN BRAIN USING PLURIPOTENT STEM CELLS	
16:45 – 17:05	**Claude Desplan** *New York University, USA* COORDINATION BETWEEN STOCHASTIC AND DETERMINISTIC CHOICES IN THE DROSOPHILA OPTIC LOBES	

SATURDAY, 29 JUNE *(continued)*

17:05 – 17:25 **Kristin Baldwin**
Scripps Research Institute, USA
DRIVING AND DEFINING NEURONAL DIVERSITY USING REPROGRAMMING
CIRM FUNDED

17:26 – 17:36 **Ralda Nehme**
Broad Institute of Harvard and MIT and Harvard University, USA
REGULATION OF GENES UNDERLYING SCHIZOPHRENIA RISK BY 22Q11.2 IN HUMAN NEURONS

17:36 – 17:47 **Joel Blanchard**
Massachusetts Institute of Technology, USA
RECONSTRUCTION OF THE HUMAN BLOOD-BRAIN BARRIER IN VITRO REVEALS THE PATHOGENIC MECHANISMS OF APOE4 IN CEREBRAL AMYLOID ANGIOPATHY

17:47 – 18:07 **Sally Temple**
Neural Stem Cell Institute, USA
STEM CELLS IN THE ADULT HUMAN RETINAL PIGMENT EPITHELIUM AND THEIR THERAPEUTIC POTENTIAL

18:07 – 18:17 **PATIENT ADVOCATE REMARKS**

Robert Klein
Americans for Cures, USA

18:17 – 18:37 **Shinya Yamanaka**
Gladstone Institutes, USA and Center for IPS Cell Research and Application, Kyoto University, Japan
RECENT PROGRESS IN IPS CELL RESEARCH AND APPLICATION

18:37 – 18:45 **POSTER AWARD ANNOUNCEMENTS AND CLOSING REMARKS**

STEM CELL REPORTS

MEET THE EDITORS

Friday, June 28, 2019

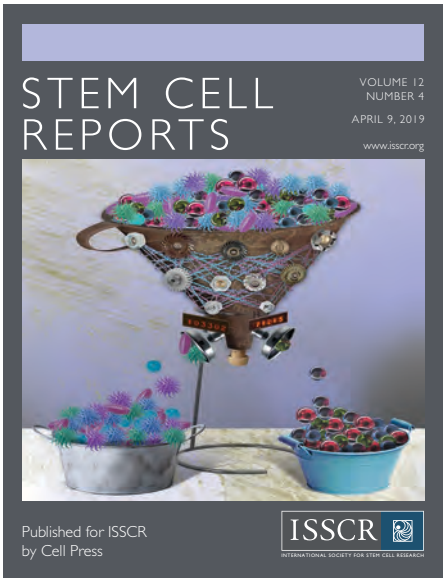
15:15 - 16:00

Meet-Up Hub in the Exhibit Hall

Editor-in-Chief
Martin Pera

Managing Editor
Yvonne Fischer

Associate Editors
Nissim Benvenisty
Thomas Graf
Christine Mummery
Jun Takahashi
Amy Wagers
Christine Wells



Stem Cell Reports is an open-access, peer-reviewed journal that offers rapid decisions for your submitted articles.

Learn more at:
cell.com/stem-cell-reports

PUBLISHED FOR THE ISSCR BY CELL PRESS

ISSCR

INTERNATIONAL SOCIETY
FOR STEM CELL RESEARCH

Exhibit & Poster Hall, Innovation Showcases

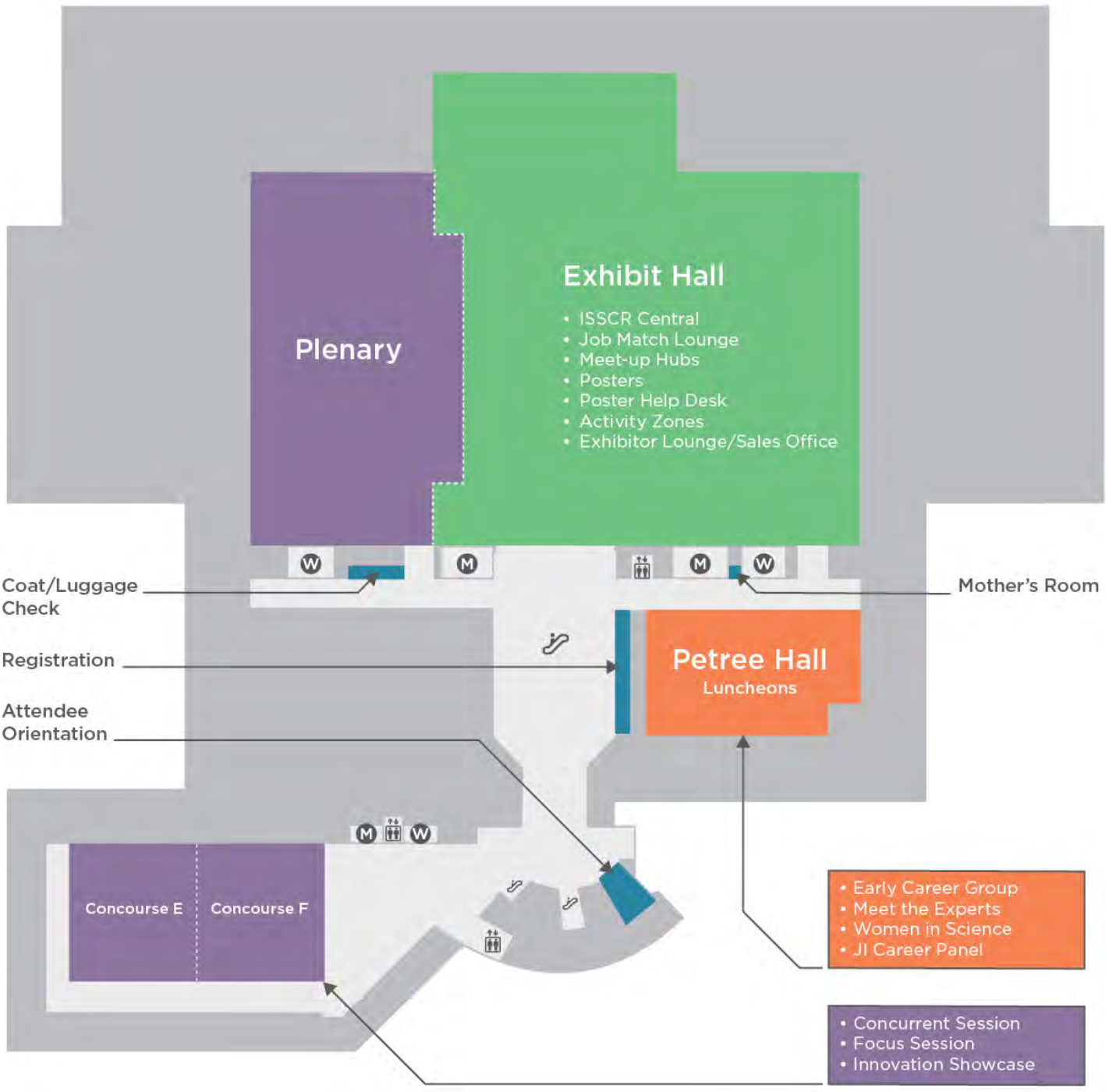
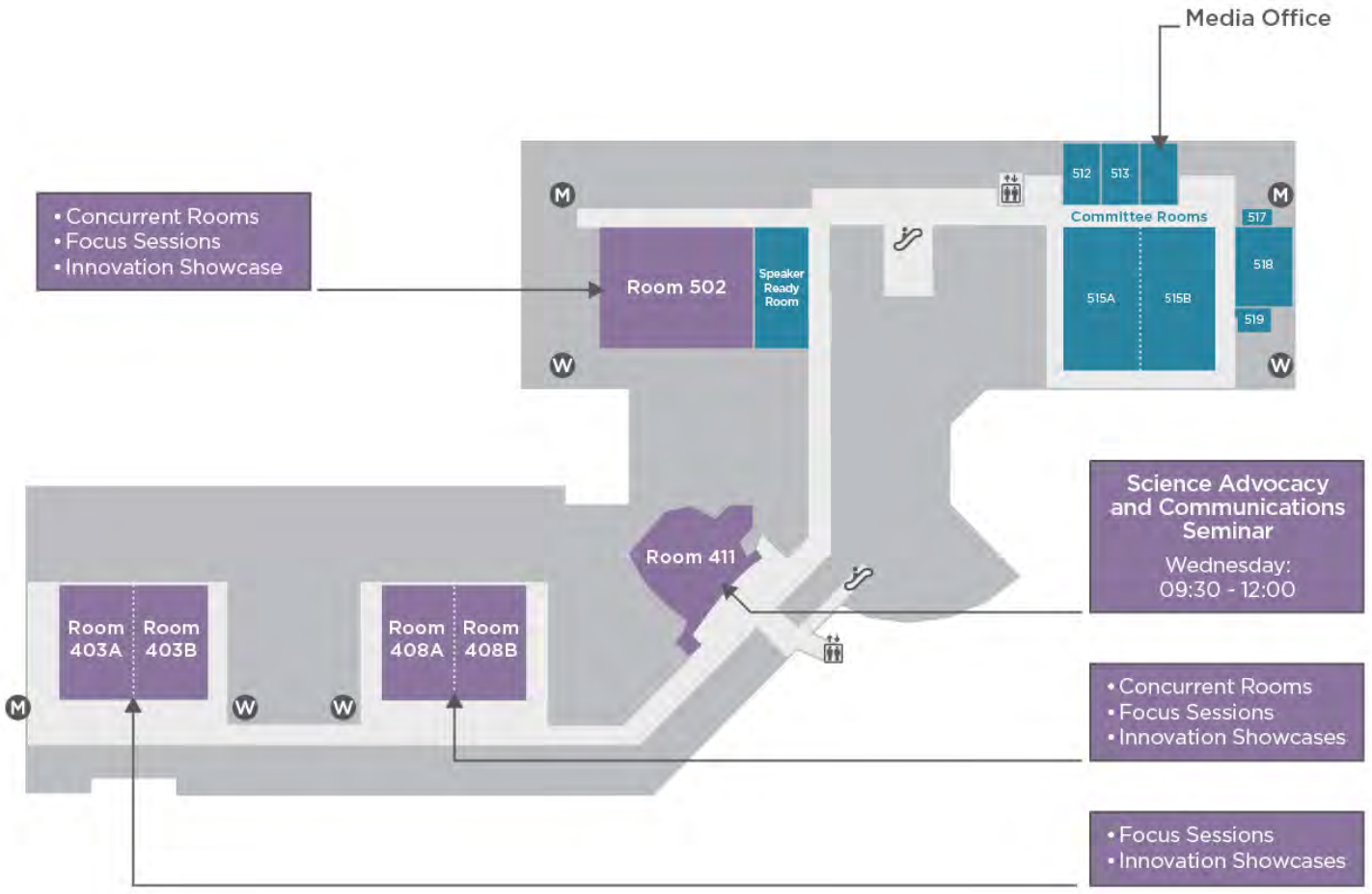
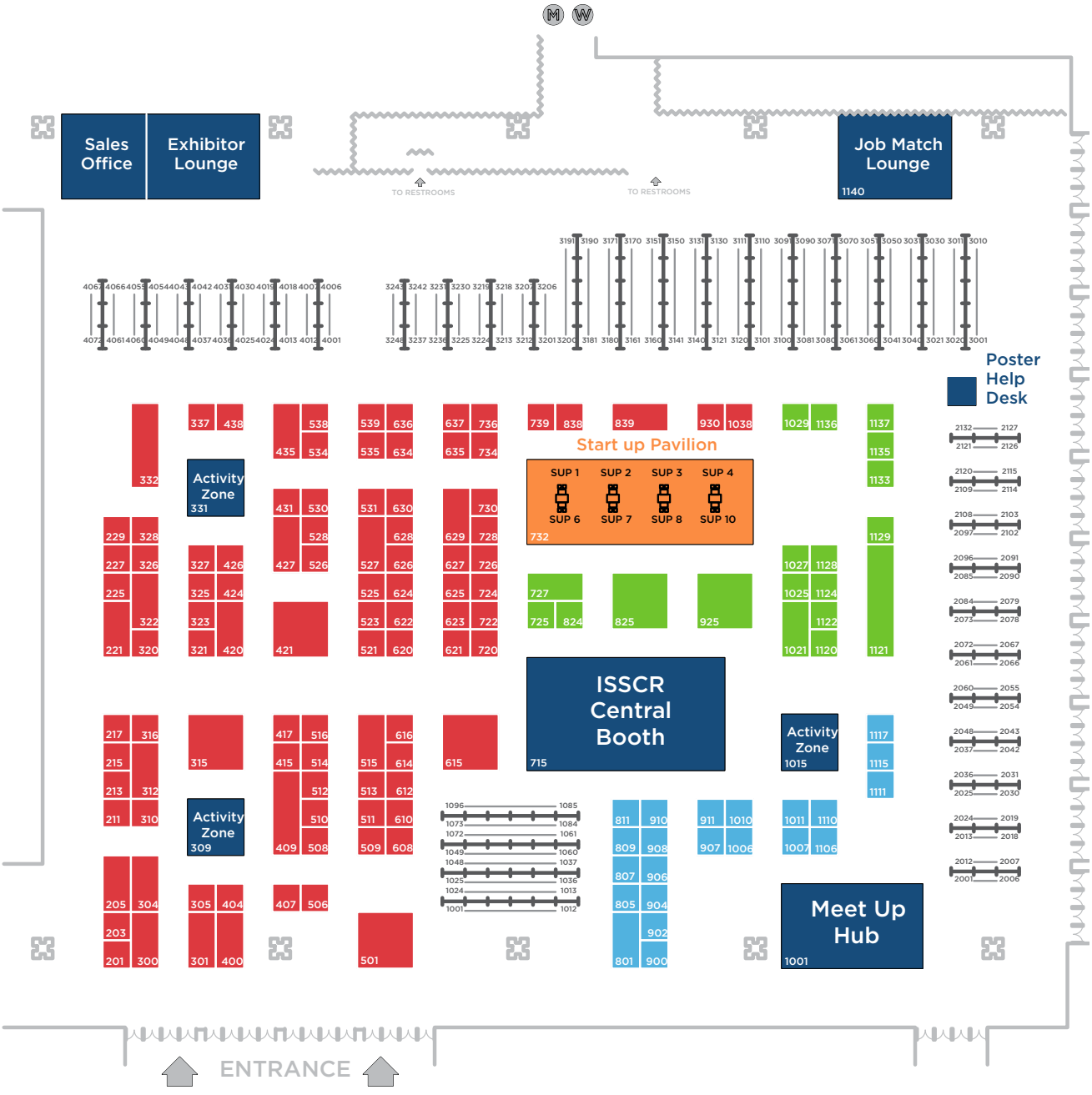

Plenary
Exhibit Hall
• ISSCR Central
• Job Match Lounge
• Meet-up Hubs
• Posters
• Poster Help Desk
• Activity Zones
• Exhibitor Lounge/Sales Office
Coat/Luggage Check
Registration
Attendee Orientation
Mother's Room
Petree Hall
Luncheons
Concourse E
Concourse F
• Early Career Group
• Meet the Experts
• Women in Science
• JI Career Panel
• Concurrent Session
• Focus Session
• Innovation Showcase

EXHIBIT & POSTER HALL





- Start Up Pavlilion
- Technology & Suppliers
- Therapeutics & Commercialization
- Academic
- ISSCR Central
- Activity Zones
- Exhibitor Lounge/Sales Office
- Job Match Lounge
- Meet Up Hub
- Poster Help Desk

POSTER BOARDS BY TOPIC

POSTER TOPICS	START NUMBER	END NUMBER
Merit Award Posters	1001	1040
Placenta and Umbilical Cord Derived Cells	2001	2005
Adipose and Connective Tissue	2006	2011
Musculoskeletal Tissue	2012	2023
Cardiac Tissue and Disease	2024	2041
Endothelial Cells and Hemangioblasts	2042	2048
Hematopoiesis/Immunology	2049	2064
Pancreas, Liver, Kidney	2065	2078
Epithelial Tissues	2079	2089
Eye and Retina	2090	2103
Stem Cell Niches	2104	2115
Cancers	2116	2129
Neural Development and Regeneration	3001	3016
Neural Disease and Degeneration	3017	3040
Organoids	3041	3058
Tissue Engineering	3059	3073
Ethical, Legal and Social Issues; Education and Outreach	3074	3080
Clinical Trials and Regenerative Medicine Interventions	3081	3086
Germline, Early Embryo and Totipotency	3087	3094
Chromatin and Epigenetics	3095	3103
Pluripotency	3104	3118
Pluripotent Stem Cell Differentiation	3119	3157
Pluripotent Stem Cell: Disease Modeling	3158	3190
Reprogramming	3191	3208
Technologies for Stem Cell Research	3209	3242
Late Breaking Abstracts	4001	4069

Click the exhibiting company name to jump to the company description.

COMPANY	STAND NUMBER
10x Genomics	420
AAAS/Science International	510
ABLE Corporation	513
Advanced Targeting Systems	608
Agilent Technologies	620
Ajinomoto Co., Inc.	509
Albumedix Ltd.	511
AllCells, LLC	431
Allele Biotech	1025
Allen Institute	427
ALS Automated Lab Solutions GmbH	521
AMSBIO	531
Amuza Inc.	527
ANALYTIK JENA US LLC	722
Applied Biological Materials Inc.	629
Applikon Biotechnology	417
Aspect Biosystems Ltd	614
Atlas Antibodies	1027
Axion Biosystems, Inc.	621
AXON MEDCHEM	739
Baker Company	530
Bio-ITech	205
Biolamina	400
BioLegend	506
Biological Industries	925
BioSpherix Ltd.	630
BioSpherix Medical	1129
Bio-techne	409
BioTek Instruments, Inc.	624
Bluechiip Limited	310
BrainXell, Inc.	612
California Institute for Regenerative Medicine	424
Cedars-Sinai, Board of Governors Regenerative Medicine Institute	1120
Cell Guidance Systems	1122

EXHIBITORS, ALPHA BY NAME

COMPANY	STAND NUMBER
Cell Line Genetics, Inc.	300
Cell Microsystems	622
Cell Press	801
Cellbox Solutions GmbH	SUP 7
CELLINK	523
The Company of Biologists	811
Corning Life Sciences	825
CYTOSMART(TM) TECH	628
Discover Echo Inc.	332
Emulate Inc.	1124
Eppendorf AG	304
The European Collection of Authenticated Cell Cultures (ECACC)	728
FroggaBio	634
FujiFilm Cellular Dynamics, Inc.	421
FUJIFILM Irvine Scientific	525
HEALIOS K.K.	1128
Healthgen Biotechnology Corp.	328
Hello Bio	SUP 1
HemaCare Corporation	535
Illumina Inc	203
INTEGRA Biosciences	627
iotaSciences	SUP 10
IXCells Biotechnologies USA, LLC	838
Jellagen	726
Kataoka-SS America Corp.	725
KEYENCE Corporation	635
Kuhner Shaker Inc.	727
LEICA MICROSYSTEMS INC	623
Logos Biosystems, Inc.	326
Lonza Pharma Bioscience Solutions	301
Mary Ann Liebert, Inc.	908
Matrigen	736
Matrixome	538
MaxWell Biosystems	435

COMPANY	STAND NUMBER
Miltenyi Biotec GmbH	315
MIMETAS	824
Mitsui Bussan Electronics Ltd. / Hitachi, Ltd.	637
Molecular Devices, LLC	407
Multi Channel Systems	508
NACALAI USA INC	539
NanoCellect Biomedical Inc	625
NanoSurface Biomedical	323
Nepa Gene Co Ltd	730
NeuroInDx	626
Nexcelom Bioscience	327
Nexus Scientific	SUP 8
The New York Stem Cell Foundation (NYSCF)	404
Nikon Instruments Inc.	322
NIPRO/CSTI	1038
Nordmark Biochemicals	636
Olympus America Inc.	316
On-chip Biotechnologies Co., Ltd	516
PAKAIR CARGO SPECIALISTS	610
PBS Biotech, Inc.	534
PeproTech Inc	501
Phase Holographic Imaging AB	337
PromoCell GmbH	320
Proteintech Group Inc	839
Qkine	SUP 6
RegMedNet	724
Reprocell	515
Rockefeller University Press	809
ROKIT Healthcare	325
RUCDR Infinite Biologics	900
Sartorius	312
S-Bio	415
ScienCell Research Laboratories	305
ShanghaiTech University	1010

EXHIBITORS, ALPHA BY NAME

COMPANY	STAND NUMBER
Shenandoah Biotechnology Inc.	512
Sino Biological	734
SPEX SamplePrep, LLC	514
Springer Nature	910
STEM CELLS Journals	911
Stem Genomics	526
StemBioSys Inc.	616
STEMCELL Technologies Inc.	615
StemExpress	321
Synthego	221
Thermo Fisher Scientific	1121
TriFoil Imaging	939
Union Biometrica, Inc.	720
UPM-Kymmene Corporation	426
USC Stem Cell	805
UTSA Brain Health Consortium	807
VectorBuilder Inc	201
WiCell	1021
Wiley	1011
Worthington Enzymes	438
Xylyx Bio, Inc.	528

ACADEMIC PAVILION

COMPANY	STAND NUMBER
Cell Press	801
The Company of Biologists	811
The Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research of USC	805
Mary Ann Liebert, Inc.	908
Olympus America Inc.	316
Rockefeller University Press	809
RUCDR Infinite Biologics	900
ShanghaiTech University	1010
Springer Nature	910
STEM CELLS Journals	911
UTSA Brain Health Consortium	807
Wiley	1011

START UP PAVILION

COMPANY	STAND NUMBER
Cellbox Solutions GmbH	SUP 7
Hello Bio	SUP 1
iotaSciences	SUP 10
Nexus Scientific	SUP 8
Qkine	SUP 6

TECHNOLOGY AND SUPPLIERS PAVILION

COMPANY	STAND NUMBER
10x Genomics	420
AAAS/Science International	510
ABLE Corporation	513
Advanced Targeting Systems	608
Agilent Technologies	620
Ajinomoto Co., Inc.	509
Albumedix Ltd.	511
AllCells, LLC	431
Allen Institute	427
ALS Automated Lab Solutions GmbH	521
AMSBIO	531
Amuza Inc.	527

EXHIBITORS, BY PAVILION

COMPANY	STAND NUMBER
ANALYTIK JENA US LLC	722
Applied Biological Materials Inc.	629
Applikon Biotechnology	417
Aspect Biosystems Ltd	614
Axion Biosystems, Inc.	621
AXON MEDCHEM	739
Baker Company	530
Bio-ITech	205
Biolamina	400
BioLegend	506
BioSpherix Ltd.	630
Bio-techne	409
BioTek Instruments, Inc.	624
Bluechiip Limited	310
BrainXell, Inc.	612
California Institute for Regenerative Medicine	424
Cell Line Genetics, Inc.	300
Cell Microsystems	622
CELLINK	523
CYTOSMART(TM) TECH	628
Discover Echo Inc.	332
Eppendorf AG	304
The European Collection of Authenticated Cell Cultures (ECACC)	728
FroggaBio	634
FujiFilm Cellular Dynamics, Inc.	421
FUJIFILM Irvine Scientific	525
Healthgen Biotechnology Corp.	328
HemaCare Corporation	535
Illumina Inc	203
INTEGRA Biosciences	627
IXCells Biotechnologies USA, LLC	838
Jellagen	726
KEYENCE Corporation	635
LEICA MICROSYSTEMS INC	623
Logos Biosystems, Inc.	326
Lonza Pharma Bioscience Solutions	301
Matrigen	736
MaxWell Biosystems	435
Miltenyi Biotec GmbH	315

COMPANY	STAND NUMBER
Mitsui Bussan Electronics Ltd. / Hitachi, Ltd.	637
Molecular Devices, LLC	407
Multi Channel Systems	508
NACALAI USA INC	539
NanoCellect Biomedical Inc	625
NanoSurface Biomedical	323
Nepa Gene Co Ltd	730
NeuroInDx	626
The New York Stem Cell Foundation (NYSCF)	404
Nexcelom Bioscience	327
Nikon Instruments Inc.	322
Nippi/Matrixome	538
NIPRO/CSTI	1038
Nordmark Biochemicals	636
On-chip Biotechnologies Co., Ltd	516
PAKAIR CARGO SPECIALISTS	610
PBS Biotech, Inc.	534
PeproTech Inc	501
Phase Holographic Imaging AB	337
PromoCell GmbH	320
Proteintech Group Inc	839
RegMedNet	724
Reprocell	515
ROKIT Healthcare	325
Sartorius	312
S-Bio	415
ScienCell Research Laboratories	305
Shenandoah Biotechnology Inc.	512
Sino Biological	734
SPEX SamplePrep, LLC	514
Stem Genomics	526
StemBioSys Inc.	616
STEMCELL Technologies Inc.	615
StemExpress	321
Synthego	221
TriFoil Imaging	939
Union Biometrica, Inc.	720
UPM-Kymmene Corporation	426
VectorBuilder Inc	201

COMPANY	STAND NUMBER
Worthington Enzymes	438
Xylyx Bio, Inc.	528

THERAPEUTIC AND COMMERCIALIZATION PAVILION

COMPANY	STAND NUMBER
Allele Biotech	1025
Atlas Antibodies	1027
Biological Industries	925
BioSpherix Medical	1129
Cedars-Sinai, Board of Governors Regenerative Medicine Institute	1120
Cell Guidance Systems	1122
Corning Life Sciences	825
Emulate Inc.	1124
HEALIOS K.K.	1128
Kataoka-SS America Corp.	725
Kuhner Shaker Inc.	727
MIMETAS	824
Thermo Fisher Scientific	1121
WiCell	1021

10X GENOMICS - STAND 420

7068 Koll Center Pkwy, Ste 401
Pleasonton, CA
94566 U.S.A.
+1 925-407-7300
+1 800-709-1208
info@10xgenomics.com

10x Genomics is committed to paving the way for a new understanding of biology, human health, and disease. The company was founded on the vision that this century will bring unprecedented advances in biomedicine to transform the way we treat diseases leading to dramatic improvements in human health. 10x products enable the acceleration of genetic discoveries through unparalleled resolution.

ABLE CORPORATION - STAND 513

7-9 Nisgigoken-cho
Shinjuku-ku
Tokyo
162-0812 Japan
+81 332600451
www.able-biott.co.jp/en

We are established company of bioreactor in Japan. Our main products are bioreactor and sensor, process controller. This exhibition, we will show the small to large scale (5mL, 30mL, 100mL, 500mL, 1500mL) of single-use bioreactor and mmultichannel magnetic stirrer for stem cell stirred suspension culture.

ADVANCED TARGETING SYSTEMS - STAND 608

10451 Roselle St
Ste 300
San Diego, CA
92121 U.S.A.
+1 619-889-2287
www.ATSbio.com

Advanced Targeting Systems, “the saporin people,” provides products and services based on an innovative targeting technology. Specifically deliver payloads to cells using receptor-mediated internalization of a targeting agent. Targeting products purify populations in cell culture or eliminate cells in vivo. The product line includes targeted toxins and antibodies. Secondary “ZAP” conjugates are useful in screening for internalization. Contract testing services also available.

AGILENT TECHNOLOGIES - STAND 620

5301 Stevens Creek Blvd.
Santa Clara, CA
95051 U.S.A.
+1 877-424-4536
www.agilent.com

Agilent Technologies Inc. is a global leader in life sciences, diagnostics and applied chemical markets. With more than 50 years of insight and innovation, Agilent instruments, software, services, solutions, and people provide trusted answers to its customers’ most challenging questions. Agilent employs about 13,500 people worldwide.

AJINOMOTO - STAND 509

15-1, Kyobashi 1-chome
Chuo-ku
Tokyo
104-8315 Japan
+1 808-827-4158
www.ajitrade.com/stemfit/products

As a world leader in amino acid research and production, Ajinomoto Co. was a natural choice for a collaborative project to develop an ideal culture medium for CiRA’s iPS cell research. Ajinomoto Co.’s line of xeno-free culture media and growth factors provide innovative solutions for iPS/ES studies, from basic research to clinical application.

ALBUMEDIX LTD - STAND 511

59 Castle Boulevard
Nottingham,
NG7 1FD UK
+44-115-9553379
www.albumedix.com

Albumedix is a science-driven, biotechnology company focused on enabling the creation of superior biopharmaceuticals utilizing our albumin-based drug enhancing technologies. We are proud to be recognized as the world leader in recombinant human albumin with products and technologies used in clinical and marketed drugs by pharmaceutical companies worldwide. We are just as passionate about albumin and albumin-enabled therapies today as we were when we started 30 years ago.

ALLCELLS, LLC - STAND 431

1301 Harbor Bay Parkway
Suite 200
Alameda, CA
94502 U.S.A.
+1 510-521-2600
www.allcells.com

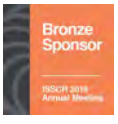
Founded in 1998, AllCells is a biotechnology company dedicated to providing researchers and biomanufacturing organizations with high quality primary cells that enable drug discovery, preclinical development, and manufacturing of cell therapies. Leveraging its adjacent blood & marrow donor collection facilities, AllCells ships cells worldwide, or fresh cells can be immediately utilized in fee-for-service.

ALLELE BIOTECH - STAND 1025

6404 Nancy Ridge Drive
San Diego, CA
92121 U.S.A.
+1 858-587-6645
www.allelebiotech.com

Allele Biotechnology and Pharmaceuticals Inc. is focused on solutions for clinical iPSC therapies, including mRNA-based iPSC generation and differentiation all under cGMP and patient derived cell models with integrated fluorescent cell sensors.

ALLEN INSTITUTE FOR CELL SCIENCE - STAND 427



615 Westlake Ave N
Seattle, WA
98109 U.S.A.
+1 206-548-7000
www.allencell.org

The Allen Institute for Cell Science aims to understand human induced pluripotent stem cells during differentiation, pathology, and other state changes by conjoining single cell genomics, live cell 3D imaging, and phenotypic activities. To accelerate biological research worldwide, the Allen Institute openly shares the cell lines, computational tools, data, and predictive models its research team produces on allencell.org.

ALS AUTOMATED LAB SOLUTIONS GMBH - STAND 521

Otto-Eppenstein-Str. 30
Jena
07745 Germany
+49 364148200
www.als-jena.com

Main product of ALS Automated Lab Solutions is the CellCelector, a multi-functional system for automated screening of cell culture plates and dishes. Target cells and colonies found during screening can be picked out of those plates fully automatically. The system can pick individual single cells, adherent cell colonies like stem cell colonies as well as colonies from semi-solid media like methylcellulose.

AMSBIO - STAND 531

1035 Cambridge St
Cambridge, MA
02141 U.S.A.
+1-800-987-0985
www.amsbio.com

AMSBIO supplies high-quality products for cell and gene therapy. Our portfolio includes stem cells from various sources, reprogramming agents, feeder cells, and GMP-qualified cryopreservation media. We offer stem cell characterization tools, differentiation reagents, unique assay platforms, and packaging of AAV and lentivirus. AMSBIO carries the industry's largest selection of recombinant ECMs, and xeno-free culture media which provide unrivalled productivity and easy of regulatory adoption.

AMUZA INC. - STAND 527

10060 Carroll Canyon Road, Suite 100
San Diego, CA
92131 U.S.A.
+1 858-225-6869
www.amuzainc.com

Amuza Inc. is a researcher-focused company. We provide instruments and support to improve productivity and outcomes for life science research and in turn, quality of life. Our unique solutions focus on driving innovation in Biology Research, Tissue Engineering, and Regenerative Medicine.

ANALYTIK JENA US LLC - STAND 722

2066 West 11th Street
Upland, CA
91786 U.S.A.
+1 909-946-3197
www.us.analytik-jena.com

Analytik Jena US LLC offers a wide range of high performance imaging systems for gel/blot applications, thermal cyclers for qPCR and standard PCR, and an assortment of ultraviolet lab equipment including PCR enclosures, transilluminators, crosslinkers and hybridization ovens. All of Analytik Jena's products are designed to fit researchers' specifications and budgets. High-throughput liquid handling/lab automation and analytical instruments complete Analytik Jena's broad product portfolio.

APPLIED BIOLOGICAL MATERIALS INC. - STAND 629

1-3671 Viking Way
Richmond, BC
V6V 2J5 Canada
+1 604-247-2416
www.abmgood.com

Applied Biological Materials (abm) Inc. is a Canadian research reagent manufacturer. Our products span from CRISPR gene editing tools, viral vector systems, to the world's largest collection of unique cell lines and NGS technologies and services. abm strives to be the 'one-stop shop' where we provide all reagents or services necessary for any project to catalyze scientific discoveries in Life Sciences and Drug Development.

APPLIKON BIOTECHNOLOGY - STAND 417

1180 Chess Dr
Foster City, CA
94404 U.S.A.
+1 617-744-9633
www.applikonbio.com

Applikon Biotechnology is a world leader in developing and supplying advanced bioreactor systems for the production of vaccines, antibodies, tissues, bio-pharmaceuticals, nutraceuticals and biosimilars in the Pharmaceutical industry, as well as enzymes, food, feed, bio-fuel, bio-chemicals and bio-plastics for Industrial Biotechnology. Applikon can guide a customer through the whole upstream process, from initial screening up to full-scale production, using the same platform.

ASPECT BIOSYSTEMS - STAND 614

1781 West 75th Avenue
Vancouver, BC
V6P 6P2 Canada
+1-604-263-0502
www.aspectbiosystems.com

Aspect Biosystems is a privately held biotechnology company pioneering microfluidic 3D bioprinting of living, human tissue. The company's proprietary technology is enabling advances in understanding fundamental biology, disease research, development of novel therapeutics, and regenerative medicine. In addition to its internal programs, Aspect is focused on strategically partnering with pharmaceutical and biotechnology companies, as well as academic researchers, to enable the creation of living, human tissues for medical research, therapeutic discovery, and regenerative medicine products.

ATLAS ANTIBODIES - STAND 1027

Voltavägen 13A
Bromma
16869 Sweden
+46 854595850
www.atlasantibodies.com

Atlas Antibodies is a Swedish manufacturer and supplier with a mission to provide customers around the world with advanced research reagents targeting all human proteins. Characterization and validation data for our antibodies can be found on our website as well as on the open access Human Protein Atlas portal.

AXION BIOSYSTEMS - STAND 621

1819 Peachtree Road NE, Suite 350
Suite 350
Atlanta, GA
30309 U.S.A.
+1 404-477-2557
www.axionbio.com

Developing electrically active cells is challenging. Enter Maestro Pro and Edge, the world's most advanced MEA platforms, designed by Axion BioSystems. Now you can track the differentiation of electroactive cells in real-time. Perfect for characterizing newly created iPSC-derived models, Maestro is an easy-to-use, cellular analysis system suitable for any lab.

AXON MEDCHEM - STAND 739

12020 SUNRISE VALLEY DR. STE100
RESTON, VA
20191 U.S.A.
+1 888-703-9861
www.axonmedchem.com

Axon Medchem is a trusted supplier of high-quality life science products, providing >2000 small molecule inhibitors and modulators as world wide recognized drug reference standards, targeting >850 biological targets. Axon Medchem is also a leading CRO in medicinal chemistry, specialized in contract research and high-quality synthesis of bio-active and/or drug-like molecules.

BAKER COMPANY - STAND 530

175 Gatehouse Road
Sanford, ME
04073 U.S.A.
+1 207-324-8773
www.bakerco.com

For over 6 decades, Baker has been at the forefront of engineering, testing, and producing reliable laboratory contamination control equipment. Our Baker Ruskinn line of precision cell culture solutions, including controlled O2, anaerobic, and microaerophilic workstations, help improve research results by providing a controlled environment for low O2 studies and systemized incubation.

BI - BIOLOGICAL INDUSTRIES - STAND 925

Kibbutz
Beit Haemek
2511500 Israel
+972-4-9960595
www.bioind.com

Biological Industries manufacturing expertise of cell culture products extends over 35 years. BI products include: The Nutristem® range of stem cell media which have become the gold standard in research and clinical applications, helping to advance stem cell based therapies.
In addition, BI supplies related products for stem cell culture and differentiation, including animal component-free freezing media, xeno-free attachment solution and animal component-free cell dissociation solutions.

BIO-ITECH - STAND 205

1208 Massachusetts Ave, Suite 3
Cambridge, MA
02138 U.S.A.
+1 617-665-5391
www.Bio-ITech.com

Bio-ITech is a Life Science IT company that provides software solutions to manage information in the workflow of laboratories worldwide. The Electronic Lab Notebook eLABJournal and the Inventory and Sample Tracking System eLABInventory are 21 CFR part 11 compliant and safeguard intellectual property with track-and-trace, versioning, and digital signatures.

BIOLAMINA - STAND 400

Löfströms alle 5A
Stockholm
172 66 Sweden
+46 858885180
www.biolamina.com

We offer an expansive portfolio of defined human recombinant laminin matrices, Biolaminins, for a variety of applications, such as expansion of human pluripotent stem cells and differentiation and maintenance of different specialised cell types. The biologically relevant cell-matrix interaction leads to improved cell functionality, robust culture systems and safe cells for therapy. BioLamina's laminin technology has been scientifically validated in many high impact journals.

BIOLEGEND - STAND 506

9727 Pacific Heights Blvd
San Diego, CA
92121 U.S.A.
+1 858-455-9588
www.biolegend.com

BioLegend develops and manufactures highly recognized, world-class antibodies and reagents at an outstanding value. Our product portfolio includes tools for research in immunology, neuroscience, cell biology, cancer, and stem cells. We offer more than 18,000 products, collectively cited in over 25,000 peer-reviewed journal publications. BioLegend is certified for ISO 13485:2003.

BIOSPHERIX LTD. - STAND 630

25 Union Street
Parish, NY
13131 U.S.A.
+1 315-387-3414
www.biospherix.com

Equipping stem cell scientists with Cytocentric Cell Incubation & Processing Systems. Manufacturer of incubators, hoods, and subchambers that provide aseptic, cell-optimized, and physiologically similar conditions to: increase proliferation, maintain pluripotency, promote correct phenotype, streamline cell reprogramming, preserve stemness, increase yield, decrease spontaneous differentiation, shorten doubling time, boost self-renewal, control lineage commitment, modulate quiescence, and enhance repopulating ability. Learn more: www.biospherix.com

BIOSPHERIX MEDICAL - STAND 1129

25 Union Street
Parish, NY
13131 U.S.A.
+1 315-625-8025
www.biospherixmedical.com

BioSpherix Xvivo SystemTM, the first cytocentric barrier isolator designed for cells. The modular design can aseptically close any cell production process, manual or automated. All analytic, automation, process equipment can be integrated. Full-time optimization of all critical cell parameters, including oxygen, produces cells with superior potency. The Xvivo SystemTM is a practical and economical alternative to cleanrooms for cGMP-compliant production of human cells and tissues.

BIO-TECHNE - STAND 409

614 McKinley Place NE
Minneapolis, MN
55413 U.S.A.
+1 612-379-2956 x6461
www.bio-techne.com

Bio-Techne empowers researchers by providing high-quality reagents, instruments, custom manufacturing, and testing services. Whether you are at the cutting-edge of academic research or at a facility that requires the highest level of diagnostic testing, our innovative products and services provide the solutions you need to succeed.

BIOTEK INSTRUMENTS INC. - STAND 624

Highland Park
Box 998
Winooski, VT
05404 U.S.A.
+1 888-451-5171
www.biotek.com

BioTek is celebrating its 50th year as a worldwide leader in the design, manufacture, and distribution of innovative life science instrumentation including cell imaging systems, microplate readers, washers, dispensers, automated incubators, stackers and pipetting systems. Our products enable life science research by providing high performance, cost-effective analysis and quantification of biomolecules, biomolecular interactions and cellular structure and function across diverse applications.

BLUECHIIP LIMITED - STAND 310

1 Dalmore Dr
Melbourne
03179 Australia
+61 397639763
www.bluechiip.com

Bluechiip is a MEMS-based technology provider that aims to be the next standard for sample identification and temperature sensing for extreme environments. The Bluechiip system can identify tags embedded in sample containers straight out of liquid nitrogen as well as covered with frost in comparison to labels or barcodes. In addition the Bluechiip tags are not affected by radiation and temperature cycles unlike RFID's.

BRAINXELL, INC. - STAND 612

455 Science Drive, Suite 210
Madison, WI
53711 U.S.A.
+1 608-220-3240
www.brainxell.com

BrainXell provides iPSC-derived human neurons to the pharmaceutical industry and other research organizations for CNS drug discovery and development. Utilizing proprietary technology developed over the last two decades by Professor Su-Chun Zhang at the University of Wisconsin, we generate subtype-specific neurons that rapidly mature. Additionally, custom neuron batches at small to very large scale can be produced from any iPSC or ESC line provided.

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE - STAND 424

1999 Harrison Street
Suite 1650
Oakland, CA
94612 U.S.A.
(Phone Missing)
www.cirm.ca.gov

porta non pulvinar neque laoreet suspendisse interdum consectetur libero id faucibus nisl tincidunt eget nullam non nisi est sit amet facilisis magna etiam tempor orci eu lobortis elementum nibh tellus molestie nunc non blandit massa enim nec dui nunc mattis enim ut tellus elementum sagittis vitae et leo duis ut diam quam nulla porttitor massa id neque aliquam vestibulum morbi blandit cursus risus at ultrices

CEDARS-SINAI, BOARD OF GOVERNORS REGENERATIVE MEDICINE INSTITUTE - STAND 1120

8700 Beverly Blvd.
Los Angeles, CA
90048 U.S.A.
+ 310-248-8072
www.cedars-sinai.edu/Research/Departments-and-Institutes/Regenerative-Medicine-Institute

The Cedars-Sinai Board of Governors Regenerative Medicine Institute brings together research faculty and clinicians to provide a true “bench to bedside” organization. We have six key program areas: Brain, Eye, Pancreas, Kidney, Liver and Gut, Blood, and Skeletal. Our core facilities focus on generating induced pluripotent stem cells from human patient blood samples and then generating tissues of interest to the six programs.

CELL GUIDANCE SYSTEMS - STAND 1122

Maia Building, Babraham Research Campus
Cambridge
CB22 3AT UK
+44-122-3967316
www.cellgs.com

Cell Guidance Systems PODS™ platform technology utilizes a patented technology to produce polyhedrin crystals containing constrained target proteins. This production process results in proteins with significantly enhanced stability in storage and greatly extended release profiles.

CELL LINE GENETICS, INC. - STAND 300

510 Charmany Drive
Suite 254
Madison, WI
53719 U.S.A.
+1 608-441-8160
www.clgenetics.com

Cell Line Genetics (CLG) is the leading provider of characterization services for regenerative medicine, cancer and cell therapy research. Our services include multi-species karyotyping, cell line authentication, Fluorescence In-Situ Hybridization (FISH), Array CGH and custom assay development. An independent vendor for large academic institutions, biotech and pharmaceutical companies, CLG delivers high-quality, unbiased results with superior turnaround time.

CELL MICROSYSTEMS - STAND 622

2 Davis Dr
Research Triangle Park, NC
27709 U.S.A.
+1 252-285-9842
www.cellmicrosystems.com

Cell Microsystems brings innovation to single cell biology, cell culture, and cloning workflows. Our CellRaft™ technology enables users to image, sort, and isolate single cells or clonal colonies. By gently sorting on our CytoSort arrays, cells are more viable and have less perturbed phenotypes compared to traditional methods. Collect single cells of interest for downstream analysis or propagate on the array to generate clonal colonies.

CELL PRESS - STAND 801

50 Hampshire Street
5th Floor
Cambridge, MA
02139 U.S.A.
+1 617-386-2121
www.cell.com

Cell Press is proud to publish Stem Cell Reports, the journal from ISSCR. Visit Cell Press booth # 801 for the latest high-quality stem cell research! Pick up free journal copies, including Stem Cell Reports, Cell, Cell Stem Cell, and Cell Reports.

CELLBOX SOLUTIONS GMBH – SUP7

Englische Planke 8
Hamburg
23552 Germany
+49 40226316410
www.cellbox-solutions.com

Cellbox Solutions GmbH is a young technology company focusing on innovative logistic solutions for the global BioMedTech industry. The company, founded in 2016, is a spin-off from the Fraunhofer Research Institution for Marine Biotechnology and Cell Technology in Lübeck, Germany. Our portable CO2 incubator, the Cellbox, provides a safe environment for the transport of living cells and biological structures under laboratory conditions.

CELLINK - STAND 523

75 Kneeland St
Boston, MA
02111 U.S.A.
+1 833-CELLINK
www.cellink.com

CELLINK is the first bioink company in the world and the leading 3Dbioprinter provider focusing on the development and commercialization of bioprinting technologies that allow researchers to 3D print human organs and tissues for the development of pharmaceutical and cosmetic treatments. Founded 2016 and active in more than 45 countries, CELLINK is changing the future of medicine as we know it. To read more: www.cellink.com.

CORNING LIFE SCIENCES - STAND 825

836 North Street
Tewskbury, MA
01876 U.S.A.
+1 978-442-2288
www.corning.com

Corning Life Sciences' line of advanced cell culture surfaces, scalable vessel platforms, and cell culture media provide innovative solutions for stem cell research and 3D cell culture. Products include Matrigel® Matrix, novel animal-free surfaces for defined stem cell expansion, like rlaminin-521 vialed and pre-coated cultureware and Corning NutriStem® media for increased expansion.

CYTOSMART(TM) TECH - STAND 628

EMMASINGEL 33
Eindhoven
5611AZ Netherlands
+31 624707248
www.cytosmart.com

CytoSMART develops smart microscope systems powered by artificial intelligence and cloud computing enabling scientist all over the world to Reduce the Time To Discovery (TTD).

DISCOVER ECHO INC. - STAND 332

9530 Padgett Street
Suite 101
San Diego, CA
92126 U.S.A.
+1 858-429-9565
www.discover-echo.com

Echo is changing the way you view science.
Our cornerstone products, the Revolve and Rebel, combine the functionality of both Upright and Inverted microscopes. Our Microscopes also leverage tablet and cloud-based technologies to capture and manage image data – setting a new precedent in microscope usability and design.
You can configure your ideal microscope in minutes: discover-echo.com/build.

EMULATE, INC. - STAND 1124

27 Drydock Ave
5th Floor
Boston, MA
02210 U.S.A.
+1 224-430-4690
www.emulatebio.com

Emulate Inc. is a privately held company that creates living products for understanding how diseases, medicines, chemicals, and foods affect human health. Our Human Emulation System™ is comprised of Organ-Chips, instrumentation, and apps, and sets a new standard for recreating true-to-life human biology.

EPPENDORF - STAND 304

Eppendorf North America
102 Motor Parkway
Hauppauge, NY
11788 U.S.A.
+49 40538010
www.eppendorf.com

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

FROGGABIO - STAND 634

3790 Commerce Court Suite 600
Wheatfield, NY
14120 U.S.A.
+1 877-318-7277
www.froggabio.com

FroggaBio is a distributor of laboratory products, supply instruments, reagents and disposables. We serve customers within academic and industrial research institutes, biotechnology and pharmaceutical companies and hospitals. FroggaBio represents numerous companies exclusively allowing us to offer a comprehensive line of products in biological, chemical, and diagnostic fields at very competitive prices includes various OEM products. We maintain close contact with our customers and stay up to date on scientific developments by attending various local and international scientific conferences.

FUJIFILM CELLULAR DYNAMICS - STAND 421

525 Science Drive
Madison, WI
53711 U.S.A.
+1 608-310-5110
www.fujifilmcdi.com

FUJIFILM Cellular Dynamics, Inc. is a developer and supplier of human cells used in discovery, toxicity testing and regenerative medicine applications. Leveraging iPSC technology, FCDI is committed to advancing life science research and transforming the therapeutic development process to improve human health. The company's iCell® and donor-specific MyCell® Products are highly pure, highly reproducible, and available in industrial quantity required for drug and cell therapy development.

FUJIFILM IRVINE SCIENTIFIC - STAND 525

1830 E. Warner Avenue
Santa Ana, CA
92705 U.S.A.
+1 800-577-6097
www.irvinesci.com

FUJIFILM Irvine Scientific has been at the forefront of cell culture media development for more than 45-years. Possessing an unrivaled heritage of innovation, superior quality, and technical expertise, the company supplies the cell therapy, immunotherapy, biopharmaceutical, cytogenetic, and Assisted Reproductive Technologies (ART) industries with a range of advanced cell culture media products and expert development, optimization, and commercial manufacturing services.

HEALIOS K.K. - STAND 1128

Hamamatsu-cho 2-4-1
Minato-ku
Tokyo
105-6115 Japan
+81-357778308
www.healios.co.jp/en

Healios is a Japan-based, global leader in the regenerative medicine field. Healios has flourished through a combination of (i)leveraging Japan's progressive regulatory framework, (ii)fostering the development of the regenerative medicine value chain and adept sourcing of stem cell platform technologies both from within and outside of Japan. Further, Healios has built a robust pipeline consisting of various iPSC and somatic stem cell therapies.

HEALTHGEN BIOTECHNOLOGY CORP. - STAND 328

No. 666 Gaoxin Avenue
East Lake High-Tech Development Zone
Wuhan
430075 China
+86 02759403932-8012
www.oryzogen.net

Healthgen Biotech is focusing on developing and manufacturing a series of animal-free and safety products by using rice endosperm expression platform. Healthgen Biotech have achievements in developing and commercializing a series of products, including recombinant human serum albumin (OsrHSA), recombinant human basic fibroblast growth factor (OsrbFGF), recombinant human epidermal growth factor (OsrEGF), recombinant human insulin-like growth factor-1 (OsrIGF-1) .

HELLO BIO - STAND SUP 1

304 Wall Street
Princeton, NJ
08540 U.S.A.
+1 609-683-7500
www.hellobio.com

Say hello to prices up to 50% less than other suppliers! We aim to offer high quality stem call research tools at prices so low that as many researchers as possible will be able to afford them. Our range includes low cost high quality small molecule inhibitors including Y-27632, CHIR 99021, PD 0325901, SB, 431542, and more. Have you said hello yet? Visit our stand!

HEMACARE CORPORATION - STAND 535

8500 Balboa Boulevard
Suite 130
Northridge, CA
91325 U.S.A.
+1 877-310-0717
www.hemacare.com

Global leader in the customization of research use and GMP-compliant human-derived biological products and services supporting drug discovery and global cell therapy from process development through commercialization with apheresis collections, enabling customers to advance both autologous and allogeneic cellular therapies. Its network of FDA-registered, GMP/GTP-compliant collection centers ensure fresh donor material is available to customers and for use within HemaCare's GMP-compliant isolation laboratory.

ILLUMINA, INC. - STAND 203

5200 Illumina Way
San Diego, CA
92122 U.S.A.
+1 858-202-4500
www.illumina.com

A global genomics leader, Illumina provides comprehensive next-generation sequencing solutions to the research, clinical, and applied markets. Illumina technology is responsible for generating more than 90% of the world's sequencing data.* Through collaborative innovation, Illumina is fueling groundbreaking advancements in oncology, reproductive health, genetic disease, microbiology, agriculture, forensic science, and beyond.

INTEGRA BIOSCIENCES - STAND 627

2 Wentworth Drive
Hudson, NH
03051 U.S.A.
+1 603-578-5800
https://www.integra-biosciences.com/united-states/en

INTEGRA is a leading provider of high-quality laboratory tools for liquid handling and media preparation. We are committed to fulfill the needs of our customers in research, diagnostics and quality control within the life science and medical industry. Visit www.integra-biosciences.com to see our new automated sample processor, the ASSIST PLUS!

IOTASCIENCES - STAND SUP 10

Begbroke
Oxford
OX51PF United Kingdom
+44-1865-309630
www.iotasciences.com

Advancing cell biology with fluid-shaping technology

IXCELLS BIOTECHNOLOGIES USA, LLC – STAND 838

10340 Camino Santa Fe, Suite C
San Diego, CA
92121 U.S.A.
+1 858-412-5988
www.ixcellsbiotech.com

iXCells Biotechnologies is a San Diego based cell biology company offering high quality primary and iPSC-derived cells, custom cell services and disease models to the academic, biotech and pharma communities to accelerate the pace of drug discovery.

JELLAGEN - STAND 726

Jellagen, Unit G5,
Capital Business Park,
Cardiff
CF3 2PX UK
+44-333-3583299
www.jellagen.co.uk

Jellagen is a UK Marine Biotechnologies Company based in Cardiff, UK, whose strategic mission is to utilise sustainable marine species and natural resources to develop a range of scientific products. Currently, Jellagen offers products in its first range of 2D & 3D Cell Culture Reagents with the second phase to include medical devices and biomaterials in the areas of wound and regenerative medicine.

KATAOKA-SS AMERICA CORP. - STAND 725

21255 Hawthorne Blvd
Torrance, CA
90503 U.S.A.
+1 310-802-7180
www.kataoka-ss.co.jp/english

Kataoka Corp. has invented the world's first high-speed device to process stem cells from observation to unnecessary cell elimination by means of Kataoka's advanced laser technologies. We provide researchers and the pharmaceutical industry with the fastest and most advanced solution for improving the human life quality, which will contribute to a gigantic step in medicine.

KEYENCE CORPORATION - STAND 635

500 Park Blvd
Suite 500
Itasca, IL
60143 U.S.A.
+1 888-539-3623
www.keyence.com

KEYENCE Corporation specializes in microscope systems for high-resolution imaging, live-cell analysis, well-plate and slide screening, and cell quantification – all within a single, easy-to-use platform. With advanced software and automated operation, researchers can dramatically improve their workflow and research efficiency.

KUHNER SHAKER INC - STAND 727

299 Old County Road
Ste 7
San Carlos, CA
94070 U.S.A.
+1 650-595-1997
www.kuhner.com

Kuhner Shaker Inc is the leading developer and manufacturer of shaking machines for the international market. From bench top shakers to orbital shaking bioreactors, Kuhner offers machines of the highest quality. We endeavor to understand your science and cultivation needs to ensure solutions accelerating your time to market and elevating your results. We commit to earning our client's trust and establishing relationships for decades.

LEICA MICROSYSTEMS INC – STAND 623

1700 Leider Lane
Buffalo Grove, IL
60089 U.S.A.
+1 800-248-0123
www.leica-microsystems.com

Leica Microsystems develops and manufactures microscopes and scientific instruments for the analysis of microstructures and nanostructures. The company is one of the market leaders in compound and stereo microscopy, digital microscopy, confocal laser scanning microscopy, electron microscopy sample preparation, optical coherence tomography, and surgical microscopes.

LOGOS BIOSYSTEMS - STAND 326

7700 Little River Turnpike STE 207
Annandale, VA
22003 U.S.A.
+1 703-622-4660
www.logosbio.com

Logos Biosystems specializes in advanced imaging tools and technologies for diverse applications including basic research, quality control, and drug discovery. High content image acquisition and analysis is simplified with the CELENA X High Content Imaging System. Automated cell counters provide cell concentration and viability data with speed, accuracy, and reliability.

LONZA PHARMA & BIOTECH - STAND 301

14905 Kirby Drive
Houston, TX
77047 U.S.A.
+1 713-568-6190
www.pharma.lonza.com

From the building blocks of life to the final drug product, our solutions are created to simplify your outsourcing experience and provide a reliable outcome, when you expect it. We continuously invest to solve the current and future manufacturing challenges. Together, we can bring your next medicine to life.

MARY ANN LIEBERT, INC. - STAND 908

140 Huguenot Street
3rd Floor
New Rochelle, NY
10801 U.S.A.
+1 914-740-2100
www.liebertpub.com

Mary Ann Liebert, Inc. is a leading independent publisher known worldwide for its prescience and establishment of authoritative peer-reviewed journals, books, and trade publications in cutting-edge fields. Just one of our over 90 publications is Stem Cells and Development which is globally recognized as the trusted source for critical, even controversial coverage of emerging hypotheses and novel findings.

MATRIGEN - STAND 736

861 6TH AVE Ste 822
SAN DIEGO, CA
92101 U.S.A.
+1 949-229-3012
www.matrigen.com

Matrigen's expansive line of hydrogel-coated wells mimic the stiffness of biological tissues. Our aim is to make cell culture more physiologically relevant, yet practical and economical.

MATRIXOME - STAND 538

1-1-1 Senju Midori-cho, Adachi
Tokyo
120-8601 Japan
+81 38885184
www.nippi-inc.co.jp

Nippi/Matrixome is specialized to produce the extracellular matrix components and related proteins for clinical use as well as DDS and drug development. Our collagen (I, II, III, IV, & V), gelatin, laminin-E8 (511, 221, 411) substrates are also used for drug discovery, microfluidic organs-on-a-chip devices.

MAXWELL BIOSYSTEMS - STAND 435

Mattenstrasse 26
Basel
04058 Switzerland
+41-615-511070
www.mxwbio.com

MaxWell Biosystems provides advanced high-resolution electrophysiology platforms to facilitate detailed investigation of cells in vitro. MaxOne and MaxTwo allow stimulation and recording of every active cell on a dish at unprecedented spatio-temporal resolution. Every cell has a story to tell. MaxWell Biosystems aims to equip everyone with tools to easily track and discover cells' functionality and maturity.

MILTENYI BIOTEC GMBH - STAND 315

Friedrich-Ebert-Straße 68
Bergisch Gladbach
51429 Germany
+49 220483060
www.miltenyibiotec.com

Miltenyi Biotec provides products that advance biomedical research and cellular therapy. Our innovative tools support research from basic research to translational research to clinical application. Our 30 years of expertise includes immunology, stem cell biology, neuroscience, and cancer. Miltenyi Biotec has 2,500 employees in 28 countries.

MIMETAS - STAND 824

JH Oortweg 19
Leiden
2333CH Netherlands
+31 858883161
www.mimetas.com

MIMETAS enables scientists to develop better predictive human tissue and disease models with organ-on-a-chip technology. Our vision is to create the simplest device for the most complex 3D biology. The OrganoPlate® platform allows perfused 3D cell culture, membrane free co-culture and culture of tubules and vessels in a throughput never seen before.

MITSUI BUSSAN ELECTRONICS LTD. / HITACHI, LTD. - STAND 637

Shiba Park Bldg, A-10F, 4-1, Shibakoen 2-chome
Minato-ku
Tokyo
105-0011 Japan
+81 6504756693
www.en.mbel.co.jp

Mitsui Bussan Electronic Ltd.'s business is the global sales & marketing of the "Automated Cell Mass Culture Equipment" manufactured by Hitachi. Ltd. This equipment is the first equipment which has the necessary functions to comply with the regulation, GCTP (Good Gene, Cellular, and Tissue-based Products Manufacturing Practice) and can be used to culture automatically a mass of iPS cells for clinical use.

MOLECULAR DEVICES - STAND 407

3860 N. 1st Street
San Jose, CA
95134 U.S.A.
+1 800-635-5577
www.moleculardevices.com

At Molecular Devices, we enable our customers to unravel the complexity of biological systems. We provide platforms for high-throughput screening, genomic and cellular analysis, colony selection and microplate detection. These leading-edge products empower scientists to improve productivity and effectiveness, ultimately accelerating research and the discovery of new therapeutics.

MULTICHANNEL SYSTEMS - STAND 508

Aspenhaustrasse 21
Reutlingen
72770 Germany
+49 71219092528
www.multichannelsystems.com

As an innovator in microelectrode array (MEA) technology, we offer the largest selection of tools for the label-free study of electroactive cells (neurons, myocytes, and organoids). From single MEAs for method development to cost-effective, reusable Multiwell (24 and 96) MEA plates in higher-throughput applications (compound screening, iPSC differentiation), we help you discover faster while extending your research budget.

NACALAI USA INC - STAND 539

10225 Barnes Canyon Rd.
Suite A103
San Diego, CA
92121 U.S.A.
+1 858-404-0403
www.nacalaiusa.com

Nacalai USA provides the highest quality research products necessary for the Life Science research such as Cell Biology and Proteomics. The products are manufactured and packaged in the high level of manufacturing facilities in Japan.

NANOCELLECT BIOMEDICAL - STAND 625

7770 Regents Rd.
113390
San Diego, CA
92122 U.S.A.
+1 877-745-7678
www.nanocellect.com

NanoCellect's mission is to modernize cell based assays by providing innovative tools for cell analysis and sorting. Our microfluidic flow cytometry platforms enable biomedical scientists to analyze and sort cells required for drug discovery, diagnostics, and basic research.

NANOSURFACE BIOMEDICAL - STAND 323

4000 Mason Road, Suite 304
Seattle, WA
98195 U.S.A.
+1 800-913-4403
www.nanosurfacebio.com

NanoSurface Biomedical, Inc. specializes in producing easy-to-use biomimetic cell culture platforms for in vitro cell biology applications. NanoSurface helps scientists produce more physiologically relevant data by recapitulating the native extracellular matrix via structural (nanotopography), mechanical, and electrochemical cues. NanoSurface Biomedical, Inc. also excels in developing products and services for drug development, disease modeling, and fundamental cell biology research.

NEPA GENE - STAND 730

3-1-6 Shioyaki
Ichikawa
272-0114 Japan
+81 473067222
www.nepagene.jp/index2.html

Nepa Gene is a scientific manufacturer of state-of-the-art laboratory instruments such as transfection systems and cell fusion systems. Nepa Gene and Bulldog Bio will present the NEPA21 Electro-kinetic Transfection System. The NEPA21 can deliver CRIPSR/Cas9, plasmid DNA and RNA molecules into tissues, organs, cell lines, stems cells, and other primary cultured cells.

NEUROINDX, INC. - STAND 626

20725 S Western Ave
Ste 100
Torrance, CA
90501-1885 U.S.A.
+1 424-731-7512
www.neuroindx.com

NeuroInDx, Inc. (NDX) was founded in 2006 with a goal to develop new instrumentation and technologies for single cell isolation and complex tissue microdissection for a range of downstream applications including genomics and single cell analysis. Based on its patented cell and tissue acquisition technology (CTAS) NDX has developed a product line of versatile instruments that are compatible with a wide range of inverted microscopes.

NEXCELOM BIOSCIENCE – STAND 327

360 Merrimack Street
Lawrence, MA
01843 U.S.A.
+1 978-809-7320
www.nexcelom.com

Headquartered in Lawrence, MA, Nexcelom Bioscience LLC is a designer, manufacturer and marketer of innovative Cellometer and Celigo image cytometry products designed for cell analysis in life science and biomedical research.

NEXUS SCIENTIFIC - STAND SUP8

745 Atlantic Ave
8th Floor
Boston, MA
02111 U.S.A.
+1 857-264-6884
www.nexusscientific.com

Nexus Scientific is a Life Science Service business providing International Trade of Analytical products and Distribution of Innovative Life Science products in the U.S.A.. As the sole US distributor of the Swiss 3D Live Cell Imaging company Nanolive S.A., Nexus provides local access to their proprietary 3D Cell Explorer product family of holographic tomography microscopes and accessory items.

NIKON INSTRUMENTS INC. - STAND 322

1300 Walt Whitman Rd
Melville, NY
11747 U.S.A.
+1 631-547-8535
www.nikoninstruments.com

Nikon Instruments Inc. is the US microscopy arm of Nikon Healthcare, a world leader in the development and manufacture of optical and digital imaging technology for biomedical applications. Leveraging our expertise in optics, image acquisition, and image analysis, Nikon Instruments is able to offer a wide range of solutions for live cell imaging and quality control in the stem cell and regenerative medicine industry. For more information, visit https://www.microscope.healthcare.nikon.com/ or contact us at 1-800-52-NIKON.

NIPRO/CSTI - STAND 1038

3-3-13, toyosaki,kita-ku
Osaka
531-0072 Japan
+81 671765399
www.nipro.co.jp/en

The company has expanded the scope of its business from glass materials to medical devices and pharmaceutical products, in pursuit of technological innovation.

NORDMARK BIOCHEMICALS - STAND 636

Pinnauallee 4
Uetersen
25436 Germany
+49 4122 712 560
www.nordmark-biochemicals.com

Nordmark Biochemicals, a division of the pharmaceutical company Nordmark, offers products for cell isolation, including Collagenase NB 6 GMP Grade for stem cell isolation and animal-free Collagenase AF-1 GMP Grade. As the world's largest manufacturer of pharmaceutical collagenase, we provide translational - research and GMP Grade - collagenases and neutral proteases for research to clinic. Supporting documentation and access to Drug Master Files are available.

OLYMPUS AMERICA INC. - STAND 316

48 Woerd Avenue
Waltham, MA
02453 U.S.A.
+1 781-419-3900
www.olympus-lifescience.com

Olympus is dedicated to your work, vision and science. Through innovation and service, we seek to aide in your discoveries, advance your research, and inspire you to explore new possibilities. Stop by the Olympus booth today or visit www.olympus-lifescience.com.

ON-CHIP BIOTECHNOLOGIES CO., LTD. - STAND 516

203 Venture Port 2-24-16, Naka-cho, Koganei-shi
Tokyo
1840012 Japan
+81 423850461
www.on-chipbio.com

On-chip Biotechnologies is the manufacturer of the world's first microfluidic chip-based flow cytometer and cell sorter. The cell sorter, "On-chip Sort", has an exchangable and disposable microfluidic cartilage as its core. This innovative technology allows for damage-free cell and large cell cluster (e.g. spheroids) recovery in sterile condition which is not attainable with conventional sorters.

PAKAIR CARGO SPECIALISTS - STAND 610

59-61 Leveson St
North Melbourne
03051 Australia
+61 400671238
www.pakairusa.com

Pakair Cargo Specialists provide fully integrated Time Critical and Temperature sensitive Courier and Cargo solutions worldwide. From BioMedical samples to Controlled substances, or Hi-Tech parts & film rushes to Food samples, Pakair is the quality choice to ensure swift delivery, specific to your independent needs.

PBS BIOTECH, INC. - STAND 534

1183 Calle Suerte
Camarillo, CA
93012 U.S.A.
+1 805-482-7272
www.pbsbiotech.com

PBS Biotech's line of innovative single-use bioreactors can provide homogeneous, low-shear, and scalable mixing across a wide range of working volumes from 100 mL to 500 L. With unmatched expertise in process development for a variety of cell therapy applications, we can fulfill your research and manufacturing scale-up needs.

PEPROTECH, INC - STAND 501

5 Crescent Avenue
PO Box 275
Rocky Hill, NJ
08553 U.S.A.
+1 800-436-9910
www.peprotech.com

PeproTech creates the building blocks of your life science research by manufacturing high-quality products that advance scientific discovery and human health. Since 1988, PeproTech has grown into a global enterprise manufacturing an extensive line of Recombinant Human, Murine and Rat Cytokines, Animal-Free Recombinant Cytokines, Monoclonal Antibodies, Affinity Purified Polyclonal Antibodies, Affinity Purified Biotinylated Polyclonal Antibodies, ELISA Development Kits, Cell Culture Media Products and GMP Cytokines.

PHASE HOLOGRAPHIC IMAGING AB - STAND 337

Scheelevagen 22
Lund
22363 Sweden
+46 386081
www.phiab.se

The HoloMonitor platform offers you a powerful and unique portfolio of cell biological applications, non-invasive, quantifiable, inside your incubator.

PPA - STAND 316

124 Old Gray Station Rd
Suite 1
Gray, TN
37615 U.S.A.
+1 423-943-1603
www.pparesearch.com

PPA Research Group established in 2009 is a one stop provider for healthy, mobilized, diseased leukopacks, bone marrow, cord blood, PBMC's, Primary Cells and custom isolations. We are dedicated to first class customer service, high quality products, and the quickest lead times in the industry.

PROMOCELL GMBH - STAND 320

Sickingenstr. 63/65
Heidelberg
69126 Germany
+49 6221649340
www.promocell.com

PromoCell is a premier manufacturer of human stem & blood cells and primary cells with optimized cell culture media. Our products provide scientists with the most physiologically accurate models to obtain better results in their research. Our solutions are ethically approved and innovative. We own the entire development and manufacturing process. We share openly our cell culture knowledge, through our PhD-qualified cell culture experts.

PROTEINTECH GROUP INC. - STAND 839

5400 Pearl Street, ste 300
Rosemont, IL
60018 U.S.A.
+1 312-455-8498
www.ptglab.com

From our bench to your bench, Proteintech manufactures all and sells only its own high quality antibodies, proteins, ELISA kits and human cell-expressed proteins allowing for unique products with superb tech support. Visit www.ptglab.com to view thousands of publications and validation data using our products. Worldwide locations offer next-day delivery.

QKINE - STAND SUP 6

80 Tennis Court Road
Cambridge
CB2 1GA UK
+44-122-3491486
www.qkine.com

Qkine is a manufacturer of high quality growth factors and cytokines for stem cell, organoid and regenerative medicine applications. We are based in Cambridge, UK.

REGMEDNET - STAND 724

Unitec House, 2 Albert Place, Finchley Central
London
N3 1QB UK
+44-208-3716090
www.regmednet.com

RegMedNet is a community site that unites the diverse regenerative medicine community.

REPROCELL INC. - STAND 515

9000 Virginia Manor Rd.
Suite 207
Beltsville, MD
20705 U.S.A.
+1 301-470-3362
www.reprocell.com

REPROCELL is a worldwide leader in iPSC and drug discovery. Our products and services, from extensive human tissue network, RNA-based reprogramming to CRISPR/Cas9 genome editing support every step of translational research. Our contract research organization expertise for neural and 3D tissue models strives to provide unrivalled solutions for pre-clinical testing.

ROCKEFELLER UNIVERSITY PRESS - STAND 809

950 Third Ave.
Floor 2
New York, NY
10022 U.S.A.
+1 212-327-8000
www.rockefeller.edu

Rockefeller University Press publishes Journal of Cell Biology (JCB), Journal of Experimental Medicine (JEM), and Journal of General Physiology (JGP), and co-publishes Life Science Alliance. RUP journals are committed to quality and integrity in scientific publishing.

ROKIT HEALTHCARE - STAND 325

B-1106, Gabul Great Valley
32, Digital-ro-9-gil
Seoula, Korea 08512
www.rokithealthcare.com
+82 10-3912-5410

ROKIT HEALTHCARE is a leading regenerative medicine biotechnology company based in South Korea. We are committed to pioneering medical treatments based on the principles of 3D bioprinting and autologous stem cell use to regenerate and restore functions of human tissues and organs. To read more: rokithealthcare.com

RUCDR INFINITE BIOLOGICS - STAND 900

145 Bevier Rd
Piscataway, NJ
08854-8082 U.S.A.
+1 848-445-7195
www.rucdr.org

RUCDR Infinite Biologics is the largest academic based repository in the US. We offer a wide range of pluripotent stem cell services and are home to several large cell line collections that are available to researchers world-wide.

SARTORIUS STEDIM BIOTECH - STAND 312

Grantham Close
York Way
Hertfordshire
SG8 5WY UK
+44-1763-227200
www.sartorius.com

We deliver and implement rapid and cost-effective Biomanufacturing solutions from early phase development through scale-up to commercial manufacturing. Benefit from the most comprehensive bioprocess technology portfolio coupled with our expertise in Single-use bioprocess engineering. Our global bioprocess teams are available to discuss your process development and manufacturing requirements.

S-BIO - STAND 415

20 Executive Drive
Hudson, NH
03051 U.S.A.
+1 603-546-6800
www.s-bio.com

S-BIO specializes in providing quality 3D cell culture labware to advance research and development in Regenerative Medicine, Oncology and Drug Screening. PrimeSurface® culture ware are ultra low attachment (ULA) dishes and plates that promote scaffold free, self-assembly of spheroid formation. ProteoSave product line prevents non-specific sticking of sample to the tubes thus avoiding sample loss. S-BIO also provides glycan characterization tools and kits for biotherapeutics and stem cell characterization.

SCIENCE/AAAS - STAND 510

1200 New York Avenue, NW
Washington, DC
20005 U.S.A.
+1 202-326-6417
www.aaas.org

Since 1848, AAAS and its members have worked together to advance science and serve society. As part of these efforts, AAAS publishes Science, a multidisciplinary peer-reviewed journal, Science Advances, an open-access online journal, Science Immunology, Science Robotics, Science Signaling, and Science Translational Medicine. AAAS also offers programs focused on science policy, international cooperation, science education, diversity, and career development for scientists.

SCIENCELL RESEARCH LABORATORIES - STAND 305

1610 Faraday Ave
Carlsbad, CA
92208 U.S.A.
+1 760-602-8549
www.sciencellonline.com

ScienCell is the world's largest cell provider. We enable the scientists of today to discover the science of tomorrow by providing a variety of high-quality normal human and animal cells, cell culture media and reagents, gene analysis tools, cell-derived molecular biology products, cell-based assay kits, and stem cell products for the research community.

SHANGHAITECH UNIVERSITY - STAND 1010

No. 393, Middle Huaxia Road
Shanghai
201210 China
+1 862-068-5017
www.shanghaitech.edu.cn

SLST aims to develop into a world-class, research-oriented school in life science and technology, drawing strength not only from its outstanding full-time faculty but also from two affiliated world-class biomedical research institutes at ShanghaiTech.

SHENANDOAH BIOTECHNOLOGY - STAND 512

101 Camars Dr.
Warwick, PA
18974 U.S.A.
+1 877-613-6020
www.shenandoah-bt.com

Shenandoah Biotechnology is a US-based recombinant protein manufacturer focused on producing a catalog of cytokines, growth factors and chemokines. Shenandoah provides lot-specific data for all products prior to purchase. Shenandoah also offers custom protein and bulk production services.

SINO BIOLOGICAL - STAND 734

1400 Liberty Ridge Drive
Suite 101
Chesterbrook, PA
19087 U.S.A.
+1 215-583-6595
www.sinobiological.com

Sino Biological offers a comprehensive set of premium quality reagents, all of which are produced in-house and cover a broad range of life science research and drug development. We also provides one-stop services for protein and antibody discovery, R&D, production and commercialization.

SPEX SAMPLEPREP - STAND 514

65 Liberty Street
Metuchen, NJ
08840 U.S.A.
+1 732-623-0465
www.spexsampleprep.com

The SPEX SamplePrep Geno/Grinder® is a high throughput homogenizer and cell lyser, it is designed for fast and effective DNA/RNA extraction. For temperature sensitive samples Kryo-Tech accessories are available. Samples are homogenized in titer plates or sample tubes up to 50 mL. Our Freezer/Mills® are designed for cryogenic grinding of tough or fibrous samples. Samples are ground in sealed vials minimizing cross contamination.

SPRINGER NATURE - STAND 910

One New York Plaza
Suite 4600
New York, NY
10004 U.S.A.
+1 212-726-9200
www.springernature.com

Springer Nature is one of the world's leading global research, educational and professional publishers, home to an array of respected and trusted brands providing quality content through a range of innovative products and services. Springer Nature is the world's largest academic book publisher and numbers almost 13,000 staff in over 50 countries. www.springernature.com.

STEM CELLS JOURNALS - STAND 911

318 Blackwell St, Ste 260
Durham, NC
27701 U.S.A.
+1 919-680-0011
www.StemCellsJournals.com

STEM CELLS and STEM CELLS Translational Medicine publishes high-impact articles in the areas of stem cell research and regenerative medicine. STEM CELLS focuses on novel and mechanistic basic stem cell biology findings. 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 to improve patient outcomes.

STEM GENOMICS - STAND 526

Institute for Regenerative Medicine & Biotherapy - Hospital Saint Eloi
80 avenue Augustin Fliche
Montpellier
34090 France
+33 642-112424
www.stemgenomics.com

Stem Genomics provides specific services to assess the genetic integrity of stem cells. We propose a new test that allows detecting more than 90% of recurrent genomic abnormalities in pluripotent stem cells, the most worrying ones. The iCS-digitalTM test (in Culture Supernatant-digital PCR test) is a rapid, sensitive, high-resolution, simple to interpret and cost-effective assay for the routine testing of your stem cells in culture. This new test is particularly suitable for screening genetically stable clones, for instance patient-derived induced pluripotent stem cell clones after reprogramming or after CRISPR-based editing.

STEMBIOSYS, INC. - STAND 616

3463 Magic Drive
Ste. 110
San Antonio, TX
78229 U.S.A.
+1 210-877-9323
www.stembiosys.com

StemBioSys, Inc., a privately held, San Antonio-based biomedical company, manufactures and develops innovative, advanced stem cell technologies to meet the promise of regenerative medicine. Market demand in stem cells has enabled StemBioSys to turn a single cell expansion platform, CELLvo™ Matrix, licensed from UT Health, into an extended line of high quality cells and cell expansion tools.

STEMCELL TECHNOLOGIES INC - STAND 615

1618 Station St
Vancouver, BC
V6A1B6 Canada
+1 604-675-7575
www.stemcell.com

At STEMCELL, science is our foundation. Driven by our mission to advance research globally, we offer over 2,500 tools and services supporting discoveries in areas such as stem cell research, regenerative medicine, immunotherapy, and disease research. With innovative culture media and techniques such as genome editing and 3D culture, we're helping scientists accelerate the pace of discovery. Inspired by knowledge, innovation, and quality, we are Scientists Helping Scientists.

STEMEXPRESS, LLC - STAND 321

1743 Creekside Drive
Suite 200
Folsom, CA
95630 U.S.A.
+1 530-626-7000
www.stemexpress.com

StemExpress provides leading biomedical researchers around the world human hematological samples at life-changing speed. Our nationwide procurement network and state-of-the-art collection centers ensure StemExpress can reliably obtain the highest quality and most varied source material, including Leukopaks, peripheral and maternal blood, and bone marrow. Isolated cell lines are purified less than 24 hours from procurement, guaranteeing the purity, viability, and quality you need.

SYNTHEGO - STAND 221

3696 Haven Ave.
Suite A
Redwood City, CA
94063 U.S.A.
+1 650-224-5459
www.synthego.com

Synthego is the genome engineering innovation company. The company's automated, full stack genome engineering platform enables broader access to CRISPR to accelerate basic scientific discovery, uncover cures for diseases, and develop novel synthetic biology applications. Headquartered in Silicon Valley, Synthego is used by scientists from the largest global biotechnology companies and global biology universities to unlock the potential of gene editing.

THE COMPANY OF BIOLOGISTS - STAND 811

Bidder Building
Station Road, Histon
Cambridge, Cambs
CB24 9LF UK
+44-122-3632878
www.biologists.com

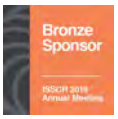
The Company of Biologists is a not for profit publishing organisation dedicated to supporting and inspiring the biological community. The Company publishes five specialist peer-reviewed journals: Development, Journal of Cell Science, Journal of Experimental Biology, Disease Models & Mechanisms and Biology Open. It offers further support to the biological community by facilitating scientific meetings and communities, providing travel grants for researchers and supporting research societies.

THE EUROPEAN COLLECTION OF AUTHENTICATED CELL CULTURES (ECACC) - STAND 728

Culture Collections (PHE)
Manor Farm Rd
Salisbury,
SP4 0JG UK
+44-198-0612462
www.phe-culturecollections.org.uk/ECACC

The European Collection of Authenticated Cell Cultures (ECACC) is one of four Culture Collections of Public Health England. We supply authenticated and quality controlled cell lines, nucleic acids and induced Pluripotent Stem Cells (iPSCs). Over the last 30 years ECACC has expanded and diversified to become one of the premier collections of authenticated cell cultures in the world.

THE NEW YORK STEM CELL FOUNDATION RESEARCH INSTITUTE - STAND 404



619 West 54th St.
3rd Floor
New York, NY
10019 U.S.A.
+1 212-787-4111
www.nyscf.org

The New York Stem Cell Foundation (NYSCF) Research Institute accelerates cures for the major diseases of our time through stem cell research and technology innovation. The NYSCF Global Stem Cell ArrayTM, a one-of-a-kind automated platform for iPSC reprogramming, has generated thousands of patient lines used by laboratories worldwide, including in NYSCF's own research on neurodegenerative diseases, cancer, diabetes, and tissue engineering. Independent and privately funded, NYSCF takes a "team science" approach, collaborating with and funding leaders throughout the biomedical research community to advance the understanding and treatment of disease.

THERMO FISHER SCIENTIFIC - STAND 1121

5781 Van Allen Way
Carlsbad, CA
92008 U.S.A.
+1 760-603-7200
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.

TRIFOIL IMAGING – STAND 939

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

TriFoil Imaging, based in Chatsworth, CA, is a technological leader in the preclinical imaging industry. TriFoil Imaging offers the InSyTe FLECT/CT, a preclinical multi-modality imaging platform that combines the strengths of optical imaging in the form of fluorescence tomography with X-ray CT. The InSyTe FLECT/CT acquires CT and fluorescence data in full 360°, an industry-first, for true 3D, complete angle fluorescence tomographic imaging.

UNION BIOMETRICA, INC. - STAND 720

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

Union Biometrica Large Particle Flow Cytometers automate the analysis and sorting of objects that are too big / fragile for traditional cytometers. Examples include large cells / cell clusters, cells in/on beads and small model organisms. COPAS and BioSorter models cover the full 10-1500um range of particle sizes. The new COPAS VISION cytometer adds brightfield image capture of selected sample objects.

UPM-KYMMENE CORPORATION - STAND 426

Alvar Aallon katu 1
PO Box 380
Helsinki
00101 Finland
+358 20415111
www.upmbiomedicals.com

UPM provides bio-friendly hydrogels extracted from birch wood, sourced from sustainably managed forests. GrowDex® is ready to use, room temperature stable hydrogel that has tunable stiffness and allows easy cell recovery with a 1 step process. Guaranteed batch consistency and versatility makes GrowDex the perfect hydrogel for 3D cell culture, organ-on-a-chip models, personalised medicine, drug release studies, 3D printing and drug discovery.

USC STEM CELL - *Meeting Co-Sponsor* - STAND 805

1425 San Pablo Street
Los Angeles, CA
90033 U.S.A.
+1 323-442-8080
www.stemcell.keck.usc.edu

The USC Stem Cell initiative unites more than 100 faculty members from disciplines across the University of Southern California. The researchers collaborate to leverage the power of stem cells to develop therapies of the future. At the hub of this effort is the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at USC, which hosts world-class scientists and shared research facilities.

UTSA BRAIN HEALTH CONSORTIUM - STAND 807

1 UTSA Circle
SRL1.126
San Antonio, TX
78249 U.S.A.
+1 210-458-7024
www.utsa.edu/bhc

The Brain Health Consortium (BHC) is a bold new, interdisciplinary research initiative at the University of Texas at San Antonio which uses the power of stem cells to discover precision therapeutics. A shared resource of the BHC is the Stem Cell Core, the first human induced pluripotent stem cell core in the University of Texas system, open to researchers across the state and beyond.

VECTORBUILDER INC - STAND 201

150 Pine Forest Dr., Ste 803
Shenandoah, TX
77384 U.S.A.
+1 800-517-2189
www.vectorbuilder.com

VectorBuilder is a revolutionary online platform aimed at providing researchers with one-stop solutions to all their vector design, custom cloning and virus packaging needs.

WICELL - STAND 1021

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

As a recognized world leader in pluripotent stem cell banking, distribution, and characterization services, WiCell provides the stem cell community with high-quality cell lines as well as accurate and reliable characterization testing.

WILEY - STAND 1011

111 River Street
Hoboken, NJ
07030 U.S.A.
+1 201-748-6000
www.wiley.com

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

WORTHINGTON ENZYMES - STAND 438

730 Vassar Ave
Lakewood, NJ
08701 U.S.A.
+1 732-942-1660
www.Worthington-Biochem.com

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

XYLYX BIO, INC. - STAND 528

760 Parkside Avenue
Suite #321
Brooklyn, NY
11226 U.S.A.
+1 212-689-9005
www.xylyxbio.com

Xylyx Bio is harnessing the power of tissue-specific extracellular matrix for both cell culture and tissue regeneration. Xylyx Bio's tissue-specific ECM substrates support cell culture models that are significantly more predictive of human physiology, thus facilitating acceleration of drug discovery and development.

THURSDAY, 27 JUNE

CELL GUIDANCE SYSTEMS

Room 408B, Level Two
8:00 AM - 8:30 AM

A NOVEL SUSTAINED RELEASE GROWTH FACTOR TECHNOLOGY FOR IMPROVED QUALITY IN STEM CELL DIFFERENTIATION AND ORGANOID CULTURE

Christian Pernstick, *PhD, Cell Guidance Systems, UK*

Stem cell culture and differentiation protocols are challenging and generally require a significant amount of time and reagents. One of the main issues is instability, i.e. the relatively short half-live of growth factors, which limit their use both in the lab and during the transition to the clinic. In collaboration with Kyoto Institute of Technology, we developed a novel sustained release growth factor technology which encapsulates growth factors in a protein shell, protecting and preserving their function. PODS® (POlyhedrin Delivery System) crystals are produced in insect cells by co-expression of polyhedrin protein with a cargo protein. Highly stable, PODS® crystals degrade slowly, resulting in steady release of embedded proteins over several weeks. Here, we outline how PODS® crystals can be applied in 3D cell differentiation as well as in culturing healthier and physiologically more relevant organoids.

UNION BIOMETRICA

Room 502, Level Two
8:00 AM - 8:30 AM

AUTOMATION FOR ANALYSIS, IMAGING, AND HANDLING OF CELL CLUSTERS, SPHEROIDS, AND ORGANOIDS IN STEM CELL RESEARCH

Rock Pulak, PhD, *Union Biometrica, Inc.***, USA**

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 some of which are studied by stem cell researchers. Sample types include embryoid bodies, neurospheres and other spheroids, and organoids. Flow cytometry data, Profiles and brightfield images of the sample constituents are collected for analysis and used to make sorting decisions. 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.

AJINOMOTO COMPANY, INC.

Room 403A, Level One
8:00 AM - 8:30 AM

DEVELOPING THE NEXT GENERATION OF IPSC CELL-BASED ADOPTIVE CELL THERAPY

Raul Vizcardo, PhD, *Surgery Branch, National Cancer Institute, NIH Center for Cell-Based Therapy, USA*

Hajime Ohnuki, *Ajinomoto Co., Inc., USA*

T cells are potentially curative for patients with metastatic cancer, but many patients have T cells that are 'terminally differentiated', a condition associated with treatment failure. We have observed that less differentiated T cells have a greater capacity to proliferate, persist and destroy large metastatic cancer deposits. Advances in regenerative medicine might allow the generation of rejuvenated T cells from induced pluripotent stem cells (iPSC). Previously reported rejuvenated T cells have limited tumor-specificity but also exhibit unconventional and NK cell-like properties demonstrating lineage diversion into alternative lymphoid development pathways, with unknown consequences for their safety and efficacy. Recently, by developing a novel 3D thymic culture system we successfully generated murine 'iPSC-derived thymic emigrants'(iTE). iTE are antigen specific CD8αβ+ T cells with phenotypic and functional characteristics very similar to natural naïve CD8αβ+ T cells, including vigorous expansion and anti-tumor activity. Although many milestones remain, our data show that 'Next-Gen' autologous tumor-specific T cells can realistically be generated from iPSC using 3D thymic organ tissue. In this session, we will show our current efforts to generate tumor antigen-specific T cells from human iPSC to treat patients with metastatic cancer because iPSC-derived T cells have unlimited capacity for proliferation, persistence and anti-tumor activity.

MOLECULAR DEVICES

Room 403B, Level Two
8:00 AM – 8:30 AM

FUNCTIONAL AND MECHANISTIC NEUROTOXICITY PROFILING USING HUMAN IPSC-DERIVED NEURAL 3D CULTURES

Cassiano Carromeau, PhD, *StemoniX, USA*

Human induced pluripotent stem cell (hiPSC)-based three dimensional (3D) platforms enable greater physiological relevance, improving performance in drug discovery and toxicology applications. These complex, biologically relevant, and predictive cell-based assays are ideal for rapidly screening environmental toxins and chemical compounds. In this Innovation Showcase, we will describe how we used the StemoniX microBrain 3D platform, a high throughput screening system comprised of human iPSC-derived homogenous 3D

neural spheroids, to screen a diverse 91 compound-library from the National Toxicology Program. Each uniform spheroid has a fully developed network of cortical neurons and astrocytes co-matured from a single donor source. Immunocytochemistry indicates that the neurons and astrocytes display key markers of cellular identity and maturity, such as synaptic proteins and glutamate transporters. With its fully functional glutamatergic and GABAergic circuitry, microBrain 3D spheroids present highly synchronized, quantifiable, robust, and uniform spontaneous calcium oscillations that can be easily reproducibly modified and screened using fluorometric imaging, kinetic high throughput readers plate readers such as the FLIPR Tetra® High-Throughput Cellular Screening System, and, at the cellular level with high-content imaging systems such as the ImageXpress® Micro Confocal High-Content Imaging System.

EPPENDORF AG

Room 408A, Level Two
8:00 AM - 8:30 AM

SMART STEM CELL CULTIVATION- A SYNTHETIC READY-TO-USE SURFACE FOR HUMAN IPS CELLS

Nadine Mellies, PhD, *Eppendorf AG, Germany*

You cultivate hiPSCs, but you are tired of lot-to-lot coating variations, tedious preparation, and increased contamination risk? Especially biological coatings may negatively impact downstream applications due to the presence of undefined ECM components and growth factors. Maybe you are also struggling with reproducibility of data due to an inherently complex and non-defined growth surface. Have you ever thought about a pre-coated synthetic surface for stable long-term expansion of stem cells? We invite you to hear about the development of an animal-component-free, ready-to-use growth surface. It is specifically designed for optimal culture of human PSCs, MSCs, and other ECM dependent primary cells. The FN1 motifs matrix is a completely synthetic coating to promote attachment and robust expansion of hiPSCs. Cells can be grown either in clumps or as homogenous monolayer enabling full applicational flexibility. Due to its compatibility with various SF, XF, and ACF media this innovative surface brings you closer to a complete defined culture system and enables you to study proliferation, self-renewal, and differentiation with a high level of consistency and reproducibility. Join our session to get to know FN1 motifs for your hiPSC expansion and differentiation, while enjoying the provided yummy breakfast.

NOVO NORDISK

Concourse E, Level One
8:00 AM – 8:30 AM

STEM CELL R&D AT NOVO NORDISK A/S

Jacob Sten Peterson, *Novo Nordisk A/S, Denmark*

Novo Nordisk has been active in stem cell research for over 20 years.

We are now looking to expand our project portfolio with potential therapies that will make a difference to patients suffering from serious chronic diseases. We are interested in, therapeutic programs at any stage, differentiation protocols for serious chronic diseases, cell encapsulation technologies, cell engraftment technologies, and other technologies to support the use of cell therapy. We can offer access to world class stem cell research facilities, production of fully differentiated, progenitor and mesenchymal cells based on our proprietary hESC technology platform, an agile Stem Cell R&D Transformational Research Unit, longstanding expertise in GMP cell production a fully GMP compliant hES cell lineand immune evasive cells.

ROKIT HEALTHCARE

Room Concourse F, Level One
8:00 AM – 8:30 AM

WHOLE HUMAN EXTRACELLULARMATRIX (HUMATEIN) AS A POTENT MULTI-PURPOSE MATERIAL FOR STEM CELL AND CLINICAL APPLICATIONS OF BIOPRINTING

Joshua Jaeyun Kim, *Director of R&D, ROKIT, Inc., Korea*

ROKIT HEALTHCARE is a leading regenerative medicine biotechnology company based in South Korea. We are committed to pioneering medical treatments based on the principles of 3D bioprinting and autologous stem cell use to regenerate and restore functions of human tissues and organs. To read more: rokithealthcare.com

MILTENYI BIOTEC GMBH

Room 408A, Level Two
11:30 AM - 12:30 PM

A THERAPY FOR PARKINSON'S DISEASE: LATEST CLINICAL RESEARCH HIGHLIGHTS AND CONCEPTS FOR MANUFACTURING OF ATMPS

Daisuke Doi, ND, PhD, *Department of Clinical Application, Center for iPS Cell Research and Application (CiRA), Kyoto, Japan*

Sebastian Knoebel, *Manager R&D, Miltenyi Biotec GmbH, Germany*

Cell therapy for Parkinson's disease (PD) based on induced pluripotent stem cell (iPSC)–derived products has finally reached clinical trials. Daisuke Doi will give an update on latest developments in the first iPSC–based clinical trial for PD in Japan. He will specifically discuss the use of the MACSQuant® Tyto®, a microfluidic and closed-system cell sorter, for selection of early dopaminergic (DA) progenitors as part of the manufacturing protocol. Sebastian Knoebel will highlight recent developments of the automated manufacturing platform for ATMPs, the CliniMACS Prodigy®. The new CliniMACS Prodigy Adherent Cell Culture System meets the needs for automated and scalable cell manufacturing. A tubing set, providing a functionally closed and sterile system, a software package adapted for adherent cells, together with high-quality QC and cell culture reagents constitute major advances for development and scaling of cell manufacturing processes. Applications include PSC expansion, differentiation into DA progenitors and cardiomyocytes, and MSC isolation from bone marrow plus subsequent cultivation.

BIOLAMINA

Room 403B, Level Two
11:30 AM - 12:30 PM

BIOLOGICALLY RELEVANT CELL CULTURE - ADVANCES IN TRANSLATIONAL RESEARCH FOR ALS, PARKINSON'S AND CARDIOVASCULAR DISEASES

Michal Izrael, PhD, *Kadimastem Ltdm, Israel*

Malte Tiburcy, MD, *University Medical Center Göttingen, Germany*

Alessandro Fiorenzano, PhD, *Lund University, Sweden*

Tissues are 3D formations of cells integrated in an extracellular matrix (ECM) with specific sites for cell anchorage, giving positional and instructive information that regulates cell behavior. A vast number of publications in the last decades have proven how the reciprocal interaction between the ECM, cytoskeleton and nuclear matrix exert a physical and chemical influence over the cellular gene expression. Thus, to culture authentic cells from which real biological questions can be answered, environmental context is pivotal. Human recombinant laminins are biologically relevant ECM protein substrates that can be used to mimic the in vivo cell niche in vitro. The laminin 521 isoform is a critical factor supporting pluripotent stem cells in culture and, given the right context, also provides support for differentiated cell types. Here, we welcome three collaborators and customers to tell the story of their advances in translational research. These are the topics: 1) THE ROAD TO CLINIC: SAFETY AND EFFICACY OF HUMAN EMBRYONIC STEM CELLS DERIVED ASTROCYTES FOLLOWING INTRATHECAL TRANSPLANTATION IN SOD1G93A AND NSG ANIMAL MODELS 2) GMP-COMPATIBLE ENGINEERED HUMAN MYOCARDIUM 3) IDENTIFICATION AND CHARACTERIZATION OF MATURE DOPAMINERGIC NEURON SUBTYPES AT SINGLE-CELL RESOLUTION IN HUMAN VENTRAL MIDBRAIN-PATTERNED ORGANOIDS

MAXWELL BIOSYSTEMS

Room 408B, Level Two
11:30 AM - 12:30 PM

HUMANAN IPSCS FOR CNS DRUG DISCOVERY – FUNCTIONAL PHENOTYPE CHARACTERIZATION AND NOVEL BIOMARKERS BY HIGH-RESOLUTION MICROELECTRADE ARRAY (MEA) TECHNOLOGY

Marie Obien, PhD*, Maxwell Biosystems, Switzerland*

Michele Fiscella, PhD, *Maxwell Biosystems, Switzerland*

We will introduce MaxTwo, the first high-throughput electrophysiology platform using high-resolution microelectrode array (MEA) technology. The platform allows access to individual cells simultaneously through 26'400 electrodes. The MaxTwo System includes "MEA Assays" that are quick and easy to execute towards obtaining high-quality results. This platform can be used to characterize iPSC-derived and primary neuron cultures (2D and 3D), organoids, cardiomyocytes, and muscle cells.We will present techniques to dissect the functional phenotype of different human iPSC-derived neurons, namely, dopaminergic neurons, glutamatergic neurons, and motor neurons. We will also show comparisons between healthy and disease models of the said neuron types. We will show how the activity of single neurons can be isolated and studied, together with subcellular details, such as the propagation of action potentials along single axons. These parameters can be used as functional readouts for evaluating the effects of compounds on single neuron and network activity.

STEMCELL TECHNOLOGIES INC.

Concourse E, Level One
11:30 AM - 12:30 PM

ORGANOID CULTURE EVOLUTION: ADVANCED CULTURE SYSTEMS ENABLING THE NEXT GENERATION OF ORGANOID APPLICATIONS

Ryan Condor, PhD, *STEMCELL Technologies Inc., Canada*

Organoid cultures have redefined the limits of the biological data that can be obtained in vitro. The past decade has seen development of organonid systems modeling a wide variety of tissues. Concurrently, researchers spanning fields have refined and adapted organoid cultures to better address their research questions. This session will give an overview of some of the most impactful applications and adaptations of organoid cultures and the methods and reagents to generate these in vitro models. Straight-forward generation of intestinal monolayers from organoids, differentiation of stem and progenitor cell-enriched organoids, culture of cancer organoids, and culture of organoids as spatially organized arrays will be discussed. A further focus will cover how organoids derived from adult tissue and hPSCs across all three germ layers are used to address questions ranging from disease mechanisms to response to pharmaceutical exposure. We will highlight available and upcoming optimized organoid media and protocols from STEMCELL Technologies that allow researchers to focus on their scientific questions, rather than establishing, maintaining or trouble-shooting their culture systems.

BIO-TECHNE

Concourse F, Level One
11:30 AM - 12:30 PM

PIONEERING SOLUTIONS FOR CELL AND GENE THERAPY MANUFACTURING - FROM GMP ANCILLARY MATERIAL TO PRODUCT ANALYSIS

Scott Schachtele, PhD, *Bio-Techne, USA*

As clinical trials for cell and gene therapies continue to show promise, the cell therapy community is dedicating more attention toward identifying innovative cell manufacturing technologies that can maintain product efficacy, decrease production time, and scale supply to meet commercial demand. This entails determining stages of the production workflow where optimization is necessary, qualifying new technologies that improve that stage of the workflow, and establishing supplier relationships to secure raw materials for scale-up. During this session we will introduce Bio-Techne as an innovative solutions provider for regulatory-compliant raw materials and instrumentation across the ex vivo manufacturing workflow for stem cell and immune cell therapies. The session will focus on: 1) manufacturing process optimization during ex vivo expansion, 2) novel tools for cell culture optimization (Cloudz™ Activation Kits, GMP small molecules) and cell characterization (Milo™ Single-cell Western and Simple Plex™ Immunoassay), and 3) considerations for raw material sourcing, including GMP small molecules and proteins.

FUJIFILM IRVINE SCIENTIFIC

Room 403A, Level Two
11:30 AM - 12:30 PM

UNDERSTANDING THE USE OF CANCER STEM CELLS IN CELL THERAPY

Vanda Lopes PhD, *FUJIFILM Irvine Scientific, USA*

Cancer is a devastating disease and a large effort has been made to develop cancer therapies. Immunotherapy has been the focus of extensive research and recently two T cell based therapies have been made available in the market. Despite the promising results, advances in the understanding of cancer biology and drug testing will continue to be crucial. Cancer stem cells (CSC), or cancer initiating cells, have been identified as cells that lead to tumor initiation and therapy failures. They are usually refractory to the most commonly used cancer therapies and their ability to self-renew, tumor initiating ability and differentiation potential lead to disease recurrence. It is thus crucial to understand CSC cell biology and develop effective strategies that target these cells. As with most of the adult stem cell populations, CSC are typically present in small numbers and require expansion and 3D structure formation for effective in vitro studies and drug development. FUJIFILM Irvine Scientific has developed a serum-free, cGMP solution that allows the expansion and formation of cancer initiating cell tumorspheres. By following a rational design media development and extensive know-how we have eliminated the need for serum in the culture process. Serum-free solutions will allow for a standardization of results among different laboratories, and provide a consistent performance product. In this presentation we will introduce our PRIME XV ® Tumorsphere SFM. We will also introduce other PRIME XV solutions that target cancer drug discovery and immunotherapy.

THERMO FISHER SCIENTIFIC

Room 502, Level Two
11:30 AM - 12:30 PM

IMPROVING HPSC-DERIVED MODELS: OPTIMAZATION OF CULTURE METHODS FOR GENE EDITING AND DISEASE MODELING USING ORGANOIDS

Madel Durens, PhD, *Hussman Institute for Autism, Baltimore, USA*

Yi-Hsien Chen, PhD, *Washington University School of Medicine, USA*

The availability of human pluripotent stem cells (hPSCs) and the ability to reliably manipulate these cells to achieve more physiologically relevant models has revolutionized disease modeling and research. In our first presentation, Dr. Yi-Hsien Chen will compare culture systems for single-cell cloning and expansion of hPSCs after genome editing and single cell sorting. Dr. Chen will describe how an optimized culture system for this application has enabled his ongoing research through workflow simplification. Our second presentation will focus on the derivation and subsequent characterization of iPSC neuronal organoids generated from individuals with Autism Spectrum Disorder (ASD). In this talk, Dr. Madel Durens will describe optimal culture conditions to generate neuronal organoids and the use of high content imaging (HCI) and multi-electrode array (MEA) to screen for phenotypes in idiopathic autism. Together, these talks aim to describe best in class culture methods for today's applications by reducing variability and ultimately enabling high throughput assay systems for drug discovery applications.

FRIDAY, 28 JUNE

CELL MICROSYSTEMS, INC.

Room 403A, Level Two
8:00 AM - 8:30 AM

HIGH VIABILITY CLONAL COLONY PROPAGATION OF STEM CELLS USING THE CELLRAFT AIR SYSTEM

Nick Trotta, PhD*, Cell Microsystems, Inc., USA*

Contemporary stem cell workflows often rely on isolating single cells for either single cell molecular analysis or clonal colony propagation. Due to stem cell-specific viability properties, isolating single cells remains a bottleneck in analytical workflows. To eliminate these cell biology limitations, Cell Microsystems has developed the CellRaft AIR System. The AIR System allows automated imaging of thousands of individual cells on a single cell culture consumable, the CytoSort Array. CytoSort Arrays come in a range of forms tailored to various laboratory workflows, each comprising thousands of microwells in which cells randomly segregate and settle. Each microwell contains a releasable plastic floor, or CellRaft, which serves as a microscale cell culture substrate. Using the AIR System software, cells on the CytoSort Array can be imaged and sorted based on fluorescence intensity in three fluorescent channels. To isolate single cells from the array, the AIR System mechanically releases the individual microscale CellRafts from each microwell and physically places them into a 96-well plate or collection tube. The CellRaft technology provides a gentle, microwell-based method for imaging, sorting and isolating stem cells for various single cell applications.

STEMBIOSYS, INC.

Room 502, Level Two
8:00 AM - 8:30 AM

DEVELOPMENT AND APPLICATION OF CELL DERIVED MATRICES FOR BIOLOGICALLY RELEVANT CELL CULTURE

Travis Block, PhD, *StemBioSys, Inc., USA*

Sy Griffey, PhD, *StemBioSys, Inc., USA*

Despite overwhelming evidence demonstrating the important role of the extracellular matrix in regulating cell behavior, traditional cell culture strategies do little to recreate a natural microenvironment. Presently, standard culture conditions inevitably lead to phenotypic drift, spontaneous differentiation, replicative senescence, and aberrant phenotypes that are unlike those found in the body. This may lead to experimental artifact in basic research or suboptimal clinical outcomes in translational research. To address this challenge, we focused our efforts on developing in vitro culture substrates that closely mimic natural microenvironments. Here we describe the development of scale-able, tissue-specific, cell-derived extracellular matrices for cell culture, and their applications in basic and translation research.

10X GENOMICS

Room 408B, Level Two
8:00 AM - 8:30 AM

THE EMERGENT LANDSCAPE OF THE MOUSE GUT ENDODERM AT SINGLE-CELL RESOLUTION

Jens Durruthy-Durruthy, PhD, *10X Genomics, USA*

Anna-Katerina Hadjantonakis, PhD, *Sloan-Kettering Institute for Cancer Research, USA*

To delineate the ontogeny of the mammalian endoderm, we used to 10x Genomics Chromium platform to generate 112,217 single-cell transcriptomes representing all endoderm populations within the mouse embryo until midgestation. We developed new graph-based approaches, to model

differentiating cells for spatio-temporal characterization of developmental trajectories and defined the transcriptional architecture that accompanies the emergence of the first (primitive or extra-embryonic) endodermal population and its sister pluripotent (embryonic) epiblast lineage. This allowed us to uncover a relationship between descendants of these two lineages, whereby pluripotent epiblast cells differentiate into endoderm at two distinct time-points, before and during gastrulation. Trajectories of endoderm cells were mapped as they acquired embryonic versus extra-embryonic fates, and as they spatially converged within the nascent gut endoderm; revealing them to be globally similar but retaining aspects of their lineage history. We observed the regionalized identity of cells along the anterior-posterior axis of the emergent gut tube, reflecting their embryonic or extra-embryonic origin, and their coordinate patterning into organ-specific territories.

XYLYX BIO, INC.

Room 408A, Level Two
8:00 AM - 8:30 AM

TISSUE-SPECIFIC ECM SUBSTRATES FOR STEM CELL AND ORGANOID CULTURES

John O'Neill PhD, *Xylyx Bio, Inc., USA*

Extracellular matrix (ECM) is a critical regulator of cell function. The biomechanical, biochemical, and ultrastructural properties of the ECM vary with tissue type (e.g., bone, heart, liver), region within an organ (e.g., kidney cortex, medulla), and state of disease (e.g., normal or fibrotic lung). Previously, we showed that tissue-specific ECM derived from heart, lung, kidney, and bone tissues can provide highly instructive substrates for 3D cell culture. Here we describe the use of tissue-specific ECM products in three formats: 3D scaffold, hydrogel, and surface coating. Tissue-specific ECM provides a physiologically relevant cell culture environment and consistently demonstrates robust support of stem cell activity and function in vitro. We also show that disease-specific ECM (e.g., from fibrotic lung, neoplastic breast) retains hallmark features of the diseased tissue. Such disease-specific ECM can be used to develop more predictive models of disease and drug screening platforms. Overall, we show multiple examples of how tissue-specific ECM products can be used to advance stem cell and organoid cultures in studies of development, regeneration, and disease.

BIOLOGICAL INDUSTRIES

Room 502, Level Two
11:30 AM - 12:30 PM

CELEBRATING 10-YEARS OF INNOVATION WITH NUTRISTEM® MEDIA: 3D CULTURE, MINIBRAIN®, AND NATURAL KILLER CELLS

Sébastien Mosser, PhD, *Neurix SA, Switzerland*

Allen Feng, *Chief Scientific Officer, HebeCell Corporation, USA*

Innovation for newer cell culture models has recently picked up steam with advancements in 3D cell culture which are beginning to transform various stem cell applications in research, therapeutic, and drug discovery. We will present two of the latest scientific discoveries where NutriStem® serves as a centerpiece to innovative workflows in regenerative medicine technologies. NEURIX specializes in neurotoxicity testing and drug efficacy assessment by offering services and tissue manufacturing through the use of in vitro 3D neural models derived from human pluripotent stem cells, called Minibrain®. Here, NEURIX will describe the Minibrain® platform which is enabling the development of brain disease models including Alzheimer's disease, glioblastoma invasion, and multiple sclerosis. Natural killer (NK) cells are cytotoxic cells critical for innate immune system function. Here, HebeCell will describe a novel 3D-bioreactor platform that can continuously generate highly pure and functional NK cells in defined conditions. First, human iPS 3D-spheres were converted to hemogenic endothelial progenitors, then further differentiated toward NK cells under specific conditions. NK cells released from these 3D-spheres can then be harvested and cryopreserved. Through establishing master iPS-CAR cell lines, this novel technology platform will provide inexhaustible sources for the generation of truly off-the-shelf CAR-NK cells for all patients.

CORNING LIFE SCIENCES

Room 403B, Level Two
11:30 AM - 12:30 PM

WHAT'S NEW AND NEXT FOR STEM CELL RESEARCH: DISSOLVABLE MICROCARRIERS FOR SCALE-UP AND ORGANOIDS FOR DISEASE MODELING AND HIGH THROUGHPUT SCREENING

Chris Saurez, *Applications Specialist, MA, USA*

Human mesenchymal stem cells (hMSCs) are commonly used for cellular therapeutics because of their regenerative properties and ability to differentiate into multiple cell lineages. Generating the quantity of hMSCs required for clinical trial usage requires technology for scaling up. From the technology to facilitate scaling up hMSCs to advanced disease modeling using induced pluripotent stem cell (iPSC) derived organoids,

this seminar will highlight the use of dissolvable microcarriers for scaling up and the importance of your surface and extracellular matrix for generating iPSC derived organoid models for high throughput screening.

STEMCELL TECHNOLOGIES

Concourse E, Level One
11:30 AM - 12:30 PM

DEVELOPMENT, COMPATIBILITY, AND APPLICATIONS OF MTESR® PLUS; AN ENHANCED MEDIUM FOR THE MAINTENANCE OF HUMAN PLURIPOTENT STEM CELLS

Melanie Kardel, PhD, *STEMCELL Technologies Inc., Canada*

Loren Ornelas, BS, MBA, *Cedars-Sinai Medical Center, USA*

Dhruv Sareen, PhD, *Cedars-Sinai Medical Center, USA*

High quality hPSC maintenance cultures are the foundation for robust and reproducible downstream applications. Traditionally, culture systems have required daily medium changes in order to replenish levels of critical components and prevent medium acidification. mTeSR™ Plus, based on the mTeSR™1 formulation, was specifically developed to ensure truly versatile feeding schedules while promoting a more consistent cell culture environment. The stabilization of components including FGF2 combined with an enhanced buffering capacity that maintains pH ≥7.0 for up to 72 hours without feeding, supports every other day or weekend-free schedules. Rigorous downstream testing has demonstrated improved cloning efficiencies and no impact on genome editing or on the efficiency of downstream differentiation protocols developed for mTeSR™1 when used with hPSCs maintained in mTeSR™ Plus.Cedars-Sinai Induced Pluripotent Stem Cell (iPSC) Core Facility uses the latest techniques to reprogram, expand, and characterize human iPSCs. They offer an iPSC repository with >700 control and diseased cell lines. This talk will feature core services, highlight key collaborations and describe the core facility's experience with mTeSR™ Plus including cell line transition and quality control. Additionally, plans to launch the Cedars-Sinai Biomanufacturing Center (CBC) to create GMP grade stem cells for research and clinical use will be described.

LONZA PHARMA & BIOTECH

Room 408B, Level Two
11:30 AM - 12:30 PM

PLURIPOTENT STEM CELL BASED THERAPIES: FROM BENCH TO COMMERCIALIZATION

Pupsa Pandey, PhD, *Lonza Pharma & Biotech, USA*

Stem cell-based therapies require innovative solutions to close the gaps existing between research and commercialization. Allogeneic cell therapy indications that target large patient populations will necessitate the use of flexible cell production platforms to meet the increasing demand of cell quantities. In addition, process control and monitoring, along with cell quality, are key parameters in clinical cell therapy product manufacturing. Human pluripotent stem cells (hPSCs) hold great promise for regenerative medicine and therefore, are a key intermediate cell therapy product. Taking advantage of scalable, stirred tank bioreactors to expand hPSCs in suspension, will not only enable the required cell quantity demand for clinical applications, but also will enhance process comparability, control and automation. Here we show that high fold expansion of hPSCs in suspension can be achieved in a bioreactor, without the need to pass the cells during culture time. Expanded hPSCs pass cell quality assays of self-renewal and pluripotency, including the expression of hPSC-associated markers, differentiation to cells of the three germ layers and retention of a normal karyotype. Expansion of hPSCs in a closed stirred tank bioreactor not only meets commercial cell quantity demand but also enables automation and inline monitoring, which enhance process control and product quality.

MATRIXOME, INC.

Concourse F, Level One
11:30 AM - 12:30 PM

LAMININ E8 TECHNOLOGY FOR STEM CELL PROLIFERATION AND DIFFERENTIATION: FROM MOLECULAR MECHANISM TO CLINICAL APPLICATION

Takuji Yamamoto, PhD, *Matrixome, Inc., Japan*

Yuhei Hayashi, PhD, *Graduate School of Medicine, Osaka University, Japan*

Yukimasa Taniguchi, PhD, *Institute for Protein Research, Osaka University, Japan*

Dr. Ryuhei Hayashi's technique for differentiating human pluripotent stem cells into ocular cells has recently been approved by Japan's Ministry of Health, Labour and Welfare for cell therapy treatment of corneal epithelial stem cell deficiency. His group has developed the culture system for self-formed ectodermal autonomous multi-zone (SEAM), cell colonies that are arranged as four concentric areas that mimic

the spatiotemporal development of the whole eye. This was accomplished with laminin E8, a recombinant laminin fragment, as the culture substrate. The group has since recently uncovered the specific isoforms of laminin E8 responsible for the induction of pluripotent stem cells to the corneal epithelium, the retina, and the epithelium of the lens. The outcome of their research underscores the importance of selecting appropriate laminin isoforms for cell culturing. The binding affinity of substrates and integrins determines the nature of expanded human pluripotent stem cell colonies in terms of cell motility, cell-cell interactions and cell density. Currently, how binding between laminin and integrin is achieved is poorly understood. Dr. Yukimasa Taniguchi will present his group's latest findings on the molecular mechanism of laminin E8-integrin interactions underlying stem cell culturing.

HEALIOS K.K.

Room 403A, Level Two
11:30 AM - 12:30 PM

THE FOREFRONT OF ORGANOID MEDICINE

Takanori Takebe, MD, PhD, *Cincinnati Children's Hospital, Tokyo Medical and Dental University, Yokohama City University, Japan*

Organoids hold great promise to revolutionize 21st century healthcare through transforming drug development, precision medicine, and ultimately, transplantation-based therapies for end stage diseases, namely an "organoid medicine". For example, transplantation of human liver organoids is capable of extending life in a mouse model of liver failure (Nature, 2013, Cell Reports, 2017). Herein, with the goal of clinical translation of organoid transplant therapy, we will discuss the practical strategies that will cover manufacturing strategies, alliance strategies and clinical study design towards regenerative applications.

THERMO FISHER SCIENTIFIC

Room 408A, Level Two
11:30 AM - 12:30 PM

A NEW HSC EXPANSION MEDIUM FOR SUPERIOR CD34+ CELL EXPANSION AND ENGRAFTMENT USED IN COMBINATION WITH A NOVEL GENE TAGGING SYSTEM FOR EFFICIENT GENE EDITING CONFIRMATION AND LINEAGE TRACKING

Curt Civin, MD, *University of Maryland School of Medicine, USA*

Jonathan Chestnut, PhD, *Thermo Fisher Scientific*

Development of ex vivo culture systems to expand human hematopoietic stem-progenitor cells (HSPCs) is critical in the development of cell and gene therapies. To address this, Thermo Fisher Scientific has developed a xeno-free, serum-free medium -- StemPro™ HSC Expansion Medium (Prototype) where culture of primary human CD34+ cells resulted in ~100-fold increase in CD34+CD45+Lin- cells and ~2000-fold increased numbers of CD34+Lin-CD90+CD45RA- cells, as compared to uncultured day 0 cells. The ex vivo-expanded CD34+ cells formed erythroid and non-erythroid hematopoietic colonies in vitro. In an ongoing hematopoietic chimera experiment, ex vivo-cultured mPB CD34+ HSPCs harbored robust in vivo-engrafting capacity at the 8-week post-transplant short-term HSC time point evaluated to date. CD34+ cells were expanded in StemPro HSC SFM and tagged with GFP using the new TrueTag system. Whereas CD34+ cell labeling has historically been inefficient, the tagged CD34+ cells generated hematopoietic colonies containing GFP+ erythroid and granulocytic/monocytic cells.

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Join us

ISSCR 2019 INTERNATIONAL SYMPOSIA

INTERNATIONAL 2019 SYMPOSIA

26–27 SEPTEMBER / 2019

SEOUL
SOUTH KOREA

Stem Cell Research: Present and Future

CO-SPONSORED BY:

KSSCR 한국줄기세포학회 KOREAN SOCIETY FOR STEM CELL RESEARCH

Poster abstract deadline: 10 July

6–8 NOVEMBER / 2019

TORONTO
CANADA

From Stem Cell Biology to New Therapies

CO-SPONSORED BY: BlueRock Therapeutics

Poster abstract deadline: 28 August

www.isscr.org/symposia

Speaker Abstracts

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

INTERNATIONAL 2020 SYMPOSIA

Join us

ISSCR 2020 INTERNATIONAL SYMPOSIA

13–15 MARCH / 2020

SHANGHAI
CHINA

CO-SPONSORED BY:

广州再生医学与健康广东省实验室
GUANGZHOU REGENERATIVE MEDICINE AND HEALTH GUANGDONG LABORATORY

中国科学院广州生物医药与健康研究院
GUANGZHOU INSTITUTES OF BIOMEDICINE AND HEALTH, CHINESE ACADEMY OF SCIENCES

上海科技大学
ShanghaiTech University

12–14 OCTOBER / 2020

PARIS
FRANCE

CO-SPONSORED BY:

BeSSCR Belgian Society for Stem Cell Research

FSSCR French Society for Stem Cell Research

www.isscr.org/symposia

WEDNESDAY, 26 JUNE, 13:00 – 15:05

PLENARY I: PRESIDENTIAL SYMPOSIUM

West Hall B, Level One
Sponsored by Fate Therapeutics

13:40 – 14:00

IS IT WORTH A RISK IN CHOOSING A PROJECT AT THE START OF YOUR CAREER?

Gurdon, John B.
University of Cambridge, UK

I am sometimes asked if I think it is worth, at an early stage in a career, taking the risk of questioning a conclusion widely accepted and reached by senior scientists. In some cases, it may be a worthwhile risk, as exemplified by the early years of somatic cell nuclear transfer. Using this as an example, I will explain current experiments that concern the residence time of cell-lineage-determining transcription factors on their specific DNA binding site. This also questions a widely-accepted current understanding in this field.

14:00 – 14:20

UNDERSTANDING HUMAN BRAIN DEVELOPMENT AND DISEASE: FROM EMBRYOS TO BRAIN ORGANOIDS

Arlotta, Paola
Harvard University, Cambridge, MA, USA

Much remains unknown regarding the mechanisms that govern the development of the human brain and the extent to which this process can be replicated outside the embryo, within brain organoids. In this lecture, I will discuss the challenges and opportunities of modeling human brain development in the dish, and the promise that organoids hold to transform our understanding of complex neuropsychiatric disease.

14:20 – 14:40

FROM HAIR CELLS TO HAIR FOLLICLES: GENERATION OF SENSORY ORGANOIDS FROM PLURIPOTENCY

Koehler, Karl
Indiana University School of Medicine, Indianapolis, IN, USA

Peripheral sensory organs, such as the inner ear and skin, arise from complex interactions between multiple cell lineages during development. To date, it has been difficult to capture the intricate cross-talk between epithelial, mesenchymal, neuronal progenitor cells needed to recreate human sensory tissue in culture models. Here, I will discuss recent work in my lab on an organoid culture model that generates complex inner ear and skin tissue from human pluripotent stem cells (PSCs). I will describe how modulating a few signaling pathways in 3D cultured PSCs initiates co-development of surface ectoderm and cranial neural crest cells—key ingredients for craniofacial development. The co-developing tissues can be steered toward an otic or epidermal fate by toggling WNT signaling. After 3-5 months in culture, inner ear organoids contain sensory hair cells similar to those in nascent balance organs. By contrast, skin organoids are composed of a cyst of stratified epidermis surrounded by dermis tissue, which generates pigmented hair follicles. Moreover, each organoid system arises with a population of sensory neurons and glial cells that form a neural network targeting sensory cells, mimicking human vestibulocochlear and touch circuitry. I will discuss how these organoids are being used to investigate developmental mechanisms, model disease processes, and generate cells for reconstructive surgery.

14:40 – 15:00

STEM CELL-BASED ORGANOIDS AS AVATARS IN HUMAN DISEASE

Clevers, Hans
Hubrecht Institute, Utrecht, Netherlands

Stem cells are the foundation of all mammalian life. Stem cells build and maintain our bodies throughout life. Every organ in our body is believed to harbor its own dedicated stem cells. These adult stem cells replace tissue that is lost due to wear and tear, trauma and disease. Adult stem cells are highly specialized and can only produce the tissue in which they reside; they are 'multipotent'. Examples are bone marrow stem cells that make all blood cells, skin stem cells and gut stem cells. Even the brain is now known to harbor its specialized stem cells. The adult stem cells allow us to live 80-90 years, but this comes at a cost: they are the cells that most easily transform into cancer cells. We have identified a gene (lgr5) that marks a series of known and novel adult stem cells, in organs such as the gut, the liver, the lung and the pancreas. We have learned to grow these stem cells in a dish into mini-versions of the human organs from which they derive. This so called organoid technology opens a range of avenues for the study of development, physiology and disease, and for personalized medicine. In the long run, cultured mini-organs may replace transplant organs from donors and hold promise in gene therapy.

WEDNESDAY, 26 JUNE, 16:00 – 18:00

PLENARY II: PLURIPOTENCY AND GERM CELLS

West Hall B, Level One
Sponsored by Takeda Pharmaceutical Co., Ltd.

16:00 – 16:20

FORMATIVE PLURIPOTENCY

Smith, Austin
University of Cambridge, UK

Pluripotent cells emerge as a naïve founder population in the mammalian blastocyst. They then develop capacity for germline and somatic specification, prior to lineage priming and differen-

tiation. Mouse embryonic stem cells and post-implantation epiblast stem cells (EpiSC) represent the early naïve and late primed stages of pluripotency respectively. Between these two stages a formative transition occurs, in vitro and in the embryo, through which the competence is acquired for multi-lineage induction. The capture of stem cells representative of the intermediate formative stage may be invaluable for exposing and dissecting the molecular machinery that actuates pluripotency.

16:20 – 16:40

EMERGENCE OF PLURIPOTENCY AND CONTROL OF TISSUE SIZE: A DYNAMIC BALANCING ACT PLAYED OUT IN THE MAMMALIAN BLASTOCYST

Hadjantonakis, Anna-Katerina, Saiz, Nestor**,** Simon, Claire**,** Garg, Vidur and Nowotschin, Sonja

Sloan-Kettering Institute, Memorial Sloan Kettering Cancer Center, New York, NY, USA

The mammalian preimplantation embryo is the site of a bona fide pluripotent cell population, the epiblast, and is also the source of embryonic stem (ES) cells. The preimplantation period is a paradigm of self-organization and regulative development; embryos can develop normally in vitro without the need for extrinsic growth factors, and they can recover from experimental perturbations, including the removal or addition of cells. The pluripotent epiblast and its sister lineage, the primitive endoderm, arise from a common progenitor population, the Inner Cell Mass, within the developing blastocyst. These blastocyst lineages are generated in precise proportions within a short period of time, suggesting the existence of mechanisms controlling tissue size, a feature critical for normal organismal development and homeostasis. In the mouse, FGF/ERK signaling activation drives primitive endoderm formation, while its inhibition promotes an epiblast fate. Assessing the spatial and temporal changes in signaling is therefore key to understanding how lineage decisions are made over time and in the correct proportions. To delineate the mechanistic control and coordination of fate specification and scaling events in vivo we are using genetic, embryological and optogenetic manipulations, combined with single-cell resolution quantitative imaging and genomic analyses. I will discuss recent results which provide insight into how individual cell fate decisions are regulated at the population level in the mouse blastocyst, and how embryos can accommodate to perturbations.

16:40 – 17:00

O'Shea, Clodagh

The Salk Institute, La Jolla, CA, USA

Title and abstract not available at time of printing

17:00 – 17:11

DDX6 CONTROLS HUMAN STEM CELL FATE BY MODULATING CHROMATIN PLASTICITY THROUGH P-BODY HOMEOSTASIS

Di Stefano, Bruno[1], Luo, En-Ching[2], Haggerty, Chuck[3], Aigner, Stefan[2], Charlton, Jocelyn[3], Brumbaugh, Justin[1], Ji, Fei[4], Rabano Jiménez, Inés[2], Clowers, Katie[4], Huebner, Aaron[1], Clement, Kendell[5], Lipchina, Inna[1], Anselmo, Anthony[1], Pulice, John[1], Gerli, Mattia[6], Gu, Hongcang[5], Gygi, Steven[4], Sadreyev, Ruslan[1], Meissner, Alexander[3], Yeo, Gene[2] and Hochedlinger, Konrad[1]

[1]Molecular Biology, Massachusetts General Hospital, Harvard University, Boston, MA, USA, [2]Cellular and Molecular Medicine, University of California, San Diego, CA, USA, [3]Genome Regulation, Max Planck Institute for Molecular Genetics, Berlin, Germany, [4]Cell Biology, Harvard Medical School, Boston, MA, USA, [5]Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [6]Regenerative Medicine, Massachusetts General Hospital, Boston, MA, USA

Transcription factors and chromatin regulators have been extensively studied during self-renewal and differentiation of pluripotent and adult stem cells. However, the mechanisms by which these factors are regulated across cell types and the involvement of RNA-binding proteins in these processes remain largely unexplored. Here, we show that the RNA helicase DDX6 is crucial for both the maintenance and dissolution of the pluripotency-specific transcriptional network in mouse and human embryonic stem cells (ESCs). We demonstrate that CRISPRi-mediated transcriptional silencing of DDX6 endows ESCs with a differentiation-resistant "hyper-pluripotent" state, which is poised to revert to a developmentally more naïve state resembling the preimplantation embryo. In addition to directing cell fate in ESCs, we find that DDX6 plays a key role in adult progenitors where it controls the balance between self-renewal and differentiation in a context dependent manner. Mechanistically, we show that DDX6 interacts with translational repressors and mRNA decay enzymes to coordinate the storage of untranslated mRNAs in P-bodies. Upon loss of DDX6 or mutation of its helicase domain, P-bodies dissolve and release mRNAs encoding fate-instructive transcription and chromatin factors that re-enter the ribosome pool. Increased expression of these targets impacts cell fate by profoundly altering the enhancer and heterochromatin landscapes of embryonic and somatic stem cells. Collectively, our data establish a novel link between P-body homeostasis, chromatin organization and cellular potency across diverse stem and progenitor cell populations.

17:11 – 17:22

HISTONE H3 ACETYLATION PLAYS IMPORTANT ROLES IN BOTH WIDE-TYPE AND SCNT PRE-IMPLANTATION EMBRYO DEVELOPMENT

Zhang, Linfeng[1], Yang, Guang[2], Chen, Jiayu[2], Jiang, Cizhong[2] and Gao, Shaorong[2]

[1]Shanghai Key Laboratory of Signaling and Disease Research, School of Life Sciences and Technology, Tongji University, Shanghai, China, [2]School of Life Sciences and Technology, Tongji University, Shanghai, China

Somatic cell nuclear transfer (SCNT) holds tremendous application potentials since this technology can reprogram highly differentiated cells into the totipotent state. However, the cloning efficiency of mammalian cells remains to be low for decades. Treatment of histone deacetylase inhibitor (HDACi) is reported to be one of the most effective ways to improve both the in vitro blastocyst formation rate and the in vivo development of full-term cloned embryos, which suggests that sufficient histone acetylation is essential for the successful cloning. However, genome-wide profile of histone acetylation during pre-implantation embryo development remains largely undefined. Moreover, to what extent the HDACi corrects histone acetylation is still unclear. Here, we used ultra-low-input micrococcal nuclease-based native chromatin immunoprecipitation (ULI-NChIP) to detect genome-wide profiling of certain core histone 3 acetylation modification during both wide-type and SCNT pre-implantation embryo development. We found that this modification is closely related to gene expression and zygotic genome activation (ZGA). Meanwhile, its distribution pattern is quite similar to H3K4 trimethylation, which may indicate a synergistic effect of both histone modifications. Further analysis has indicated a crucial role of this histone 3 acetylation modification during the SCNT process, which is found to be deficient in the reprogramming resistant regions (RRRs) of SCNT embryos.

Funding Source: National Key R and D Program of China (2015CB964800) and the National Natural Science Foundation of China (31721003 and 31871446).

17:22 – 17:33

BETA-CATENIN ASSOCIATED PROTEIN COMPLEX MAINTAINS GROUND STATE MOUSE EMBRYONIC STEM CELL BY RESTRICTING LINEAGE DIFFERENTIATION

Tao, Fang[1], Gao, Xin[1], Chen, Shiyuan[1], Hu, Deqing[2], Zhao, Chongbei[1], Zhao, Meng[3], Qian, Pengxu[4], Li, Zhenrui[1], Venkatraman, Aparna[1], Parmely, Tari[1], Zhang, Da[5], He, Xi[1], Zeitlinger, Julia[1], McMahon, Andrew[6] and Li, Linheng[1]

[1]Stowers Institute, Kansas City, MO, USA, [2]Cell Biology, Tianjin Medical University, Tianjin, China, [3]Third Affiliated Hospital, Sun Yat-sen University, Guangdong, China, [4]Stem Cell and Regenerative Medicine, Zhejiang University, Hangzhou, China, [5]Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, MO, USA, [6]Stem Cell Biology, University of Southern California, Los Angeles, CA, USA

Mouse embryonic stem cells (ESCs) cultured in defined medium with MEK and GSK3 inhibitors(2i) resemble the pre-implantation epiblast in the ground state, with full developmental capacity including the somatic lineages and the germline. Although β-catenin is known to be crucial for naive pluripotency of mouse ESCs, the underlying mechanism is not fully understood. Here we showed that β-catenin interacted with a repressive protein complex to maintain the ground state of mouse ESCs by fine-tuning their lineage development potential. Absence of β-catenin impaired mouse ESC self-renewal without anticipated decrease in the protein levels of core Oct4-Sox2-Nanog regulatory factors. However, β-catenin-depleted ESCs showed a primed state transcriptional signature with perturbed expression of germline and neuronal lineage genes. Knockdown of T-cell factor 3 (Tcf3), the repressor in canonical Wnt signaling pathway, did not completely rescue the β-catenin-depleted phenotype of ESCs. Mechanistically, β-catenin formed a novel protein complex with E2F6, HP1γ and HMGA2 to restrain ESCs from differentiation via occupying the promoters of germline and neuronal lineage regulatory genes. Overall, our work showed that β-catenin maintained ground state mouse ESCs by restricting the immediate lineage fate towards primed state through forming a repressive protein complex with E2F6, HP1γ and HMGA2.

17:33 – 17:53

ANNE MCLAREN MEMORIAL LECTURE: OOCYTES: THE ULTIMATE STEM CELLS

Spradling, Allan, Deluca, Steven, Greenblatt, Ethan and Niu, Wanbao

Carnegie Institution for Science, Baltimore, MD, USA

Oocytes are large cells uniquely capable of developing into complete metazoan animals. Oocytes are produced using a special cell cycle, meiosis, and with extensive assistance from other cell types. We have characterized how primordial germ cells become follicular oocytes in both mice and Drosophila, and find evidence that the process of female gametogenesis has been extensively conserved during evolution. The formation of repressive domains by epigenetic modification is needed to imprint mammalian X chromosome inactivation in mice, and to restrict transposon activity, recombination and gene expression during Drosophila oogenesis. We inserted more than 100 tester genes throughout chromosomal repressive domains to determine at single cell resolution during Drosophila development when specific domains become functionally repressive. Comparing functional and epigenetic changes with protein binding provided new insights into the formation mechanism and function of Polycomb and HP1 domains in female germ cells. Mechanisms that maintain mature quiescent oocytes are critically important for female reproductive competence. We developed methods to accurately measure quiescent oocyte aging and to identify genes, including fragile X mental retardation 1 (Fmr1), required to maintain oocyte function. Fmr1 encodes a protein functionally interchangable between humans and Drosophila that binds mRNAs in stored oocytes and neural synapses, but whose targets and mode of action are poorly understood. Fmr1 mutation is the largest cause of inherited mental disability/autism and of premature ovarian failure. We show that Fmr1 is maternally required for neural development in embryos that develop from aged eggs and acts to maintain the translation of large proteins important for neural and oocyte function, possibly by controlling their repression by P bodies.

THURSDAY, 27 JUNE, 09:00 – 11:15

PLENARY III: MECHANISMS AND APPLICATIONS OF MESODERMAL TISSUES I

West Hall B, Level One

9:15 – 9:35

BUILDING THE KIDNEY IN VITRO FROM PLURIPOTENT STEM CELLS

Nishinakamura, Ryuichi

Kumamoto University, Kumamoto, Japan

Organogenesis generates higher-order structures containing functional subunits, connective components, and progenitor niches. Despite recent advances in organoid-based modeling of tissue development, recapitulating these complex configurations from pluripotent stem cells (PSCs) has remained challenging. The kidney derives from the embryonic metanephros, which develops by the reciprocal interactions between the nephron progenitor and ureteric bud. We previously identified the distinct origins of these two precursor tissues and generated the nephron progenitor from mouse and human PSCs. The induced nephron progenitors readily formed glomeruli and renal tubules in vitro, and upon transplantation, human glomeruli were vascularized with the host mouse endothelial cells. More recently, we reported an induction protocol for the ureteric bud from mouse and human PSCs, by studying the developmental processes of this second lineage, which contains epithelial kidney progenitors that undergo branching morphogenesis and thereby plays a central role in orchestrating organ geometry. Importantly, mouse organoids reassembled from the differentially induced ureteric bud and nephron progenitors developed the inherent architectures of the embryonic kidney, including the peripheral progenitor niche and internally differentiated nephrons that were interconnected by a ramified ureteric epithelium. This selective induction and reassembly strategy will be a powerful approach to recapitulate organotypic architecture in PSC-derived organoids.

9:35 – 9:55

LINEAGE-DETERMINING TRANSCRIPTION FACTOR TCF-1 INITIATES THE EPIGENETIC IDENTITY OF T CELLS

Vahedi, Golnaz

Perelman School of Medicine, University of Pennsylvania, PA, USA

T cell development is orchestrated by transcription factors that regulate the expression of genes initially buried within inaccessible chromatin, but the transcription factors that establish the regulatory landscape of the T cell lineage remain unknown. Profiling chromatin accessibility at eight stages of T cell development revealed the selective enrichment of TCF-1 at genomic regions that became accessible at the earliest stages of development. TCF-1 was further required for the accessibility of these regulatory elements and at the single-cell level, it dictated a coordinate opening of chromatin in T cells. TCF-1 expression in fibroblasts generated de novo chromatin accessibility even at chromatin regions with repressive marks, inducing the expression of T cell-restricted genes. These results indicate that a mechanism by which TCF-1 controls T cell fate is through its widespread ability to target silent chromatin and establish the epigenetic identity of T cells.

9:55 – 10:06

A SPATIAL, TRANSCRIPTOMIC, MOLECULAR, AND GENE NETWORK BLUE-PRINT FOR THE HUMAN NEPHROGENIC PROGRAM

Lindstrom, Nils O.[1], Sealfon, Rachel[2], Chen, Xi[2], Parvez, Riana[1], De Sena Brandine, Guilherme[3], Hill, Bill[4], Ransick, Andrew[1], Grubbs, Brendan[5], Thornton, Matthew[5], McMahon, Jill[1], Zhou, Jian[2], Smith, Andrew[3], Ruffins, Seth[1], Armit, Chris[4], Troyanskaya, Olga[2] and McMahon, Andrew[1]

[1]USC Stem Cell, University of Southern California, Los Angeles, CA, USA, [2]Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, NJ, USA, [3]Molecular and Computational Biology, University of Southern California, Los Angeles, CA, USA, [4]IGMM, University of Edinburgh, UK, [5]Maternal Fetal Medicine Division, University of Southern California, Los Angeles, CA, USA

Advances in stem-cell derived organoids that recapitulate developmental differentiation trajectories are built on a robust understanding of how these differentiation programs occur in vivo. This requires a cellular level integration of spatial, structural, and molecular data, where structure-function relationships are particularly important for delineating the development of anatomically complex tissues such as the nephron – the filtration apparatus of the kidney. Though partial success has been achieved in producing kidney-like cell types in the renal organoid, the normal development and organization of precursors that form mature functional cells remain unresolved. Thus, unbiased assessment of cell-type fidelity in the organoid has not been performed. Here, we present a unified model for the development of the human and mouse nephron based on four-dimensional analyses of hundreds of nephrons. We describe a pipeline to register nephrons into quantitative models, show that the morphogenetic program is largely conserved between human and mouse, and that nephrogenesis follows a tightly regulated developmental progression with species-specific differences in timing, cellularity, and signaling domains. We describe a novel lineage trajectory prediction of human nephron precursor diversification using scRNA-seq data and extract probabilistic maps from registered human nephrons using machine learning. This is integrated, by spatial mapping, to new predicted precursor domains in order to build a full transcriptomic map of the human nephron. These data provide an unprecedented understanding of how nephrons form during human embryogenesis and act as an atlas for the underlying transcriptional programs the drive cellular diversification in the early nephron. Importantly, our studies serve as a blueprint for how kidney developmental differentiation trajectories can be replicated in vitro.

10:06 – 10:17

IMMUNE REJECTION OF ALLOGENEIC MOUSE AND HUMAN CELL TRANSPLANTS DERIVED FROM IPSCS IS PREVENTED BY GENETIC ENGINEERING

Deuse, Tobias[1], Hu, Xiaomeng[2], Gravina, Alessia[2], Wang, Dong[2], Tediashvili, Grigol[2], De, Chandrav[3], Thayer, William[3], Wahl, Angela[3], Garcia, Victor[3], Reichenspurner, Hermann[4], Davis, Mark[5], Lanier, Lewis[6] and Schrepfer, Sonja[2]

[1]Cardiothoracic Surgery, University of California, San Francisco, CA, USA, [2]Surgery, University of California, San Francisco, CA, USA, [3]Infectious Diseases, University of North Carolina School of Medicine, Chapel Hill, NC, USA, [4]Cardiac Surgery, University Heart Center Hamburg, Hamburg, Germany, [5]Immunology, Stanford University, Stanford, CA, USA, [6]Immunology, University of California, San Francisco, CA, USA

Patient-specific autologous induced pluripotent stem cell (iPSC)-derived products pose technical and manufacturing challenges and will probably not be economically suitable to treat a big patient population. These shortcomings can only be overcome with prefabricated ready-to-use cell products of allogeneic origin, but the vigorous immune response against any type of histoincompatible cells so far prevents this approach. We thus aimed to engineer hypoimmunogenic iPSCs that would not exert any allo-immune response. Applying features of fetomaternal tolerance, we inactivated both major histocompatibility complex (MHC) class I and II genes in mouse iPSCs and over-expressed CD47. Such gene-edited hypoimmunogenic iPSCs lost their immunogenicity but fully retained their pluripotency and could be differentiated into cell types of cardiac tissue. Hypoimmunogenic endothelial cells, smooth muscle cells, or cardiomyocytes reliably evaded immune rejection in fully MHC-mismatched allogeneic recipients, showed long-term survival without using any immunosuppression, and endothelial cells even formed primitive vessels. A battery of immune assays showed no immune cell infiltration in hypoimmunogenic cell grafts, no T and NK cell activation and no inflammatory environment. Their wild-type counterparts underwent rapid rejection with all features of cellular and humoral activation. We then similarly engineered hypoimmunogenic human iPSCs using the same engineering steps. HLA I and II-deficient and CD47 overexpressing human iPSC-derived endothelial cells and cardiomyocytes did not elicit any cellular or humoral immune response in allogeneic humanized NSG-SGM3 mice, while their wild-type counterparts triggered vigorous allo-immune activation. Survival was assessed in two humanized mouse models, the triple transgenic NSG-SGM3 mice and the BLT mice, which allow for T cell maturation in human thymic tissue and permit HLA restricted T cell responses. Hypoimmunogenic endothelial cells and cardiomyocytes showed long-term survival in fully allogeneic humanized recipients without using immunosuppression. Collectively, our findings suggest that hypoimmunogenic cell grafts can be engineered that allow universal transplantation, irrespective of the recipient's histocompatibility antigen type.

Funding Source: A.W.: NIH (AI123010). J.V.G. : NIH (AI111899 and MH108179). L.L.L.: NIH (AI068129). S.S. and T.D.: California Institute for Regenerative Medicine (CIRM; Grant Number DISC1-09984) and the NHLBI (R01HL140236).

10:17 – 10:28

AN INTEGRATED MYELOID ATLAS REVEALS CULTURE CONDITIONING IS A MAJOR PHENOTYPE THAT DISCRIMINATES IN VIVO FROM PLURIPOTENT-DERIVED MACROPHAGES

Wells, Christine A.[1], Rajab, Nadia[2], Angel, Paul[2], Rutar, Matthew[2] and Choi, Jarny[2]

[1]Faculty of Medicine Dentistry and Health Sciences, University of Melbourne, Australia, [2]Centre for Stem Cell Systems, The University of Melbourne, Australia

Macrophages have an integral role in the development and homeostasis of human tissues, but models of human macrophage biology have relied heavily on ex-vivo differentiation of peripheral blood monocytes. Pluripotent-derived myeloid cells may better approximate the ontogeny of tissue resident macrophages. Using the Stemformatics stem cell data platform, we built an atlas of primary monocytes, tissue macrophages and dendritic cells from public studies. This provides a map of myeloid biology constituted from 1000s of donors. We show that cultured monocytes rapidly adopt a distinct 'adhesion' phenotype, which precedes inflammatory gene expression that is associated with exposure to pathogen or cytokine. Pluripotent derived monocytes map closely to cultured monocytes and activated macrophages, but do not approximate the in vivo circulating cell. PS-derived macrophages have an additional phenotype consistent with an altered metabolic status of high lipid catabolism and altered redox activity. The atlas and underlying data can be interrogated in the Stemformatics resource, providing a platform for researchers to upload and benchmark their own PS-derived macrophage data.

Funding Source: NR has a scholarship from the CSIRO Synthetic Biology Future Science Platform. The Stemformatics resource is funded by the Australian Research Council (FT150100330) and Stem Cells Australia (SR110001002) to CAW.

10:28 – 10:48

DECODING HUMAN HEMATOPOIETIC STEM CELL SELF-RENEWAL

Mikkola, Hanna

University of California, Los Angeles, CA, USA

Limited knowledge of the mechanisms governing human hematopoietic stem cell (HSC) self-renewal have impeded the generation and expansion of HSCs in vitro for therapeutic use. Our prior studies identified SCL/TAL1 as a key factor that specifies the hematopoietic lineage in the endothelium, and the activation of HOXA genes is a critical indicator of the definitive hematopoietic fate. To identify factors that sustain HSC stemness and might

improve the function of cultured HSC, we defined genes differentially expressed between the self-renewing HSC in human fetal liver and their non-self-renewing progeny, and genes dysregulated in cultured HSPC (fetal liver and PSC-derived). These studies uncovered MLLT3 as a critical HSC regulator highly enriched in human fetal, neonatal and adult HSCs, but downregulated in culture. MLLT3 is a component of the Super-elongation (SEC) and DOT1L complexes, which regulate transcription elongation and chromatin accessibility. Lentiviral shRNA knockdown of MLLT3 prevented the maintenance of human hematopoietic stem/progenitor cells (HSPC) in culture and their engraftment in vivo, confirming necessity for HSC function. Strikingly, stabilizing MLLT3 levels in cultured cord blood HSPC enabled >12-fold expansion of transplantable HSC that provided balanced multilineage reconstitution in primary and secondary recipients. In other words, MLLT3 enabled symmetric self-renewal of HSCs during culture. Lentivirally expressed MLLT3 displayed highly similar DNA binding pattern as the endogenous MLLT3, localizing to promoters of genes that were accessible and expressed in HSPC. Co-operating with DOT1L, MLLT3 protected HSC transcriptional program in culture by maintaining H3K79me2 levels in HSC regulatory genes. Knockdown of MLLT3 targets MECOM and HLF attenuated the effects of MLLT3 on HSPC expansion, nominating them as crucial MLLT3 downstream effectors in HSCs. MLLT3 thus acts as HSC maintenance factor that links histone reader and modifying activities to maintain HSC stemness. MLLT3-controlled HSC program also serves as an indicator for human HSC identity, and enables the monitoring of human HSC development in vitro using fluorescent hESC reporter lines, and in vivo using scRNA sequencing. These findings open new avenues to generate or expand HSC for transplantation.

10:48 – 11:08

NORMAL AND NEOPLASTIC STEM CELLS

Weissman, Irving L.

Stanford University, Stanford, CA, USA

Stem cell isolation and transplantation is the basis for regenerative medicine. We isolated mouse then human hematopoietic stem cells (HSCs). Importantly, the transplantation of purified HSCs results in complete regeneration of the blood and immune systems without causing graft vs, host disease, and can induce permanent transplant tolerance of any organ or cell from the HSC donor. HSC transplantation offers a curative treatment for a wide range of hematological and immune disorders, however the main barrier to a broad clinical application is the high toxicity of current conditioning regimens. To make HSC transplantation a safe, well-tolerated procedure, our group has been developing antibody-based non-toxic conditioning methods to replace chemotherapy and radiation. To study the relationship between stem cells and cancer, we followed the preleukemic progression from hematopoietic stem cells (HSCs) to myelogenous leukemias and found that the developing pre-cancerous HSC clones gradually accumulate mutations, with the last mutation giving rise to leukemia stem cells (LSC). The LSCs are downstream oligolineage or multilineage progenitors that have acquired self-renewal and evaded programmed cell death and programmed cell removal. A checkpoint inhibitor for innate immunity macrophages: By comparing LSC to HSC, we identified CD47 overexpression on LSC, and then on all cancers tested, and showed that it is a cell surface molecule used by live cancer cells to evade macrophage phagocytosis by binding to SIRPa, its inhibitory receptor on macrophages. CD47 is the first target that is expressed on all human cancers tested. Humanized clinical grade IgG4 anti-CD47 Abs are in phase 1/2 clinical trials. anti-CD47 combination with Rituximab led to responses in patients with highly aggressive lymphomas who were relapsed and refractory to Rituxan and chemotherapy (Advani et. al, 2018 NEJM); The combined response rate was nearly 50%, 70-80% of these achieved complete remission.

THURSDAY, 27 JUNE, 13:15 – 15:15

CONCURRENT IA: ENGINEERING TISSUES AND ORGANS

Concourse E, Level One

13:15 – 13:20

Topic Overview

Srivastava, Deepak

Gladstone Institutes, San Francisco, CA, USA

13:20 – 13:40

NEXT-GEN ORGANOIDS FROM PLURIPOTENCY: NARRATIVE ENGINEERING

Takebe, Takanori

Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA and Tokyo Medical and Dental University, Yokohama, Japan

Dynamic multicellular self-organization in organoids seems to have unique aspects that are not commonly studied in decades of "tissue engineering" . One of key features is the "narrative" element, where the group of cells, radically change along the temporal axes in a context-dependent manner, for instance, during organogenesis. Biological self-organization arises from successive local interactions between cells of an initially disorganized system by environmental fluctuations, amplified by positive feedback. Thus, controlling biological history (or "narrative") awaits a new design strategy in order to enhance the robustness and complexity of self-organizing systems. Narrative engineering is an engineering principle to enhance the robustness of tissue self-organization both in time and space such includes patterning, assembly, morphogenesis and growth as an interface principle of biology and engineering. Key design elements of Narrative Engineering: 1. Space design: Tissue designed as a spatial default. 2. Proactive design: Biological environmental control. 3. Active design: Synthetic environmental control. Herein, we discuss the three general design strategies, based largely on the example of how hepatobiliary organs are assembled during embryonic development, have been (can be) adopted for the robust creation of complex liver organoid systems from pluripotent stem cells.

13:40 – 13:51

SELF-ORGANIZATION OF SPATIAL PATTERNS IN ARTIFICIAL HUMAN EMBRYOS AND ORGANOIDS

Etoc, Fred[1,2] and Brivanlou, Ali H.[1,2]

[1]Laboratory of Stem Cell Biology and Molecular Embryology, The Rockefeller University, New York, NY, USA, [2]Rumi Scientific, New York, NY, USA

Harnessing the potential of human embryonic stem cells to mimic normal and aberrant development with highly reproducible, quantitative and standardized models is a pressing challenge. I will show that self-organization can be induced to generate artificial human embryos and organoids starting from human embryonic stem cell (hESCs) assemblies grown under defined architectures and stimulated with simple chemical cues. This leads to the formation of complex structures with many cell types that not only carry the molecular signature of the in-vivo counterparts, as quantified by single-cell RNA sequencing, but also present a layered tri-dimensional organization which closely resembles the embryonic context. We most recently applied this strategy to early human neurulation, generating "neuruloids" which harbor ectodermal derivatives within the same self-organized tissue: neural progenitors, neural crest, sensory placode, and epidermis. This work led to the first molecular signature of the lineages involved in human neurulation in the context of the entire ectodermal compartment. Moreover, using an isogenic series of hESCs modeling the genetic basis of Huntington's Disease (HD), we were able to reveal subtle phenotypic signatures associated with HD in a human developmental context. Finally, we turned these phenotypic readouts into highly quantitative screening platforms by integrating machine learning algorithms for unbiased phenotypic analysis, which will allow an unbiased identification of therapeutics for HD. This illustrates the clinical relevance of our disruptive new platforms.

Funding Source: This work, in part, was funded by the NIH and private sources.

13:51 – 14:02

DERIVATION OF FOLLICULOGENIC DERMAL PAPILLA CELLS FROM HUMAN IPSC

Pinto, Antonella[1], Chermnykh, Elina[2], Kalabusheva, Ekaterina[2], Vorotelyak, Ekaterina[2], Steiger, Wolfgang[3], Ovsianikov, Aleksandr[3], Chaffoo, Richard[4] and Terskikh, Alexey[1]

[1]Neuroscience, Aging and Stem Cell Research Department, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA, USA, [2]Koltzov Institute of Developmental Biology, Russian Academy of Sciences, Moscow, Russia, [3]Bioengineering Science, Technische Universität Wien, Wien, Austria, [4]Plastic Surgery and Cosmetic Dermatology, La Jolla Skin, La Jolla, CA, USA

Human induced Pluripotent Stem Cells (iPSCs) have been directed to various cell fates, however, the derivation of Dermal Papilla (DP) cells from iPSCs was challenging. DP plays a dominant role during hair follicle morphogenesis and is critical in defining hair thickness, length, and hair cycle. We report, for the first time, the derivation of functional human DP cells from iPSCs using a Neural Crest (NC) cell intermediate. We investigated the effect of growth factors such as Wnt, FGF, BMP, and R-spondin on the differentiation of iPSC-derived NC cells into DP cells. We observed that the activation of the Wnt pathway enhances the differentiation process, as demonstrated by the expression of classical DP cell markers (Versican and Alkaline Phosphatase) and the up-regulation of relevant DP genes (Nexin, Corin, LEF1, SDC1, HEY1, EGR3). To confirm the identity of iPSC-DP cells in vitro, we compared, at a single cell level, the gene expression profile of iPSC-DPs with that of freshly isolated human adult DP cells including the 3D environment-induced modulation of gene expression. Transplantation of human iPSC-derived DP cells aggregated with mouse E18.5 epithelial cells inside the microscaffolds into the skin of Nude mice resulted in prolonged and robust hair growth. The ability to regenerate hair follicles from cultured iPSC-induced human cells will transform the management of hair loss disorders, which represent an unmet medical need. In addition, modeling of hair growth using organoids will advance the field of regenerative medicine and patient-derived organoids could be used to interrogate drug response for the purpose of personalized medicine.

Funding Source: The work was funded by the Russian Science Foundation (Project No16-14-00204).

14:02 – 14:13

SELF-ASSEMBLED EMBRYO-LIKE STRUCTURES COMPRISING THREE TYPES OF BLASTOCYST-DERIVED STEM CELLS

Han, Jianyong

College of Biological Sciences, State Key Laboratory for Agrobiotechnology, China Agricultural University, Beijing, China

Spatially ordered assembled embryos comprising blastocyst-derived stem cells are pursued to mimic embryogenesis in vitro. However, assembly system and development potential of the structures need to be further studied. Here, we show that reconstructed structures can be self-assembled with embryonic stem cells (ESCs) and extra-embryonic endoderm stem cells (XENCs), termed EXE-embryos; or, interestingly, with ESCs, trophoblast stem cells (TSCs) and XENCs (ETX-embryos) through their self-recognition and aggregation under no-adherent suspension shaking culture condition, and the morphogenesis of these structures are similar to that of natural embryos. In EXE-embryos, the ESCs, which are surrounded by XENCs, can give rise to polarized rosette-like structures and undergo cavitation, similar to how the epiblast structure develops in natural embryos. When developed in vitro, the ETX-embryos exhibit lumenogenesis, asymmetrical expression of mesoderm and primordial germ cell (PGC) markers as well as formation of anterior visceral endoderm-like tissues. After transplantation into the uterus of pseudopregnant mice, the ETX-embryos efficiently initiated implantation. The ability of the three distinct stem cell types to undergo spatially

ordered self-assembly and development in vitro provides new insights into studies of embryogenesis.

Funding Source: This work was supported by China National Basic Research Program (2016YFA0100202), National Natural Science Foundation of China (31571497, 31601941 and 31772601).

14:13 – 14:24

3D BIOPRINTING A CONTRACTILE VENTRICLE USING HUMAN STEM CELL-DERIVED CARDIOMYOCYTES

Lee, Andrew, Bliley, Jacqueline, Shiwarski, Dan, Tashman, Josh, Hudson, Andrew, Hinton, Thomas and Feinberg, Adam

Department of Biomedical Engineering, Carnegie Mellon University, Pittsburgh, PA, USA,

Myocardial infarction is a leading cause of death due in large part to the limited regenerative capacity of the adult heart. Human embryonic and induced pluripotent stem cell-derived cardiomyocytes have provided a new way to rebuild the myocardium, but these cells are phenotypically immature and difficult to organize into functional muscle. Tissue engineering promises to replace scar with aligned, contractile cardiac tissues, but to date has been limited to simple geometries and fabrication processes that lack scalability towards more complex organ-scale constructs. Here we report the development of a 3D model of the left ventricle using the Freeform Reversible Embedding of Suspended Hydrogels (FRESH) 3D bioprinting technique. FRESH is a 3D bioprinting approach specially developed for cells and hydrogels, and works by printing within a temperature sensitive support material that is gently melted away after the printing process. We used FRESH in a dual material strategy that printed collagen type I bioink as a structural material and a high-density cellular bioink composed of human embryonic stem cell-derived cardiomyocytes (hESC-CMs) as the contractile component. The ventricle was designed on the scale of an embryonic heart as an ellipsoidal shell 8 mm from base to apex and 7 mm at its largest diameter. The ventricle was printed with high fidelity, and after 7 days in culture had visible, synchronized contractions. A dense layer of interconnected and striated hESC-CMs was found throughout the ventricle, confirmed by immunofluorescent of sarcomeric alpha-actinin. The ventricles had a baseline spontaneous beat rate of ~0.5 Hz and using field stimulation could be captured and paced up to 2 Hz. Calcium imaging of the spontaneous contractions revealed propagation of calcium waves with conduction velocities of ~1 cm/s. Finally, we observed wall thickening of ~13% at 1 Hz pacing and a decrease in cross-sectional area of the ventricular chamber, suggesting we were able to achieve similar contractility to native myocardium. Together, these results demonstrate that collagen and hESC-CMs can be bioprinted together into ventricular constructs that exhibit key functional metrics of that heart, including synchronized contraction, action potential propagation, and wall thickening.

Funding Source: NIH award numbers DP2HL117750 and R21HD090679, NSF award number CMMI 1454248, the Office of Naval Research award number N00014-17-1-2566, and CMU Bioengineered Organs Initiative.

14:24 – 14:35

SYNTHETIC GENETIC CIRCUITS TO CONTROL STEM CELL PROGRAMS IN TISSUE ASSEMBLY

Morsut, Leonardo

Stem Cell Biology and Regenerative Medicine, Keck School of Medicine, University of Southern California (USC), Los Angeles, CA, USA

Current technologies and protocols for directing stem cells into tissue and organs in vitro are based on providing the right combination of external stimuli: growth factor signals, scaffold/matrix interactions, cell-cell interactions, and others. Collectively, these inputs can instruct and influence the endogenous self-organization potential of the system. To overcome current limitations in in vitro grown tissues (e.g. lack of vascularization, poor cellular-scale geometric recapitulation of in vivo counterparts), we have developed genetic technologies in stem cells that program their self-organization potential itself. I will present the use of a combination of synthetic reprogramming pathways and genetic circuits that drive self-organization in complex cellular patterns. The platform offers a powerful new layer of intervention for spatial and temporal control of stem cell differentiation. Using synthetic Notch (synNotch) receptors as sensors, and master transcription factors as outputs, we engineered stem cells or fibroblasts to undergo controlled differentiation in response to synthetic ligands presented by neighboring cells or extracellular scaffolds. Fibroblasts were reprogrammed to multinucleated, contractile, skeletal myoblasts or cardiomyocytes, and human iPSCs to functional motorneurons and endothelial cells. By combining synthetic reprogramming with genetic circuits, spatial and temporal patterning can be set completely autonomously or can adopt scaffold-directed geometries. We have successful implemented the programmed organization of multi-layered structures including multi-polar structures in 2D and 3D, and tubular structures within solid tissues. We are harnessing these technologies to establish vascularized muscular tissue and neuromuscular junctions in the tissue culture dish. Controlled tissue assembly in vitro can be used to explore cell-cell interactions, study and model disease, and facilitate drug development.

Funding Source: Research is supported by an R00 grant from the National Institute of Biomedical Imaging and Bioengineering (4R00EB021030-03).

14:35 – 14:46

LONG-TERM PERFORMANCE OF IMPLANTED BIOPRINTED HUMAN LIVER TISSUE IN A REGENERATIVE MOUSE MODEL OF LIVER FAILURE

Crews, Leslie A.[1], Jamieson, Catriona[1], Joshi, Vaidehi[2], Ma, Wenxue[1], Mondala, Phoebe[1], Shepherd, Benjamin[2] and Wiese, Julie[2]

[1]Division of Regenerative Medicine, University of California, San Diego, La Jolla, CA, USA, [2]Therapeutics, Organovo Holdings, Inc., San Diego, CA, USA

Regenerative medicine and tissue engineering approaches to treating liver diseases and injury are limited by relatively low graft durability as well complications like portal hypertension. Bioengineered regenerative medicine technologies, such as 3D bioprinting, are an essential step towards the clinical success of cellular therapeutics and may have broad applicability ranging from treatment of inborn errors of metabolism to acute or chronic liver failure. Mutations in the fumarylacetoacetate hydrolase (FAH) gene cause Tyrosinemia I, an inborn error of metabolism characterized by increased tyrosine levels in blood and urine. Here, we report implantation and engraftment of human bioprinted therapeutic liver tissue (BTLT) containing human umbilical vein and liver endothelial cells, hepatic stellate cells (HSC) and hepatocytes in a mouse model of Tyrosinemia I. Following BTLT implantation on the surface of the liver in FRG knockout (FAH-/- / Rag2-/-/Il2rg-/-) mice, circulating human albumin was detected as early as 9 days, with increasing levels detected for at least 35 days post-implantation. In addition, fluorescent dye-labeled BTLT could be detected by in vivo imaging (IVIS), indicating successful engraftment and retention of the implanted tissue patch in a model of injury. FRG mice require supplementation with the tyrosine catabolism inhibitor, nitisinone (NTBC), to support long-term survival. Following implantation, survival analysis showed an increase in overall survival in mice treated with BTLT implants as compared to sham-operated controls. Higher body weights and lower alanine aminotransferase (ALT) levels were observed in animals that received BTLT implants compared to controls. Histopathologic evaluation of implanted BTLT revealed integration of the fabricated tissues with the host liver, and human hepatocytes in the BTLT also stained positive for albumin. Early indication of decreased tyrosine levels were also seen in treated animals. The rapid vascularization, durable tissue engraftment, cell retention, and improvement in overall animal health reveal a promising approach to treating Tyrosinemia I that will facilitate translation of novel regenerative medicine strategies for a variety of liver diseases.

Funding Source: Organovo Holdings, Inc.

14:46 – 15:06

FORCING TUMOR INITIATION AND PROGRESSION

Weaver, Valerie

University of California, San Francisco, CA, USA

Cells experience force and possess mechanotransduction machinery to detect physical cues from their microenvironment and to transduce and biochemically amplify these signals to modulate their fate and tissue development. Tumors are stiffer, show increased cell and tissue level forces and transformed cells exhibit a perturbed mechanophenotype. We have been studying how cells transduce mechanical cues to regulate their behavior and how altered force compromises tissue homeostasis to drive malignancy and metastasis. We found that the tumor ECM is remodeled and stiffened and that the magnitude of the ECM stiffening and the nature of the collagen crosslinks correlate with tumor progression and aggression. A stiffened ECM compromises tissue differentiation and organization by promoting integrin focal adhesion assembly that potentiates transmembrane receptor signaling and inducse cytoskeletal remodeling and actomyosin contractility. Sustained mechanosignaling synergizes with cancer oncogenes and reduces tumor suppressor gene levels to drive transformation and an epithelial to mesenchymal transition. We determined that cells respond to a stiffened ECM by “tuning” the magnitude of their actomyosin tension to align with the stiffness of their microenvironment. Elevated cell tension fosters focal adhesion assembly and activates ion channels to enhance transmembrane receptor signaling that promote proliferation, survival, and invasion. A stiff tissue also expands the tumor glycocalyx and increases the frequency of tumor stem-like cells that contributes to tumor aggression, treatment resistance and tumor recurrence. We discovered that a stiff ECM can also expand the frequency of stem-like cells in a normal tissue. We found that women with high mammographic density with a fourfold increased risk to malignancy have 4 times the number of stem-like cells. The stiff breast stroma in these women modifies progesterone transcription in their breast cells to increase RANKL expression that expands the stem cell frequency, as illustrated in experimental models. Current studies are now being directed to determine how these findings could be used to identify new biomarkers, treatment modalities to potentiate current therapies and for chemoprevention.

THURSDAY, 27 JUNE, 13:15 – 15:15

CONCURRENT IB: STEM CELL-BASED DISEASE MODELING

Concourse F, Level One

13:20 – 13:40

MODELING DISEASE BIOLOGY WITH HUMAN STEM CELL-DERIVED CELLS TO ENABLE DRUG DISCOVERY

Engle, Sandra J., Mekhoubad, Shila and Kleiman, Robin

Biogen, Norfolk, MA, USA

The use of human iPSC-derived cells to develop physiologically relevant in vitro models to enable drug discovery has been a goal since the inception of the technology. Making that goal a reality has been a journey. It has required the confluence of numerous other technologies in order to lay the groundwork for success. More significantly it has required those of us involved in drug discovery to think differently about what we model and how we do it. In this presentation, I will focus on how human stem cell-derived cells are becoming an integral component of the drug discovery process, drawing form examples in neuroscience and highlighting where the technology may evolve.

13:40 – 13:51

MODELING THE EFFECTS OF CHOLESTEROL ON ALZHEIMERS DISEASE PATHOGENESIS IN IPSC DERIVED NEURONS

Langness, Vanessa[1], Das, Utpal[1], van der Kant, Rik[2] and Wang, Louie[1]

[1]Cell and Molecular Medicine, University of California, San Diego (UCSD), La Jolla, CA, USA, [2]Department of Functional Genomics, Center for Neurogenomics and Cognitive Research, Amsterdam Neuroscience, VU University Amsterdam, Netherlands

Alzheimer's disease (AD) is a progressive neurodegenerative disease that results in loss of neurons and synapses. Brains from human patients with AD exhibit two defining pathological changes: Accumulation of extracellular amyloid plaques which are composed of amyloid beta (Aß) and accumulation of intracellular neurofibrillary tangles which are made up of hyperphosphorylated tau (pTau) protein. These changes are toxic and contribute to the devastating neurodegeneration that occurs in AD. Recent developments in disease modeling using human induced pluripotent stem cells (hiPSCs) have allowed for modeling of Alzheimer's disease in human neurons in a dish. We can measure Aß and pTau levels in these hiPSC derived neurons allowing us to study how the levels of these proteins become dysregulated in AD. Genetic, biochemical, pharmacological, and epidemiological data suggest a role for cholesterol in AD pathogenesis. Recent studies have shown that amyloid precursor protein (APP), the precursor to Aß contains a cholesterol binding site. We use cholesterol lowering drugs and CRISPR/CAS9 genome editing to study how cholesterol levels and mutations that abolish APP-Cholesterol binding influence Aß and pTau burden. Our data indicate that cholesterol levels influence levels of these toxic proteins and thus could lead to new therapeutic avenues for AD treatment.

13:51 – 14:02

SKEWED FATE CHOICE AND DELAYED NEURONAL MATURATION OF NEURAL STEM CELLS FROM AN AUTISM PATIENT WITH BI-ALLELIC NRXN1 MUTATION REVEALED BY SINGLE CELL RNA-SEQ

Falk, Anna

Neuroscience, Karolinska Institutet, Stockholm, Sweden

To investigate the role for NRXN1 in early human brain development we generated human iPS derived neural stem cells and differentiated cells (neurons and glia) from a healthy control individual and an individual with autism spectrum disorder carrying bi-allelic NRXN1-alpha deletion. We investigated the expression of NRXN1-alpha during neural induction of iPS cells and during neural stem cell differentiation and observed a key role for NRXN1-alpha. Single cell RNA-sequencing showed that NRXN1-alpha deleted neural stem cells shifted fate towards radial glia-like cell identity. One month differentiation of the patient neural stem cells revealed considerably higher proportion of astroglia differentiation with a ratio of 50/50 neurons versus glia, compared to control cell culture that harbored mostly neurons at this time point. Further, the NRXN1-alpha deleted cells differentiated towards neurons were more immature when compared to neuronal control cells shown both by gene expression and by function confirmed by significant depression of calcium signaling activity. Our observations propose that NRXN1-alpha have an important role for efficient establishment of neural stem cells and in differentiation of functional neuronal cells.

14:02 – 14:13

SURF1 MUTATIONS CAUSATIVE OF LEIGH SYNDROME IMPAIR HUMAN NEUROGENESIS

Prigione, Alessandro[1], Inak, Gizem[1], Lisowski, Pawel[1], Mlody, Barbara[1] and Schuelke, Markus[2]

[1]Neuroproteomics, Max Delbrueck Center for Molecular Medicine, Berlin, Germany, [2]Neuropediatrics, Charité University, Berlin, Germany

Mutations in the mitochondrial complex IV assembly factor SURF1 represent a major cause of Leigh syndrome (LS), a rare fatal neurological disorder. SURF1-deficient animals failed to recapitulate the neuronal failure of LS, which is considered an early-onset neurodegeneration. We generated induced pluripotent stem cells (iPSCs) from LS patients carrying homozygous SURF1 mutations and corrected the mutations on both alleles with CRISPR/Cas9. We discovered that aberrant bioenergetics initiates in neural progenitor cells (NPCs), leading to an impairment of neuronal maturation, branching, and activity. iPSC-derived cerebral organoids recapitulated the neurogenesis defects and appeared smaller with reduced cortical thickness. Our data imply that SURF1 deficiency causes a failure in the development of maturing neurons rather than an early-onset degeneration of already fully functional neurons. Using NPC function as an interventional target, we identified SURF1 gene augmentation as a strategy for restoring neural function in this fatal disease.

14:13 – 14:24

GENE REGULATION BY TRANSCRIPTION FACTOR DOSAGE IN A HUMAN CELLULAR MODEL OF CONGENITAL HEART DISEASE

Kathiriya, Irfan[1], Rao, Kavitha[1], Garay, Bayardo[1], Lai, Michael[1], Goyal, Piyush[1], Akgun, Gunes[1], Iacono, Giovanni[2], Bernard, Laure[1], Wasson, Lauren[3], Sukonnik, Tatyanna[1], Heyn, Holger[2], Seidman, Jonathan[3], Seidman, Christine[4] and Bruneau, Benoit[1]

[1]Gladstone Institute of Cardiovascular Disease, J. David Gladstone Institutes, San Francisco, CA, USA, [2]Centre for Genomic Regulation, Barcelona Institute of Science and Technology, Barcelona, Spain, [3]Department of Genetics, Harvard Medical School, Boston, MA, USA, [4]Cardiovascular Genetics Center, Brigham and Women's Hospital, Boston, MA, USA

Cellular responses of gene expression to changes in gene dosage are not understood. Many human mutations that lead to congenital heart disease (CHD) cause a reduction in gene dosage. Heterozygous mutations in the T-box transcription factor (TF) gene TBX5 lead to haploinsufficiency, which causes CHDs and

arrhythmias in humans and mice. Homozygous deletion of Tbx5 in mice leads to severe malformations of the developing heart, and in humans, is presumed to cause fetal demise. It remains unknown how reducing cardiac TF dosage causes aberrant cardiac gene regulation and heart defects. In a human cellular disease model, we attempt to define human cell types that are vulnerable to reductions in TBX5 gene dosage. We engineered and isolated an allelic series of isogenic human iPSCs with heterozygous or homozygous loss of function mutations for TBX5. We differentiated these iPSCs to cardiomyocytes (CM) in vitro and deployed single-cell RNA-seq to follow the consequences of reducing gene dosage on gene expression in individual cells. We observed a TBX5 dose-dependent delay in the onset of beating, impaired differentiation efficiency, and electrophysiologic abnormalities. We used this platform to examine the effects of TF dosage on human gene regulation in single cells. We profiled nearly 80,000 cells by single cell RNA-seq at three time points across the TBX5 allelic series. We discovered discrete responses to TBX5 dosage among specific cell populations, as well as classes of dosage-sensitive gene expression dynamics in a subset of cardiomyocytes. Thus, we define gene regulation networks that respond to altered TBX5 dosage in a human disease model at single-cell resolution. Our results reveal unforeseen complexity of human in vitro differentiation and an exquisite sensitivity in discrete cell populations to graded TBX5 dosage. These findings uncover molecular insights underlying gene dosage, gene regulation and the development of human CHD.

14:24 – 14:35

IN VIVO TUMOR FORMATION OF HUMAN NEUROBLASTOMA IN INTERSPECIES CHIMERAS

Cohen, Malkiel A.[1], Zhang, Shupei[1], Sengupta, Satyaki[2], Ma, Haiting[1], Horton, Brendan[3], George, Rani[2], Spranger, Stefani[3] and Jaenisch, Rudolf[1]

[1]Massachusetts Institute of Technology, Whitehead Institute for Biomedical Research, Cambridge, MA, USA [2]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA, [3]Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, MA, USA

Interspecies chimeras represent a promising experimental system for studying human development and disease and may provide the most physiologically relevant environment to study human disease in an in vivo context by overcoming some of the limitations of conventional animal models. We have previously described the generation interspecies neural crest (NC) chimeras from pluripotent stem cells. We showed that human pluripotent stem cells-derived human NC cells, when injected into the gastrulating mouse embryo, migrated along the dorso-lateral migration route contributing to the pigment system of the mouse, suggesting that this platform may use to model neurocristopathies in vivo. Neuroblastoma (NB), derived from the NC, is the most common pediatric extracranial solid tumor. Here we report the establishment of a platform that allows studying human NBs in mouse-human NC chimeras. Chimeric mice were produced by injecting human NCs carrying NB relevant oncogenes in utero into gastrulating mouse embryos. The mice developed tumors composed of a heterogeneous cell population that closely resembled that seen in primary NBs of patients but were significantly different from homogenous tumors formed in xenotransplantation models. The human tumors emerged in immunocompetent hosts and were extensively infiltrated by mouse cytotoxic T cells reflecting a vigorous host anti-tumor immune response. However, the tumors blunted the immune response by inducing infiltration of regulatory T cells and expression of immune checkpoints similar to escape mechanisms seen in human cancer patients. Thus, this experimental platform allows studying human tumor initiation, progression, manifestation and tumor – immune-system interactions in an animal model system. This chimeric model may further allow the study other neurocristopathies, providing in vivo readouts, drug efficacy and toxicity, with relevant clinical value.

Funding Source: This work was supported by grants from the Emerald Foundation, the LEO Foundation (L18015), the St. Baldrick's Foundation and by the R37HD045022, 1R01-NS088538 and 5R01-MH104610 NIH grants.

14:35 – 14:46

CHEMICAL INDUCTION OF AGING PHENOTYPES IN STEM CELL-DERIVED NEURONS FOR MODELING NEURODEGENERATIVE DISEASES

Fathi, Ali, Petersen, Andrew, Harder, Cole, Block, Jasper, Miller, Julia, Bhattacharyya, Anita and Zhang, Su-Chun

Waisman Center, School of Medicine and Public Health, University of Wisconsin-Madison, WI, USA

Modeling age-related neurodegenerative disorders with human stem cell-differentiated neurons is challenging due to the embryonic age of stem cell derived neurons. Genetic introduction of aging related genes like progerin endows young cells with aging phenotypes and enhances phenotypic presentation from patient stem cell-derived neurons, but such a strategy is complicated by changes associated by the transgene. To overcome this issue, we developed a chemical cocktail to induce cellular senescence in iPSC-derived neurons. We first screened small molecules that induce embryonic fibroblasts to exhibit age-related features as presented by aging fibroblasts, including changes in chromatin methylation and senescence associated proteins. We then optimized a cocktail of small molecules that induces aging related changes in fibroblasts and cortical neurons without causing apoptosis. The utility of the "aging cocktail" was validated in motor neurons derived from ALS patient iPSCs. In the presence of the "aging cocktail", ALS patient iPSC-derived motor neurons exhibited protein aggregation and axonal degeneration substantially earlier than those without the treatment of the cocktail and isogenic control neurons. Our "aging cocktail" will likely enhance the manifestation of disease-related phenotypes in neurons derived from iPSCs with a range of neurological disorders in a consistent manner, enabling the generation of reliable drug discovery platforms.

Funding Source: This study was supported in part by a core grant to the Waisman Center from the National Institute of Child Health and Human Development (U54 HD090256)

14:46 – 15:06

CHALLENGES FOR IN VITRO MODELING OF HUMAN BRAIN DISEASE

Kriegstein, Arnold R., Bhaduri, Aparna**,** Andrews, Madeline**,** DiLullo, Elizabeth and Pollen, Alex

Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research and Department of Neurology, University of California, San Francisco, CA, USA

Patient-derived cerebral organoids are an exciting in vitro model that enable long term culture and functional investigation of the process of brain development and the pathophysiology of diseases that are otherwise inaccessible in primary human tissue. But how closely do the in vitro models resemble normal human brain development? To evaluate the fidelity of cerebral organoids to primary developing human cortex, we performed single-cell RNA sequencing of 200,000 cortical organoid cells across developmental stages generated with a range of protocols, from undirected signaling to strongly directed forebrain protocols. Using this dataset, as well as published sequencing datasets from cortical organoids, we compared cell type identity and molecular signatures of the organoid model to primary developing human cortex single-cell RNA sequencing data obtained in our laboratory. Molecular trajectories indicate that while cerebral organoids effectively recapitulate neuronal differentiation programs, the precise specification of radial glia and neuronal subtypes observed in normal human development is obscured in the organoid model. Comparisons of molecular maturation states between organoids and primary samples indicate that the cortical organoid models mature substantially faster than primary developing cortical counterparts. Interestingly, area-specific neuronal signatures are a hallmark of primary human newborn neurons, and in some cases the organoid newborn neurons recapitulate these identities, but in most cases, they express no previously characterized area-specific neuronal transcriptomes. Across all organoid datasets explored, we find a significantly higher expression of markers of glycolysis and endoplasmic reticulum stress in cortical organoids compared to primary developing cortex that we subsequently validate with immunohistochemistry. Together, these findings highlight that although there are important benefits to in vitro cerebral organoid models, their fidelity to normal developmental processes could be improved and the differences between organoids and primary tissue should be accounted for when designing and interpreting disease mechanisms.

THURSDAY, 27 JUNE, 13:15 – 15:15

CONCURRENT IC: STEM CELL AGING

Room 502, Level Two

13:20 – 13:40

ADULT STEM CELL CLOCKS IN HOMEOSTASIS AND AGING

Aznar Benitah, Salvador

Institute for Research in Biomedicine (IRB Barcelona), Spain

We interested in studying how adult stem cells maintain tissue homeostasis, and why and how their striking regenerative capacity is altered during aging. We have previously shown that the activity of adult stem cells is under robust circadian control. This allows not only allows stem cells to anticipate correct functions according to the time of the day, but also to temporally segregate functions that would cause harm if coincident. Importantly, we and others have shown that stem cell circadian arrhythmia leads to a premature ageing phenotype and shortened lifespan. Moreover, our recent results show that the oscillating transcriptome is extensively reprogrammed in physiologically aged stem cells, switching from genes involved in homeostasis to those involved in tissue-specific stresses. I will discuss the functional consequence of circadian rewiring in several tissues, how it is influenced by dietary interventions, and present new data using a novel mouse model of reverse circadian arrhythmia to define its consequences on tissue and organismal ageing.

13:40 – 13:51

A SINGLE-CELL TRANSCRIPTOMIC ATLAS OF ARTERIAL AGING OF CYNOMOLGUS MONKEY

Zhang, Weiqi[1], Qu, Jing[2] and Liu, Guang-hui[3]

[1]Beijing Institute of Genomics, Institute of Biophysics, Chinese Academy of Sciences, Beijing, China, [2]Institute of Zoology, Chinese Academy of Sciences, Beijing, China, [3]Institute of Biophysics, Chinese Academy of Sciences, Beijing, China

Our understanding of how human aging affects the cellular and molecular components of the vasculature and contributes to cardiovascular disease is still limited. Here we report a single-cell transcriptomic survey of aortic arches and coronary arteries in young and old cynomolgus monkeys. Our data defined the molecular signatures of specialized arteries, and identified eight novel markers for experimentally discriminating aortic and coronary vasculature. Gene network analyses characterized transcriptional landmarks that regulate vascular senility, and positioned FOXO3A, a longevity-associated transcription factor, as a master regulator gene that was downregulated in six subtypes of monkey arterial cells during aging. Targeted inactivation of FOXO3A in human vascular endothelial cells recapitulated the major phenotypic defects observed in aged monkey arteries, verifying that FOXO3A is a functional geroprotective factor in endothelial cells. Our study provides a critical resource for understanding the principles underlying arterial aging and contributes important clues for future treatment of age-associated vascular disorders.

13:51 – 14:02

THE IDENTIFICATION OF A NOVEL PERI-ARTERIAL SKELETAL STEM/PROGENITOR CELL IN ADULT BONE MARROW

Shen, Bo and Morrison, Sean

Children's Research Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA

Leptin Receptor-expressing (LepR+) stromal cells in adult bone marrow are highly enriched for skeletal stem cells and are a ma-

jor source of osteoblasts and adipocytes. We discovered that these cells produce a previously uncharacterized bone-forming growth factor, Clec11a/Osteolectin, which promotes the osteogenic differentiation of LepR+ cells and is required for the maintenance of adult skeletal bone mass. Osteolectin-deficient mice appeared developmentally normal but exhibited accelerated bone loss during adulthood. Osteolectin promotes osteogenic differentiation by binding to alpha11 integrin and promoting integrin signaling, leading to Wnt pathway activation. Conditional deletion of alpha11 integrin in LepR+ cells phenocopies Osteolectin deficiency, leading to accelerated bone loss during adulthood. To test if Osteolectin expression could refine the identification of skeletal stem/progenitor cells in vivo, we generated a knock-in tdTomato reporter. We found that Osteolectin was expressed by only a subset of LepR+ cells. Interestingly, Osteolectin was exclusively expressed by peri-arterial LepR+ cells. RNA-seq analysis comparing Osteolectin+ and Osteolectin- stromal cells showed that Osteolectin+ cells were highly enriched for osteogenic gene expression. Osteolectin+ cells formed CFU-F colonies in culture that could be passaged multiple times. The Osteolectin+ cells exhibited robust osteogenic and chondrogenic differentiation in culture, but limited adipogenic differentiation. To test if these Osteolectin+ cells function as skeletal stem/progenitor cells in vivo, we generated a knock-in creER allele. Fate-mapping revealed that Osteolectin+ cells contribute significantly to bone regeneration. The discovery of a previously unrecognized peri-arteriolar skeletal stem/progenitor cell suggests the existence of a peri-arteriolar niche for skeletal stem/progenitor cells in the bone marrow.

Funding Source: NHLBI (1F32HL139016-01) for Bo Shen HHMI and NIA (R37 AG02494514) for Sean J Morrison

14:02 – 14:13

SUPPRESSION OF THE ACTIVITY OF SMALL RHO GTPASE CDC42 AMELIORATES INTESTINAL STEM CELL AGING

Nalapa Reddy, Kodanda, Geiger, Hartmut[1], Hassan, Aishlin[2], Sampson, Leesa[2] and Zheng, Yi[1]

[1]Experimental Hematology, Cancer Biology and Stem Cell Biology, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, USA, [2]Experimental Hematology, Cincinnati Children's Hospital and Medical Center, Cincinnati, OH, USA

The regenerative potential of intestine declines upon aging. This is in part due to a decline in the function of intestinal stem cells (ISCs). The activity of the small Rho GTPase Cdc42 is critical for intestinal homeostasis. However, it is not known whether there is a role for Cdc42 in aging-associated changes in the function ISCs. Our data demonstrate that the activity of Cdc42 is increased upon aging in the intestine. Constitutive activation of Cdc42 in young animals in gene-targeted mice carrying null alleles of cdc42gap, a negative regulator of Cdc42, resulted in aging phenotypes in the intestine along with a decline of the regenerative function of ISCs. Pharmacological inhibition of the aging-associated elevated Cdc42 activity in organoid cultures from aged animals, or an administration of the inhibitor to aged animals in vivo, ameliorated the aging-associated decline of the regenerative function of ISCs. Together, this study provides evidence for a causative role of the Rho GTPase Cdc42 and its aging-associated activity in the functional decline of ISCs upon aging. Targeting the age-elevated activity of Cdc42 might thus be a novel avenue to ameliorate intestinal stem cell aging.

Funding Source: This work was supported by funds from CCHMC.

14:13 – 14:24

AGED MACROPHAGES DRIVE PERSISTENT INFLAMMATION ALTERING STEM CELL FATE DURING MOUSE MUSCLE REGENERATION

Blanc, Romeo S., Bachman, John, Paris, Nicole and Chakkalakal, Joe

Pharmacology and Physiology, University of Rochester Medical Center, Rochester, NY, USA

Aging is associated with regenerative deficits and a functional decline in resident stem cells that lead to delays in recovery from injury or permanent loss of tissue. In aged skeletal muscle, delayed regeneration occurs due to both aberrant extrinsic factors and cell-autonomous defective mechanisms. However, it is uncertain whether one predominates. Although aged human skeletal muscle can regenerate, delays in this process cause persistent physical discomfort that compromises recovery, mobility, and independence in the growing elderly population. During aged muscle regeneration, we identified macrophages as a source of aberrant inflammatory signals regulating muscle stem and progenitor cell (MSPC) fate. We tied elevated inflammation in aged regenerating muscle to reduced macrophage-mediated phagocytosis and increased expression of chemokines. Identified chemokines induced p38 mitogen-activated protein kinase (p38MAPK) signaling in MSPCs and inhibited myogenic differentiation. Accordingly, opportune inhibition of the chemokine activity or downstream p38MAPK signaling during myogenesis enhanced aged muscle regeneration. Despite the intrinsic advantages of young MSPCs, successful engraftment into an aged regenerating muscle host was only achieved when pre-treated with the chemokine inhibitor. These results illustrate the impact of the inflammatory milieu on MSPC fate and the requirement for precise manipulation of this micro-environmental component to stimulate aged tissue regenerative potential. As such, specific manipulation of the inflammatory niche provides an effective means to direct stem and progenitor cell fate, promote tissue regeneration, and accelerate regimens of recovery in aged individuals.

Funding Source: This work was supported by the NIA/NIH.

14:24 – 14:35

OVERCOMING THE AGED NICHE TO IMPROVE SKELETAL MUSCLE REGENERATION

Palla, Adelaida R., Ho, Andrew T.V., Holbrook, Colin, Yang, Ann, Kraft, Peggy and Blau, Helen

Microbiology and Immunology, Stanford University, Stanford, CA, USA

Muscle repair after injury entails an immune response that promotes efficacious regeneration. As we age, infiltration of inflammatory cells, fibroadipogenic progenitors and senescent cells leads to a deleterious microenvironment that impedes skeletal muscle regeneration. Muscle stem cells are key for regeneration, but their function and numbers decrease as we age, to great extent due to these extrinsic niche changes. Previously, we have shown Prostaglandin E2 (PGE2) is essential for skeletal muscle stem cell function in regeneration in young mice. Here we identify PGE2 signaling is dysregulated in aged skeletal muscle. By treatment with a small molecule, this aberrant signaling is surmounted, and muscle strength and regenerative capacity of aged mice are increased. Our data show a new role for PGE2 signaling in aging, and the importance of restoration of EP4 signaling to improve skeletal muscle regeneration in the aged.

14:35 – 14:46

STEM CELL COMPETITION AND DIVISION GOVERN SKIN HOMEOSTASIS AND AGEING

Matsumura, Hiroyuki[1], Liu, Nan[1], Kato, Tomoki[1], Ichinose, Shizuko[2], Takada, Aki[1], Namiki, Takeshi[3], Asakawa, Kyosuke[1], Morinaga, Hironobu[1], Mohri, Yasuaki[1], Arcangelis, Adèle[4], Labouesse, Elisabeth[4], Nanba, Daisuke[1] and Nishimura, Emi[1]

[1]Department of Stem Cell Medicine, Medical Research Institute, Tokyo Medical and Dental University, Tokyo, Japan, [2]Division of Human Gene Sciences Research, Research Center for Medical and Dental Sciences, Tokyo Medical and Dental University, Tokyo, Japan, [3]Department of Dermatology, Tokyo Medical and Dental University, Tokyo, Japan, [4]Institut de Génétique et de Biologie Moléculaire et Cellulaire, Development and Stem Cells Department, Université de Strasbourg, France

Stem cells maintain tissue homeostasis, yet the actual stem cell dynamics during aging and its relevance to organ aging are still unknown. Here we report that the expression of Collagen XVII (COL17A1), a hemidesmosome component, by epidermal stem cells fluctuates physiologically through genomic/oxidative stress-induced proteolysis and that the resulting differential expression of COL17A1 in individual stem cells generates a driving force for cell competition. In vivo clonal analysis in mice and in vitro 3D modeling revealed that COL17A1+ clones that divide symmetrically outcompete adjacent COL17A1 low/- stressed clones that divide asymmetrically to eliminate them. Stem cells with higher potential/quality are thus selected for homeostasis, yet their eventual loss of COL17A1 limits their competition causing aging. The resultant hemidesmosome fragility and stem cell delamination depletes adjacent melanocytes and fibroblasts to promote skin aging. Conversely, the forced maintenance of COL17A1 rescues skin organ aging thereby opening a new horizon for anti-aging therapeutic intervention.

14:46 – 15:06

UNDERSTANDING MUSCLE STEM CELL REGENERATIVE DECLINE WITH AGING

Muñoz-Cánoves, Pura

Pompeu Fabra University, ICREA and CNIC, Barcelona, Spain

Skeletal muscle has a remarkable capacity to regenerate by virtue of its resident Pax7-expressing stem cells (satellite cells), which are normally quiescent in the adult. Upon injury, quiescent satellite cells activate and proliferate, to subsequently differentiate and form new myofibers or self-renew to restore the quiescent satellite cell pool. Through a combination of global gene expression/bioinformatics and molecular/cellular in vitro and in vivo assays, we found that resting adult satellite cells have basal autophagy activity and are subjected to circadian control, and that they undergo circadian reprogramming with aging. Interestingly, autophagy was identified as one of the intracellular processes that are oscillatory in adult, but not aged, muscle stem cells. Thus, we propose that, through controlling distinct activities, proteostasis maintains muscle stem cell homeostasis and rhythmicity, while its decay is causally implicated in stem cell aging, a process that can be targeted for rejuvenation.

THURSDAY, 27 JUNE, 13:15 – 15:15

CONCURRENT ID: STEM CELL HETEROGENEITY

Room 408A, Level Two

13:20 – 13:40

A NEW MECHANISM UNDERLYING HETEROCHROMATIN FORMATION DURING EMBRYONIC STEM CELL DIFFERENTIATION

Plath, Kathrin

University of California, Los Angeles School of Medicine, Los Angeles, CA, USA

One of critical questions of embryonic stem cell (ESC) differentiation is how gene silencing and heterochromatin are established. Conversely, during reprogramming to iPSCs, heterochromatin represents a barrier to the process and needs to be erased. We study the X-chromosome-inactivation (XCI) process, mediated by the lncRNA Xist, to understand how heterochromatin is formed during differentiation and reset during reprogramming. We uncovered a function for several Xist-interacting proteins in XCI. We show that these factors directly bind Xist and engage in functional RNA-protein and protein-protein interactions that seed the formation a higher-order condensate within the inactive X-chromosome in a time-dependent manner. The formation of this assembly is required to maintain Xist localization and complete and sustain transcriptional silencing during the initiation of XCI. Our work shows that RNA binding proteins, known for their function in RNA splicing and processing, have a critical role in

heterochromatin formation, and suggests an essential function for phase-separation in gene regulation.

13:40 – 13:51

LOCATION-DEPENDENT MAINTENANCE OF AN INTRINSIC, DIFFERENTIAL SUSCEPTIBILITY TO MTORC1-DRIVEN TUMOR GROWTH IN A PERSISTENT STEM CELL NICHE

Ihrie, Rebecca[1], Rushing, Gabrielle[1], Brockman, Asa[1], Bollig, Madelyn[2], Chervonski, Ethan[2], Leelatian, Nalin[3], Mobley, Bret[4], Irish, Jonathan[1], Fu, Cary[5] and Ess, Kevin[5]

[1]Cell and Developmental Biology, Vanderbilt University, Nashville, TN, USA, [2]Neuroscience Program, Vanderbilt University, Nashville, TN, USA, [3]Cancer Biology Program, Vanderbilt University, Nashville, TN, USA, [4]Pathology, Microbiology, and Immunology, Vanderbilt University Medical Center, Nashville, TN, USA, [5]Neurology, Vanderbilt University Medical Center, Nashville, TN, USA

The neural stem cells of the ventricular-subventricular zone (V-SVZ) have a 'positional identity' imparted by developmental programming - their location within different zones of this physically extensive stem-cell niche predicts the type and location of the mature progeny produced. These fate differences were first defined by the localized expression of transcription factors; however, whether a cell's location of origin within the V-SVZ results in differential post-translational signaling activity or tumor formation when a neoplastic mutation is introduced was unknown. We used a novel approach to measure phosphorylation events at the single cell level in these populations. This revealed previously unappreciated differences in mTORC1 signaling, a central pathway vital for controlling cell size and protein translation, in dorsal versus ventral V-SVZ stem/progenitor cells in both mouse and human brain. Further, we demonstrated that this difference links directly to preferential tumor development by cells from the ventral V-SVZ. Using a mouse model of the mTORC1-driven disorder Tuberous Sclerosis Complex, we demonstrated that ventral progenitor cells preferentially proliferate and form tumors upon mutation induction while dorsal cells do not. Complementing this finding, periventricular tumors found in Tuberous Sclerosis Complex patients highly express markers of ventral neural stem cell identity. Thus, per-cell quantification of signal transduction intermediates in freshly dissociated V-SVZ tissues and cultured stem/progenitor cells led to the demonstration of a positionally defined V-SVZ subpopulation preferentially forming tumors in a mouse model of a human disorder. This work provides a provocative model to understand differing stem cell responses after assault by a common genetic mutation, and reveals a new feature which may be used to selectively target tumor-forming cells while sparing the normal stem-cell niche. More broadly, this concept is potentially relevant to tumor types outside the brain, including those in the skin and GI tract, where progenitor cells display transcriptional and post-translational differences at different physical locations within these complex and constantly renewing tissue types.

13:51 – 14:02

HUMAN BASAL PROGENITOR CELL DIVERSITY AND INVOLVEMENT IN LUNG REMODELLING

Carraro, Gianni[1], Mulay, Apoorva[1], Petrov, Martin[1], Konda, Bindu[1], McQualter, Jonathan[2] and Stripp, Barry[1]

[1]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [2]Cell Biology and Anatomy, RMIT University, Melbourne, Australia

Hyperplasia of basal cells is pathognomonic of several lung diseases, including cystic fibrosis, chronic obstructive pulmonary disease, and interstitial lung diseases. In the normal lung basal cells function as a progenitor cell for maintenance of pseudostratified airways. To characterize how basal cells change in chronic lung disease we have used a combination of FACS and single cell RNA sequencing. This approach allowed to reveal the diversity of basal cell types in normal human airways. We reconstructed basal cell heterogeneity in the normal lung and through use of novel surface markers for fractionation of basal cell subsets have used three-dimensional organoid culture models to reveal their distinct functional properties. Novel disease-dependent changes in the molecular phenotype of basal cells raise the possibility of previously unappreciated roles for basal cells in coordination of repair and remodelling responses in chronic lung disease.

Funding Source: Supported by funding from California Institute for Regenerative Medicine (CIRM), the NIH (NHLBI), and the Cystic Fibrosis Foundation (CFF).

14:02 – 14:13

FUNCTIONAL PROGENITOR CELL HETEROGENEITY IN THE MOUSE ESOPHAGEAL EPITHELIUM

Grommisch, David[1], Giselsson, Pontus[2] and Genander, Maria[1]

[1]Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden, [2]Automatic Control, Lunds Tekniska Högskola, Lund, Sweden

The esophageal epithelium possesses a remarkable proliferative capacity. A single progenitor cell population is believed to maintain the epithelium during homeostasis. However, the studies from which this hypothesis arose is based on lineage tracing data generated from randomly recombined progenitors at single cell density, and do not formally exclude the existence of functionally distinct subpopulations of esophageal progenitor cells. Here we describe a subpopulation of esophageal progenitor cells characterized by the expression of tumor necrosis factor superfamily member 19 (Tnfrsf19, Troy). We have identified single epithelial Troy+ cells scattered in the normal mouse esophageal progenitor layer. Utilizing genetic in vivo labelling and in situ hybridization, we show that Troy is expressed in ~5% of progenitor cells. Characterization of Troy+ progenitors reveal that they are slow cycling and symmetrically dividing within the basal layer. Genetically labelled single Troy+ progenitor cells are able to give rise to large long-lasting clones (<1 yr) which expand within the basal layer and consist of progenitor and differentiated cells. We demonstrate that Troy+ progenitor cells comprise a distinct, slow

cycling, progenitor population with the ability to contribute to the esophagus long-term, challenging the current progenitor cell model proposed for the esophagus.

14:13 – 14:24

EVIDENCE FOR TWO DEVELOPMENTALLY DISTINCT SKELETAL STEM CELL POPULATIONS

Ambrosi, Thomas H., Lopez, Michael, Koepke, Lauren, Hoover, Malachaia, Longaker, Michael and Chan, Charles

Department of Surgery, Stanford University, Stanford, CA, USA

Skeletal health is maintained by a balance between bone formation and resorption perpetuated by resident stem cells and their downstream cell populations. During aging and some skeletal diseases, skeletal tissue homeostasis shifts from osteochondrogenic to adipogenic fates. However, the cellular and molecular events underlying this change are not well understood. Recently, the mouse skeletal stem cell (mSSC - CD45-Tie2-CD51+CD90-6C3-CD105-) and a stem cell-like multipotent skeletal pericyte (MSP - CD45-CD31-Sca1+C24+; formerly called MSC) occupying discrete anatomical niches and displaying disparate adipogenic potentials have been reported. Here we perform detailed characterization of distinct stem/progenitor populations in bone to clearly elucidate the developmental relationship between mSSC and MSP. Experiments confirmed that mSSCs and MSPs exhibit hallmarks of adult stem cell properties in vitro and in vivo upon transplantation including self-renewal. Lineage output analysis of freshly isolated cells transplanted under the renal capsule further revealed that the two cell populations never gave rise to each other. Flow cytometry of developmentally staged tissues demonstrated that mSSCs are the main source of bone formation during embryogenesis and persist in reduced numbers throughout life. Strikingly, in contrast to MSPs they never acquire the ability to form fat in vitro or in vivo, even during advanced age. MSPs first appear shortly after blood vessel infiltration at E14.5 and peak shortly before birth. In line, subcutaneously transplanted E13.5 limbs did not contain adipocytes six weeks after, while limbs of more advanced ages did. Gene expression and gene ontogeny analysis assigned classical stem cell- and osteogenesis-related expression signatures to both cell types, while sinusoidal MSPs particularly expressed a high number of genes associated with metabolic activity, suggesting distinct niche functions of the two cell populations. This study provides evidence for the existence of two previously unappreciated developmentally distinct osteochondrogenic and adipogenic stem cell populations in long bones. These findings may inform development of therapeutic strategies to stimulate SSCs mediated bone formation while inhibiting MSP-derived adipogenesis in skeletal tissues.

14:24 – 14:35

IDENTIFICATION OF A NOVEL BASAL STEM CELL SUB-POPULATION IN THE PROSTATE

Zhu, Helen H.[1], Wang, Xue[2] and Gao, Wei-Qiang[3]

[1]Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, China, [2]School of Medicine, Shanghai Jiao Tong University, Shanghai, China, [3]School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

The prostate basal cell compartment is postulated to contain stem/progenitors due to its resistance to castration, capability to differentiate into basal, luminal and neuroendocrine cells, and susceptibility to oncogenic transformation. However, basal cells are heterogenous and the stem cell subpopulation within basal cells is not well elucidated. Here we uncover that the core epithelial-to-mesenchymal transition (EMT) inducer Zeb is exclusively expressed in a prostate basal cell subpopulation. The Zeb1+ basal cells possess greater efficiency to produce prostate organoids in vitro, can undergo self-renewal, and generate functional prostatic glandular structures with all three cell lineages in vivo at the single cell level. Genetic ablation studies reveal an indispensable role for Zeb1 in prostate basal cell development. In addition, utilizing unbiased single cell transcriptomic analysis of over 9000 mouse prostate basal cells, we find that Zeb1+ basal cell subset shares gene expression signatures with both epithelial and mesenchymal cells and stands out uniquely. The single cell sequencing data analysis reveals that key components of the WNT signaling pathway are enriched in Zeb1+ basal cells, and Zeb1+ prostate basal cells are expanded in APCmin mice. Moreover, Zeb1 expressing epithelial cells can be detected in human prostate samples. Our data demonstrate that these Zeb1+ cells are bona fide PSCs in the basal cell compartment. Identification of the PSC and its expression profile is crucial to advance our understanding of prostate development and tumorigenesis.

Funding Source: The study is supported by funds to by funds from the National Key RandD Program of China (2017YFA0102900), NSFC (81772743 and 81872406), Shanghai Municipal Education Commission—Gaofeng Clinical Medicine Grant Support (20181706).

14:35 – 14:46

TRACING THE HETEROGENEITY OF MOUSE SKELETAL STEM CELLS

Shu, Hui S. and Zhou, Bo

Department of Cell Biology, Shanghai Institute of Biochemistry and Cell Biology (SIBCB), Shanghai, China

Skeletal stem cells (SSCs), also known as bone marrow mesenchymal stem cells (BM-MSCs), reside in postnatal bone marrow and give rise to cartilage, bone and marrow adipocytes. SSCs have been identified in many anatomical regions of the bone, such as perivascular regions, growth plate, growth cartilage, endosteum and periosteum. Our laboratory is interested in the phenotypic and functional heterogeneity of SSCs. By genetic lineage tracing, we found that adult Lepr+ cells were multipotent progenitors of osteoblasts and marrow adipocytes. Neonatal

Col2+ chondrocytes contributed to most osteoblasts and Lepr+ stromal cells in adults. In contrast, adult Col2+ chondrocytes only contributed to a small subset of osteoblasts and Lepr+ stromal cells. c-kit was not expressed by postnatal SSCs, but by some fetal chondrocytes. Lineage-tracing of fetal, but not postnatal, c-kit+ cells marked ~20% of SSCs, generating 45% of all osteoblasts and 40% of marrow adipocytes. Conditional deletion of Kitl (c-kit ligand) from fetal, but not adult bone marrow stromal cells, markedly augmented the osteogenic and adipogenic differentiation of SSCs. Taken together, our studies highlight the heterogeneity of SSC population during development and aging.

14:46 – 15:06

Rajewsky, Nikolaus

Max Delbrück Center for Molecular Medicine, Berlin, Germany

Title and abstract not available at time of printing

THURSDAY, 27 JUNE, 13:15 – 15:15

CONCURRENT IE: NON-MAMMALIAN MODEL ORGANISMS FOR STEM CELL BIOLOGY

Room 408B, Level Two

13:20 – 13:40

HARNESSING THE REGENERATIVE ABILITY OF ZEBRAFISH TO TRANSFORM ORTHOPEDIC MEDICINE

Galloway, Jenna

Harvard Medical School and Massachusetts General Hospital, Boston, MA, USA

Tendons and ligaments are crucial for movement and providing stability to our musculoskeletal system. Injuries to these tissues affect a significant portion of the population and can be caused by trauma, sports-related overuse, and aging. In many cases these injuries also lead to osteoarthritis and eventually the need for joint replacement surgery. An understanding of the pathways that regulate tendons would have significant implications in regenerative biology applications for injury and disease in humans. Central to this challenge is to uncover new mechanisms regulating tendon cells and to define the signaling pathways and cellular events involved in their regeneration. Zebrafish and mammalian tendons are similar in their gene expression, developmental regulation, ultrastructure, and mechanical properties. As most research has focused on tendons in non-regenerative mammalian models, our understanding of the mechanisms regulating regenerative tendon healing is limited. Therefore, we have turned to the zebrafish system to establish a tendon regeneration model. We found that zebrafish have robust abilities to regenerate tendon composition and pattern after ablation of all tendon cells. Tendon cell loss disrupts the morphology of cartilage and muscle, but these defects are restored upon tendon regeneration. Using genetic lineage tracing and functional analysis, we also identify the developmental lineage relationships and pathways important for the regenerative process. In addition, the zebrafish system enables high-throughput chemical screens for compounds that promote musculoskeletal fates. A recent screen of known bioactive compound libraries identified tendon and cartilage promoting compounds with conserved activities in mammalian cell culture. Current efforts are focused on manipulating these new pathways to direct the differentiation of human pluripotent stem cells to tendon tissue. Collectively, this work introduces a new platform to study tendon regeneration using the zebrafish model and establishes a framework to identify new regulators of tendon biology that have application to humans. Together, these approaches in the zebrafish model will impact the design of therapies for Orthopaedic injury and disease in humans.

13:40 – 13:51

CALCINEURIN SCALES REGENERATING ZEBRAFISH FINS BY REGULATING THE BIOELECTRICAL PROPERTIES OF THEIR CELLS

Antos, Christopher L.[1], Al-Far, Ezz Al-Din Ahmed[2], Wagner, Michael[2] and Yi, Chao[1]

[1]School of Life Science and Technology, ShanghaiTech University, Shanghai, China, [2]Pharmacology and Toxicology, Technische Universitaet Dresden, Germany

Tissue regeneration and engineering requires coordinated scaling of all stem and progenitor cells of each tissue within an organ. This control on proportional growth is a fundamental yet poorly understood phenomenon. We previously found that the phosphatase calcineurin regulates scaling of regenerating zebrafish fins, but the mechanism through which calcineurin regulated the proportional growth remained unknown. We now show that calcineurin controls proportional growth by regulating the activity of Kcnk5b, a potassium leak channel that regulates membrane potential, and that this control of the bioelectrical properties of this channel regulates specific signal transduction pathways. Electrophysiology measurements of cells overexpressing Kcnk5b show that increasing calcineurin activity inhibits channel-mediated conductance at the plasma membrane; whereas, inhibiting endogenous calcineurin activity increases Kcnk5b activity. Interaction studies indicate that calcineurin interacts with Kcnk5b, and removal of predicted consensus calcineurin binding sites makes KcnK5b activity refractory to calcieneurin. Furthermore. we found that a phosphorylation mimic at serine 345 (Kcnk5bS345E) not only increased conductance but also made the activity of the channel resistant to calcineurin inhibitory effects, while the converse dephosphorylation mimic of the channel Kcnk5bS345A decreased channel conductance. Mimics at other serines did not have these effects and were still regulated by calcineurin. Transgenic overexpression of the mutant serine channels in vivo indicate that serine345 regulates the scaling of the fish appendages. In addition, we found that actiivation of this channel leads to the induction of conical Wnt and sonic hedgehog signaling, arguing that kcnk5b's control of tissue scaling involves more than the control of proliferative growth. Thus, we found that calcineurin

contols bioelectrical properties of cells to scale tissues by regulating specific developmental signals.

Funding Source: Deutsche Forschungsgemeinschaft Shanghaitech University

13:51 – 14:02

SINGLE-CELL DECOMPOSITION OF VERTEBRATE CELL FATE HIERARCHIES, DEVELOPMENTAL PLASTICITY, AND CONTROL LOGIC

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

Systems Biology, Harvard Medical School, Boston, MA, USA

A fundamental motivation in developmental biology is to understand the detailed molecular progression of cellular lineages, from pluripotency to adulthood. Here, using zebrafish as a model, I demonstrate a powerful application of high-throughput single-cell transcriptomics: “shotgun” reconstruction of whole-embryo developmental fate landscapes. The resulting landscape view of development provides a comprehensive molecular atlas of the emerging vertebrate body plan, facilitating cell-by-cell or tissue-by-tissue gene discovery efforts, and quantitative mapping of both mutant phenotypes and cell lineage relationships. I will discuss new topological insights gained from this view of development, new opportunities for decoding messy “salt & pepper” fate specification events, and a novel framework for studies of developmental compensation, tissue scaling, and growth control.

Funding Source: D.E.W. is supported by a K99/R00 award from NIGMS (1K99GM121852-01)

14:02 – 14:13

INVESTIGATING THE MECHANISM OF ANTERIOR-POSTERIOR AXIS FORMATION DURING REGENERATION IN THE ACOEL WORM HOFSTENIA MIAMIA

Ramirez, Alyson[1], Gehrke, Andrew[2] and Srivastava, Mansi[2]

[1]Molecular and Cellular Biology, Harvard University, Somerville, MA, USA, [2]Organismic and Evolutionary Biology, Harvard University, Cambridge, MA, USA

Despite their capacity for extensive wound healing, most vertebrate species have limited regenerative potential. Whole body regeneration, or the process of rapidly replacing missing tissue following amputation, requires the integration of patterning information along with stem cell activation. To study this process and identify mechanisms of regeneration that are potentially conserved between vertebrates and highly regenerative organisms, alternative model systems must be considered. The acoel worm Hofstenia miamia is capable of whole body regeneration due to an adult stem cell population that replaces lost tissues in response to injury. The extensive regenerative capacity of this acoel worm, coupled with additional tools including accessible embryos and a sequenced genome, make Hofstenia an ideal model system for studying regeneration, stem cell activation, and the re-establishment of patterning information following amputation. From previous studies, we show that Wnt signaling is required for establishing anterior-posterior fates during whole body regeneration. However, factors regulating the onset of Wnt signaling in the proper orientation during the early wound response and how those factors interface with the stem cell population remain unknown. Using an RNAseq time course dataset during Hofstenia regeneration, we identified several candidates acting as potential regulators of the polarity decision. Here, I present our findings on how these putative regulators are involved in regeneration and in establishing anterior from posterior. I also show evidence for polarity regulators as members of a putative gene regulatory network tied to the early wound response. This work represents, to our knowledge, one of the first demonstrated links between these processes during whole-body regeneration, revealing how these signaling pathways could instruct stem cells to respond to regenerative cues following wounding.

14:13 – 14:24

MOLECULAR SIGNATURES OF CHORDATE DEVELOPMENT: TWO DISPARATE PATHWAYS, ONE CHORDATE

Kowarsky, Mark A.[1], Anselmi, Chiara[2], Hotta, Kohji[3], Rosental, Benyamin[4], Neff, Norma[5], Ishizuka, Katherine[4], Palmeri, Karla[4], Okamoto, Jennifer[5], Gordon, Tal[6], Weissman, Irving[4], Quake, Stephen[7], Manni, Lucia[2] and Voskoboynik, Ayelet[4]

[1]Physics, Stanford University, Stanford, CA, USA, [2]Biology, Padova University, Padova, Italy, [3]Biosciences and Informatics, Keio University, Keio, Japan, [4] Institute of Stem Cell Biology and Regenerative Medicine, Stanford University, Stanford, CA, USA, [5]BioHUB, Chan Zuckerberg BioHub, San Francisco, CA, USA, [6]Zoology, Tel Aviv University, Tel-Aviv, Israel, [7]Applied Physics and Bioengineering, Stanford University, Stanford, CA, USA

Sexual development in chordates is well-described by embryogenesis. Other developmental pathways including asexual reproduction and whole body or tissue regeneration differ in origin but share essential processes such as establishment of the body axes, morphogenetic patterning and organ formation. Although studies have identified conserved aspects of embryogenesis across and within phyla, this pathway has not been linked to the other developmental pathways. In particular, it is unknown whether and how organogenesis differs during sexual, asexual and regenerative processes, how the stem cells that mediate them differ and if convergent morphology implies convergent molecular mechanisms. Colonial tunicates provide a key to answering these questions, they are unique amongst chordates in possessing two disparate developmental pathways that produce the adult body, either sexually through embryogenesis, or through a stem cell mediated asexual renewal termed, blastogenesis. Using the model organism Botryllus schlosseri we have combined transcriptome sequencing of major embryonic and blastogenic stages and multiple tissues and stem cell populations with confocal, two-photon and electron microscopy to characterize the molecular and morphological signatures along both developmental pathways. We identify de novo periods of transcriptional transition and shared molecular characteristics including stem cell associated transcription factors. We also identified the developmental origin of hematopoiesis, germ cells and central nervous system organogenesis timeline. This study generated the most complete

gene profile database produced to date on the entire embryogenesis process and the first to describe asexual development to a similar resolution. By combining microscopy with transcriptome sequencing, it demonstrates the extent to which convergent morphology implies convergent molecular mechanisms and reveals the basic principles and evolutionary conserved elements of chordate development. It also uncovered the exact time when tissue specific precursor cells emerge in both developmental pathways, suggesting a link between embryonic and adult tissue specific stem cells.

Funding Source: NIH R56AI089968, R01AG037968 RO1GM100315 , 5T32AI07290-28, T32 HL120824-03, Virginia and D. K. Ludwig Fund for Cancer Research, Steinhart-Reed grant and Chan Zuckerberg Biohub Research Award.

14:24 – 14:35

OCCLUDING JUNCTIONS COORDINATE EPITHELIAL INTEGRATION WITH GROWTH OF STEM CELL PROGENY DURING INTESTINAL TURNOVER IN DROSOPHILA

O'Brien, Lucy Erin[1], Moreno-Roman, Paola[1], Su, Yu-Han[1] and Koloteuva, Irina[2]

[1]Molecular and Cellular Physiology, Stanford School of Medicine, Stanford, CA, USA, [2]Electron Microscopy Facility, Universite de Lausanne, Switzerland

The intestinal epithelium forms a barrier between the external environment and the interior body. This barrier is created by a closed network of occluding junctions, which must be dynamically maintained during organ turnover. How new stem cell progeny integrate into this junctional network is poorly understood. Examining the intestinal epithelium of adult Drosophila, we find that new progeny achieve seamless integration by coordinating growth, polarization, and differentiation with biogenesis of occluding junctions de novo. The core occluding junction proteins Snakeskin, Mesh, and Tetraspanin2a are missing in stem cells but activated in terminal enteroblast daughters. As an enteroblast differentiates, these proteins localize to the apical-most tip of the growing cell, forming a nascent plaque that induces remodeling of and coalesces with the mature junctional network. When we prevent enteroblasts from forming septate junctions, cells grow but cannot integrate or generate apical polarity. Instead, they become squamous and accumulate under the basal epithelium. Conversely, when we block TOR-dependent enteroblast growth, junction biogenesis is partially inhibited. By using de novo biogenesis of occluding junctions to drive integration of stem cell progeny, the intestinal epithelium incorporates new replacement cells without compromising barrier function.

14:35 – 14:46

DECIPHERING THE EMBRYONIC ORIGINS AND THE GENETIC REGULATION OF SKELETAL STEM CELLS IN THE ZEBRAFISH SKULL

Farmer, D'Juan T.[1], Crump, Gage[1], Maxson, Robert[2], Teng, Camilla[1] and Ting, Man-Chun[2]

[1]Department of Stem Cell Biology and Regenerative Medicine, University of Southern California, Los Angeles, CA, USA, [2]Department of Biochemistry and Molecular Biology, University of Southern California, Los Angeles, CA, USA

In the vertebrate skull, skeletal stem cells reside in fibrous joints called sutures and ensure the long-term growth and separation of skull bones. Humans with Saethre-Chotzen syndrome lose these skeletal stem cells at the coronal suture, leading to a malformed skull and a heightened risk of impaired brain development. Genetics studies have demonstrated that mutations in two bHLH transcription factors, TWIST1 and TCF12, cause Saethre-Chotzen syndrome, but the developmental origins of coronal synostosis has remained elusive. We utilize the unique genetic and imaging strengths of zebrafish to determine the embryonic origins and genetic regulation of long-term stem cells that grow and maintain the vertebrate skull. Simultaneous deletion of twist1b and tcf12 in zebrafish leads to the same coronal synostosis seen in humans. Sequential live bone staining in mutant zebrafish reveals an initial increase in the growth of all skull bones, which correlates with increased number of proliferative osteoblasts. Intriguingly, stalled bone growth arises only at the coronal suture, and the severity of bone growth stalling predicts coronal synostosis. RNAscope in situ for skeletal stem cell markers uncovers a depletion of the number of progenitor cells that separate neighboring skull bones at the coronal suture of mutant zebrafish. Altogether, these data suggest that alterations in progenitor dynamics cause the coronal synostosis observed in Saethre-Chotzen syndrome. Current work focuses on integrating complex genetics tools, live imaging, and genomic technologies to uncover the precise progenitor dysfunction that cause coronal synostosis and the twist1b/tcf12 dependent regulatory networks that control coronal suture development.

Funding Source: National Institutes of Health Helen Hay Whitney Foundation Howard Hughes Medical Institute

14:46 – 15:06

MAINTENANCE OF GENOMIC INTEGRITY IN PROLIFERATING BLASTEMA CELLS OF REGENERATING AXOLOTL LIMBS

Whited, Jessica, Sousounis, Konstantinos**,** Bryant, Donald**,** Martinez Fernandez, Jose**,** Eddy, Samuel**,** Tsai, Stephanie and Levin, Michael

Harvard University, Boston, MA, USA

A fundamental question in regenerative biology and medicine is how stem and progenitor cells can function effectively throughout the lifetime of the organism, or while being cultured in vitro, without compromising genomic integrity. Profoundly regenerative

creatures, such as axolotl salamanders, offer an experimental space to explore this concept and to ask what happens at the extreme end of the spectrum, when multiple tissues must be replaced in a short amount of time, on a very large scale, and at mature ages. Axolotls are capable of regenerating entire limbs—as well as many other tissues and organs—throughout life, with perfection. This process is mediated by formation of a transient structure composed of activated progenitor cells, the blastema, that develops beneath a specialized wound epidermis. Our laboratory has been characterizing gene expression in pre-blastema-stage and blastema-stage tissues from normally-regenerating limbs as well as limbs subjected to repeated injury and other experimental perturbations to learn more about how blastemas are built and what might limit their creation. We uncovered a role for the Eyes absent 2 (Eya2) protein in the maintenance of genomic integrity within blastema cells. Using loss-of-function genetics and pharmacological inhibition, we demonstrate that Eya2 activity modulates phosphorylation state of the histone H2AX in the regenerating limb and that it promotes blastema cell proliferation and survival. We also show this factor is required for normal limb regeneration. This example highlights the axolotl model and the kinds of experimental manipulations now possible in it as a forum for exploring concepts of progenitor cell biology, regenerative mechanisms, and constraints.

THURSDAY, 27 JUNE, 16:00 – 18:00

CONCURRENT IIA: MECHANISMS OF PLURIPOTENCY AND IPS CELL REPROGRAMMING

Concourse E, Level One

16:05 – 16:25

THINK GLOBAL ACT LOCAL: DO LOCAL MORPHOLOGICAL CHANGES INFLUENCE DIFFERENTIATION OF PLURIPOTENT CELLS?

Lowell, Sally, Blin, Guillaume**,** Wisniewski, Darren**,** Punovuori, Karolina and Malaguti, Mattias

MRC Centre for Regenerative Medicine, University of Edinburgh, UK

We are interested in the mechanisms that make early development robust and reproducible in the face of fluctuating or imprecise signals. As pluripotent tissues move towards differentiation they experience morphological rearrangements that are driven by changes in cell adhesion. We will present evidence that these changes in cell adhesion and polarity modulate the ability of pluripotent cells to respond to extrinsic cues. This tells us that changes in cell adhesion are not simply a passive consequence of differentiation, but rather that they actively feed back into the decision making process through unknown mechanisms. We propose a model in which pro-differentiation transcription factors regulate changes in adhesion and polarity that help to 'filter' the extrinsic information that feeds back into the pro-differentiation transcriptional network. This 'filtering' mechanism could operate either through direct interactions between cell adhesion molecules and signalling components, or else indirectly through changes in cellular organisation. This process would help to stabilise particular cell fate decisions at the appropriate time and place, whilst protecting against alternative fates. In order to address this hypothesis we are developing image analysis tools that allow us to quantify changes in cellular organisation. I will describe the key features of these tools, which we hope will be useful to others within the Developmental Biology community.

16:25 – 16:36

DEFINING ESSENTIAL REGULATORS OF HUMAN NAÏVE PLURIPOTENT STEM CELL REPROGRAMMING USING GENOME-WIDE CRISPR-CAS9 SCREENING

Rugg-Gunn, Peter[1], Collier, Amanda[1], Fabian, Charlene[1], Tilgner, Katarzyna[2], Bendall, Adam[1], Wojdyla, Katarzyna[1], Semprich, Claudia[1], Malcolm, Andrew[1], Serena Nisi, Paola[1] and Yusa, Kosuke[2]

[1]Epigenetics Programme, The Babraham Institute, Cambridge, UK, [2]Cellular Genetics, The Sanger Institute, Cambridge, UK

Naïve and primed human pluripotent stem cells (hPSCs) differ substantially in molecular and functional properties that reflect their discrete developmental identities. Investigating these cell types has the potential to uncover the pathways that define how human pluripotent cell identity is controlled and in particular how naïve pluripotency is acquired and stabilised during cell reprogramming. Towards these goals, we have completed an unbiased, genome-wide, loss-of-function CRISPR-Cas9 screen that has identified genes that are involved in primed to naïve hPSC reprogramming. These results enabled us to define several hundred genes that are essentially required for successful reprogramming, and a similar number of genes that appear to normally impede reprogramming and whose targeted deletion led to enhanced reprogramming. The identified genes are strongly enriched for roles that are associated with transcriptional regulation and chromatin remodelling. Furthermore, the screen identified many, sometimes all, factors within a particular complex, implicating not just individual genes but whole complexes in reprogramming. We generated knockout primed hPSC lines for several of the newly identified essential genes and confirmed a requirement for those factors in naïve cell reprogramming. Detailed molecular analyses of the cell lines have shed light on the mechanisms through which these factors normally operate in reprogramming, with a common theme being the role of chromatin modifying complexes to facilitate transcriptional activation at an early stage of reprogramming. In addition, treating hPSCs with small molecule inhibitors of reprogramming impediments increased the efficiency of naïve cell reprogramming, and are of practical benefit that can improve on current reprogramming methods. Taken together, we have defined a comprehensive set of factors that control the entry of human cells into naïve pluripotency, and in doing so have newly identified molecular pathways that define human pluripotent cell identity and state transitions.

16:36 – 16:47

DISSECTING THE MOLECULAR MECHANISM UNDERLYING THE DISTINCT FUNCTIONS OF GSK3ALPHA AND GSK3BETA USING MOUSE EMBRYONIC STEM CELLS

Chen, Xi[1], Park, Haeyoung[1], Chadarevian, Jean Paul[2], Wang, Duo[1], Jing, Xueyuan[1], Vonk, Ariel[1], Zhang, Chao[2] and Ying, Qilong[1]

[1]Department of Stem Cell Biology and Regenerative Medicine, University of Southern California, Los Angeles, CA, USA, [2] Department of Chemistry, University of Southern California, Los Angeles, CA, USA

Glycogen synthase kinase 3 (GSK3) plays a central role in multiple cellular processes. In mammals, GSK3 has two highly homologous isozymes, GSK3α and GSK3β. Studies have reported many essential and non-redundant roles of GSK3 isozymes during development and many disease-relevant contexts. However, despite their important roles in biology, no specific inhibitors has been developed to distinguish between the two isozymes. Previously, we found that genetically-engineered selective inhibition of GSK3β is sufficient to maintain mouse embryonic stem cell (mESC) self-renewal, whereas GSK3α inhibition promotes mESC differentiation towards neural lineages. In this study, we aim to dissect the molecular mechanism underlying the distinct functions of GSK3α and GSK3β. Domain-swapping strategy was applied to generate various chimeric GSK3 with a mix of GSK3α and GSK3β sequences. A morphological screening system was established to determine the key region related to the distinct phenotype of GSK3α and GSK3β in mESCs. Surprisingly, the key region responsible for GSK3β-specific function is located within the C-terminal kinase region, which contains only a few amino acid differences between the two isozymes. Molecular analysis indicates that this small region could be related to the preferential interaction of GSK3β towards β-catenin. More importantly, preliminary attempts to overexpress peptides mimicking this region were able to improve self-renewal in mESCs, resembling the effect of selective inhibition of GSK3β. On the other hand, using a chemical-genetic approach coupled with RNA-seq and phosphor-proteomic analysis, we found that GSK3α inhibition induced hyperphosphorylation of various GSK3β-mediated substrates. To support this finding, overexpression of GSK3β promoted mESC differentiation towards neural lineage, whereas overexpression of GSK3α pushed mESCs towards non-neural lineage. To understand the mechanism of hyperphosphorylation upon GSK3α inhibition, we established a tet-ON inducible system to control the expression of ectopic GSK3α/β and found that upregulation of GSK3α downregulated the endogenous level of GSK3β. Currently, we are focusing on identifying the key region of GSK3α responsible for this regulatory role using the same domain-swapping strategy previously mentioned.

Funding Source: This study is supported by NIH-R01-GM129305.

16:47 – 16:58

DISTINCT EARLY EMBRYONIC PREIMPLANTATION DEVELOPMENTAL PROGRAMS DRIVE REPROGRAMMING INTO PRIMED AND NAIVE INDUCED PLURIPOTENCY

Liu, Xiaodong[1], Ouyang, John[2], Rossello, Fernando[1], Rackham, Owen[2] and Polo, Jose[1]

[1]Department of Anatomy and Developmental Biology, Development and Stem Cells Program, Monash Biomedicine Discovery Institute, Australian Regenerative Medicine Institute, Monash University, Melbourne, Australia, [2]Program in Cardiovascular and Metabolic Disorders, Duke-National University of Singapore Medical School, Singapore

Reprogramming of somatic cells in defined conditions can give rise to primed and naive human induced pluripotent stem cells (hiPSCs) that recapitulate pre-implantation and post-implantation epiblasts respectively. However, the molecular events underpinning these processes are largely unexplored, impeding further rational optimisation of the reprogramming protocols. In this study, we reconstruct high-resolution molecular roadmaps of primed and naive human reprogramming at the single-cell level, and show distinct and independent cell fate transitions along each of the reprogramming trajectories. This revealed that reprogramming into primed and naive human pluripotency initially follows a shared trajectory before bifurcating into the two distinct pluripotent states, with neither states requiring a transition through the other. By extracting cell surface marker profiles of intermediate populations during the cellular transitions, we isolated and profiled reprogramming intermediates under several other naive as well as extended pluripotent conditions throughout reprogramming. We find each of them follow either of the bifurcated trajectories. Furthermore, using the same isolation strategy, we profiled genome-wide chromatin accessibility of reprogramming intermediates uncovering both individual intronic regulatory elements in core pluripotency markers, as-well-as a global association of increased chromatin accessibility with trophectoderm (TE) and epiblast (EPI) lineage-related transcription factors during the divergence into naive human pluripotency. Taken together, our comprehensive analyses of human primed and naive reprogramming reveal a remarkable and unexpected role of the TE-lineage associated regulatory program play during this process, providing novel insights to study early human lineage specification.

16:58 – 17:09

A COMMON MOLECULAR LOGIC DETERMINES EMBRYONIC STEM CELL SELF-RENEWAL AND REPROGRAMMING

Dunn, Sara-Jane[1], Li, Meng Amy[2], Carbognin, Elena[3], Smith, Austin[2] and Martello, Graziano[3]

[1]Biological Computation, Microsoft Research, Cambridge, UK, [2]Wellcome-MRC Cambridge Stem Cell Institute, University of Cambridge, UK, [3]Department of Molecular Medicine, University of Padua, Italy

Published experimental protocols demonstrate our ability to induce cell identity via differentiation or reprogramming. Yet despite

this wealth of research, an explanation of how such cell state conversions arise remains fragmentary. Ideally, we would like to understand the complex, dynamic interplay of genetic components that manifests as cell fate conversions. To address this gap, computational analyses can be combined with mathematical modelling to interrogate experimental data and generate testable hypotheses on how a program of genetic interactions governs cell identity. We have demonstrated that such an interdisciplinary approach can be applied to understand the biological program governing self-renewal and reprogramming to naïve pluripotency in mouse embryonic stem cells (ESCs). We find that a Boolean network architecture defined for maintenance of naïve pluripotency also explains transcription factor behaviour and potency during resetting from primed pluripotency. The network predicts gene activation trajectories that were experimentally substantiated at single-cell resolution by RT–qPCR. Furthermore, it reveals the contingency of factor availability and explains the counterintuitive observation that Klf2, which is dispensable for ESC maintenance, is required during resetting. Finally, we show that this network explains and predicts experimental observations of somatic cell reprogramming. In summary, we tested 124 predictions formulated by the dynamic network, yielding a predictive accuracy of 77.4%. We conclude that a common deterministic program of gene regulation is sufficient to govern both maintenance and induction of naïve pluripotency. Moreover, the iterative computational methodology we employed, which is made freely available to the community, could be applied generally to delineate network trajectories that mediate other cell fate transitions and lineage reprogramming.

Funding Source: Giovanni Armenise-Harvard Foundation; Telethon Foundation (TCP13013); BBSRC; Wellcome Trust; Medical Research Council; University of Cambridge Institutional Strategic Support Fund.

17:09 – 17:20

KLF4 AND TFCP2L1 IN HUMAN PRIMORDIAL GERM CELL DEVELOPMENT

Hancock, Grace[1], Chen, Dee[2], Peretz, Lior[2], Plath, Kathrin[3], Chitiashvili, Tsotne[1] and Clark, Amander[2]

[1]Molecular Biology Institute, University of California, Los Angeles, CA, USA, [2]Molecular, Cell, and Developmental Biology, University of California, Los Angeles, CA, USA, [3]Biological Chemistry, University of California, Los Angeles, CA, USA

Germline cells are critical for human reproduction, as they pass genetic and epigenetic information from one generation to the next. The first germline cells to develop in the human embryo are called human primordial germ cells (hPGCs), which are specified shortly following embryo implantation. Newly specified hPGCs are unique in that they contain cellular and molecular hallmarks that are similar to a naïve state in human embryonic stem cells (hESCs). These characteristics include two active X chromosomes, DNA hypomethylation, and a naïve-specific transpososome, which distinguish them from the surrounding somatic cells that are rapidly differentiating. To identify transcription factors responsible for re-establishing and maintaining a naïve-like state in hPGCs, ATAC-sequencing of hPGCs and hPGC-like cells (hPGCLCs) differentiated from hESCs was performed. Though this screen, we found the Kruppel-like family (KLF) and a naïve transcription factor called TFCP2L1 to have uniquely open binding motifs in hPGCs and hPGCLCs compared to hESCs. Additionally, we found RNA expression of both TFCP2L1 and members of the KLF family including KLF4 to be up-regulated with hPGCLC differentiation. Using CRISPR/Cas9 to make hESC knockout lines for each gene, we found that null mutations in KLF4 or TFCP2L1 did not affect PGCLC specification. To evaluate the potential role of each transcription factor at later stages in vivo, we used immunofluorescence staining in male and female PGCs at the late and advanced stages. Here we saw KLF4 and TFCP2L1 expressed in CKIT+ and VASA+ late and advanced-stage germ cells. Given the expression of these factors in this later stage of PGC development, but lack of role in early specification, we aim to further characterize the role of each transcription factor in the mutant lines using extended culture systems and genomic characterization including RNA-sequencing.

17:20 – 17:31

DEFINING EPIGENETIC CONTROL OF PLURIPOTENCY WITH SINGLE CELL ANALYSIS

Sridharan, Rupa[1], Tran, Khoa[1], Pietrzak, Stefan[1], Zaidan, Nur Zafirah[1], McKalla, Sunnie Grace[1], Siahpirahi, Ali[2], Iyer, Gopal[1] and Roy, Sushmita[1]

[1]Cell and Regenerative Biology, Wisconsin Institute for Discovery, University of Wisconsin-Madison, WI, USA, [2]University of Wisconsin -Madison, WI, USA

Elucidating the mechanism of reprogramming is confounded by heterogeneity due to the low efficiency and differential kinetics of obtaining induced pluripotent stem cells (iPSCs) from somatic cells. Therefore, we increased the efficiency with a novel combination of epigenetic and signaling molecules and profiled the transcriptomes of individual reprogramming cells. Contrary to the established temporal order, somatic gene inactivation and upregulation of cell cycle, epithelial, and early pluripotency genes can be triggered independently such that any combination of these events can occur in single cells. The down regulation of mesenchymal gene expression continues to be a barrier late into the reprogramming process and is incompatible with sustained expression of Nanog causing cells to exit the trajectory toward the pluripotent state. We identify a role for transiently modulated genes such as Ehf, and translation initiation factor Eif4a1 for progress towards iPSCs. Using regulatory network analysis, we identify a critical role for signaling inhibition by 2i in repressing somatic expression and synergy between the epigenetic modifiers ascorbic acid (AA) and a Dot1L inhibitor for pluripotency gene activation. Kdm3b, a histone H3K9me2 demethylase is a critical mediator of AA effects and transcriptionally controls expression of the DNA demethylase Tet1. Tet- mediated DNA demethylation involves a transient 5-hydroxymethyl cytosine (5hmC) state. Remarkably, in Kdm3b-deleted cells, the chromosomal sites that transiently gain 5hmC are trapped and do not resolve into demethylated cytosine. The trapped 5hmC precludes binding of the pluripotency factor Oct4 and the respective loci are rendered resistant to Oct4-mediated transcriptional activation. Furthermore we demonstrate a specific role for Tet1, but not Tet2, in pluripotency gene activation. Thus, these studies reveal the functional

relevance of epigenetic mechanisms that control the unraveling of cell identity.

17:31 – 17:51

OVERLAPPING FUNCTION OF KLF FAMILY MEMBERS AND TBX3 PREVENTS SELF-DESTRUCTION OF MOUSE ES CELLS BY ACTIVATION OF FOXD3

Niwa, Hitoshi

Kumamoto University, Kumamoto, Japan

Mouse ES cells self-renew with keeping naïve pluripotency by the activity of naïve-state-specific transcription factor network under the LIF signal. Three Klf family members Klf2, Klf4 and Klf5 show overlapping function to activate a set of naïve-specific transcription factors including Nanog, Esrrb and Tbx3. Tbx3 acts as a mediator of the LIF signal in parallel to Klf4. To investigate the parallel function of the Klf family members and Tbx3, a series of a combinatorial inducible-knockout ES cells were generated for these 4 transcription factors with Cre-loxP system and analyzed for their phenotypes. Among them, all single and double knockout ES cells continue self-renewal. In the triple knockout, Klf2/Klf4/Klf5 and Klf2/Klf4/Tbx3 knockout result in the cease of self-renewal. When the gene expression changes were analyzed in these two triple knockout events, several genes were identified for their specific down-regulation in Klf2/Klf4/Tbx3 knockout ES cells, suggesting the overlapping regulation of particular targets by these three transcription factors. Among them, Foxd3 was chosen for the functional analysis. The transgenic expression of Nanog/Esrrb/Foxd3 restored self-renewal of Klf2/Klf4/Tbx3 knockout ES cells. Since the previous report demonstrated the up-regulation of the apoptosis-related genes in Foxd3-null ES cells, the functional relation between Foxd3 expression and prevention of apoptosis was addressed. Interestingly, the combination of Nanog/Esrrb/apoptosis inhibitor also sustained self-renewal of Klf2/Klf4/Tbx3 knockout ES cells. The enhancer analysis revealed the overlapping function of Klf2, Klf4 and Tbx3 to activate transcription of Foxd3. These data indicated that the overlapping function of the Klf family members and Tbx3 converge to the activation of Foxd3 to control self-destruction of aberrant ES cell population.

THURSDAY, 27 JUNE, 16:00 – 18:00

CONCURRENT IIB: MOLECULAR AND CELLULAR DYNAMICS

Concourse F, Level One

16:05 – 16:25

CELLULAR AND MOLECULAR DYNAMICS OF INDIVIDUAL STEM CELLS IN THE BRAIN

Jessberger, Sebastian

University of Zurich, Switzerland

Neural stem cells generate new neurons in distinct regions of the mammalian brain throughout life. This process, called adult neurogenesis, is critically involved in certain forms of learning and memory. In addition, failing or altered neurogenesis has been associated with a number of neuro-psychiatric diseases such as major depression and epilepsy. However, the mechanisms underlying life-long neurogenesis on a single cell level remain poorly understood due to a lack of longitudinal observations of individual neural stem cells and their progeny within their endogenous niche. Here we present new approaches to study the cellular principles underlying neurogenesis within the endogenous adult hippocampal niche. Further, we provide evidence for novel molecular mechanisms governing the neurogenic process in the adult brain. Thus, the data presented provide new insights into the cellular principles of hippocampal neurogenesis and identify novel mechanisms regulating the behavior of rodent and human neural stem cells.

16:25 – 16:36

INDUCED 2C EXPRESSION AND IMPLANTATION-COMPETENT BLASTOCYST-LIKE CYSTS FROM PRIMED PLURIPOTENT STEM CELLS

Kime, Cody[1] and Tomoda, Kiichiro[2]

[1]Center for Biosystems Dynamics Research, RIKEN, Kobe, Japan, [2]Pharmacology, Osaka Medical College, Osaka, Japan

Soon after fertilization, the few totipotent cells of mammalian embryos diverge to form a structure called the blastocyst (BC). Although numerous cell types, including germ cells and extended pluripotency stem cells, have been developed from pluripotent stem cells (PSCs) in-vitro, generating functional BCs only from PSCs remains elusive. Here we describe induced self-organizing 3D BC-like cysts (iBLCs) generated from mouse PSC culture. Resembling natural BCs, iBLCs have a blastocoel-like cavity and were formed with outer cells expressing trophectoderm lineage markers and with inner cells expressing pluripotency markers. iBLCs transplanted to pseudopregnant mice uteruses implanted, induced decidualization, and exhibited growth and development before resorption, demonstrating that iBLCs are implantation-competent. iBLC precursor intermediates required the transcription factor Prdm14 and concomitantly activated the totipotency-related cleavage stage MERVL reporter and 2C genes. Modified experiments induce semi-stable atypical 2C-expressing subpopulations of larger cells that also enrich 2C genes. Thus, our systems may contribute to understanding molecular mechanisms underpinning totipotency, embryogenesis, and implantation.

16:36 – 16:47

REGULATION OF HSC FUNCTION BY MITOCHONDRIAL DYNAMICS

Justino De Almeida, Mariana[1], Luchsinger, Larry[2] and Snoeck, Hans-Willem[2]

[1]Microbiology and Immunology, Columbia University, New York, NY, USA, [2]Medicine, Columbia University, New York, NY, USA

Hematopoietic stem cells (HSCs) sustain the life-long production of blood. Despite their established therapeutic potential, HSC biology is poorly understood and the field remains limited by the inability to maintain HSCs in vitro or prevent functional decline with age. Since several signaling pathways and biological processes converge onto the mitochondrion, often in association with prevailing aging theories, particular aspects of this organelle have been investigated in HSCs but found to be largely dispensable. However, recent studies revealed elevated mitochondrial content and an essential role for mitochondrial respiration in HSCs, contradicting previous views and warranting additional research. In this study we investigate the function of mitochondria in HSCs through disruption of mitochondrial fusion by generating a mouse model with conditional hematopoietic deletion of two key facilitators of this process: Mitofusins (Mfn) 1 and 2. Although these mice display normal Mendelian ratios, they die prior to completing gestation. The mutant embryos are paler in appearance and display an increase in immature erythroid populations, both indicative of anemia. Analysis of HSCs by phenotypic markers in the fetal liver (FL) reveals an expansion of this compartment both in frequency and absolute numbers. However, examination of HSC function in vivo by transplantation and in vitro by colony forming assay reveals a complete failure of HSCs to reconstitute lymphoid and myeloid lineages in recipient mice or to form colonies. To gain insight into the mechanisms underlying this functional phenotype, we have examined processes known to be affected by dysfunctional mitochondrial fusion and to be tightly regulated in HSCs. We have identified a collapse of the mitochondrial network, a reduction in mitochondrial content, an increase in HSC cycling, and altered metabolism. Interestingly, one allele of Mfn1 is sufficient to completely rescue Mfn1/2-DKO HSC function in vivo and lethality, while one allele of Mfn2 only rescues myeloid reconstitution. In conclusion, our findings highlight the importance and complexity of mitochondrial function and dynamics in HSCs and point to a novel role for mitochondria in lineage specification and HSC function.

16:47 – 16:58

EARLY MOUSE EMBRYOGENESIS INVOLVES A SWITCH IN CHROMATIN ORGANIZATION FROM PREFORMED ASYMMETRIC COMPARTMENTS TO DE NOVO DOMAINS

Collombet, Samuel[1], Ancelin, Katia[2], Fraser, Peter[3], Heard, Edith[1], Nagano, Takashi[4], Ranisavljevic, Noemie[2] and Varnai, Csilla[4]

[1]Genome Biology, EMBL, Heidelberg, Germany, [2]Biologie du Développement, Institut Curie, Paris, France, [3]Biological Sciences, Florida State University, Tallahassee, FL, USA, [4]Epigenetics, Babraham Institute, Cambridge, UK

Upon fertilisation the two parental genomes must undergo a complete reprogramming to reconcile their epigenetic landscapes. The associated dynamic of chromosome organisation, and its link with chromatin and transcriptional changes are still poorly understood. Here we use allele-specific, single cell HiC to map the structure of both parental genomes during early mouse development, from the zygote to the blastocyst stages. Prior to embryonic genome activation, a remarkable asymmetry was found, with most structure on maternal chromosomes, that are organised into domains coinciding with stretches of polycomb-associated H3K27me3. These appear to be local repressive compartments and result in biased gene expression during early embryogenesis. The boundaries of these polycomb domains define precise regions of transient imprinting, such as at the maternally repressed Xist locus on the X chromosome. These transient imprinted domains disappear or transform into symmetric domains, joining newly established topologically associated domains that emerge from around the 4-cell stage, to form the classical active and inactive compartments. We find that by the blastocyst stage, local chromosome structure (loops, TADs) is associated with active chromatin and gene expression, while it is lost at silenced loci as in the case of the paternal X chromosome that becomes silenced due to X inactivation. This study offers a roadmap of chromosomes organisation in mouse early embryos, and unveils an unanticipated early asymmetry in structural domains that are associated with transient imprinting of developmental genes.

16:58 – 17:09

CALCIUM OSCILLATIONS COORDINATE CHICKEN FEATHER MESENCHYMAL CELL MOVEMENT BY SHH/WNT DEPENDENT MODULATION OF GAP JUNCTION NETWORKS

Li, Ang[1], Chuong, Cheng-Ming[2], Chow, Robert[3], Cho, Jung-Hwa[4], Zhao, Min[5], Zhou, Yu-Bin[6], Li, Yu-Wei[7], Widelitz, Randall[2], Wu, Ping[2], Yeh, Chao-Yuan[2], He, Lian[6], Reid, Brian[5], Tan, Peng[8] and Tseng, Chun-Chih[9]

[1]Kinesiology, University of Texas, Arlington, TX, USA, [2]Pathology, University of Southern California, Los Angeles, CA, USA, [3]Physiology, University of Southern California, Los Angeles, CA, USA, [4]Porter Neuroscience Research Center, National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, [5]Dermatology, University of California, Davis, Sacramento, CA, USA, [6]Center for Translational Cancer Research, Texas AandM University, Houston, TX, USA, [7]The Division of Biology and Biological Engineering, California Institute of Technology, Pasadena, CA, USA, [8]Center for Inflammation and Epigenetics, Houston Methodist Hospital, Houston, TX, USA, [9]Biochemistry and Molecular Medicine, University of Southern California, Los Angeles, CA, USA

Collective cell migration mediates multiple tissue morphogenesis processes. Yet how multidimensional mesenchymal cell movements are coordinated remains mostly unknown. Here we report that coordinated mesenchymal cell migration during chicken feather elongation is accompanied by dynamic changes of bioelectric currents. Transcriptome profiling and functional assays implicate contributions from functional voltage-gated Ca2+ channels (VGCCs), Connexin-43 based gap junctions, and Ca2+ release activated Ca2+ (CRAC) channels. 4-Dimensional Ca2+ imaging reveals that the Sonic hedgehog-responsive mesenchymal cells display synchronized Ca2+ oscillations, which expand progressively in area during feather elongation. Inhibiting VGCCs, gap junctions, or Sonic hedgehog signaling alters the mesenchymal Ca2+ landscape, cell movement patterns and feather bud elongation. Ca2+ oscillations induced by cyclic activation of

opto-cCRAC channels enhance feather bud elongation. Functional disruption experiments and promoter analysis implicate synergistic Hedgehog and WNT/β-Catenin signaling in activating Connexin-43 expression, establishing gap junction networks synchronizing the Ca2+ profile among cells, thereby coordinating cell movement patterns.

Funding Source: C-.M.C., A.L., R.B.W. and P.W. are supported by NIAMS R01-AR47364, AR60306, GM125322. A.L. is also supported by CIRM training grant TG2-01161 and Doerr Stem Cell Challenge Grant.

17:09 – 17:20

REAL-TIME KINETICS OF NOTCH-MEDIATED FATE DECISIONS IN THE DROSOPHILA ADULT INTESTINE

Sanders, Erin N.[1,2], Martin, Judy[2], Du, XinXin[2] and O'Brien, Lucy[2]

[1]Department of Developmental Biology, Stanford University, Stanford, CA, USA, [2]Molecular and Cellular Physiology, Stanford University, Stanford, CA, USA

In an adult organ, balance of cell fates at a whole-organ level is necessary for homeostasis, yet fate-determining signaling events occur within individual stem cells. Although much has been learned about which signals contribute to a stem cell's fate decision, little is known about how cells control when and how fast a fate decision is made. This is in part because of challenges inherent to monitoring the real-time kinetics of fate decisions in vivo. Here we use the intestine of adult Drosophila to examine the live kinetics of a Notch-controlled fate decision in vivo. In the fly intestine, Delta-expressing stem cells activate Notch on daughter cells to drive differentiation into terminal enteroblasts. Using a new protocol for long-term imaging within live adults, we monitored real-time Notch activity in stem and daughter cells with a sensitive GFP reporter. Our analyses reveal first insights into the kinetics of individual fate decisions in a homeostatic organ. Cross-correlation of GFP levels with hallmarks of stemness demonstrate that enteroblasts can be functionally distinguished from stem cells by a quantitative threshold of Notch activation. This threshold remains constant in opposing tissue states of homeostasis and growth, which suggests that the relationship between enteroblast identity and Notch signaling is absolute. By measuring Notch activation in single cells over time, we found that cells require multiple hours to acquire enteroblast identity and that differentiation kinetics vary between individual cells. These slow, variable kinetics may give newborn cells greater flexibility in deciding fates, ensuring that the right cell type is produced according to overall tissue needs.

Funding Source: NSF GRFP DGE-1656518 and NIH 2T32GM00779038 to E.N.S. Supported by NIH R01GM116000-01A1 to L.E.O.

17:20 – 17:31

RNA POLYMERASE II PAUSING REGULATES FGF4 SIGNALING IN THE MOUSE PRE-IMPLANTATION EMBRYO

Abuhashem, Abderhman A. and Hadjantonakis, Anna-Katerina

Cell and Developmental Biology, Sloan-Kettering Institute for Cancer Research, New York, NY, USA

FGF signaling is instrumental to many aspects of biology in health and disease. Despite the identification of several regulation points, we still fail to understand how the FGF pathway is tightly regulated and fine-tuned to produce precise outcomes in many scenarios. Recent studies suggested that RNA polymerase II pausing may be crucial to fine-tuning signaling pathways in complex model systems. However, the nature and relevance of this regulation have not been explored. We wanted to investigate whether RNA polymerase II pausing plays a role in regulating FGF signaling in vivo. We utilized the mouse pre-implantation embryo, where FGF4 governs the specification of the inner cell mass (ICM) to epiblast (Epi) and primitive endoderm (PrE) lineages in a tightly regulated manner, asynchronously, over roughly 24 hours (E 3.5 – E4.5). We deployed quantitative imaging methods to dissect the specification process at single-cell resolution in embryos lacking the Negative elongation factor-b (Nelf-b), a required subunit for the pausing complex, between E 3.5 and E 4.5. Surprisingly, Nelf-b-/- embryos are able to specify both lineages successfully. However, the tight ratio of PrE to Epi, ~1.5 PrE/Epi, in wild type embryos is lost in Nelf-b-/- embryos and a random wide range is observed, 0.7 – 2.5 PrE/Epi. In order to gain insight into the underlying mechanism, we analyzed the dynamics of ICM specification in Nelf-b-/- embryos and found that these embryos lose their ICM population rapidly before the embryos reach 70 cell stage, as opposed to 90-100 cell stage in wild type embryos. Simultaneously, the specified PrE and Epi are reaching peak expression and subsequent downregulation of key transcription factors (NANOG for Epi and GATA6 for PrE) at earlier stages than wild type embryos. Taken together, these findings suggest that Nelf-b-/- embryos are more sensitive to FGF4, which results in premature assignment of the ICM to Epi and PrE lineages and inability to tightly control the final ratios of these lineages. Our data introduces RNA polymerase II pausing as a novel critical player in fine-tuning FGF4 signaling in early mammalian development.

Funding Source: National Institute of General Medical Sciences of the National Institute of Health under award number T32GM007739

17:31 – 17:51

HEALTHY AND MALIGNANT HAEMATOPOIESIS IN THE BONE MARROW: DYNAMIC CELLS IN AN EVOLVING ENVIRONMENT

Lo Celso, Cristina

Imperial College London, UK

Haematopoietic stem cells (HSCs) sustain the turnover of all our immune cells, red blood cells and platelets throughout our

lives. Their output is adjusted depending on demand, for example emergency granulopoiesis has been described as a result of infections, and healthy haematopoiesis is lost as a consequence of leukaemia growth. HSC function depends on their ability to self-renew and differentiate in a balanced manner, and is regulated by complex and dynamic interactions with stroma and haematopoietic cells that surround them in the bone marrow, collectively known as the HSC niche. Despite an ever-growing number of studies, we still understand little about the nature of the HSC niche, whether there are multiple types of niches with specific functions, or whether there may not be a physical niche at all. My research group has been studying how HSCs interact with multiple components of the bone marrow microenvironment and how these interactions change at time of stress, may this be infection, leukaemia development or bone marrow transplantation. We take advantage of an interdisciplinary approach combining intravital microscopy of mouse bone marrow, quantitative image analysis, in vivo and ex vivo assays and mathematical modelling to understand the cellular and molecular dynamics driving healthy and malignant haematopoiesis, with the view of identifying suitable targets to develop improved therapies and preventative approaches for haematological disease, especially leukaemia and infection-driven HSC exhaustion. Through these studies, the bone marrow microenvironment has been emerging as a novel and promising therapeutic target for strategies aimed at supporting and improving HSC fitness.

THURSDAY, 27 JUNE, 16:00 – 18:00

CONCURRENT IIC: STEM CELL NICHES

Room 502, Level Two

16:05 – 16:25

REVITALIZATION OF HSC NICHE ACTIVITY BY REPROGRAMMING MSC FUNCTION

Frenette, Paul S.

Gottesman Stem Cell Institute, Albert Einstein College of Medicine, Bronx, NY, USA

Hematopoietic stem cells (HSCs) are maintained in specific niches whose identities have been the subject of intense studies. While the perivascular stromal cell population marked by Nestin-GFP transgenic mice expresses very high levels of the major niche factors, their expression is markedly downregulated upon culture following the removal of niche cells from their natural environment. We have hypothesized that the transcriptional rewiring of mesenchymal-derived stromal cells (MSCs) occurring in culture conditions may contribute to their reduced ex vivo HSC maintenance potential. Using an RNA sequencing screen, we have identified 5 transcription factors (Klf7, Ostf1, Xbp1, Irf3, Irf7) that can restore HSC niche function in cultured BM-derived MSCs. These revitalized MSCs (rMSCs) exhibited enhanced synthesis of HSC niche factors while retaining their mesenchymal differentiation capacity. By contrast to HSCs co-cultured with control MSCs, HSCs expanded with rMSCs showed higher repopulation capacity and protected lethally irradiated recipient mice. Competitive reconstitution assays revealed ~7-fold expansion of functional HSCs by rMSCs. rMSCs prevented the accumulation of DNA damage in cultured HSCs, a hallmark of aging and replication stress. Analysis of the reprogramming mechanisms uncovered a role for myocyte enhancer factor 2c (Mef2c) in the revitalization of MSCs. These results provide insight in the transcriptional regulation of the niche with implications for stem cell-based therapies.

16:25 – 16:36

CHARACTERIZATION OF "OOGONIAL STEM CELLS" ISOLATED BY DDX4 ANTIBODY BASED FACS IN THE HUMAN OVARY

Wagner, Magdalena[1], Panula, Sarita[1], Damdimopoulos, Tassos[2], Douagi, Iyadh[3], Hovatta, Outi[4], Lanner, Fredrik[1] and Damdimopoulou, Pauliina[1]

[1]Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden, [2]Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden, [3]Department of Medicine, Karolinska Institutet, Stockholm, Sweden

The presence of oogonial stem cells (OSCs) capable of forming functional follicles with oocytes in the adult human ovary has been reported. These putative stem cells are purified from human ovaries by FACS targeting DDX4, a germ line marker usually expressed in the cell cytoplasm. Following the published protocol, we have isolated a "DDX4 positive" and negative cell populations from human ovarian tissue. The cells in our hands do not express DDX4 at an RNA level, and neither do they form follicles when xenografted into immunodeficient mice within human ovarian cortical pieces. In spite of these negative results, our flow cytometry-based analysis shows that the DDX4 antibody recognizes a distinct cell population among ovarian cells. We compared isolated "DDX4 positive" cells to the negative population using single cell mRNA sequencing and cell surface antigen profiling via FACS. The expression of 616 genes differed significantly between the two cell populations. Our results further suggest that 40 cell surface antigens are consistently expressed in the human ovarian cortex, and among those, twelve markers are brightly expressed on "DDX4 positive" cells while eight markers are absent. We next carried out single-cell profiling of human ovarian cortical tissue and compared the profiles of DDX4-positive cells to the general cell population in the ovary. We discovered two distinct clusters of cells that overlap with the RNA and cell surface antigen expression profiles of the DDX4-positive cells. These clusters do not express a germ cell marker profile and are currently under investigation. Our data thus far suggest that the "DDX4 positive" cells are not oogonial stem cells but rather a heterogeneous population of diverse cell types within the ovarian cortex. Since these cells are already used in fertility treatments, their further characterization is urgently needed.

16:36 – 16:47

PSYCHOLOGICAL STRESS DRIVES MELANOCYTE STEM CELL EXHAUSTION THROUGH ACTIVATION OF THE SYMPATHETIC NERVOUS SYSTEM

Zhang, Bing[1], Baral, Pankaj[2], Choi, Sekyu[1], Shwartz, Yulia[1], Chiu, Isaac[2] and Hsu, Ya-Chieh[1]

[1]Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Harvard University, Cambridge, MA, USA, [2]Department of Microbiology and Immunobiology, Harvard Medical School, Boston, MA, USA

Psychological stress negatively affects tissue homeostasis and regeneration, but whether and how stress perception leads to profound changes in tissue biology remains poorly understood. Here, we investigate this question in the skin. Psychological stress has been anecdotally associated with hair graying, but a scientific evidence linking the two is lacking. By adapting approaches to induce stress in mice, including physical pain and restraining, we showed that psychological stress leads to gray hair formation through rapid depletion of melanocyte stem cells (MeSCs). Combining denervation, endocrine surgeries, cell ablation, and cell-type specific gene deletions, we showed that stress-induced hair graying is independent of stress hormones or the immune system, but relies on the activation of the sympathetic nervous system. Sympathetic nerve terminals innervate the MeSC niche. Under stress, sympathetic nerve activation leads to burst release of neurotransmitter norepinephrine, which targets MeSCs directly. Norepinephrine drives MeSCs proliferation, leading to their rapid exhaustion. Inhibition of MeSC proliferation or MeSC-specific deletion of norepinephrine receptors rescue stress-induced hair graying. Our study shows that psychological stress-induced neural activity can alter somatic stem cells directly, and identifies strategies that might be exploited for therapeutic purposes in the future.

16:47 – 16:58

NEUREGULIN1 PROMOTES INTESTINAL STEM CELL PROLIFERATION AND EPITHELIAL REGENERATION FOLLOWING INJURY

Abud, Helen E.[1], Jarde, Thierry[2], Rosello, Fernando[2], Kurian Arackal, Teni[2], Chan, Eva[2], Donoghue, Jacqueline[3], Abe, Shin-ichi[4], Flores, Tracy[2], Giraud, Megane[2], Prasko, Mirsada[2], Richards, Elizabeth[2], Phesse, Toby[5], Nefzger, Christian[2] and Polo, Jose[2]

[1]Biomedicine Discovery Institute, Monash University, Clayton, Australia, [2]Anatomy and Developmental Biology, Monash University, Clayton, Australia, [3]Centre for Cancer Research, University of Melbourne, Parkville, Australia, [4]Department of Biological Sciences, Graduate School of Science and Technology, Kumamoto University, Kumamoto, Japan, [5]European Cancer Stem Cell Research Institute, Cardiff University, Cardiff, UK

Identifying strategies to enhance intestinal stem cell proliferation may enable regeneration of the epithelium to be manipulated in degenerative diseases and intestinal pathologies. Using intestinal organoids grown ex vivo, we have defined Neuregulin1/ERBB signalling as a strong driver of cell proliferation in the intestinal epithelium. We defined the localisation of Neuregulin1 and interacting receptors in the intestine using immunofluorescence and qRT-PCR. We observed that supporting niche cells express Neuregulin1, while stem cells express ERBB receptors, supporting a model where Neuregulin1/ERBB signalling directly regulates stem cells. The role of Neuregulin1 was also investigated in vivo using both a gene knockout approach in different cellular compartments and a model where activation of Neuregulin1/ERBB signalling was achieved in mice injected with 15ug Nrg1 for 5 days. Elevation of signalling increased cell proliferation in crypts, altered cellular differentiation and promoted regeneration. Loss of Neuregulin1 resulted in a significant decrease in cell proliferation within crypts in both stem and progenitor cells. The molecular changes induced by Neuregulin1 were examined using RNA sequencing which defined a strong impact on the cell cycle and conversion of progenitor cells to an intestinal stem cell identity. This was reinforced by examining the ability of single intestinal stem and progenitor cells to generate organoids. The action of Neuregulin 1 during tissue regeneration was investigated using two mouse models of injury/regeneration, irradiation and 5-FU-induced damage. Neuregulin 1 treatment in both these models effectively enhanced tissue regeneration. Overall, these studies reveal Neuregulin 1 is a potent niche signal that drives proliferation and stem cell identity in intestinal crypts.

Funding Source: This research was supported by the National Health and Medical Research Council (Australia).

16:58 – 17:09

INHIBITION OF SEMAPHORIN 3A PROMOTES VASCULAR AND HEMATOPOIETIC STEM CELL REGENERATION

Himburg, Heather, Fang, Tiancheng, Pang, Amara, Zhang, Yurun, Kim, Mindy, Roos, Martina, Termini, ChristinaSasine, Joshua and Chute, John

Division of Hematology/Oncology, Department of Medicine, University of California, Los Angeles, CA, USA

Hematopoietic stem cells (HSCs) are depleted by myelosuppressive chemotherapy and irradiation and chemotherapy utilized in the curative treatment of patients with cancer, increasing risk of complications including infection, hemorrhage, long-term hematopoietic failure and secondary leukemia. HSC regeneration and hematopoietic reconstitution following myelosuppressive chemo- and/or radiotherapy are dependent on extrinsic signals from the bone marrow (BM) microenvironment. However, the precise niche-derived mechanisms that control HSC regeneration following myelosuppression remain poorly understood. We discovered that BM vascular endothelial cells (ECs) upregulate expression and secretion of semaphorin 3a (SEMA3A), a protein with anti-angiogenic properties, following irradiation or chemotherapy. We hypothesized that SEMA3A promotes EC apoptosis and delays BM vascular niche regeneration. Here, we show SEMA3A promotes EC apoptosis following irradiation, whereas antibody blockade of Neuropilin 1 (Nrp1), the receptor for SEMA3A, suppresses BM EC apoptosis and accelerates BM vascular niche regeneration in irradiated mice. Commensurate with BM vascular

niche regeneration, irradiated mice treated with anti-NRP1 displayed early recovery of peripheral blood white blood cells and HSCs capable of long-term competitive repopulation in recipient mice. These results suggest that inhibition of SEMA3A – NRP1 signaling in ECs has potent regenerative potential for the vascular niche and HSCs. In order to confirm these findings, we inducibly deleted Nrp1 in VEcadherin+ ECs using VEcadCre;Nrp1 fl/fl mice and discovered that Nrp1 deletion in ECs accelerated BM vascular regeneration, HSC regeneration and hematopoietic recovery following TBI. Mechanistically, SEMA3A promotes EC apoptosis following irradiation via activation of Cdk5 and p53, whereas inhibition of SEMA3A – NRP1 signaling blocked p53 activation and decreased EC apoptosis. These results suggest that SEMA3A - NRP1 signaling is an autocrine mechanism that inhibits BM EC and vascular niche regeneration following myelosuppressive injury. Targeted inhibition of SEMA3A - NRP1 signaling in BM ECs drives BM vascular niche regeneration following injury, thereby accelerating HSC regeneration and hematopoietic reconstitution.

Funding Source: This work was supported by NHLBI grant HL-086998-06 (JPC), NIAID grants AI-067769 (JPC), AI-107333 (JPC), the California Institute for Regenerative Medicine Leadership Award LA1-08014 (JPC), NIAID grant AI-138331 (HAH).

17:09 – 17:20

RESCUE OF OSTEONECROSIS BY TRANSPLANTATION OF INTACT BLOOD VESSEL STEM CELL NICHES

Zhao, Liming[1], Hoover, Malachia[1], Murphy, Matthew[1], Koepke, Lauren[1], Lopez, Michael[1], Ambrosi, Thomas[1], Marecic, Owen[1], Steininger, Holly[1], Deleon, Nestor[1], Nguyen, Patricia[2], Longaker, Michael[1] and Chan, Charles[1]

[1]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University, Palo Alto, CA, USA, [2]Department of Medicine, Division of Cardiovascular Medicine, Stanford University, Palo Alto, CA, USA

Osteonecrosis is a common bone disease characterized by death of bone cells and collapse of bone structures. In the United States, there are an estimated twenty to thirty thousand newly diagnosed patients each year, with even larger numbers worldwide. Osteonecrosis is an extremely painful condition and leads to significant disability as the disease worsens. Osteonecrosis often stems from a loss of blood supply to the bone which be caused by multiple conditions, including infection, injury, auto-immune, steroid treatment and alcohol abuse. Treatment options are limited, and the condition contributes to approximately 10 percent of all total hip replacements in the US. Whether restoring the blood supply to the affected bone could treat osteonecrosis is currently a hot topic of research We have observed that vessels are composed of stem cell as well as niche populations, and co-transplanting vessel stem cells (VSCs) with niches results in formation of intact vessels cable of rescuing ischemic damage. We hypothesized that co-isolation and transplanting intact VSCs with niches will lead to optimal neovascularization and improvement of blood supply to ischemic bone tissue. In the present study, we established a new microfluidic based method (On-chip Sort) to purify intact VSCs clusters with or without niches and tested their ability to form vessels in vivo. We further tested transplanting of intact VSCs/Niches clusters in a mouse model of ischemic osteonecrosis. After 1-2-4-6 weeks of surgery, laser Doppler imaging was used to measure the blood flow of ischemic tissue, and micro CT was used to assess changes to the bone structure. Histologic analysis was also performed to show the bone cell death and bone structure change. We observed that purified intact VSCs/Niches clusters gave rise to a higher frequency of host-derived intact vessel formation compared to VSCs along group. In addition, transplanting of VSCs/Niches clusters resulted in restoration of blood flow around the cauterized vessel to supply the distal tissue. Finally, the bone cell viability and bone structure in ischemic area were remarkably improved in the VSCs/Niches clusters transplanting group. In conclusion, our findings describe a new approach to rescue osteonecrosis by co-isolation and transplanting VSCs/niches units as their intact organization.

Funding Source: This study was supported by Siebel Fellowship, PCF YI Award, Stinehart/Reed, Stanford Cardiovascular Institute Funding and NIH NIAK99AG049958-01A1 to Charles Chan.

17:20 – 17:31

WNT4 FROM THE NICHE CONTROLS THE MECHANO-PROPERTIES AND QUIESCENCE OF MOUSE MUSCLE STEM CELLS

Eliazer, Susan[1], Muncie, Jon[2], Christensen, Josef[3], Sun, Xuefeng[1], D'Urso, Rebecca[1], Weaver, Valerie[4] and Brack, Andrew[1]

[1]Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research/ Department of Orthopaedic Surgery, University of California, San Francisco, CA, USA, [2]Center for Bioengineering and Tissue Regeneration, University of California San Francisco and University of California Berkeley, San Francisco, CA, USA, [3]Center for Regenerative Medicine, Massachusetts General Hospital, Boston, MA, USA, [4]Center for Bioengineering and Tissue Regeneration, Department of Surgery, Department of Anatomy, Department of Bioengineering and Therapeutic Sciences, Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, and Helen Diller Comprehensive Cancer Center, University of California, San Francisco, CA, USA

Wnt signaling is a paracrine-acting signaling cascade that plays a critical role in stem cell-niche biology. In comparison to the intracellular components of Wnt signaling in the receiving cell, the Wnt ligands, their cell source and mechanism of action remain poorly understood. In the adult muscle, tissue resident stem cells (or satellite cells, SCs) remain in a quiescent state. In response to muscle injury, the SCs exit quiescence, transition towards cell cycle entry through an mTORC1-intermediate state, leading to replication, migration to the injury site and either self-renewal or differentiation. The specific paracrine agents and niche cells that maintain the quiescent state during tissue homeostasis remain unknown. Here we present evidence that Wnt4 from the muscle fiber, maintains SC quiescence through the cytoskeletal regulator, Rho. Using cell specific inducible gene deletion to delete Wnt4

from adult muscle fibers, we find that SCs increase in number and proliferation during homeostasis. Wnt4 activates Rho in SCs to maintain mechanical strain and restrict movement in the niche. Transient deletion of Wnt4 from the niche prior to injury, increases SC function and accelerates muscle regeneration. Wnt4- Rho regulated activation of SCs is independent of mTORC1 signaling and functions through the upregulation of hippo signaling pathway. Wnt4 also prevents activation of human SCs maintaining their quiescent state. These experiments identify Wnt4 secreted from the muscle fiber directly regulates the mechano-properties of the quiescent SC during tissue homeostasis.

17:31 – 17:51

TRACING THE ORIGIN OF ADULT STEM CELLS

Jensen, Kim B.

Biotech Research and Innovation Centre (BRIC), Copenhagen, Denmark

Tissues such as the epidermis and the intestinal epithelium are maintained throughout adult life by specialised stem cells located in defined niches. During tissue homeostasis the balanced contribution from resident stem cells sustains normal tissue turnover. Yet, it remains largely unknown when these stem cells are defined during development, and how they change their behaviour as the tissue transitions from morphogenesis to steady state homeostasis. In order to address these pertinent questions and to establish a framework for cell behaviour, we have taken advantage of quantitative in vivo fate mapping analysis in combination with biophysical modelling. Our analysis reveals that the epidermis and intestine use different mechanisms to transition from morphogenesis into homeostasis and that the chosen mechanism largely defines the subsequent behaviour of cells within their respective stem cell niches of fully functional organs in homeostasis. This has important implications for generating adult tissues from pluripotent stem cells, add a framework for addressing how specific gene perturbations affect cell behaviour and provides novel insights into potential disease mechanisms.

THURSDAY, 27 JUNE, 16:00 – 18:00

CONCURRENT IID: TISSUE REGENERATION AND HOMEOSTASIS

Room 408A, Level Two

16:05 – 16:25

MESENCHYMAL PROGENITORS AS ORGANIZERS OF THE REGENERATIVE PROCESS

Rossi, Fabio

University of British Columbia, Vancouver, BC, Canada

Mesenchymal stem cells and mesenchymal progenitors are highly studied but poorly defined cell types. Most of our knowledge on their functions and properties stems from in vitro work, and provides a limited view of the true role of these cells in physiological conditions. We have generated a number of transgenic tools to probe the functions of mesenchymal progenitors in vivo, in homeostasis and regeneration. I will present three distinct "case studies" highlighting their roles in pathology, in instructing the inflammatory environment during regeneration, and in tissue maintenance at homeostasis. In most cases, these functions are carried out by signalling to other cell types through secreted molecules that represent therapeutic targets.

16:25 – 16:36

IDENTIFICATION OF A LIF-RESPONSIVE REPLICATION-COMPETENT SUBPOPULATION OF HUMAN BETA CELLS

Rosado-Olivieri, Edwin A., Ahmed, Idil and Melton, Douglas

Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Cambridge, MA, USA

Beta cell replication is the main mechanism controlling beta cell mass yet the molecular underpinnings controlling this process are elusive. To gain insight into novel regulators of cell cycle re-entry in human beta cells, we capitalized on a YAP overexpression system to induce the proliferation of stem cell derived-beta cells and performed droplet-based single cell RNA-sequencing analysis. We single cell profiled 11,517 control and replicating human beta cells and identified gene expression modules that correlate with the cell cycle re-entry observed upon YAP overexpression. Computational prediction of gene co-expression networks and cis-regulatory sequence analysis identified a set of 15 transcription factors whose gene networks are predicted to be active in replicating beta cells. Three of these transcription factors, SOX11, ASCL1 and CEPBD, are sufficient to induce beta cell replication in a cell type-specific manner. Our analysis also identified an upregulation of components of the leukemia inhibitory factor (LIF) pathway in replicating beta cells. Activation of the LIF pathway by its ligand LIF and related cytokines induce the replication and expansion of stem cell derived-beta cells in vitro in a STAT3-dependent manner. LIF pathway activation also increases the expression of CEBPD, a transcription factor that preferentially induces cell cycle re-entry in beta cells identified by our computational gene network analysis. In both stem cell derived- and adult human beta cells, the expression of LIFR, a receptor of the LIF signaling pathway, is restricted to a small subset of beta cells and is indispensable for beta cell replication in vitro. Our analysis shed light into regulatory networks and pathways that control beta cell replication and revealed an unprecedented heterogeneity in LIF-responsiveness and replication competence in beta cells.

Funding Source: JPB Foundation, HSCI, NIH, AstraZeneca

16:36 – 16:47

NEURONAL COORDINATION OF TASTE RECEPTOR CELL REGENERATION

Lu, Wan-Jin, Baghel, Ankit and Beachy, Philip

Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA

Taste reception and discrimination is critical for survival, requiring robust mechanisms for replacement of taste receptor cells

(TRCs) within the taste sensory organs by stem and progenitor cells from the surrounding epithelium. The maintenance of taste sensory organs in the tongue was shown 140 years ago to depend on innervation from distant ganglion neurons, but the underlying mechanism regulating adult stem cell niches in the taste bud has remained unknown. We found that Sonic hedgehog (Shh), which encodes a secreted protein signal, is expressed in these sensory neurons, and that experimental ablation of neuronal Shh expression causes loss of taste receptor cells (TRCs). TRCs are also lost upon pharmacologic blockade of Hedgehog pathway response, accounting for the loss of taste sensation experienced by cancer patients undergoing Hedgehog inhibitor treatment. We found that TRC regeneration following such pharmacologic ablation requires neuronal expression of Shh and can be substantially enhanced by pharmacologic activation of Hedgehog response. Our findings illustrate a new biological principle, namely, that stable and robust organ patterning in tissues with a high rate of turnover can be specified by neuronal delivery of an essential regenerative signal to precise locations. In addition, our findings suggest that pharmacologic Hedgehog pathway activation may provide a means to accelerate taste recovery in the ~85% of cancer patients that lose taste sensation when they undergo chemotherapy.

Funding Source: This work was supported by postdoctoral fellowships to W.-J.L. from Damon Runyon Cancer Research Foundation, California Institute for Regenerative Medicine, the Siebel Foundation, and NIH [R21 NS093556, R01 DC016892 (to P.A.B.)].

16:47 – 16:58

THY1.2 MARKS A DISTINCT STEM CELL POPULATION THAT CONTRIBUTES TO EPIDERMAL HOMEOSTASIS AND REPAIR

Fuchs, Yaron[1], Feldman, Alona[1], Yosefzon, Yahav[1], Kadosh, Avichai[1], Gerstberger, Stefanie[2], Shemesh, Tom[1] and Steller, Hermann[3]

[1]Biology, Technion-Israel Institute of Technology, Haifa, Israel, [2]Medicine, Columbia University, New York, NY, USA, [3]Strang Laboratory of Apoptosis and Cancer Biology, Rockefeller University, New York, NY, USA

The epidermis consists of three main compartments: the hair follicle, sebaceous gland and the interfollicular epidermis (IFE). In recent years it has become clear that under normal conditions each of these epidermal compartments is discretely maintained by distinct populations of stem cells (SCs). In contrast to the hair follicle, which has been extensively investigated and shown to house various subpopulations of SCs, the identity of the SCs that maintain the IFE is poorly understood. Here we report the identification on a unique SC population, marked by Thy1.2, that plays a key role in IFE homeostasis and repair. Thy1.2+ SCs are homogenously distributed in the basal layer of the dorsalskin and are located in the label retaining zone of the tailskin. Thy1.2+ SCs express a unique gene signature, can be easily expanded and retain label for extended periods of time. Advanced multicolor lineage-tracing analysis and ablation experiments reveal that Thy1.2+ SCs are key in replenishing the IFE. Furthermore upon injury, Thy1.2+ SCs contribute to epidermal repopulation and scar maintenance, indicating they play a crucial role in epidermal homeostasis and tissue regeneration.

16:58 – 17:09

HIGH CPSF EXPRESSION IN HUMAN EPIDERMAL PROGENITORS SUPPRESSES TERMINAL DIFFERENTIATION THROUGH ALTERNATIVE POLYADENYLATION

Bao, Xiaomin[1,2], Chen, Xin[1] and Lloyd, Sarah[1]

[1]Molecular Biosciences, Northwestern University, Evanston, IL, USA, [2]Dermatology, Northwestern University, Evanston, IL, USA

Alternative polyadenylation (APA) is a regulatory mechanism that controls gene expression level and function through the usage of different transcription termination sites, which can locate in introns in addition to 3'TURs. APA events have been identified in nearly 70% of human protein-coding genes. However, how APA is regulated to influence epithelial tissue differentiation remains under-characterized. Using human epidermal tissue as a research platform, here we show that more than 2000 genes alter polyadenylation site (PAS) usage during epidermal differentiation. These genes include the differentiation activator GRHL3, which features both proximal PAS (~5 kb downstream of the transcription start site in the first intron) and distal PAS (produces full-length mRNA). In undifferentiated (UD) keratinocytes the proximal PAS is used >40 times more frequently, suppressing the production of full-length GRHL3 mRNA. To determine how these alternative PASs are regulated, we examined the expression of the Cleavage and Polyadenylation Specificity Factor (CPSF) complex, which binds to the polyadenylation signal (AAUAAA) and cleaves nascent RNA to facilitate polyadenylation. We find that CPSF is expressed ~3 times higher in UD than differentiated (DF) keratinocytes. Suppression of CPSF using RNAi or CRISPRi strongly impaired epidermal regeneration with upregulation of terminal differentiation marker gene expression. Mechanistically, we identified that CPSF suppression decreased the usage of the GRHL3 proximal PAS and upregulated full-length GRHL3 mRNA production. Knockdown of GRHL3 in the context of CPSFi partially restored differentiation marker gene expression. Using complex purification, we identified 66 CPSF-interacting proteins (CIPs) in UD but not DF keratinocytes. RNA binding proteins are overrepresented in these CIPs. Thus, our data suggest a model where high CPSF expression drives its association with RNA-binding proteins, which alters CPSF binding preference and PAS choices to suppress epidermal terminal differentiation.

Funding Source: This work is supported by a NIH K99/R00 Award (R00AR065480), the Searle Leadership Fund and the Northwestern Skin Disease Research Center Pilot and Feasibility Award to X. B., as well as a NIH CMBD training grant to S.M.L.

17:09 – 17:20

THE PRRX1 LIMB ENHANCER MARKS AN ADULT POPULATION OF INJURY-RESPONSIVE, MULTIPOTENT DERMAL FIBROBLASTS

Currie, Joshua D.[1], Grosser, Lidia[2], Michel, Martin[3], Murawala, Prayag[2], Scheuz, Maritta[3], Tanaka, Elly[2] and Sandoval-Guzman, Tatiana[3]

[1]Department of Cell and Systems Biology, University of Toronto, ON, Canada, [2]Institute of Molecular Pathology, Vienna, Austria, [3]Center for Regenerative Therapies, Technische Universität, Dresden, Germany

The heterogeneity of adult tissues has been posited to contribute toward the loss of regenerative potential in mammals. Here we characterize an adult population of dermal fibroblasts that maintain expression of a Prrx1 enhancer which originally marked mesenchymal limb progenitors. Prrx1 enhancer-positive cells (Prrx-1enh+) make up a small subset of adult dermal cells (~0.1%) and reside mainly within specific dermal perivascular and hair follicle niches. Upon injury, however, Prrx1enh+ cells readily migrate into the wound bed and amplify on average 16-fold beyond their uninjured numbers. Additionally, Prrx1enh+ cells emigrate out of their dermal niches following wounding and contribute to subcutaneous tissue. Prrx1enh+ cells are uniquely injury-responsive and do not contribute to tissue homeostasis or enriched by neonatal-like Wnt signaling. Prrx1enh+ cells represent a potent regenerative cell population that, despite being a meager minority in adult skin, demonstrate the potential to tip the balance of mammalian wound healing toward scar-free healing.

17:20 – 17:31

ROBUST REGENERATION OF LIGAMENTS AND ARTICULAR CARTILAGE IN THE ADULT ZEBRAFISH JAW JOINT

Smeeton, Joanna, Natarajan, Natasha, Fabian, Peter, Nelson, Nellie, Tseng, Kuo-Chang and Crump, Gage

Stem Cell Biology and Regenerative Medicine, University of Southern California (USC), Los Angeles, CA, USA

Mammalian ligaments and joint cartilage have a poor intrinsic capacity for repair, which helps to explain the high incidence of arthritis world-wide. Here, we tested whether, unlike mice and humans, zebrafish can regenerate joint tissues as adults. To do so, we developed a surgical technique to destabilize the zebrafish jaw joint via transection of the major joint-supporting ligament, the interopercularmandibular (IOP). Unilateral transection of the IOP in adult fish results in a marked reduction of articular cartilage by 14 days post-transection (dplt). Remarkably, articular cartilage fully recovers by 28 dplt, which correlates with regeneration of the IOP ligament. Functional recovery of the IOP can be observed as early as 7 dplt, including the ability to open the jaw and re-expression of the key ligament gene scleraxis. During the early phase of ligament regeneration, live imaging reveals downregulation of scleraxis in ligamentocytes near the injury site, as well as the proliferative expansion and infiltration of neural crest-derived cells that bridge the injury. Single-cell RNA sequencing captured both a novel population of stem cells during ligament regeneration, as well as shifts in the gene expression profile of mature ligamentocytes that suggest de-differentiation as a contributing mechanism to regeneration. During articular cartilage regeneration, we observe upregulation of sox10 throughout the joint surface. Along with Sox9a, Sox10 is a member of the SoxE transcription factor family critical for vertebrate cartilage development. Using a conditional transgenic ablation strategy, we find that loss of Sox10+ cells prior to ligament transection effectively blocks cartilage regeneration. Our data reveal robust regeneration of ligaments through resident stem cells and de-differentiation of existing ligamentocytes, and joint cartilage through a subset of Sox10+ chondrocytes that may retain developmental potential. Creation of a joint regeneration model in zebrafish should aid in developing new approaches toward endogenous repair of arthritic joints in humans.

17:31 – 17:51

SUBEPITHELIAL TELOCYTES CONSTITUTE THE INTESTINAL STEM CELL NICHE

Shoshkes Carmel, Michal

Hebrew University of Jerusalem, Israel

Stem cell niches provide essential signals and growth factors to sustain proliferation and self-renewal of stem cells in continuously self-renewing organs such as the intestine. We identify large mesenchymal cells expressing the winged-helix transcription factor forkhead box l1 (Foxl1) and the surface platelet derived growth factor a (PDGFRa). These cells are telocytes which have a unique cell structure with long processes that extends hundreds of micrometers. Foxl1+ telocytes cover the entire gut epithelium from crypt base into the villus tips and are expressing key signaling pathway molecules such as members of the Wnt, BMP, Shh, FGF and TGFb gene families in a localized fashion. Ablation of Foxl1+ telocytes or Wnt protein secretion within these cells causes loss of proliferating cells in the crypt compartment, rapid crypt collapse, and death of the mutant mice within a few days. Thus, Foxl1+ telocytes constitute the intestinal stem cell niche which is absolutely required for stem cell function.

THURSDAY, 27 JUNE, 16:00 – 18:00

CONCURRENT IIE: LINEAGE CHOICE AND ASYMMETRIC CELL DIVISION

Room 408B, Level Two

16:05 – 16:25

PUMILIO PROTEINS ARE KEY POST-TRANSCRIPTIONAL REGULATORS OF EMBRYONIC STEM CELL PLURIPOTENCY AND EARLY EMBRYOGENESIS

Lin, Haifan[1,2,3], Uyhazi, Katherine[1], Yang, Yiying[2], Liu, Na[1], Qi, Hongying[1], Huang, Xiao[1], Mak, Winifred[1,3], Weatherbee, Scott[1] and Song, Xiaoling[2]

[1]Yale Stem Cell Center, Yale University, New Haven, CT, USA, [2]ShanghaiTech University, Shanghai, China, [3]Yale University School of Medicine, New Haven, CT, USA

Gene regulation in embryonic stem cells (ESCs) has been extensively studied at the epigenetic-transcriptional level; however post-translational regulation remains largely unexplored. Pumilio (Pum) proteins are among the few known translational repressors required for stem cell maintenance in invertebrates and plants. Here we report the essential function of two mammalian Pum proteins, Pum1 and Pum2, in mouse early embryogenesis and ESCs. Pum1/2 double mutants are developmentally delayed at the morula stage and lethal by e8.5. Consistently, Pum1/2 double mutant ESCs display severely reduced capacity of self-renewal and differentiation, revealing the function of Pum1 and Pum2 in ESC pluripotency. Remarkably, Pum1-deficient ESCs show increased expression of pluripotency genes but not differentiation genes, indicating that Pum1 mainly promote differentiation; whereas Pum2-deficient ESCs show decreased pluripotency markers and accelerated differentiation, indicating that Pum2 promotes self-renewal. Thus, Pum1 and Pum2 contribute to two complementary aspects of pluripotency. Furthermore, we demonstrate that Pum1 and Pum2 achieve such functions not only by the repressing the translation of a subset of their target mRNAs but also by promoting translation and regulating mRNA stability of other subsets of their target mRNAs. In addition, Pum1 and Pum2 bind to their own mRNA, each other's mRNA, and negatively regulate each other's expression. Thus, Pum1 and Pum2 appear to form a negative auto- and inter-regulatory feedback loop that regulates the translation and stability of many target mRNAs involved in self-renewal and differentiation to achieve ESC pluripotency and embryogenesis.

16:25 – 16:36

REGULATION OF THE MOUSE SKELETAL MUSCLE STEM CELL NICHE DURING HOMEOSTASIS AND REGENERATION

Tajbakhsh, Shahragim[1], Evano, Brendan[1] and Almouzni, Genevieve[2]

[1]Department of Developmental and Stem Cell Biology, Pasteur Institute, Paris, France, [2]Department of Developmental and Stem Cell Biology, Institut Curie, Paris, France

Regulation of skeletal muscle stem cells during homeostasis and regeneration involves the interplay between extrinsic and intrinsic cues. The mechanisms by which niche molecules and intrinsic factors regulate muscle stem cell quiescence and properties remain largely unknown. In a series of studies, we investigated Notch as a key mediator of muscle stem cell stability and fate through extrinsic regulation of extracellular matrix, and internal regulation of cell migration via the mirtron mir708. Using static and live imaging, these observations led us to propose a two-step mechanism where the final mitosis before cellular quiescence and cell migration need to be independently regulated prior to niche occupancy by the stem cell. Using cell lineage reporter mice, our data show that muscle stem cells exit from the cell cycle first, continue to migrate, then arrest and occupy the niche under the regulation of two Notch mediated axes. In parallel, we developed a novel in vivo clonal cell lineage method using Pax7 reporter mice to mark all muscle stem cells, and combined this with transcription factor readouts (Pax7, MyoD and Myogenin as stem and differentiating markers) to assess division asymmetry. Our ex vivo live imaging of artificial niches on fibronectin coated micropatterns, and in vivo clonal analyses show for the first time that asymmetric and symmetric cell divisions both contribute to the self-renewal process in vivo. This division asymmetry was examined in more detail using H3.1-SNAP transgenic mice that we generated that allow tracking of old and new histone pools. Using this transgenic in combination with clonal lineage studies in vivo, we show that in contrast to the fly germ line where this histone variant was reported to segregate asymmetrically, we observe symmetric distribution of H3.1 during muscle stem cell asymmetric cell divisions. Taken together, we show that muscle stem cell regulation is dynamic during homeostasis and regeneration and we propose a model of how the asymmetry apparatus engages in cell fate decisions during muscle stem cell self-renewal and differentiation during tissue regeneration.

Funding Source: Institut Pasteur, Laboratoire d'Excellence Revive, Investissement d'Avenir, Association Française contre les Myopathies and the European Research Council (Advanced Research Grant).

16:36 – 16:47

DEFINING ESSENTIAL GENES FOR NEUROECTODERM

Yilmaz, Atilgan, Tsypin, Anna and Benvenisty, Nissim

The Azrieli Center for Stem Cells and Genetic Research, The Hebrew University of Jerusalem, Israel

Human embryonic stem cells (hESCs) have the potential to differentiate to every cell of the body. Understanding the developmental processes of these cells will contribute to the design of novel cell therapies and the generation of better models for human diseases. Previous studies suggested several genes that have a role in the differentiation of hESCs into the ectodermal lineage. However, the complete gene networks that are essential for these early differentiation events are yet to be determined. Here, we aimed to identify the subset of genes that are essential for the differentiation of hESCs into the neuroectodermal lineage. To this end, we have utilized a genome-wide loss-of-function library covering all 18,000 coding genes, generated in haploid hESCs by CRISPR/Cas9 technology and an established differentiation protocol for neural progenitor cells (NPCs). We differentiated the mutant hESC library into NPCs and analyzed the depletion and enrichment of mutant clones in the NPC population as compared to their representation in the hESC population. We have shown that 2.9% of all genes were significantly depleted within the NPC population, but not in the hESC population suggesting that these genes are specifically essential for the development of NPCs. In contrast, we have also demonstrated that 2.8% of the genes were enriched within the NPC population, implying that these genes inhibit NPC development. We have identified two close homologs from the homeobox-containing transcription factor family, namely POU3F2 and POU3F3, as essential genes for NPC development. In order to validate our screen results, we have utilized CRISPR/Cas9 mutagenesis and generated a POU3F2 null hESC line, which, upon differentiation to NPCs, exhibited downregulation of neural differentiation markers. Our work maps essential genes for the formation of neuroectoderm and may serve as reference for future studies on human neural development.

16:47 – 16:58

DISSECTING THE REGULATORY PRINCIPLES OF ES CELL DIFFERENTIATION

Leeb, Martin

MFPL Max F. Perutz Laboratories, University of Vienna, Austria

The exit from naïve pluripotency is the initial cell fate decision towards differentiation of mouse embryonic stem cells (ESCs). Using genome-wide genetic screens in haploid ESCs, we have revealed several hundred factors required for the exit from pluripotency. However, the genetic relays downstream of these factors and the relevant causal consequences of their deregulation remain unexplored. Therefore, we have combined CRISPR/Cas9 based gene-disruption with large scale transcriptomics and systems biology approaches to dissect the gene-regulatory circuit directing ESC differentiation. Specifically, we have genetically disrupted 74 candidate genes in diploid bi-parental ESCs and obtained RNASeq profiles of cells growing in 2i or after 24h of differentiation. This allowed us to assess the impact of specific gene depletions on gene expression in self-renewal and their impact on differentiation. By genetic interference with multiple pathways known to regulate differentiation (e.g. Fgf/ERK, Wnt, Notch and mTOR) we were able test whether and to what extent the differentiation defects of KO ESCs (deficient for unrelated factors) are funneled through these known differentiation regulators. Interestingly, a large number of differentiation defective ES cells showed upregulation of a cohort of LIF responsive genes already in 2i. We propose that this stabilization of the naïve pluripotency network contributes to the differentiation delays in these KOs. Dissecting network behavior upon multiple genetic and environmental perturbations, we identified a set of naïve pluripotency associated genes (NAGs) that showed strikingly similar expression dynamics and amplitude between our in vitro system and the in vivo pre- to post- implantation transition. We propose NAGs as an integral part of the naïve ES cell specific transcriptional circuitry. To highlight the functional relevance of this group of genes we performed a clonal 3D-differentiation based screen for synthetic interactions between a defined set of candidate genes. Indeed, we found that the combinatorial activity of several NAGs is sufficient to maintain self-renewal capacity in the absence of LIF or 2i. In summary, our results provide novel and relevant insights into the mechanisms employed to dismantle naïve pluripotency.

16:58 – 17:09

MIXL1 ORCHESTRATES CELL FATE DECISIONS DURING MOUSE AND HUMAN GASTRULATION: A MULTIOMIC STUDY

Osteil, Pierre, Knowles, Hilary, Salehin, Nazmus, Santucci, Nicole, Studdert, Joshua and Tam, Patrick

Department of Embryology, Children's Medical Research Institute, Wentworthville, Australia

During early embryonic development, mammalian embryos undergo a critical transition to form the three germ layers, the originators of the body plan organisation. How a pluripotent cell decides on its fate remains a partially unsolved question. A number of studies have deciphered upstream signalling pathways that enable specification toward a particular germ layer. However, despite tremendous efforts in the field, multiple gaps remain in our understanding of the gene regulatory networks (GRN) that governs lineage specification. Our work is focused on the specification of the ectoderm versus the mesendoderm, the latter of which emerges from a common region called the primitive streak (PS). We recently unveiled the importance of inhibiting WNT signalling during ectoderm layer formation and neurogenesis in the mouse embryo. Subsequently, we focused our interest on the formation of the endoderm layer. To unravel the molecular tools operating during such an important process we scrutinized Mixl1, a gene which, when disrupted, prevents endoderm formation. To achieve this goal, ChIP-seq, RNA-seq and ATAC-seq data on gastrulating cells were combined. In addition, our lab has developed a new ATAC-seq footprinting pipeline that allows us to rapidly build secondary levels of regulation downstream of Mixl1 by predicting transcription factor regulation in open chromatin regions. Using this strategy, we have discovered that Mixl1 driven WNT signalling is responsible for mesendoderm specification in the PS. Unexpectedly, our unique multiomic approach has led to the discovery of an important regulation of Notch signalling, known to drive ectoderm differentiation when overstimulated. Our work suggests Mixl1 could play the role of a conductor in cell fate decisions for the three germ layers. We further pinpointed a conserved mechanism in human induced pluripotent stem cells (hiPSC). MIXL1 appears to have a critical role for endoderm specification and its pattern of expression may lead to different cell fates, similar to

the mouse. To unravel the MIXL1 GRN, we undertook a similar multiomic approach using RNA-seq and ATAC-seq. Altogether, our results indicate Mixl1/MIXL1 is a major driving force behind cell fate decisions.

17:09 – 17:20

THE ROLE OF FEZF2 IN REGULATING NEURAL STEM CELL FATE IN THE POSTNATAL VENTRICULAR ZONE

Akhtar, Aslam A.[1], Saxon, David[2], Ho, Ritchie[3], Park, Hannah[3], Levy, Rachelle[3], Yang, Amy[3], Svendsen, Clive[3], Danielpour, Moise[3] and Breunig, Joshua[3]

[1]School of Medicine, George Washington University, Arlington, VA, USA, [2]Department of Medicine, Georgetown University, Washington DC, USA, [3]Regenerative Medicine Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

The postnatal cortical (dorsal) ventricular zone (VZ) is a native stem cell niche containing multipotent precursors capable of differentiating into cortical astrocytes/oligodendrocytes and olfactory bulb (OB) neurons. A large subset of these precursors in the postnatal mouse brain express the embryonic master regulator factor fez family zinc finger 2 (Fezf2), yet precious little has been done to determine if and how Fezf2 regulates their fate. Due to its proximity to the cortex, elucidating the molecular mechanisms underpinning the specification of these cells are of increased interest, as these precursors may be directed to specific fates lacking in the diseased or damaged neocortex. Our results suggest that postnatal cortical VZ precursors express varying levels of Fezf2 and increasing Fezf2 expression in the overall postnatal VZ precursor population virtually blocks neurogenesis and gliogenesis, maintaining these cells in a stalled progenitor-like state. Using STEp-seq (Somatic Transgenic Electroporation-defined single-cell RNA sequencing), we generated a whole transcriptome dataset after Fezf2 gain-of-function (GOF) and loss-of-function (LOF) in VZ precursors. These data suggest that Fezf2 expression levels in VZ precursors may be an important factor in directing cell fate, and may function through repressing Notch and Olig2, key regulators of cell fate in the perinatal cortex. When Fezf2 is overexpressed independently in conjunction with Notch or Olig2, aspects of the Fezf2-induced stalled phenotype are rescued and gliogenesis ensues. Thus, we identify a critical role of Fezf2 in this postnatal germinal stem cell niche.

Funding Source: Regenerative Medicine Institute, UCLA CTSI, NIH Innovative Molecular Analysis Technologies

17:20 – 17:31

SINGLE-CELL TRANSCRIPTOMIC DISSECTION OF CELL FATE DETERMINING MOLECULAR SWITCHES IN MOUSE PAX7-EXPRESSING SOMITIC MESODERM

Wu, Angela R.[1], Fung, Cheuk Wang[2], Wu, Zhenguo[2], Zhou, Shaopu[2] and Zhu, Han[3]

[1]Division of Life Science/Department of Chemical and Biological Engineering, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, [2]Division of Life Science, Hong Kong University of Science and Technology, Clear Water Bay, Hong Kong, [3]Department of Pediatrics, University of California, San Diego, La Jolla, CA, USA

Pax7-expressing progenitor cells in the somitic mesoderm are known to differentiate into multiple lineages, such as brown adipose tissue, dorsal dermis, as well as muscle in the dorsal trunk and the diaphragm; however, the precise molecular characteristics of the cellular intermediates, as well as key molecular switches that determine and control the process of lineage commitment and cell fate are not well understood. Lineage tracing studies have already shown that the lineage potency of Pax7-expressing cells changes over developmental time, but the regulatory mechanism of this lineage restriction is not fully understood. To probe the mechanisms behind this process, we dissected transgenic mouse embryos wherein the cellular descendants of Pax7-expressing progenitors are YFP-labelled, and subject these YFP-expressing Pax7-descendents to single-cell RNA profiling. We observed that a subpopulation of cells differentiates into the myogenic lineage, showing Myf5 expression as early as E12.5, whereas the rest of the population is fibroblast-like and has high collagen expression. This fibroblast-like population appears to be the early stage of the adipocyte and dermal lineages. Cells at E14.5 have distinct myogenic populations that express Myod1 and Myog; we also identified other populations with Ebf2 or Twist2 expression which could belong to brown adipose and dermal lineage respectively. One subpopulations of cells at E16.5 show a marked increase in expression of distinct brown adipose tissue markers; while another subpopulation maintains expression of dermal markers. Further analysis of their gene expression pattern confirms the important role of Notch signaling in the myogenic populations, and also identified candidate transcription factors that could play a role in regulating the lineage commitment decision. Importantly, we also identified novel surface markers for the dermal and BAT intermediate subpopulations that allowed us to sort and culture these cells in-vitro. This discovery will enable further functional evaluation of these newly identified cell types.

Funding Source: Hong Kong Research Grants Council (RGC): ECS 26101016, GRF 16101118, CRF C6002-17G; Hong Kong Research Block Grants to HKUST: start-up and initiation grants; HKUST BDBI lab; Hong Kong Epigenomics Project LKCCFL18SC01-D

17:31 – 17:51

RIBOSOMAL DNA AND THE RDNA-BINDING PROTEIN INDRA MEDIATE NON-RANDOM SISTER CHROMATID SEGREGATION IN DROSOPHILA MALE GERMLINE STEM CELLS

Yamashita, Yukiko

University of Michigan, Ann Arbor, MI, USA

Although non-random sister chromatid segregation has been proposed to underlie asymmetric cell divisions, the underlying biological significance or mechanisms remained elusive. Here we show that non-random sister chromatid segregation during asymmetric division of Drosophila male germline stem cells is mediated by ribosomal DNA (rDNA) loci, consisting of hundreds of tandemly repeated rDNA units. We identify a novel zinc-finger protein CG2199/Indra that binds to rDNA and control non-random sister chromatid segregation. Our data indicate that non-random sister chromatid segregation may reflect the segregation of sister chromatids with different rDNA copy numbers after unequal sister chromatid exchange to maintain rDNA copy number through generations. To our knowledge, this is the first study to provide mechanistic insights into the mechanism of non-random sister chromatid segregation.

FRIDAY, 28 JUNE, 09:00 – 11:20

PLENARY IV: STEM CELLS AND REGENERATION OF ENDODERMAL ORGANS

West Hall B, Level One
Sponsored by Semma Therapeutics

9:00 – 9:20

THE DRIVING FORCE OF ALVEOLAR DEVELOPMENT AND REGENERATION

Tang, Nan

National Institute of Biological Sciences, Beijing, China

Many organs, and especially the lung, have unique mechanical properties and are exposed to ever-present mechanical forces. It is therefore important to carefully consider the influence of mechanical forces when investigating the mechanisms that control tissue development and regeneration in such organs. A new generation of live-imaging techniques is now enabling life scientists to properly consider questions about the interface of cell biology and biophysics. We used an integrated combination of live imaging, mouse genetics, lineage tracing, and quantitative cell biology to demonstrate pulmonary alveolar development and regeneration are synergistically controlled by both mechanical forces and local growth factors. Our study highlights the essential need to consider the coordinated influences of both mechanical forces and growth factors to obtain a comprehensive and thus accurate understanding of the development and regeneration of tissues and organs. Insights gained from studies that account for these multiple regulatory influences will very likely lead to important breakthroughs in our ability to successfully engineer tissues and organs in the future.

9:20 – 9:40

A UNIVERSAL SYSTEM FOR PHARMACOLOGICAL SELECTION OF GENE EDITED HEPATOCYTES

Grompe, Markus, Nygaard, Sean**,** Vonada, Anne and Tiyaboonchai, Amita

Oregon Health and Science University, Portland, OR, USA

Many promising new strategies for liver directed cell transplantation and gene therapy are hampered by their inherent inefficiency. Targeted gene editing of specific loci by homologous recombination is one example. While gene disruption can be quite efficient in the liver, gene repair is not efficient. Lentiviral gene transfer to the liver, also a promising method, is restricted by the fact that the vector dose required to achieve therapeutic levels of gene transfer in the liver is high, making production for clinical use cost prohibitive. Cell transplantation into the liver is also inefficient. In hematopoietic stem cell transplantation, host conditioning and selection of therapeutic donor cells is key for success. Here we report the development of an analogous system for the liver. The approach relies on the knockout of a gene required for the hepatotoxic transformation of an otherwise harmless medication. Knockout of the gene renders modified hepatocytes resistant to the toxic metabolite, allowing for the selection and proliferation of transduced hepatocytes when the medication is given. Specifically, our method employs the widely used fever medicine acetaminophen (APAP). The parent drug APAP itself has no liver toxicity, but at high doses it can be metabolized to NAPQI, a hepatotoxic compound, by the cytochrome p450 (Cyp) enzymes Cyp1A2, 2E1 and 3A4. NADH-cytochrome p450 reductase (Cypor in mice/POR in humans) is an obligatory cofactor of this reaction. Hepatocytes lacking Cypor are positively selected in vivo with APAP and can replace up to 40% of the liver. Cypor deficiency is achieved by either shRNA knockdown or CRISPR/cas9 mediated gene knockout. We have developed integrating AAV and lentiviral vectors in which the Cypor gene knockdown/knockout is linked in cis to a therapeutic gene, human factor 9. Administration of APAP to mice treated with these vectors resulted in >100x expansion of the transgene bearing hepatocytes, reaching therapeutic levels of cell replacement. We conclude that APAP mediated hepatocyte selection can be used to achieve therapeutic levels of gene replacement in the context of both gene therapy and cell transplantation. The mechanisms of APAP toxicity are identical in mice and humans and therefore this approach has clinical potential for a broad array of liver diseases.

9:40 – 10:00

REGENERATION ON A CHIP: MICROFLUIDIC VASCULARIZED HUMAN HEPATIC ENSEMBLES

Bhatia, Sangeeta, Chhabra, Arnav**,** Song, Hyun-Ho and Chen, Christopher

Massachusetts Institute of Technology, Cambridge, MA, USA

The liver is uniquely able to regrow within a short period after tissue loss. Liver regeneration is commonly modelled by partial hepatectomy, a surgical procedure first described in rats in 1931 in which both biochemical and fluid forces are acutely altered, promoting regeneration primarily via paracrine signals between parenchymal hepatocytes and vascular endothelial cells. While animal models have provided insight into liver regeneration, the exact mechanisms and interactions in humans are less clear. Thus, we sought to establish a human 3D culture system that incorporates fluid forces and paracrine interactions between hepatocytes and endothelial cells. We developed a microfluidic device, called SHEAR (structurally-vascularized hepatic ensembles for analyzing regeneration), that enables modulation of hemodynamic and biochemical inputs, while also allowing paracrine, multicellular interactions. Specifically, microfluidic SHEAR devices were fabricated with lumenized endothelial channels, and embedded with parenchymal microtissues: microfabricated 3D ensembles of primary human hepatocytes and human dermal fibroblasts. To model key aspects of regeneration, we modulated fluid flow through the device and stimulated the system by including combinations of cytokines in the media, and found that exposing the endothelium to flow rates consistent with physiologically relevant shear stresses led to an increased secretion of angiogenesis- and regeneration-associated factors. Addition of cytokines known to be important during regeneration not only amplified the secretory response, but also induced cell cycling of primary human hepatocytes within the device. Unsupervised ma-

chine learning-based assays of the secretome in stimulated devices detected additional endothelial-derived, shear-dependent mediators that independently stimulate proliferation of human hepatocytes in both 2D and 3D configurations. Collectively, the data presented here underscore the importance of multicellular models that integrate tunable biochemical and fluid forces, and demonstrate that the SHEAR device can be used to discover and validate conditions that promote human liver regeneration.

10:00 – 10:11

DEVELOPING A HUMAN HEPATOBLAST ORGANOID MODEL TO STUDY DEVELOPMENT, SCREEN MEDICAL COMPOUNDS, AND DEVELOP POTENTIAL CELL BASED THERAPIES

Ross, Alexander D.[1], Wesley, Brandon[1], Saxton, Sarah[2], Kraiczy, Judith[3], Morell, Carola[1], Muraro, Daniele[4], Tomaz, Rute[1], Ortmann, Daniel[1], Stevens, Kelly[2], Zilbauer, Matthias[5] and Vallier, Ludovic[1]

[1]Cambridge Stem Cell Institute, University of Cambridge, UK, [2]Departments of Bioengineering and Pathology, University of Washington, Seattle, WA, USA, [3]Dana Farber Cancer Institute, Harvard University, Cambridge, MA, USA, [4]Cellular Genetics, Wellcome Trust Sanger Institute, Hinxton, UK, [5]University Department of Paediatrics, University of Cambridge, UK

Organoid systems have revolutionised the way in which we are able to study human development and provide a unique ability to expand large quantities of functional primary cell types. Previously, it has only been possible to culture the differentiated cell types of the liver, i.e. from either ductal or more recently fetal hepatic lineages. Here, we performed detailed characterisation of the first trimester human liver, including single cell RNA sequencing analyses, demonstrating for the first time the specific cellular landscape at this crucial stage. We went on to extract the hepatoblast population described in the primary liver and successfully generated bipotential human hepatoblast organoids (HO). These HO were able to be expanded long term in culture (>1 year) and could be differentiated to a defined lineage, i.e. either cholangiocytes or hepatocytes. Upon transplantation in vivo, HO were furthermore able to differentiate into three dimensional aggregates containing both cell types, allowing the complex cellular interactions between the daughter cell types to occur in response to innate hepatic developmental programmes. Furthermore, transplanted constructs demonstrated hepatic function in vivo, crucially generating human albumin secreted into the mouse blood stream.HO offer a unique opportunity to perform detailed analysis of the processes involved in hepatic development, provide functional differentiated cell types for drug toxicology screening, and offer a potential cell based therapy for liver disease.

10:11 – 10:22

CO-REPRESSORS MTG8 AND MTG16 REGULATE NICHE EXIT AND EARLY FATE DECISION OF MOUSE INTESTINAL STEM CELLS

Li, Vivian[1], Baulies, Anna[2] and Angelis, Nikolaos[1]

[1]The Francis Crick Institute, London, UK, [2]Stem Cell and Cancer Biology Laboratory, The Francis Crick Institute, London, UK

Notch signals are crucial to maintain intestinal stem cells (ISCs). Upon niche exit, lateral Notch inhibition between early progenitors at position +4/5 results in binary (secretory vs enterocyte) lineage specification. Transcription factor Atoh1, repressed by Notch in ISCs, specifies secretory lineage upon its de-repression in 'Notch-off' progenitors. It remains unclear what drives the ISC-to-progenitor transition, and how binary fate decision is established. Here we find that the transcriptional co-repressors Mtg8 and Mtg16 are uniquely expressed in +4/5 early progenitors. We show that Notch represses Mtg8 and Mtg16 via Atoh1. Deletion of Mtg8 and Mtg16 induces hyperproliferation and expansion of ISCs. Chromatin immunoprecipitation shows that Mtg16 binds to numerous stem cell-signature gene promoters (e.g. Lgr5, Ascl2) for their transcriptional repression. Importantly, the co-repressor also binds to the previously reported Atoh1-bound enhancer regions of delta-like (Dll) Notch ligands, implying a role in Notch-mediated lateral inhibition. We conclude that the co-repressors Mtg8 and Mtg16 play central roles in the earliest progenitors to repress the ISC programme for niche exit and control binary fate decision by repressing Atoh1 target genes.

Funding Source: Cancer Research UK, Wellcome Trust, RCUK Medical Research Council

10:22 – 10:33

ENDOGENOUS METABOLITES HELP INSTRUCT INTESTINAL STEM CELL FATE

Yilmaz, Omer

Koch Institute, Massachusetts Institute of Technology, Cambridge, MA, USA

Little is known about how endogenous small molecule metabolites regulate tissue stem and progenitor cell function. Here we show that in mouse and human intestine, the expression of Hmgcs2 (3-hydroxy-3-methylglutaryl-CoA synthetase 2)—the gene encoding the rate-limiting enzyme in the production of ketone bodies, including beta-hydroxybutyrate (βOHB)—distinguishes the rapidly self-renewing Lgr5+ stem cells from progenitor and differentiated cell types, highlighting that ketone production by intestinal stem cells (ISCs) plays a role in maintaining their stemness. The intestinal specific deletion of Hmgcs2 depletes βOHB levels in the crypt and induces the premature differentiation of Lgr5+ ISCs into secretory cells, which compromises Lgr5+ ISC numbers and function. These changes can be rescued by exogenous βOHB as well as class I histone deacetylases (HDACs) inhibitor treatment in organoid assays and in vivo. Furthermore, a ketogenic diet enhances Lgr5+ ISC numbers and function by strongly elevating intestinal Hmgcs2 expression, crypt βOHB levels, and Notch activity. Mechanistically, βOHB acts by inhibiting HDACs

to enhance Notch signaling in ISCs, thereby influencing the balance between stem cell self-renewal and lineage-balanced differentiation. These findings reveal ISC derived ketone bodies as cell-autonomous signaling metabolites that help instruct stem cell fate to maintain intestinal maintenance in homeostasis and in regeneration.

10:33 – 10:53

PLURIPOTENT STEM CELL-DERIVED GASTROINTESTINAL ORGANOIDS AS NEW MODELS TO STUDY HUMAN DEVELOPMENT AND DISEASE

Wells, James M.

Cincinnati Children's Hospital, Cincinnati, OH, USA

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 of embryonic organ development. We have used principles of organogenesis to generate complex, three-dimensional human gastrointestinal organ tissues from PSCs in vitro. We have done this by focusing on the signaling pathways that drive anterior-posterior and dorsal-ventral patterning of the developing endoderm. We can now generate organoids representing all of the organs of the gastrointestinal tract including esophagus, gastric fundus, gastric antrum, small intestine and colon. GI organoids contain complex epithelial structures and diverse cell types that are unique to their representative organ; esophageal organoids develop a stratified squamous epithelium, gastric organoids have a glandular epithelium that secrete digestive enzymes, hormones, and acid, and intestinal organoids additionally absorb nutrients. While the first generation of GI organoids had epithelium and mesenchyme, they were lacking important cell types and functions. We have now engineered additional cellular complexity into organoids, such as small intestinal organoids with a functional enteric nervous and colonic organoids with functional immune cells capable of triggering an inflammatory cascade in response to pathogenic bacteria. Ongoing studies include PSC-derived organoids to identify the underlying mechanisms behind birth defects including Hirschsprung's disease and esophageal atresia, to identify new pathologies in patients with complex GI diseases. Lastly we are using human organoids to investigate the how the GI endocrine system modulates a broad array of metabolic functions including nutrient sensing and absorption.

10:53 – 11:13

THE ISSCR AWARD FOR INNOVATION LECTURE: STEM CELLS PLAY A ROLE IN HUMAN LEUKEMIA FROM THE BEGINNING TO THE END

Dick, John E.

Princess Margaret Cancer Centre and McEwen Stem Cell Institute, University Health Network and Department of Molecular Genetics, University of Toronto, ON, Canada

Individual cancer cells exhibit functional heterogeneity of many cancer hallmarks including the capacity for sustaining long-term clonal maintenance, a stemness property involving self-renewal. Our studies established that only rare AML cells possessed such leukemia stem cell (LSC) properties and that AML is a cellular hierarchy. LSC were found to be highly relevant to human disease as gene signatures specific to LSC were much more predictive of patient response to therapy and overall survival compared to the bulk non-LSC AML cells. We have now provided insights into how LSC develop during leukemogenesis. Through sequencing of purified populations of normal blood cells, AML cells, and xenografts from paired diagnosis/relapse AML samples, we tracked the full arc of leukemia development in humans: from the cell of origin (an HSC) that acquires the first genetic mutation; to pre-leukemic clonal expansion of HSC; the generation of genetically diverse LSC; and finally to the cellular origin of relapse (rare LSC subclones) within the diagnosis sample. Similar studies have been undertaken in B-ALL where relapse-fated subclones were found within the diagnosis sample before exposure to chemotherapy. These clones possess distinct epigenetic and metabolic properties that underlie their partially resistance to chemotherapy and they possess stemness signatures that drive their ability to regenerate relapse disease. Finally, the identification of clonally expanded pre-leukemic HSPC in the diagnosis blood sample of many AML samples predicted that it should be possible to identify individuals who are at risk for progressing to AML long before AML develops. We genotyped individuals from the general population who were enrolled in the large cohort (EPIC) who eventually developed AML and compared them to the enrollment sample of others who never progressed to AML. We have found a clear signature that is able to predict with high accuracy those individuals who have age related clonal hematopoiesis who progress to AML, almost 10 years prior to AML development. This is distinct from individuals who have benign clonal hematopoiesis who never progress. These new findings offer the potential for future intervention to permit AML prevention trials.

FRIDAY, 28 JUNE, 13:15 – 15:15

CONCURRENT IIIA: ORGANOID MODELS

Concourse E, Level One

13:20 – 13:40

MODELING COLORECTAL CANCER PROGRESSION THROUGH ORTHOTOPIC IMPLANTATION OF ENGINEERED ORGANOIDS

de Sauvage, Frederic

Genentech, Inc., South San Francisco, CA, USA

Colorectal cancer (CRC) is a leading cause of cancer related death and is largely thought to progress through the acquisition of specific genetic alterations, including functional loss of the tumor suppressors APC, TP53, and SMAD4 as well as activating mutations in oncogenes such as KRAS or BRAF. Despite extensive biological, molecular and clinical knowledge, CRC remains a high unmet medical need. This is especially the case once the tumor has disseminated beyond their primary site. Indeed, patients that present with metastatic disease, in particular to the liver, have a poor prognosis. Hence, a better understanding of the processes

that drive CRC progression and metastatic dissemination are key to enable the development of novel and effective therapies. To do so, pre-clinical in vivo models that faithfully recapitulate the human disease are critically needed. Despite the availability of xenograft, chemical-induced and genetically-engineered mouse models of CRC, these models fail to recapitulate full disease progression, including dissemination to the liver, the most relevant site of metastasis of human CRC. To overcome these limitations, we have developed orthotopic implantations of engineered intestinal organoids. Introduction of organoids with increasing number of mutations lead to a corresponding increase in tumor growth rate and to spontaneous metastatic dissemination to the liver and lung. This approach enables the study of each and every step of the metastatic process as well as the testing of therapeutic modalities.

13:40 – 13:51

CARDIAC- BUT NOT DERMAL FIBROBLASTS INDUCE STRUCTURAL AND FUNCTIONAL MATURATION OF HIPSC-DERIVED CARDIOMYOCYTES IN 3D MICROTISSUES

Giacomelli, Elisa[1], Meraviglia, Viviana[1], Campostrini, Giulia[1], Garcia, Ana Krotenberg[1], van Helden, Ruben[1], Giera, Martin[2], Jost, Carolina[3], Koster, Abraham[3], Kostidis, Sarantos[2], van Meer, Berend[1], Mei, Hailiang[4], Miguez, David[5], Mircea, Maria[6], Mulder, Aat[3], Ledesma-Terron, Mario[5], Sala, Luca[1], Semrau, Stefan[6], Slieker, Roderick[3], Tertoolen, Leon[1], Orlova, Valeria[1], Bellin, Milena[1] and Mummery, Christine[1]

[1]Anatomy and Embryology, Leiden University Medical Center, Leiden, Netherlands, [2]Center for Proteomics and Metabolomics, Leiden University Medical Center, Leiden, Netherlands, [3]Department of Cell and Chemical Biology, Leiden University Medical Center, Leiden, Netherlands, [4]Sequencing Analysis Support Core, Leiden University Medical Center, Leiden, Netherlands, [5]Centro de Biologia Molecular Severo Ochoa, Departamento de Física de la Materia Condensada, Instituto Nicolas Cabrera and Condensed Matter Physics Center (IFIMAC), Universidad Autónoma de Madrid, Spain, [6]Leiden Institute of Physics, Leiden University, Leiden, Netherlands

Human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) in vitro are structurally and functionally immature, unless incorporated into engineered tissues or forced to undergo cyclic contraction. In this study, we showed that cardiac fibroblasts derived from hiPSC-epicardium induced structural, electrical, mechanical and metabolic maturation of hiPSC-CMs in scaffold-free, three-dimensional microtissues containing hiPSC-cardiac endothelial cells. Three-cellular paracrine signals and direct coupling between hiPSC-CMs and cardiac fibroblasts appeared to contribute to hiPSC-CM maturation. hiPSC-CMs in microtissues containing cardiac endothelial cells and cardiac fibroblasts showed increased nuclear size and sarcomere length, T-tubule-like structures, enhanced contractility and mitochondrial respiration, and were electrophysiologically more mature than microtissues with just two cell types. Primary adult cardiac- but not dermal fibroblasts could replace hiPSC-cardiac fibroblasts. Single-cell RNA-sequencing revealed that hiPSC-CMs in microtissues clustered together with adult human cardiomyocytes. Using just 5000 cardiac-specific cells per microtissue, we were thus able to induce structural, electrical, mechanical and metabolic maturation of hiPSC-CMs.

13:51 – 14:02

HUMAN STEM CELL-DERIVED PODOCYTES IN DEVELOPMENTAL BIOLOGY AND DISEASE MODELING

Tran, Trinh Khiet (Tracy)[1], Lindström, Nils[1], Ransick, Andrew[1], De Sena Brandine, Guilherme[1], Guo, Qiuyu[1], Albert, Kim[1], Smith, Andrew[2], Thornton, Matthew[3], McMahon, Jill[1] and McMahon, Andrew[1]

[1]Department of Stem Cell and Regenerative Medicine, University of Southern California, Los Angeles, CA, USA, [2]Molecular and Computational Biology, University of Southern California, Los Angeles, CA, USA, [3]Maternal Fetal Medicine Division, University of Southern California, Los Angeles, CA, USA

The renal corpuscle of the kidney comprises a glomerular vasculature embraced by podocytes and supported by mesangial myofibroblasts. From the earliest stages of development, there is a close interplay amongst these cell types. In the functional kidney, their combined actions are essential for the formation of an acellular plasma filtrate that passes through the podocyte-generated slit diaphragm, into the nephron. Mutations in a spectrum of podocyte-expressed genes lead to chronic disease. An enhanced understanding of podocyte development and function, and the creation of biologically relevant podocyte cell culture models is a clinical imperative. To characterize human podocyte development, single cell RNA-sequencing (scRNA-seq) was performed on human fetal kidneys. Distinct transcriptional signatures were identified that accompanied the differentiation of podocyte progenitors to functional podocytes. Interestingly, organoid-generated podocytes exhibited highly similar progressive transcriptional profiles despite an absence of vascular endothelial cells. On transplantation into the kidney of immunocompromised mice, human organoid derived podocytes recruited the host vasculature and transcriptional profiles were partially corrected. Thus, much of human podocyte development is likely an intrinsic regulatory program where vascular interactions refine the mature podocyte state. These studies support the application of organoid-derived podocytes to model development and diseases and to restore or replace normal kidney functions. However, in vitro analyses highlight differences in gene regulation between in vitro generated podocytes and in vivo counterparts that likely reflect epigenetic differences in regulatory program. To this end, we are employing a variety of strategies to identify the cis-regulatory modules and gene regulatory networks orchestrating human podocyte development, and generating approaches for systematic interrogation of regulatory actions in kidney organoid cultures. We expect these studies will provide new mechanistic insights into development of a key disease-associated cell type in the human kidney. Further, a better understanding of podocyte programming will facilitate engineering of effective renal filtration devices.

14:02 – 14:13

SELF-ORGANIZATION AND SYMMETRY BREAKING IN MOUSE INTESTINAL ORGANOID DEVELOPMENT

Serra, Denise[1], Mayr, Urs[1], Boni, Andrea[2] and Liberali, Prisca[1]

[1]Friedrich Miescher Institute, Basel, Switzerland, [2]Friedrich Miescher Institute, Viventis Microscopy, Basel, Switzerland

Intestinal organoids are complex three-dimensional structures that mimic cell type composition and tissue organization of the intestine by recapitulating the self-organizing capacity of cell populations derived from a single stem cell. Crucial in this process is a first symmetry-breaking event, in which only a fraction of identical cells in a symmetrical sphere differentiate into Paneth cells, which in turn generates the stem cell niche and leads to asymmetric structures such as crypts and villi. In our work we combine a quantitative imaging approach with single-cell gene expression to characterize the development of mouse intestinal organoids from a single cell. We show that intestinal organoid development follows a regeneration process driven by transient Yap1 activation. Cell-to-cell variability in Yap1, emerging in symmetrical spheres, initiates a Notch/Dll1 lateral inhibition event driving the symmetry-breaking event and the formation of the first Paneth cell. Our findings reveal how single cells exposed to a uniform growth-promoting environment have the intrinsic ability to generate emergent, self-organized behavior resulting in the formation of complex multicellular asymmetric structures.

Funding Source: This work was supported by National Science Foundation and European Research Council (ERC) under the European Union's Horizon 2020 research and innovation programme

14:13 – 14:24

MODELING OVARIAN CANCER USING BRCA1 MUTANT IPSC-DERIVED 3D HUMAN FALLOPIAN TUBE

Yucer, Nur[1], Ahdoot, Rodney[1], Kathleen, Kurowski[1], Liang, Victoria[1], Karlan, Beth[2] and Svendsen, Clive[2]

[1]Board of Governors Regenerative Medicine Institute, Cedars-Sinai Health System, Los Angeles, CA, USA, [2]Women's Cancer Program, Samuel Oschin Comprehensive Cancer Institute, Cedars-Sinai Medical Center, Los Angeles, CA, USA

High-grade serous cancer (HGSC) is the most common and malignant form of ovarian cancer with the highest incidence of mortality. Recent studies strongly suggest that HGSC originates from the neighboring fallopian tube epithelia (FTE). The discovery of serous tubal intraepithelial carcinoma (STIC) lesions, a preneoplastic finding in the fallopian tube fimbriae of patients with breast cancer gene (BRCA) mutations, supports the model of FTE origin of serous "ovarian" carcinoma. Germline mutations in BRCA genes are the greatest risk determinant for developing HGSC, however little is known about other specific drivers of the transformation of normal FTE to STICs and HGSC. Importantly, the absence of relevant in vitro human models that can recapitulate tissue-specific architecture has hindered our understanding of FTE transformation and initiation of HGSC. In this study, we aimed to investigate early genomic alterations and disease progression seen in patients with a BRCAmut using an iPSC-based disease model. Toward this goal, we developed a rapid and efficient method to create an iPSC-derived 3D human FTE organoid in vitro containing the relevant cell types of the human fallopian tube as well as a luminal architecture that closely reflects the organization of fallopian tissues in vivo. We generated three different BRCAmut -iPSC cell lines from patients with early onset of cancer and create three different BRCAmut -3D-human FTE. Our recent data demonstrate that BRCAmut -3D-human FTE organoid show structural abnormalities, including cellular crowding, loss of polarity and severe atypia of the nuclei which are signatures of Tubal Intraepithelial Carcinoma (TIC). Our data suggest that we recapitulated cancer initiating events and created an in vitro system to model ovarian cancer with the BRCA1 mutation. Currently, we are characterizing molecular signatures of this initial event in BRCA1 mutant organoids and the effect of oscillating hormones such as estrogen and progesterone on neoplastic transformation. Our novel human-derived FTE organoid model can be used to identify the critical sequence of genetic alterations involved in high-grade serous carcinogenesis and to identify specific biomarkers of early fallopian tube epithelial cell transformation.

Funding Source: Ovarian Cancer Research Fund Ann and Sol Schreiber Mentored Investigator Award, Gilda Radner Hereditary Cancer Program and Regenerative Medicine Institutional Fund at Cedars-Sinai Medical Center

14:24 – 14:35

SNAKE VENOM GLAND ORGANOIDS

Puschhof, Jens, Post, Yorick, Beumer, Joep and Clevers, Hans

Hubrecht Institute, Utrecht, Netherlands

Recent advances in organoid technology have proven this system to be a valuable tool in understanding human organ development and pathologies. These adult stem cell derived cultures closely recapitulate structural and functional properties of their organ of origin. Here, we expand the organoid technology toolbox by describing a protocol to culture non-mammalian organoids derived from a snake venom gland. The complexity of venom production, composition and function remains largely unknown for many species. Organoids derived from an Aspidelaps lubricus venom gland can be long-term expanded and histologically resemble the gland. Expression of typical venom-related transcripts (3FTx and Kunitz-type protease inhibitors) can be detected in proliferating organoids with RNA sequencing. Single cell RNA sequencing reveals distinct venom expressing cell types, as well as proliferating cells with features of mammalian stem cells. Using mass spectrometry, we identify peptides in the culture medium supernatant that match the composition of the crude venom of the same species. Venom gland organoids furthermore consist of specialized secretory cells visible by transmission electron microscopy. The system enables investigation of venom production and function on a cellular level in controlled conditions and without the need of experimental animals. This study describes the adaption of

organoid technology to a non-mammalian species, providing a model to understand the complexity of the snake venom gland.

14:35 – 14:46

TFAP2C IS A CRITICAL INDICATOR AND REGULATOR OF RELIABLE AND EFFICIENT FOREBRAIN ORGANOID DIFFERENTIATION FROM HUMAN PLURIPOTENT STEM CELLS

Watanabe, Momoko[1], Vishlaghi, Neda[1], Haney, Jillian[1], Turcios, Felix[1], Buth, Jessie[1], Miranda, Osvaldo[1], Ohashi, Minori[1], Gu, Wen[3], Taniguchi-Ikeda, Mariko[4], Chen, Di[5], Sabri, Shan[3,4], Plath, Kathrin[3], Christofk, Heather[3], Clark, Amander[5], Gandal, Michael[2] and Novitch, Bennett[1]

[1]Neurobiology, University of California, Los Angeles, CA, USA, [2]Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, CA, USA, [3]Biological Chemistry, University of California, Los Angeles, CA, USA, [4]Clinical Genetics, Fujita Health University, Aichi, Japan, [5]Molecular, Cell, and Developmental Biology, University of California, Los Angeles, CA, USA

The human forebrain has many structural and functional features that are distinct from lower species traditionally used for medical research. To identify mechanisms of human forebrain development and find cures for human-specific neurological disorders such as autism, we ideally need a human brain model. However, experimentation with human brain tissue, particularly at fetal stages, is inherently challenging, curtailing long-term gene manipulation studies and environmental perturbations. Cerebral organoids generated from human pluripotent stem cells (hPSC) are thus emerging as a promising alternative system for studying human neocortical development and disease. While progress in organoid technology is rapidly advancing, many challenges remain including rampant batch-to-batch and line-to-line variability and irreproducibility, as well as unwanted differentiation into different classes of neural cells and other tissue types. In our previous work, we established reproducible and efficient methods for cortical organoid differentiation that faithfully recapitulate in vivo neocortical development. However, optimal results are achieved only when hPSCs are grown under particular feeder-supported conditions. Here, we define differences in the transcriptional state of hPSC maintained under different conditions and demonstrate how this in turn relates to success or failure in cerebral organoid development. Utilizing this information, we identified four TGFβ superfamily molecules that can significantly enhance forebrain neuroepithelial organoid formation even from feeder free cultures. Of note, high expression of some naïve signature genes in the hPSC state correlates with reliable and efficient forebrain organoid formation. One of these genes, TFAP2C, is highly upregulated by the four TGFβ factors across multiple hPSC lines and its function is essential for efficient forebrain organoid formation. Together, our findings illustrate how different hPSC culture methods impact their developmental potential, and identify TFAP2C as a both a prognostic marker and critical effector needed to achieve reproducibility and consistency in cerebral organoid production.

Funding Source: B.G.N. from the NINDS (R01NS089817), CIRM (DISC1-08819), and the UCLA Broad Stem Cell Research Center (BSCRC). M.W. from the UCLA Brain Research Institute, the Uehara Foundation, the UCLA BSCRC, and the NICHD (K99HD096105).

14:46 – 15:06

CELL-CELL INTERACTIONS IN NORMAL HUMAN EMBRYONIC LUNG DEVELOPMENT

Rawlins, Emma

Gurdon Institute, University of Cambridge, UK

Extensive work on mouse lung morphogenesis has shown that the branching tips of the developing epithelium comprise a multipotent progenitor population. These distal tip progenitors are maintained throughout embryonic development and initially generate bronchiolar-fated and subsequently alveolar-fated progeny. Many of the developmental cues which regulate lung branching, epithelial and mesenchymal differentiation and subsequent maturation have been investigated in the mouse lung. How many of the morphogenetic events and signals are conserved in human lung embryonic development? Can we develop improved models of in vitro human lung development that will facilitate drug screening and disease modelling? And gain insights from lung regeneration? To address these questions, we have been studying human embryonic lung development with a focus on the multipotent distal epithelial progenitor cells. Transcriptional analysis revealed broad similarity between the mouse and human tip epithelial populations, but with some surprising differences. To be able to perform functional experiments, we have developed an organoid-based culture system in which we can grow human embryonic distal tip cells isolated from 6-8 week gestation human lungs. We can self-renew these epithelial tips as karyotypically stable, genetically manipulable, organoids for at least 12 months allowing us to expand the scarce starting material. Moreover, we have developed methods for in vitro and in vivo differentiation of the cells, providing new platforms specifically for the study of human lung development.

FRIDAY, 28 JUNE, 13:15 – 15:15

CONCURRENT IIIB: EPIGENETIC REGULATION OF CELL IDENTITY

Concourse F, Level One

13:20 – 13:40

EPIGENETIC INHERITANCE AND REPROGRAMMING DURING EARLY MAMMALIAN DEVELOPMENT

Xie, Wei

Tsinghua University, Beijing, China

Drastic chromatin reorganization occurs during mammalian early embryogenesis to convert terminally differentiated gametes to a totipotent embryo. Deciphering the molecular events underlying these processes is crucial for understanding both developmental biology, stem cell biology, and infertility. Previously, we have reported chromatin reprogramming during early mammalian development for chromatin accessibility, histone modifications, and 3D architecture. These studies unveiled highly dynamic and non-canonical chromatin regulation during maternal-to-zygotic transition and zygotic genome activation. Here, I will present our recent research progress in understanding the epigenetic reprogramming on how the oocyte epigenome, including genomic imprints, is established through extensive crosstalks of chromatin modifications. We show that defects in maternal epigenome exert a profound impact on mammalian embryonic development in both preimplantation and postimplantation development. These data demonstrate at the molecular level how epigenetic reprogramming and inheritance play a critical role in promoting parental-to-zygotic transition during early development.

13:40 – 13:51

EPIMOGRIFY: A SYSTEMATIC APPROACH TO IDENTIFYING CELL MAINTENANCE FACTORS AND CELL CONVERSION FACTORS BY MODELLING THE CELL'S EPIGENETIC LANDSCAPE

Kamaraj, Uma Sangumathi[1], Chen, Joseph[2], Ouyang, John[1], Polo, Jose[2], Petretto, Enrico[1] and Rackham, Owen[1]

[1]Cardiovascular and Metabolic Disorders Programme, Duke NUS Medical School, Singapore, [2]Biochemistry and Molecular Biology, Monash University, Melbourne, Australia

The ability to derive and culture various cell/tissue types in vitro have led to an increase in the development of new technologies to control and fine-tune cell states. However, discovering new culture conditions for optimal cell maintenance and directed differentiation is often time-consuming and laborious. This poses a great challenge in the advancement of cell therapies and clinical applications of cell cultures as they require more chemically defined conditions. Hence, we have developed a new computational approach, EpiMogrify, to identify signalling molecules that could facilitate the formulation of a more chemically defined cell culture condition. Our method is able to capture a cell's identity or a change in its identity to predict signalling molecules for cell maintenance or cell conversion respectively. We developed a statistical approach to model and characterize a cell's state, utilizing the presence of broad H3K4me3 histone modifications to mark the cell identity genes. For 111 human cell/tissue types made available by the ENCODE and Roadmap consortia, EpiMogrify predicts signalling molecules that can facilitate the development of chemically defined cell maintenance and differentiation media. We further validated the signalling molecules predicted for astrocyte cell maintenance in vitro by supplementing the predicted factors to establish culture conditions, showing that our predicted factors were able to improve the growth rate of astrocytes by at least two-fold. Moreover, EpiMogrify can also prioritize other protein types such as transcription factors (TFs) or epigenetic remodelers for cell maintenance or cell conversion. We verified the accuracy of TFs predicted for cell conversion in silico through comparison with known TFs used in experimentally validated cell conversions. EpiMogrify is the first computational method to systematically address and predict signalling molecules for cell maintenance and directed differentiation. With this approach, we are able to facilitate the identification of key components for chemically defined cell culture conditions in a multitude of cell types.

Funding Source: Duke-NUS PhD Fellowship

13:51 – 14:02

GLOBAL DNA DEMETHYLATION OF HUMAN NEURAL PROGENITOR CELLS LEADS TO ACTIVATION OF NEURONAL GENES VIA EVOLUTIONARILY YOUNG LINE-1 ELEMENTS

Jonsson, Marie E.[1], Brattas, Per Ludvik[1], Gustafsson, Charlotte[2], Petri, Rebecca[1], Yudovich, David[3], Verschuere, Shana[1], Madsen, Sofia[1], Hansson, Jenny[4], Larsson, Jonas[3], Mansson, Robert[2], Meissner, Alexander[5] and Jakobsson, Johan[1]

[1]Laboratory of Molecular Neurogenetics, Lund University, Lund, Sweden, [2]Center for Hematology and Regenerative Medicine Huddinge, Karolinska Institutet, Stockholm, Sweden, [3]Division of Molecular Medicine and Gene Therapy, Lund University, Lund, Sweden, [4]Laboratory of Proteomic Hematology, Lund University, Lund, Sweden, [5]Department of Genome Regulation, Max Planck Institute for Molecular Genetics, Berlin, Germany

DNA methylation is an epigenetic modification that plays a crucial role in gene regulation throughout development and in adulthood. It contributes to the maintenance of genomic integrity in somatic cells, in part through the silencing of the potentially harmful transposable elements (TEs). However, TEs may also be beneficial for the host through the influence on transcriptional networks by acting as hubs for epigenetic marks. In this study we used CRISPR/Cas9 technology to delete the DNA methyltransferase (DNMT) mainly responsible for maintaining DNA methylation during replication (DNMT1) which resulted in viable, proliferating cells despite the global loss of DNA methylation. These DNMT1-KO cells allowed us to study the role of DNA methylation in silencing TEs during neural development. DNA demethylation led to specific transcriptional activation and chromatin remodeling of evolutionarily young, hominoid-specific LINE-1 elements, while older LINE-1s and other classes of TEs remained silent. The activated LINE-1s acted as alternative promoters for several protein-coding genes involved in neuronal functions, revealing a hominoid-specific LINE-1 based transcriptional network controlled by DNA methylation that influences neuronal protein-coding genes. Our results provide mechanistic insight into the role of DNA methylation in silencing TEs in somatic human cells, as well as further implicating LINE-1s in human brain development and disease.

Funding Source: The Swedish Childhood Cancer Fund, The Swedish Cancer Society

14:02 – 14:13

RONIN MEDIATES PROMOTER-PROMOTER INTERACTIONS THAT INFLUENCE GENE REGULATION IN PLURIPOTENCY

Zwaka, Thomas P.[1], Dejosez, Marion[1], Ramamoorthy, Mahesh[1], Hogan, Megan[1], Brosh, Ran[1], Ying, Xing[1], Weintraub, Abraham[2], Hnisz, Denes[2] and Young, Richard[2]

[1]Huffington Foundation Center for Cell-Based Research in Parkinson's Disease, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Department of Biology, Massachusetts Institute of Technology, Whitehead Institute for Biomedical Research, Cambridge, MA, USA

In most contemporary models of stem cell gene control, enhancers interact with promoters to mediate transcription. Here we report a new paradigm for the transcriptional regulation of developmental genes. It centers around a novel class of DNA-folding proteins (Thanatos-associated proteins, or THAPs)—Ronin in particular—that evolved from an ancestor of the P-element transposase. Our data suggest that the molecular domestication of THAPs was driven by the proclivity of the transposase to bind to promoters and induce DNA looping. Whereas transcription factor binding typically stimulates promoter-enhancer interaction, Ronin and other THAPs organize promoters into hierarchical clusters in which several promoters are tethered to one or more "hub" promoters. These novel genomic structures entrap RNA polymerase II, subsequently form concentrated networks of promoters including their associated genes and regulatory elements. We propose that Ronin and other THAPs enable cells to draw from a radically different logic of combinatorial gene regulatory space that is based on direct promoter-promoter interactions. This evolutionary maneuver may have been pivotal in generating the diverse cell types and body plans typical of metazoans.

14:13 – 14:24

AN MICRORNA PROCESSING MECHANISM TARGETING CRYPTOCHROME CIRCADIAN REGULATOR 2 MODULATES MYOGENESIS

Hu, Ping and Yang, Lele

Shanghai Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

Cry2 (Cryptochrome Circadian regulator 2) is an important circadian regulator. It has a wide range of functions in regulating sleep, body temperature, metabolism. It is also a critical player in adult myogenesis. We found that Cry2 was significantly upregulated during myogenesis. Further analysis indicates that Cry2 is the target of miR7 and negatively regulated by the microRNA. Though microRNA metabolism and processing has been shown to be critical in many physiological processes, its functions in myogenesis remains to be elusive. We explored the regulatory mechanism of miR7 processing and found that a pair of RNA binding proteins, Msi2 and HuR, served as negative regulators of the maturation of miR7 and therefore improve the expression of Cry2 in aged muscles. In summary, we identified a new signaling pathway modulating microRNA processing and circadian gene expression to regulate myogenesis.

14:24 – 14:35

EPIGENOME DYNAMICS REVEAL NEW INSIGHTS INTO HUMAN ISLET DIFFERENTIATION AND MATURATION

Alvarez-Dominguez, Juan R.[1], Donaghey, Julie[1], Kenty, Jennifer[1], Niloofar, Rasouli[1], Helman, Aharon[1], Charlton, Jocelyn[2], Straubhaar, Juerg[1], Meissner, Alexander[2] and Melton, Douglas[1]

[1]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [2]Department of Genome Regulation, Max Planck Institute for Molecular Genetics, Berlin, Germany

Pancreatic islets control glucose homeostasis primarily through α cells, which secrete glucagon in response to low blood glucose to promote its release by the liver, and β cells, which secrete insulin in response to high blood glucose to promote its uptake by other tissues. β-cell loss or dysfunction is accompanied by defects in other islet cell types and underlies diabetes, which affects >400 million people worldwide. Diabetics could be cured through transplantation of new islets generated in vitro, but this approach has been limited by an incomplete understanding of the mechanisms driving islet cell specification and functional maturation. To better understand these mechanisms, we exploited the stepwise differentiation of islet cells from human stem cells and devised methods to purify developmental intermediates, including endocrine progenitors and stem cell-derived β (SC-β) and polyhormonal (insulin+ glucagon+) cells, which enabled global DNA methylation, chromatin accessibility, histone modification, and RNA expression profiling. We thus elucidate the landscape of regulatory domains, the pioneer factors that establish them, and their dynamics throughout human islet development. We find that endocrine specification involves de novo establishment of enhancer repertoires and is foreshadowed by priming of lineage-specifying loci. Accordingly, we identify polyhormonal cells as α cell progenitors by showing that priming of α cell-specific enhancers steers them toward an α-cell fate in vivo. We further define core regulatory circuits for each islet developmental stage by dissecting autoregulatory loops formed by super-enhancer-driven transcription factors. These include both known and unexpected regulators such as LMX1B, which we validate as critical for endocrine differentiation both in vitro and in vivo. Finally, by contrasting epigenomes of maturing SC-β with their in vivo counterparts, we uncover a role for circadian rhythms in eliciting mature glucose responsiveness. Metabolically synchronized SC-β show rhythmic expression of genes controlling insulin release and rhythmic insulin secretion with an increased glucose threshold, a hallmark of functional maturity. This work forms a basis for understanding genetic and epigenetic mechanisms controlling human islet cell fate and function.

Funding Source: Juan R. Alvarez-Dominguez is a Howard Hughes Medical Institute Fellow of the Life Sciences Research Foundation. This work was supported by grants from the Harvard Stem Cell Institute, NIH, and the Howard Hughes Medical Institute.

14:35 – 14:46

EPIGENETIC CONTROL OF CELLULAR PLASTICITY BY MANIPULATING CHROMATIN ORGANIZATION PATHWAYS

Cheloufi, Sihem[1], Livelo, Yiming[1], Rockne, Russell[2], Roe, Jae Seok[3], Sykes, David[4] and Vakoc, Chris[3]

[1]Biochemistry Department and UCR Stem Cell Center, University of California, Riverside, CA, USA [2]Mathematical Oncology, City of Hope, Duarte, CA, USA, [3]CSHL Cancer Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA, [4]Center For Regenerative Medicine, Massachusetts General Hospital, Boston, MA, USA

Epigenetic wiring of the genome is a process involving discrete interactions between proteins and nuclear DNA that determines and maintains the identity of each cell type. Although human diseases are typically linked to genetic mutations, many can arise solely from epigenetic aberrations. Therefore, there is a need to develop strategies to reverse epigenetic vulnerabilities in human disease by manipulating cell fate. We have recently implicated histone chaperones as epigenetic regulators of cellular plasticity in the context of pluripotent stem cells and nuclear reprogramming. Histone chaperones are proteins that associate with histones and other co-factors in the nuclear space to organize and maintain the architecture of our genome. They are functionally and structurally diverse and orchestrate several fundamental processes in the cell such as DNA replication, transcription and repair. Recent studies found a number of histone chaperones either mutated or dysregulated in various types of cancers and developmental disorders. However, these findings are purely correlative and the role of histone chaperones as epigenetic drivers of cell fate reprogramming or differentiation is poorly understood. To address this problem, we systematically dissected histone chaperone vulnerabilities during cellular reprogramming and differentiation. More specifically, we conducted a focused loss of function genetic screen of all known histone chaperones candidates during two cell fate change paradigms: reprogramming somatic cells to pluripotency and myeloid differentiation from hematopoietic progenitors. Our results reveal intriguing similarities and differences in the histone chaperone pathways that are in place to either safeguard cell identity or promote cell fate change. We further dissect these pathways by studying the underlying transcriptional programs driving these processes at the single cell level. We will present how manipulating a single histone chaperone can instruct canonical and alternate transcriptional programs to mediate cell fate change.

14:46 – 15:06

SUPER-RESOLUTION IMAGING OF TRANSCRIPTION IN LIVE MAMMALIAN CELLS

Cissé, Ibrahim

Massachusetts Institute of Technology, Cambridge, MA, USA

Protein clustering is a hallmark of genome regulation in mammalian cells. However, the dynamic molecular processes involved make it difficult to correlate clustering with functional consequences in vivo. We developed a live-cell super-resolution approach to uncover the correlation between mRNA synthesis and the dynamics of RNA Polymerase II (Pol II) clusters at a gene locus. For endogenous β-actin genes in mouse embryonic fibroblasts, we observe that short-lived (~8 s) Pol II clusters correlate with basal mRNA output. During serum stimulation, a stereotyped increase in Pol II cluster lifetime correlates with a proportionate increase in the number of mRNAs synthesized. Our findings suggest that transient clustering of Pol II may constitute a pre-transcriptional regulatory event that predictably modulates nascent mRNA output.

FRIDAY, 28 JUNE, 13:15 – 15:15

CONCURRENT IIIC: STEM CELLS AND CANCER

Room 502, Level Two

Sponsored by EMBO Molecular Medicine

13:20 – 13:40

CANCER STEM CELLS, RIBOSOMAL BIOGENESIS AND PROTEIN SYNTHESIS

Batlle, Eduard

Institute for Research in Biomedicine, (IRB Barcelona), Barcelona, Spain

The Cancer Stem Cell (CSC) concept states that tumor growth, analogous to renewal of healthy tissues, is fueled by small numbers of dedicated stem cells. It provides attractive explanations for the clinical behavior of cancers and inspires treatment strategies that specifically target CSCs, the 'beating heart' of the tumor. Over the past years, an avalanche of studies has identified CSCs by expression of individual marker genes but the nature and features of these cells remain largely uncharacterized. As a matter of example, LGR5 has been established as a bonafide marker of CSCs in colorectal cancer (CRC). Many CRCs contain abundant LGR5+ cells yet clonal analysis suggests that only a small proportion of these cells function as CSCs. It is also known that many CRCs contain few o no LGR5+ cells, yet these tumors may still exhibit a hierarchical organization. Here, I will discuss the identification of CSCs in CRCs based on their biosynthetic capacities.

13:40 – 13:51

RADIAL GLIA CONTRIBUTE TO TUMORIGENESIS IN ADULT GLIOBLASTOMA

Tabar, Viviane[1], Hemberg, Martin[2], Laughney, Ashley[3], Pe'er, Dana[4], Sharma, Roshan[4], Shen, Xiaojuan[2] and Wang, Rong[1]

[1]Neurosurgery, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Sanger Institute, Wellcome Trust, London, UK, [3]Cancer Biology, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [4]Computational Biology, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Glioblastomas (GBM) exhibit significant heterogeneity and a hierarchy of cell functions. Tumor initiating cells may represent a source of persistent growth of GBM, however their identity is not resolved. Recent data have suggested that tumor hierarchies relate significantly to conserved developmental programs that seem to be maintained despite the genetic heterogeneity within and across tumors. Hence, it can be postulated that primitive tumor-initiating cells may exist within glioblastomas, that support tumor cell hierarchy and fuel it with proliferative progenitors. Characterization of the specific cell type and differentiation state of tumor initiating cells will facilitate our understanding of the pathogenesis of brain tumors, thereby providing potential therapeutic targets for early detection and prevention of this devastating disease. Radial Glia (RG) cells are the first neural stem cells to appear during embryonic development, and are thought to disappear in the mammalian cortex postnatally. Here we demonstrate that adult human glioblastoma tumors harbor a population of tumor RG-like cells with unique RG morphology and markers. The cells, monitored by time-lapse video imaging exhibit the classic and unique mitotic behavior of normal radial glia, including mitotic somal translocation and interkinetic nuclear migration, in a cell autonomous manner. Single cell RNASeq analyses of glioblastoma cells reveal transcriptionally diverse clusters of RG-like cells of confirmed neoplastic origin, that share transcriptional profiles with normal human fetal radial glia and that reside in non-cycling (dormant/quiescent) and cycling states. An analysis of signaling pathways followed by functional assays showed a role for interleukin in triggering exit from dormancy into active cycling, suggesting a role for inflammation in tumor progression. Copy number variation analysis confirms the tumor origin of the RG like cells and show a lower burden of copy number alterations in some RG clusters. These data are consistent with the possibility of persistence of radial glia into adulthood and their involvement in tumor initiation or maintenance. They also provide a cellular basis for the persistence of normal developmental programs in adult tumors.

13:51 – 14:02

TARGETING THE MTF2-MDM2 AXIS SENSITIZES REFRACTORY ACUTE MYELOID LEUKEMIA TO CHEMOTHERAPY

Stanford, William L.

Regenerative Medicine Program, Ottawa Hospital Research Institute, Ottawa, ON, Canada

Acute myeloid leukemia (AML) is the most common adult blood cancer. While relapse is believed to be driven by therapy-resistant leukemic stem cells, up to a third of AML patients fail to respond to the standard of care treatment, induction chemotherapy. These refractory AML patients have survival rates hovering around 10% even with hematopoietic stem cell transplant. While deep sequencing has identified the common leukemogenic driver mutations, none of these mutations predict response to therapy. Thus, we reasoned that refractoriness is driven by the epigenome rather than genome mutations. We demonstrate that Metal Response Element Binding Transcription Factor 2/Polycomblike 2 (MTF2/PCL2) plays a fundamental role in the Polycomb repressive complex 2 (PRC2) and the loss of MTF2 by hypermethylation of the MTF2 promoter elicits an altered epigenetic state underlying refractory AML. Unbiased systems analyses identified the loss of MTF2-PRC2 repression of MDM2 as central to, and therefore a biomarker for, refractory AML. Thus, immature MTF2-deficient CD34+CD38- cells overexpress MDM2, thereby inhibiting p53 that leads to chemoresistance due to defects in cell cycle regulation and apoptosis. Targeting this dysregulated signaling pathway by MTF2 overexpression or MDM2 inhibitors sensitized refractory patient leukemic cells to induction chemotherapeutics and prevented relapse in AML patient-derived xenograft (PDX) mice, suggesting this novel therapeutic regimen targets the leukemic stem cell. Therefore, we have uncovered a direct epigenetic mechanism by which MTF2 functions as a tumor suppressor required for AML chemotherapeutic sensitivity and identified a potential therapeutic strategy to treat refractory AML.

14:02 – 14:13

IDENTIFICATION OF HUMAN CIRCULATING BREAST CANCER STEM/PROGENITOR CELLS THAT SURVIVE CHEMOTHERAPY, INITIATE EX VIVO TUMOR GROWTH AND SHOW ELEVATED METASTATIC GENE EXPRESSION

Pommier, SuEllen, Limbach, Kristen, Mattert, Rachel, Jackson, Cynthia and Pommier, Rodney

Surgery, Oregon Health and Science University, Portland, OR, USA

Breast cancer stem/progenitor cells (BCSC) show variable expression of CD44/CD49f/CD24 and EpCAM, oncogenic mutations and drive breast cancer development. Following neoadjuvant chemotherapy (NAC), 70% of patients have residual disease (RD). The presence of BCSCs in RD and in circulation (cBCSC) may measure therapeutic resistance and metastatic spread. 63 specimens were obtained from patients with stage 0-IV breast cancer (8 ductal carcinoma in situ (DCIS), 50 invasive ductal and 5 invasive lobular). 28 samples were chemotherapy-naïve and 35 were collected as RD following NAC. 30mL of blood were obtained before and after NAC. Tumor cells and circulating CD49f+CD24-, CD49f-CD24+, CD49f-CD24- cells (all CD45/CD31/CD34-negative) were collected by fluorescence-activated cell sorting and analyzed for metastatic gene expression (MET) by qRT-PCR. Three different tumor BCSC and 3 different blood cBCSC populations were collected and examined for each patient sample (total 378 discrete samples). Approximately 300 circulating CD49f+/- CD24+/- cells were cultured in Matrigel/Mammocult and stained with DAPI, CD44, panCK, EpCAM and vimentin and imaged by confocal microscopy. The percentage of patients with cBCSC-initiated EpCAM, vimentin and panCK positive tumors, >50 uM were: in the Chemotherapy-Naïve group: DCIS=0%, stages I=20%, II=100% III=67%, IV=50% (stage I vs stages II-IV growth $p<0.01$). Growth arose predominantly from CD49f-CD24+ cells. In the NAC group: stages I=60%, II=34%, III=65%, IV=76% (stages 1-II vs III-IV growth $p<0.01$). Growth originated equally from CD49f+CD24-, CD49f-CD24+ and CD49f-CD24- cells. Tumor initiating cBCSCs recapitulated invasive ductal or lobular morphology of their primary tumors and showed >4-fold over-expression of CD44, FGFR4, FXYD5, MMPs, PLAUR and SET compared to non-tumor initiating

cBCSC. While having some shared metastatic gene expression, cBCSCs had increased expression compared to patient-paired tumor BCSCs. In summary, BCSCs are often present in RD and circulation after NAC, demonstrating that NAC does not completely eradicate BCSCs. While circulating epithelial cells were found in many breast cancer patients, ex vivo growth identified a subset of cBCSCs with true de novo tumor initiating potential. Their association with increasing stage underscores their clinical relevance and role in metastasis. That DCIS demonstrated no tumor growth and different MET compared to invasive cancers, suggests a discriminatory assay for early detection of invasive breast cancer.

14:13 – 14:24

CHARACTERISING STEM CELL BEHAVIOUR IN KRASG12D PRO-ONCOGENIC FIELDS OF THE MOUSE INTESTINE CHARACTERISING STEM CELL BEHAVIOUR IN KRASG12D PRO-ONCOGENIC FIELDS OF THE MOUSE INTESTINE

Thorsen, Ann-Sofie[1], Kemp, Richard[1], Lourenco, Filipe[1], Morrissey, Edward[2] and Winton, Doug[1]

[1]Cancer Research UK, Cambridge Institute, University of Cambridge, UK, [2]MRC WIMM, Centre for Computational Biology, University of Oxford, UK

The classical pathway to colorectal cancer development is viewed as a sequential acquisition of oncogenic mutations in the colonic epithelium that alters the tissue from normal to cancerous. The common view is that this transition from normal to cancerous is initiated by mutations in the APC gene and that genes such as Kras are only mutated later in the cascade. However, our lab has previously shown that mutations of amino acid residues 12 and 13 in Kras, e.g. KrasG12D, are found in a subset of healthy human colons, allowing the inference that Kras mutations are present in large patches of intestinal crypts. This creates potentially pro-oncogenic fields in healthy colon tissue. These areas could prime cancer development. Here we develop a mouse model that utilises two different DNA recombinases to disconnect an initial KrasG12D recombination event and subsequent lineage-tracing. Using this model, we show that crypts in KrasG12D+ epithelium have a markedly higher monoclonal conversion rate than crypts in wild-type epithelium. Furthermore, we show that the increased monoclonal conversion rate in the KrasG12D+ epithelium is dependent on Mek and that treatment with the Mek inhibitor AZD6244 reduces the conversion rate in KrasG12D+ crypts without affecting wild-type crypts. These results suggest that KrasG12D+ fields in the intestinal epithelium fixes secondary mutations at an accelerated rate and could represent pro-oncogenic areas. Collectively, this new transgenic mouse model allows in-dept investigation of stem cell behaviour in pro-oncogenic KrasG12D fields and aids the understanding of how such fields might lead to colon cancer in some patients.

Funding Source: Cancer Research UK.

14:24 – 14:35

THE ROLES OF POLYPLOIDY IN MOUSE LIVER CANCER AND REGENERATION

Lin, Yu-Hsuan and Zhu, Hao

Children's Research Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA

Polyploidy refers to cells with whole genome duplications. In cancer cells, polyploidy is seen as a precarious precursor to genome instability. Surprisingly, polyploidy is a normal state in organisms such as plants and fish. In mammals, more than 50% of hepatocytes are tetraploid, octaploid, or greater, but putative liver stem cell populations are thought to be diploid. We have tested several genetic pathways to interrogate roles for polyploidy, which have remained obscure. Knocking down E2f8, a transcription factor required for polyploidization, or Anillin, a cytoskeletal protein required for cytokinesis, can decrease or increase ploidy, respectively. We developed a dox-inducible shRNA mouse against Anillin that permits reversible knockdown and massive polyploidization without permanent disruption of Anillin. These super-polyploid mice were potently protected from tumorigenesis induced by a single mutagen dose. However, it is unknown how polyploids react to chronic proliferative demands, which are characteristic of clinically relevant chronic diseases. What if damaged polyploids that divide result in chromosomally unstable daughter cells? Thus, we used persistent chemical injuries to induce damage and proliferation. Surprisingly, super-polyploid mice were again protected from cancer. We tested if tumor protection could be caused by gene expression changes, but RNA-seq showed no differences between ploidy states. Moreover, diploid and polyploids showed no differences in tissue damage as measured by serum tests, histology, and fibrosis. We also detected no significant differences in mitosis frequency between diploid and polyploid livers. In summary, polyploid hepatocytes readily divide and regenerate while being buffered from tumor suppressor loss of heterozygosity and tumorigenesis. Our work implies that therapeutic polyploidization could protect livers from cancer while preserving the astounding regenerative capacity of this organ.

14:35 – 14:46

TRIM32 SUPPRESSES PROLIFERATION OF CEREBELLAR GRANULE CELL PROGENITORS AND MEDULLOBLASTOMA FORMATION IN THE MOUSE BY DEGRADING GLI1/SONIC HEDGEHOG SIGNALING

Gao, Wei-Qiang

School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai, China

Sonic hedgehog (SHH) signaling is crucial for the maintenance of the physiological self-renewal of granule neuron progenitor cells (GNPs) during cerebellar development, and its dysregulation leads to tumorigenesis. However, how SHH signaling is controlled during cerebellar development is poorly understood. Here, we show that Trim32, a cell fate determinant, is distributed asymmetrically in the cytoplasm of mitotic GNPs, and that genetic knockout of Trim32 keeps GNPs at a proliferating and undif-

ferentiated state. In addition, Trim32 knockout enhances the incidence of medulloblastoma (MB) formation in the Ptch1 mutant mice. Mechanistically, Trim32 binds to Gli1, an effector of SHH signaling, via its NHL domain and degrades the latter through its RING domain to antagonize the SHH pathway. Therefore, these findings indicate that Trim32 may be a vital cell fate regulator by antagonizing the SHH signaling to promote GNPs differentiation and a tumor suppressor in MB formation.

Funding Source: This study was supported by funds from Ministry of Science and Technology of the People's Republic of China (2017YFA0102900), National Natural Science Foundation of China (81872406 and 81630073) and KC Wong foundation.

14:46 – 15:06

INTERDEPENDENCE OF MALIGNANT MYELOID CELLS AND THEIR NICHE: "IT TAKES TWO TO TANGO"

Bonnet, Dominique

The Francis Crick Institute, London, UK

The bone marrow (BM) niche is the spatial environment where hematopoietic stem cells (HSCs) reside. Multiple components of the niche regulate HSC quiescence, activation and mobilization, however many of them remain poorly characterized. Recent findings point towards the existence of an active crosstalk between the niche and the hematopoietic compartment during leukemia. Therefore, a thorough characterization of the BM niche alteration is required to better understand the mechanisms of leukemogenesis. In this talk, we will summarize our published data concerning the effect of AML on the vascular niche and how by dissecting the molecular mechanisms involved in vascular leakage, we were able to impede indirectly on AML development. We will also describe our new humanised 3D scaffold system, which mimic the human BM niche, and show examples of its utility. We will discuss unpublished data related to our effort to provide a global picture of the BM niche, using high-throughput omics and computational tools to analyse multiple environmental components and decipher their mutual interactions in the context of leukemic development. Gene expression dynamics across different stromal components will be described, uncovering their relationships in the context of AML.

FRIDAY, 28 JUNE, 13:15 – 15:15

CONCURRENT IIID: INFLAMMATION AND MICROBIOME

Room 408A, Level Two

13:20 – 13:40

Geissmann, Frederic

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Title and abstract not available at time of printing

13:40 – 13:51

CONTROL OF IMMUNE RESPONSE IN THE CELL THERAPY FOR PARKINSON'S DISEASE

Morizane, Asuka, Doi, Daisuke, Kikuchi, Tetsuhiro and Takahashi, Jun

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

The first clinical trial of the iPS-based cell therapy for Parkinson's disease has been started in Japan. Although brain is considered as immunologically privileged, there are evidences that immune reaction occurs after cell transplantation. There are several strategies to prevent immune response. First, iPSC technology provides the possibility of autologous transplantation. Secondly, the "stock project" with human leukocyte antigen (HLA)-homo iPSCs enables the HLA-matched transplantation for the selected subjects. Thirdly, we can use the immunosuppressive drugs as used in organ transplantations such as kidney, bone marrow, heart, etc. We performed the non-clinical study for these three strategies with non-human primates. Autologous, MHC-matched, and allogeneic (MHC-mismatched) transplantations were compared with iPSC-derived dopamine neurons originated from cynomolgus monkeys. Based on the non-clinical results, we adopt the HLA-homo iPSCs derived from the "stock project" that has the most popular HLA haplotype in Japan with an immunosuppressive drug, Tacrolimus. The trial recruited the recipients regardless of their HLA haplotypes. Tacrolimus is used to all the recipients for at least one year. The imaging analyses including positron emission tomography (PET) are performed to monitor the graft survival and immunological rejection. In this presentation we will show the non-clinical research data and the protocol of the clinical trial in Japan regarding the control of immune response.

Funding Source: This study was supported by a grant from the Network Program for Realization of Regenerative Medicine from the Japan Agency for Medical Research and Development (AMED).

13:51 – 14:02

CUSTOM DISRUPTION OF HLA GENES IN HUMAN IPS CELLS BY CRISPR-CAS9 GENOME EDITING TO SUPPRESS T AND NK CELL ALLO-REACTIVITY

Hotta, Akitsu[1], Xu, Huaigeng[2], Wang, Bo[2], Ono, Miyuki[2], Kagita, Akihiro[2], Fujii, Kaho[2], Sasakawa, Noriko[2], Ueda, Tatsuki[2], Gee, Peter[2], Nishikawa, Misato[2], Nomura, Masaki[2], Kitaoka, Fumiyo[2], Okita, Keisuke[2], Yoshida, Yoshinori[2] and Kaneko, Shin[2]

[1]Department of Clinical Application, [2]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan, [2]Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan

Derivatives from pluripotent stem cells, such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), have been utilized for cell therapy in various conditions. However, one major concern that must be overcome before their widespread clinical use is potential HLA mismatching, which can be a cause of immune rejection. To eliminate surface expression of all the class I HLA molecules, B2M gene knockout has been demonstrated to circumvent allo-reactivity of cytotoxic T cells, but this approach may induce NK cell activity and fail to present antigens through class I HLAs. At CiRA, Kyoto university, HLA-homozygous iPSCs have been generated, but it is challenging to recruit rare homozygous donors. In this study, we investigated CRISPR-Cas9 mediated HLA editing approaches for enhancing T cell compatibility while suppressing NK cells' missing-self immunity. First, we prepared CRISPR-sgRNA library to target specific HLA haplotype and optimized Cas9/sgRNA RNP transduction protocol in iPSCs. Then, we disrupted both HLA-A and -B genes bi-allelically but retain HLA-C mono-allelically to generate "HLA-C-retained" iPSCs to suppress the NK cell response and retain antigen presentation. We differentiated our "HLA-C-retained" iPSC lines into CD43+ monocytes and measured the activities of CD8+ cytotoxic T cells and NK cells. Importantly, our iPSC-derived monocytes could evade immunological activities of cytotoxic T and NK cells measured by CSFE proliferation assay, CD107a degranulation marker assay, and 51Cr release cytotoxicity assay. In addition, our approach can be combined with elimination of class II HLAs to suppress CD4+ helper T cells. Notably, our whole exome sequencing analysis of the 13 HLA-edited iPSC lines identified no obvious indels or mutagenesis on predicted off-target sites. Lastly, when our HLA-edited iPSCs were transplanted into immunodeficient mice and challenged with allogenic human T or NK cells, our HLA-edited cells survived better than non-edited iPSCs in vivo. Given the lower variations of HLA-C haplotypes, we estimated that only 12 lines of the HLA-C retained iPSCs would be sufficient to cover over 90% of the HLA haplotypes in the world-wide population. We believe our custom editing of HLA approach would greatly facilitate cell therapy applications of iPSCs and beyond.

Funding Source: This work was supported by Japan AMED grants for the Core Center for iPS cell Research, Research Center Network for Realization of Regenerative Medicine and JSPS KAKENHI.

14:02 – 14:13

LOW DOSE KINASE INHIBITOR TREATMENT RESCUES THE PRIMARY CILIUM AND ITS FUNCTION IN OBESE ADIPOSE-DERIVED MESENCHYMAL STEM CELLS

Ritter, Andreas[1], Kreis, Nina-Naomi[2], Louwen, Frank[2], Solbach, Christine[2] and Yuan, Juping[2]

[1]Molecular Obstetrics, University Hospital, Frankfurt, Germany, [2]Department of Gynecology and Obstetrics, J. W. Goethe-University, Frankfurt, Germany

Obesity negatively affects a variety of cell types including adipose-derived mesenchymal stem cells (ASCs). Previous studies demonstrated that obese ASCs have reduced differentiation capacity, decreased motility, impaired immunomodulation and a hampered replicative capacity. We illustrated that some of these defects are associated with defective primary cilia, which are unable to properly convey and process signals. Additionally, we show the rescue of primary cilia in subcutaneous and visceral ASCs by inhibiting Aurora A with MLN8054 or extracellular-signal regulated kinase 1/2 (Erk1/2) with PD98059. The treatment with these inhibitors increased the length of the primary cilium, restored the invasion and migration potential and improved the differentiation capacity of obese ASCs. Associated with enhanced osteogenic and adipogenic differentiation ability. The cells displayed an increased expression of stemness related genes like SOX2, OCT4 and NANOG. This work describes a novel phenomenon whereby the primary cilium of obese ASCs is rescuable by Aurora A or Erk1/2 inhibition, resulting in more functional ASCs. These cells might be able to improve tissue homeostasis in obese patients and thereby ameliorate obesity associated-diseases. Additionally, these functionally restored obese ASCs could be useful for novel autologous mesenchymal stem cell-based therapies.

14:13 – 14:24

EFFICIENTLY RECONSTITUTING THE STEPWISE DEVELOPMENT OF DEFINITIVE BLOOD PROGENITORS FROM HUMAN PLURIPOTENT CELLS VIA AN ARTERY-LIKE INTERMEDIATE

Loh, Kyle M.[1], Fowler, Jonas[1], Chen, Angela[1], Nguyen, Alana[1], Ang, Lay Teng[1] and Weissman, Irving[2]

[1]Institute for Stem Cell Biology & Regenerative Medicine/ Department of Developmental Biology, Stanford University School of Medicine, Stanford, CA, USA, [2]Institute For Stem Cell Biology & Regenerative Medicine/Departments Of Pathology and Developmental Biology, Stanford University School of Medicine, Stanford, CA, USA

It is currently challenging to generate blood-forming stem cells from human pluripotent stem cells (hPSCs) owing to incomplete knowledge of how blood progenitors arise during development. Indeed over the past century, multiple precursors to blood stem cells have been proposed, including hemangioblasts, hemogenic endothelium or arteries; however, the relationships between these cell-types and their lineage potentials remain controversial. Here we reconstituted the stepwise development of hPSCs into

primitive streak, lateral mesoderm, arteries, hemogenic endothelium and finally, blood progenitors in defined, monolayer culture over 9 days of in vitro differentiation. Starting from day 2 hPSC-derived lateral mesoderm populations, we leveraged SOX17 as a marker of definitive blood formation and generated >90% pure SOX17+CD34+ definitive blood intermediates by day 3 of hPSC differentiation. These SOX17+CD34+ intermediates resembled arteries, and could further mature into candidate hemogenic endothelium with stepwise upregulation of RUNX1, GFI1 and GFI1B on days 4, 5 and 6 of differentiation, respectively. By day 9 of differentiation, a >50% pure population of CD43+CD45+CD34+CD144+ blood progenitors emerged. These hPSC-derived blood progenitors could generate myeloid and lymphoid cells in vitro and their in vivo engraftment potential is currently being explored. We suggest arteries and hemogenic endothelium are separable entities, and that arteries are transiently competent to be diverted into hemogenic endothelium. Transition through an intervening artery-like intermediate may be an obligatory step to establish competence for definitive blood development, with ramifications for our ability to efficiently and rapidly generate blood progenitors from hPSCs.

Funding Source: This work was supported by the NIH Director's Early Independence Award, Stanford Beckman Center, and the Anonymous, Baxter, DiGenova and Siebel families (to K.M.L.) and the California Institute for Regenerative Medicine (to I.L.W.).

14:24 – 14:35

THYMOPOIESIS IN TIME AND SPACE - DECIPHERING THE IMPACT OF DEVELOPMENTAL TIMING ON LYMPHOCYTE OUTPUT IN THE EMBRYONIC MOUSE THYMUS

Elsaid, Ramy[1], Yang, Junjie[1], Brulen-Defranoux, Odile[1], Da-Silva, Francisca[1], Iturri, Lorea[2], Freyer, Laina[2], Vieira, Paulo[1], Rodewald, Hans-Reimer[3], Gomez Perdiguero, Elisa[2] and Cumano, Ana[1]

[1]Department of Immunology, Institut Pasteur, Courbevoie, France, [2]Development and Stem Cell Biology, Institut Pasteur, Paris, France, [3]Cellular Immunology, DKFZ, Heidelberg, Germany

During embryonic development multiple waves of hematopoietic progenitors with distinct lineage potential are differentially regulated in time and space. Consistent with that view, two waves of distinct thymic settling progenitors (TSPs) colonize the fetal thymus where they contribute to thymic organogenesis. TSPs of the first and second wave generate specialized lymphocyte subsets which are produced during embryogenesis and remain in tissues throughout life. While growing evidence of the heterogeneity and layered organization of the hematopoietic system is leading to a common speculation that the first TSPs may be derived independently of hematopoietic stem cells (HSCs), it has remained unclear what is the relative contribution of the HSC-independent progenitors and fetal HSCs to lymphopoiesis and tissue resident innate-like lymphocytes throughout life? Addressing this question highlights a critical challenge in the understanding of lymphopoiesis. Spatiotemporal analysis allowed us to trace the lymphoid site of origin and its contribution in an efficient and precise fashion. Although multi-lineage yolk sac (YS) derived progenitors express lymphoid-associated genes (Il7ra, Rag1 and Rag2), they are devoid of lymphoid potential indicating that lineage-associated genes could be expressed with no further consequences on cell fates during early stages of development. In addition, only fetal HSCs but not YS-progenitors initiate thymopoiesis in a fetal thymic microenvironment. Moreover, in vivo fate-mapping directly demonstrate that TSPs and lymphoid progenitors originate from HSCs, thus settling the controversy over the origin of the first TSPs. Furthermore, we found the first TSPs are generated through a unique developmental program initiated in multipotent lymphoid primed progenitors, which exhibit a partial lymphoid lineage bias in the fetal liver then migrate to the thymus to give rise to embryonic T cell and innate lymphoid cells (ILC). Further analysis showed that while cells in the first wave were T cell-ILC-restricted with bias towards the ILC3 lineage, TSPs from the second wave were multipotent with T-cell, B-cell, ILC and myeloid potential. Our work provide a detailed analysis of thymopoiesis during embryogenesis and shed new light on the multi-layered immune system development.

14:35 – 14:46

A HUMAN INDUCED PLURIPOTENT STEM CELL BASED IN VITRO MODEL FOR AUTOIMMUNE TYPE-1 DIABETES

Sintov, Elad[1], Leite, Nayara[1], Babon, Jenny Aurielle[2], Kent, Sally[2], Brehm, Michael[2] and Melton, Douglas[1]

[1]Harvard Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [2]Diabetes Center of Excellence, UMass Medical School, Worcester, MA, USA

Type 1 diabetes (T1D) is an autoimmune disorder leading to the destruction of insulin-producing β-cells in the pancreas. Despite recent scientific advances, questions remain regarding the initial trigger and the mechanisms of disease. The development of human induced pluripotent stem cells (hiPSCs) opened new opportunities for cell replacement therapy of T1D. Using a large-scale production strategy, therapeutic quantities of human stem cell-derived β-cells (SC-β) can be attained in vitro following a step-wise differentiation protocol. Yet, preventing immune rejection of grafted cells without the use of immunosuppressant drugs remains a major challenge. To date, only murine systems exist for modeling T1D and no human model has been developed to sufficiently capture autoimmune responses, selectively triggered by β-cells. In the current research, we have developed a human in vitro platform in an autologous setting that recapitulates the effector/target interactions in an autoimmune response. To create target cells for in vitro autoimmune assays, hiPSCs were reprogrammed from healthy or T1D patients, expanded in 3D suspension cultures and differentiated to human pancreatic endocrine cells by implementing SC-β and SC-α differentiation protocols. A donor-matched response against target hiPSC-derived β-cells was achieved by co-cultures with either an autologous CD8+ T cell line specific to a known diabetogenic peptide or perihelial blood mononuclear cells (PBMCs) derived from the same donors' blood. Immune responses were quantified by means of T-cell effector activation signatures, inflammatory cytokine secretion, and

loss of cell-type specific target cells by killing. Results show that under specific environmental conditions, both CD4+ and CD8+ T-cells exhibit a stronger activation phenotype when stimulated against iPSC-derived β-cells compared to iPSC-derived α-cells. Furthermore, HLA-I blocking experiments demonstrate that T-cell responses are mediated by T-cell receptor (TCR) to MHC-I interactions. The in vitro model designed in this research can serve as a multi-purpose platform to study mechanisms of T1D autoimmunity, functionally evaluate cell replacement therapies and screen for immunomodulatory drugs or CRISPR-edited gene perturbations.

14:46 – 15:06

INFLAMMATORY TUNING OF EPITHELIAL STEM CELLS

Naik, Shruti

New York University School of Medicine, New York, NY, USA

Our body's epithelia are barriers that interface with the terrestrial environment and routinely experience inflammation. Although a vast majority of these inflammatory reactions resolve, they imprint the tissue with a memory. Cells of the immune system are traditionally thought to be the bearers of this memory, allowing them to react faster to subsequent inflammatory pressures. Yet, barrier tissues are composites of epithelial, mesenchymal, nervous, vascular, and immunological networks working in unison to sustain optimal function. I discuss the enduring impact of inflammatory exposures on the skin epithelia and in particular on their long-lived stem cells, which replenish this tissue in health and disease.

FRIDAY, 28 JUNE, 13:15 – 15:15

CONCURRENT IIIE: STEM CELL ETHICS

Room 408B, Level Two

13:20 – 13:40

STRATEGIES FOR PAYMENT REFORM IN AN ERA OF TRANSFORMATIVE THERAPIES: MOVING FROM VOLUME TO VALUE

Hamilton Lopez, Marianne

Duke-Robert J. Margolis, MD, Center for Health Policy, Washington, DC, USA

An increasing number of "transformative" therapeutic innovations are emerging that aim to provide durable responses for serious diseases, and disrupt the current treatment paradigm for genetic disorders, cancers, and other chronic conditions. However the potentially high value and high cost of such technologies creates challenges in volume-based, fee-for-service (FFS) health care reimbursement systems. Payers concerns include the impact on budgets; uncertainty about the long-term effectiveness and durability of the therapy; and beneficiary enrollment shifts that disconnect the long-term financial benefits from the payer that bore the cost of the intervention. Continuing within the current FFS system may lead to limited reimbursement for the high, upfront costs of transformative therapies, which in turn may result in a loss of investment in and access to innovative therapies. These challenges are not just the challenges of tomorrow's health system, but obstacles for patients today. This presentation will: 1. Summarize the transformative therapies environment; as well as relevant national and state policies focused on addressing drug and device payment and prices. 2. Explore the barriers related to coverage of high-cost transformative therapies within Medicare and commercial insurance, including uncertainty in long-term results; uncertainty in recouping investment with a fragmented payer system; concern about cumulative budgetary impact; and concern about the potential cumulative impact of multiple pipeline therapies arriving on the market concurrently. 3. Highlight potential new payment strategies, including value-based payment arrangement for medical devices meant to align pricing and payments to expected or observed value in a population with the goal of reducing the uncertainty and risk in payments. 4. Present recommendations for identifying a path forward for new access and payment needs.

13:40 – 13:51

EDUCATING PATIENTS ABOUT UNAPPROVED STEM CELL TREATMENTS: EVALUATING A REGENERATIVE MEDICINE CONSULTATION SERVICE

Master, Zubin[1], Martin Lillie, Charlene[2], Dens Higano, Jennifer[3], Smith, Cambray[1], Phu, Sydney[4], Arthurs, Jennifer[5], Shapiro, Shane[6] and Turner, Leigh[7]

[1]Biomedical Ethics Research Program, Mayo Clinic, Rochester, MN, USA, [2]Center for Regenerative Medicine, Mayo Clinic, Rochester, MN, USA, [3]Mayo Clinic Alix School of Medicine, Mayo Clinic, Rochester, MN, USA, [4]School of History, Philosophy, and Religion, Oregon State University, Corvallis, OR, USA, [5]Center for Regenerative Medicine, Mayo Clinic, Jacksonville, FL, USA, [6]Orthopedic Surgery, Mayo Clinic, Jacksonville, FL, USA, [7]Center for Bioethics, School of Public Health, and College of Pharmacy, University of Minnesota, Minneapolis, MN, USA

Over 700 clinics in the U.S. market direct-to-consumer unlicensed stem cell-based interventions (SCBIs). Prior work shows the use of inaccurate information to advertise SCBIs and increased distrust of physicians as reliable information sources. In 2011, Mayo Clinic-Minnesota created the Regenerative Medicine Consultation Service (RMCS) with the goal of providing education about SCBIs, dispelling misinformation, and helping patients consider evidence-based options. In 2016, Mayo Clinic-Florida created a similar service focused mostly on orthopedic conditions. To date, over 3,500 consults have been conducted by both services. Here, we describe the RMCS by analyzing databases and electronic medical records of consultations. Results show that most consults were by phone (91% MN, 96% FL) with slightly more male patients (56% MN). Most patients were 60 years or older (65% MN, 71% FL). RMCS-MN received calls from 48 states and 8 different countries and RMCS- FL received calls from 33

states and 4 countries. RMCS-MN patients inquired on over 150 distinct conditions (43% orthopedic, 19% cardiology, 15% neurology, and 11% pulmonology) whereas 93% of RMCS-FL consults were orthopedics-related. Nearly all patients (99%) asked about SCBIs for their condition, and consultants discussed the unapproved SCBI industry in 37% of consults. Consultants described the state of stem cell research in 93% of consults and provided additional educational materials in 13% of consults. Patients were offered medical (29%) and clinical research referrals (37%) when appropriate. Patients reported performing research on a specific SCBI clinic in 16% of cases and stated they were actively considering an unproven SCBI in 13% of cases. Of these, 17% of patients reported they would no longer pursue an unproven SCBI after the consult. From pilot interviews, patients report the service as useful and the consultant knowledgeable. A limitation of our analysis is that consultants may not provide details of the discussion in the consult note. Our analysis suggests that the RMCS provides information and offers some additional options. Future work to improve the RMCS and determine whether it can deter patients from seeking unapproved SCBIs will be discussed.

Funding Source: CTSA UL1 TR002377 (Small Grants Program), National Center for Advancing Translational Sciences

13:51 – 14:02

WEIGHING UP THE EVIDENCE USED BY DIRECT-TO-CONSUMER STEM CELL CLINICS IN THE SOUTHWEST US

Nadone, Haley[1], Richey, Alexandra[2], Muldoon, Anna[3], Krum, Logan[4], Williams, Paige[5], Becker, Bryson[4], Nelson, J.P.[3], Brafman, David[2] and Frow, Emma[2,3]

[1]School of Life Sciences and School of Politics and Global Studies, Arizona State University, Tempe, AZ, USA, [2]School of Biological and Health Systems Engineering, Arizona State University, Tempe, AZ, USA, [3]School for the Future of Innovation in Society, Arizona State University, Tempe, AZ, USA, [4]School of Life Sciences, Arizona State University, Tempe, AZ, USA, [5]School of Human Evolution and Social Change, Arizona State University, Tempe, AZ, USA

In the US, there are currently hundreds of businesses advertising stem-cell-based treatments that have not undergone regulatory approval by the Food and Drug Administration (FDA). These clinics use a variety of strategies in marketing their treatments directly to prospective patients. Here we map and analyze the different types of evidence used by stem cell businesses on their websites. We use the subset of businesses operating in the Southwest US (n=169) as our initial case study. We present an overview of the different forms of evidence mobilized to support and lend credibility to clinic practices, and provide a snapshot of the frequency with which they are used by stem cell businesses. The forms of evidence we identify range from more 'scientifically' accepted metrics (including registered clinical trials, published research papers, and lists of physicians' professional accreditations) to 'less scientific' data (such as patient testimonials and references to celebrities who have had stem cell treatments). Almost all businesses make use of at least one type of evidence in marketing their treatments. We find that 'less scientific' evidence is presented more often than 'more scientific' types of data. We also dig deeper into forms of evidence that might be considered 'more scientific', to evaluate how well the information provided supports the stem-cell-based treatments being offered by a given business. Specifically, we analyze over 350 abstracts from research papers posted on clinic websites, to evaluate whether the findings provide clinically relevant support for the treatments being offered. We also catalog the medical specialties, professional certifications and affiliations of doctors practicing in stem cell clinics. Our findings suggest the need to exert caution in treating these forms of 'scientific' data as evidence in support of the stem-cell-based treatments on offer by clinics. We use these findings to make suggestions for how the International Society for Stem Cell Research (ISSCR) might update their recommended list of questions for prospective patients considering stem cell treatments.

14:02 – 14:13

ETHICAL TRADEOFFS IN THE MANUFACTURING OF AUTOLOGOUS CELL THERAPIES

Levine, Aaron D.

School of Public Policy, Georgia Institute of Technology, Atlanta, GA, USA

In recent years, advances in basic and pre-clinical stem cell research, combined with rapid improvements in gene editing technologies, have moved novel autologous stem cell and combined cell and gene therapies closer to the clinic. Yet despite this progress, the development of manufacturing processes remains a substantial obstacle to the successful translation and commercialization of these therapies. The manufacturing of autologous cell therapies is complex. It typically includes extracting cells from the patient, transporting these cells to a manufacturing facility (perhaps at a substantial distance away), and manipulating and growing cells over an extended period, before transporting the cells back to a medical facility for treatment. To the extent that manufacturing concerns are considered in the development of these therapies, the focus has traditionally been on process optimization and reducing the cost of good sold. Yet the extended and distributed manufacturing process associated with these novel therapies raises several challenging and under-explored ethical concerns. In this presentation, I will draw on the results of a novel simulation model of an autologous cell therapy supply chain to summarize the manufacturing choices available to firms developing autologous cell therapies and identify the ethical tradeoffs among access, cost, and product quality inherent in these manufacturing design choices. I will highlight these ethical tradeoffs for the case of chimeric antigen receptor T cell therapy, a form of combined cell and gene therapy that was first approved by the U.S. Food and Drug Administration in 2017 and argue that ethical considerations merit placement alongside cost and regulatory issues as a key criterion for the design of cell manufacturing processes. I will conclude by discussing the importance of addressing these manufacturing considerations early in the translation process if personalized stem cell therapies are to be both a medical and commercial success.

Funding Source: This material is based upon work supported by the National Science Foundation under Grant No. EEC-1648035.

14:13 – 14:24

MIND THE GAP: TRAINING NEXT-GENERATION PHYSICIANS IN REGENERATIVE MEDICINE AND SURGERY

Wyles, Saranya P.[1], Hayden, Richard[2], Meyer, Fredric[3] and Terzic, Andre[4]

[1]Center for Regenerative Medicine, Mayo Clinic, Rochester, MN, USA, [2]Department of Otolaryngology, Mayo Clinic, Phoenix, AZ, USA, [3]Department of Neurologic Surgery, Mayo Clinic, Rochester, MN, USA, [4]Division of Cardiovascular Diseases, Mayo Clinic, Rochester, NY, USA

Regenerative sciences are poised to transform clinical practice. The quest for regenerative solutions has however exposed a major gap in current healthcare education. A call for evidence-based adoption has underscored the necessity to establish rigorous regenerative medicine educational programs early in training. Here, we present a patient-centric regenerative medicine curriculum embedded into medical school and residency core learning. Launched as a dedicated portal of new knowledge, learner proficiency was instilled by means of a discovery-translation-application blueprint. Using the "from the patient to the patient" paradigm, student and resident experience recognized unmet patient needs, evolving regenerative technologies, and ensuing patient management solutions. Targeted on the deployment of a regenerative model of care, complementary subject matter included ethics, regulatory affairs, quality control, supply chain, and biobusiness. Completion of learning objectives was monitored by online tests, group teaching, simulated clinical examinations along with longitudinal continuity across medical school and residency training. Success was documented by increased awareness and proficiency in domain-relevant content, as well as specialty identification through practice exposure, research engagement, clinical acumen and education-driven practice advancement. Self-reported learner proficiency based on subject-matter familiarity in all course objectives improved significantly from pre-course to post-course (n=151). Early incorporation into mainstream medical education offers a tool to train next-generation healthcare providers equipped to adopt and deliver validated regenerative medicine solutions.

Funding Source: Funding from Regenerative Medicine Minnesota, National Institutes of Health (HL134664), Marriott Foundation, and Michael S. and Mary Sue Shannon Family is deeply acknowledged.

14:26 – 14:46

THE ETHICS AND ECONOMICS OF PRICE-SETTING FOR STEM CELL PRODUCTS

Sipp, Douglas

RIKEN Center for Biosystems Dynamics Research and Keio University School of Medicine, Kobe, Japan

Rising drugs prices have been a topic of international concern in recent years. While much of the focus has been on novel small chemical drugs and advanced cancer therapies, the prospect of a new generation of stem cell-based therapeutics appears to be on the near horizon. Achieving a balance between affordability and sustainability in medical product pricing is a challenge for all fields, and is made even more complex in cell-based drugs due to the historically large outlays of public funding for RandD and the climate of international economic competition in this arena. I will provide a brief review of key issues in the drug pricing debate with a focus on issues specific to stem cell biologics.

14:46 – 15:06

Speaker to be named

FRIDAY, 28 JUNE, 16:00 – 18:00

PLENARY V: MECHANISMS AND APPLICATIONS OF MESODERMAL TISSUES II

West Hall B, Level One

16:10 – 16:30

JOHN MCNEISH MEMORIAL LECTURE: USHERING IN A NEW ERA OF MEDICINE: THE PROMISE OF CELL THERAPIES

Plump, Andrew

Takeda Pharmaceutical Company, Cambridge, MA, USA

Takeda isn't new to the area of cell therapies; we've long believed in the promise and curative potential of this emerging modality. In 2015 we established a Regenerative Medicine Unit (RMU) in Shonan, Japan to support T-CiRA, our joint research program with Kyoto University's Center for iPS Cell Research Application. Over the years, through T-CiRA and our close partnership with Professor Shinya Yamanaka we've progressed several exciting projects. In addition to our T-CiRA collaboration, Takeda has made investments and formalized collaborations with several emerging companies to develop next-generation chimeric antigen receptor (CAR) T-Cell technologies. More recently, Takeda executed a new alliance with Memorial Sloan Kettering Cancer Center (MSKCC) to discover and develop novel CAR-T cell products for the potential treatment of several cancers. This broad, multi-faceted collaboration pairs Takeda with Dr. Michel Sadelain, MD, PhD, Director of the Center of Cell Engineering & Gene Transfer and Gene Expression Laboratory at MSKCC. And finally, this spring, after a two-year joint development effort, Takeda and TiGenix received EU approval for Alofisel, a new treatment option for patients suffering from one of the most disabling complications of Crohn's disease. This is a significant milestone as Alofisel is the first allogeneic stem cell therapy to receive central marketing authorization in Europe. We've since acquired the company because we believe in the potential of TiGenix's stem cell platforms and we're excited about the opportunity to gain first-hand experience in the production, distribution and delivery of these unique and sensitive therapeutic products. In a short period of time, we've generated significant expertise and research momentum in the area of cell therapies and we're now turning our attention toward optimizing our infrastructure so that we may propel our efforts forward at an even faster pace.

16:30 – 16:50

ANGIOGENESIS REVISITED: ROLE AND (THERAPEUTIC) IMPLICATIONS OF ENDOTHELIAL METABOLISM

Carmeliet, Peter

VIB-KU Leuven Center for Cancer Biology, Leuven, Belgium

The past 40 years of research in the angiogenesis field have focused on identifying genetic signals such as VEGF and Notch, which determine vessel sprouting. However, the role and therapeutic potential of targeting endothelial cell (EC) metabolism have been largely overlooked. We have recently reported that ECs are glycolysis addicted and that glycolysis importantly co-determines vessel sprouting downstream of VEGF and other pro-angiogenic signals. In addition, we documented that ECs are rather unique in utilizing fatty acid-derived carbons for the de novo synthesis of deoxyribonucleotides for DNA synthesis during EC proliferation when vessels sprout and found particular roles for enzymes involved in amino acid metabolism in EC proliferation, migration and survival. Moreover, targeting (blocking) glycolysis and fatty acid oxidation inhibit pathological angiogenesis and induce tumor vessel normalization (thereby reducing metastasis and improving chemotherapy), suggesting that these metabolic pathways are new targets for anti-angiogenic drug development without evoking systemic side effects. Furthermore, lymphatic ECs differ from other EC subtypes in their metabolic requirements for lymphangiogenesis. Since many of these metabolic targets are pharmacologically druggable, these metabolic pathways represent a new promising target for therapeutic anti-angiogenesis.

16:50 – 17:10

ES CELLS BASED GASTRULOIDS AS A PLATFORM TO STUDY DEVELOPMENTAL GENE REGULATION

Duboule, Denis, Beccari, Leo**,** Rekaik, Hocine and Bochaton, Celia

Ecole Polytechnique Fédérale, Lausanne, Switzerland

During vertebrate development, clustered Hox genes are controlled by enhancers acting over very long distances and localized within two large and distinct regulatory landscapes flanking the gene cluster. The proper implementation of these complex long-range regulations is key to the general organization of the animal body plan. However, molecular genomics studies of these regulations in living specimens are made difficult by the early developmental stages considered, the heterogeneity of the tissues and the low number of cells. In this context, we use ES cells-based gastruloids to try to overcome some of these problems. These biological objects display many features of an elongating post-occipital mammalian trunk and can thus be used as a surrogate system to challenge particular mechanisms at work during the dynamic development of posterior body parts. Comparative data regarding Hox gene regulation between gastruloids and the mouse embryo will be discussed as well as the necessary complementarity between these two approaches.

17:10 – 17:21

DIFFERENTIATION OF BROWN ADIPOCYTE PROGENITORS OF MOUSE IN VIVO: NEW CONCEPTUAL ADVANCES IN STEM CELL METABOLISM

Mayeuf-Louchart, Alicia[1], Lancel, Steve[2], Sebti, Yasmine[2], Pourcet, Benoit[2], Loyens, Anne[3], Eeckhoute, Jérôme[2], Vincent, Stéphane[4], Staels, Bart[2] and Duez, Hélène[2]

[1]Institut Pasteur de Lille, INSERM U1011, Universite de Lille-Egid, Lille, France, [2]UniversiteLille, Inserm, CHU Lille, U1011 – EGID, Institut Pasteur de Lille, France, [3]UMR-S 1172-JPArc Centre de Recherche Jean-Pierre Aubert Neurosciences et Cancer, University Lille, France, [4]CNRS, UMR7104, INSERM U1258, Université de Strasbourg, IGBMC, Illkirch, France

Browning induction or transplantation of brown / beige adipocytes derived from progenitors or iPs cells represents a powerful strategy to treat metabolic diseases. However, our poor understanding of the mechanisms that govern the differentiation and activation of brown adipocytes limits the development of such therapy. The transcription factor Prdm16 was identified as a master regulator of brown adipose tissue differentiation. Number of studies have also identified factors involved in the differentiation program of brown adipocytes, but most of them were done on ex vivo pre-adipocyte culture and mechanisms controlling brown adipocyte differentiation from progenitors in vivo still remains unknown. Understanding these processes are nevertheless essential for the development of iPs strategies. In this study, we have followed the development of brown adipocytes within their physiological environment in the mouse embryo. We have identified the genes and pathways involved in the differentiation of brown-preadipocytes, providing a transcriptomic database which will serve as a reference for the scientific community and notably for the generation of brown adipocytes from iPs cells. In addition, our work highlights a new mechanism in the formation of multiple lipid droplets, which characterise differentiated brown adipocytes. We demonstrate how lipid droplets form thanks to a novel ex-vivo brown adipose tissue explant model, which allows molecular manipulations. This model is of great interest to the stem cell scientific community and can be used as a new tool for studying the differentiation of brown pre-adipocytes under more phyiological conditions than cultured cell lines. Our results on lipid droplet biogenesis change the standard view of stem cell cellular metabolism and this study provides new insights into the mechanisms controlling the differentiation of brown adipocyte progenitors in vivo.

17:21 – 17:32

DEK-MEDIATED INTRON RETENTION REGULATES MOUSE MUSCLE STEM CELL QUIESCENCE TO ACTIVATION TRANSITION

Yue, Lu, Wan, Raymond, Luan, Shaoyuan and Cheung, Tom

Life Science, Hong Kong University of Science and Technology, Hong Kong

Adult stem cells are essential for tissue homeostasis and regeneration. Dysregulation of signaling pathways that regulate adult

stem cell quiescence to activation leads to stem cell pool depletion and impaired tissue regeneration. A subset of adult stem cells remain in a quiescent state for a prolonged period of time with the ability to respond to external stimuli rapidly. The mechanisms of such rapid activation of quiescent stem cells remain elusive. Using skeletal muscle stem cells, also called satellite cells (SCs), we showed that intron retention (IR) is prevalent in the quiescent satellite cell (QSC) transcriptome. Genes possessing IR are essential for various fundamental cellular functions including RNA splicing, protein translation, cell cycle entry and lineage specification. Further analysis revealed that IR is a post-transcriptional regulation that regulates QSC quiescence to activation transition and it is dependent on the phosphorylated-Dek protein. While Dek protein is absent in QSCs, overexpression of Dek in QSC in vivo results in a global decrease of IR, SC quiescence exit and cell cycle entry, and consequently undermine muscle regeneration. Altogether, these findings illuminate a conserved post-transcriptional regulation of that plays an important role for adult stem cell to transit from quiescence to activation.

17:32 – 17:52

ASSESSING GENOMIC INTEGRITY FOR STEM CELL CLINICAL TRIALS

Murry, Charles E, MacLellan, Robb**,** Nelson, Stanley**,** Fields, Paul and Thies, Scott

University of Washington, Seattle, WA, USA

For a cell-based therapy that may persist for the life of the patient, the integrity of the genome is of clear importance. Since there is no established definition of genomic integrity, we are developing a practical pipeline for screening. We selected three lines of human embryonic stem cells (hESCs) and subjected them to 10-15 serial passages in 3-5 different commercial media under standard monolayer culture conditions. Two of the lines demonstrated recurrent, low-level karyotypic abnormalities. In contrast, the RUES2 line showed a consistently normal 46XX karyotype and was studied further. We performed exome sequencing and screened for potentially deleterious germline variants. From the Network of Cancer Genes 5.0 database, 1571 known or suspected cancer genes were identified, and 46 of these had variant alleles in RUES2 cells. Literature review demonstrated that only 1 of these allelic variants was associated with cancer (colon, breast and neuroendocrine). Since our clinical target is heart regeneration, we then tested for deleterious cardiac variants in 652 cardiac genes obtained by intersecting all commercial cardiac genetic tests and interrogating the OMIM and HGMD databases. Twelve variants were identified and classified as low risk based on conservative amino acid changes or a high allelic frequency in the general population. Finally, since this is a female cell line, we assessed for erosion of X-inactivation by bisulfite sequencing. Globally, the RUES2 line showed only modest erosion of X-inactivation. Eight cancer or cardiac promoters were hypomethylated but were judged to be of low risk based on known biological variables in cancer or cardiac disease. Ongoing studies are using targeted deep sequencing to assess the frequency of somatic mutations within the stem cell population during genomic editing, expansion in culture and after transplantation. We suggest that molecular genetics provides a rational basis for evaluating the genomes of therapeutic stem cells, allowing researchers to choose the best lines and optimize their protocols to ensure genomic health of a cellular graft.

SATURDAY, 29 JUNE, 09:00 – 11:20

PLENARY VI: FROM BENCH TO BEDSIDE: SURFACE ECTODERM AND ENDOCRINE ORGANS

West Hall B, Level One
Sponsored by Semma Therapeutics

9:00 – 9:20

MESENCHYMAL NICHE HETEROGENEITY GOVERNS REGIONAL EPITHELIAL REGENERATION AND DISEASE INITIATION

Chen, Ting

National Institute of Biological Sciences, Beijing, China

Niche cells play dominant roles in instructing the activity of stem cells and progenitor cells. However the principles governing organ level niche cells heterogeneity and functional diversity are largely unknown. Previously we discovered that the mesenchymal niche cells can be reprogrammed to change the regeneration landscape of skin hair follicle stem cells. Our transcriptome screen revealed that the expression of Hoxc genes in adult skin dermis uniquely correlates with the regional regeneration pattern of hair follicles. Disrupting the region specific expression pattern of Hoxc genes by either decreasing epigenetic repression through loss of Bmi1, or ectopic interaction of the Hoxc locus with an active epigenetic region, leads to ectopic HF regeneration. In vivo single Hoxc gene is sufficient to convert dormant dermal papilla niche into active one through regulating canonical Wnt signaling. Our current study further indicates mesenchymal fibroblasts influence immune cells aggregation in skin disease that demonstration regional patterns. Further study will be focused on understanding the molecular mechanism and regulatory method that can be used for effective disease treatment.

9:20 – 9:40

GENERATION OF FUNCTIONAL ORGANS VIA INTERSPECIES BLASTOCYST COMPLEMENTATION

Nakauchi, Hiromitsu

University of Tokyo, Japan and Stanford University, USA

Despite numerous efforts, in vitro derivation of truly functional, clinically relevant organs from PSCs has been difficult. Using interspecies blastocyst complementation, we demonstrated the generation of functionally normal rat pancreas by injecting rat PSCs into Pdx1-/- (pancreatogenesis-disabled) mouse embryos. Furthermore, we succeeded in generating functional mouse pancreas by injecting mouse PSCs into Pdx1-/- rat embryos. When islets obtained from these mouse pancreas generated in rats were transplanted to streptozotocin-induced mouse, blood glucose levels of recipient mice were normalized over a year without immunosuppression. These data provided proof-of-concept for the use of patient's iPSC-derived islets generated in xenogenic environment for the treatment of diabetes. With generation of human organs in animals as an ultimate goal, we have been making many intra- as well as inter-species chimeras. Our interspecies chimeras exhibit donor chimerism (DC) lower than that of intra-species chimeras. Interspecies chimeras with high DC also suffer embryonic lethality and are malformed. Interestingly, we find drastic organ-to-organ variation in extent of DC, suggesting that environmental factors influence proliferation and differentiation of xenogenic PSC-derived cells. Interspecies chimeras provide a novel and unique tool to generate PSC-derived organs, compare cell potency/function and to probe signaling pathways during development.

9:40 – 10:00

CHROMATIN DYNAMIC STRATEGIES DURING SURFACE ECTODERM COMMITMENT

Oro, Anthony, Pattison, Jillian**,** Piekos, Samantha**,** Li, Lingjie**,** Gaddam, Sadhana**,** Collier, Annie**,** Torkelson, Jessica and Wernig, Marius

Program in Epithelial Biology and Department of Dermatology, Stanford University School of Medicine, Stanford, CA, USA

Recent advances in genome editing technologies, induced pluripotent stem (iPS) cells, and tissue engineering have opened the door to keratinocyte-based tissue replacement for patients with diseases where palliation remains the only option such as Recessive Dystrophic Epidermolysis bullosa (RDEB). Because clinical production requires a defined differentiation protocol, we have used multi-dimensional genomics, chromatin conformational analysis and proteomics, along with network inference modeling to identify a two-step chromatin dynamic mechanism for keratinocyte differentiation from ES/iPS cells. We have uncovered unexpected dependencies of master regulators on local morphogenic signaling that explain how a key regulator can specify diverse surface ectoderm transcriptional programs based on the chromatin landscape induced by the local morphogen exposure. These insights have allowed acceleration of clinical development of new cell-based therapies for RDEB.

10:00 – 10:11

CAPTURING EPITHELIAL-IMMUNE INTERACTIONS TO MAINTAIN TISSUE HOMEOSTASIS

Park, Sangbum, Martone, Catherine and Greco, Valentina

Genetics, Yale University, New Haven, CT, USA

Skin protects our body against the outer environment, and its ability to repair upon injury is directly connected to both disease and survival. Despite recent advances in our understanding of skin homeostasis, it is still unclear how stem cells interact with their niche to sustain this process in a live mammal. The critical barrier to addressing these fundamental questions lies in the inability to simultaneously follow behaviors of different cell types and to define their functional interactions in vivo. Skin epidermis is an ideal system because of its accessibility and well-characterized epithelial stem cells and coexisting epidermal immune cells. In the epidermis, epithelial stem cells are closely intermingled with two resident immune cell populations: Dendritic epidermal T cells

(DETCs) and Langerhans cells (LCs). Intravital imaging platform with multiphoton microscope allows us to dissect the coordination and functional significance of distinct cell activities, populations and interactions during homeostasis in live mice. In addition to immune surveillance, our data show that both immune populations can perceive and respond to the changes of their neighbors. Epidermal immune cells actively retain spatial organization within their own population while neighboring epithelial stem cells continuously divide and differentiate. Furthermore, skin epithelial stem cells act as regional checkpoints for the organization and number of epidermal immune populations, but not vice versa. This study reveals new principles of immune organization within the epidermis and elucidates dynamic epithelial-immune interactions that are in place to maintain homeostasis of the epidermis.

Funding Source: Sangbum Park is is a New York Stem Cell Foundation-Druckenmiller Fellow. Research supported by The New York Stem Cell Foundation.

10:11 – 10:22

STEM CELLS DYNAMICS AND SIGNALLING CONTROLLING MECHANICAL FORCE-MEDIATED MOUSE SKIN EPIDERMAL EXPANSION

Aragona, Mariaceleste[1], Simons, Benjamin[2] and Blanpain, Cedric[1]

[1]Stem Cells and Cancer Lab, Université Libre de Bruxelles, Belgium, [2]Cavendish Laboratory, Department of Physics, University of Cambridge, UK

The ability of the skin to expand in response to stretching has been used for decades in reconstructive surgery. Several studies have investigated the response of stretching epidermal cells in vitro. However, it remains unclear how mechanical forces affect epidermal stem cell behaviour in vivo. Here we develop a mouse model allowing the study of the temporal cellular and molecular consequences of stretching the skin epidermis. Using multidisciplinary approaches combining clonal analysis and mathematical modelling, we show that mechanical stretching induces skin expansion by promoting the renewal of epidermal stem cells. This occurs through a structured response in which cell fates are coordinated locally by coupled pairs of stem cells that switch between states primed for renewal or differentiation. With single cells RNA-seq and transcriptional and chromatin profiling we identify the temporal activation of the gene regulatory networks modulated by mechanical forces. Using combination of pharmacological inhibition and several conditional gene loss-of-function mouse mutants, we dissect the signalling pathways and transcription factors that control force-mediated tissue expansion.

10:22 – 10:32

PATIENT ADIPOSE STEM CELL-DERIVED ADIPOCYTES REVEAL GENETIC VARIATION THAT PREDICTS ANTI-DIABETIC DRUG RESPONSE

Hu, Wenxiang[1], Jiang, Chunjie[1], Guan, Dongyin[1], Dierickx, Pieterjan[1], Zhang, Rong[2], Moscati, Arden[3], Nadkarni, Girish[3], Steger, David[1], Loos, Ruth[3], Hu, Cheng[2], Jia, Weiping[2], Soccio, Raymond[1] and Lazar, Mitchell[1]

[1]School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, [2]Shanghai Diabetes Institute, Shanghai Jiao Tong University Affiliated Sixth People's Hospital, Shanghai, China, [3]The Charles Bronfman Institute for Personalized Medicine, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Thiazolidinedione drugs (TZDs) target the transcriptional activity of PPARg to reverse insulin resistance in type 2 diabetes, but side effects limit their clinical use. Here, using human adipose stem cell-derived adipocytes, we demonstrate that single-nucleotide polymorphisms (SNPs) were enriched at sites of patient-specific PPARg binding, which correlated with the individual-specific effects of TZD rosiglitazone (rosi) on gene expression. Rosi induction of ABCA1, which regulates cholesterol metabolism, was dependent upon SNP rs4743771, which modulated PPARg binding by influencing the genomic occupancy of its cooperating factor NFIA. Conversion of rs4743771 from the inactive SNP allele to the active one by CRISPR/Cas9-mediated editing rescued PPARg binding as well as rosi-induction of ABCA1 expression. Moreover, rs4743771 is a major determinant of undesired serum cholesterol increases in rosi-treated diabetics. These data highlight human genetic variation that impacts PPARg genomic occupancy and patient responses to antidiabetic drugs, with implications for developing personalized therapies for metabolic disorders.

10:33 – 10:53

DEVELOPMENT OF A STEM CELL DERIVED ISLET CELL THERAPY FOR THE TREATMENT OF DIABETES

Pagliuca, Felicia

Semma Therapeutics, Boston, MA, USA

Recent advances in the directed differentiation of pluripotent stem cells into functional human pancreatic islets have set the stage for development of a novel cell therapy for the treatment of diabetes. Type 1 diabetes results from the destruction of the insulin-producing beta cells in the pancreatic islet. The development of replacement sources of beta cells, combined with effective methods of delivery back into the patient's body, has the potential to provide a functional cure for this disease. In order to facilitate clinical translation, further optimization and innovation in differentiation technologies, manufacturing process and scale-up, and characterization of stem cell derived islets in preclinical studies have been performed. In parallel, innovative encapsulation solutions using novel materials and device configurations have been developed to solve the challenge of protecting these therapeutics

from immune destruction. Together these technological advances set the stage for the first clinical tests of stem cell-derived islets.

10:53 – 11:13

ISSCR DR SUSAN LIM AWARD FOR OUTSTANDING YOUNG INVESTIGATOR LECTURE: RECONSTRUCTING DEVELOPMENT AND REGENERATION USING SINGLE-CELL GENOMICS

Treutlein, Barbara

Department of Biosystems Science and Engineering, ETH Zurich, Basel, Switzerland

In biology, there are many scenarios where cells transit from one cell state or identity to another. During development, stem cells make fate decisions and differentiate into various mature cell types within a complex organ. During regeneration, differentiated cells can acquire a stem cell state and re-differentiate along multiple lineages. Single-cell genomics provides a set of powerful methods to illuminate the intermediate states that cells go through during these transitions of cellular identities. Here I will discuss our work using single-cell genomics to reconstruct molecular paths during organ development and regeneration. First, I will present our work using single-cell transcriptomics to reconstruct human organoid development and to compare these systems with their primary counterparts. We are now manipulating these systems to study gene function during human development and disease. Second, I will discuss our work exploring regeneration of the axolotl forelimb, where we found that connective tissue cell types in the uninjured adult limb revert to multipotent progenitor states that re-pattern and execute genetic programs observed in the embryonic limb.

SATURDAY, 29 JUNE, 13:15 – 15:15

CONCURRENT IVA: ROAD TO THE CLINIC

Concourse E, Level One

Sponsored by The New York Stem Cell Foundation

13:20 – 13:40

DEVELOPMENT OF TURBULENCE-BASED PRODUCTION OF IPSC-DERIVED PLATELETS TOWARDS CLINICAL APPLICATION AND BEYOND

Eto, Koji

Center for IPS Cell Research and Application (CIRA), Kyoto University, Kyoto, Japan

Induced pluripotent stem cell (iPSC) derived-platelet like particle product (iPS-platelets) is aimed to complement the current blood donor-dependent system, which is expecting the shortage of blood donors in the younger population due to the aging societies in developed countries and platelet transfusion refractoriness due to alloimmune responses. Based on our previous establishment of expandable megakaryocyte cell lines, imMKCLs, from iPSCs, we sought to develop a clinical scale iPS-platelet manufacturing system. However, optimal cultivation of imMKCLs in bioreactors to mature and efficiently yield intact iPS-platelets in feeder cell-free liquid culture remained unsuccessful. To overcome this issue and complete the production system of iPS-platelets, we performed in vivo assay to find a clue and eventually developed a bioreactor based on the novel concept of turbulence. Live imaging of mouse bone marrow showed the presence of turbulence adjacent to megakaryocytes actively releasing platelets. Accordingly, a turbulent flow incorporated bioreactor enabled to efficiently produce intact iPS-platelets. Furthermore, turbulent energy and shear stress were identified as the determinant parameters of the turbulent flow. By scaling up of the bioreactor with those parameters in optimal range, more than 100 billion iPS-platelets were produced for a one unit platelets concentrate (300 billion of platelets, USA). In vitro and in vivo evaluation of iPS-platelets showed the functionality comparable with donor-derived platelets. Interestingly, megakaryocytes released soluble factors MIF, IGFBP2 and NRDC which in turn enhanced the maturation. In conclusion, we achieved the clinical scale production of iPS-platelets using turbulent-flow based bioreactor. We further plan to establish the proof-of-concept of the universal HLA class-I knocked out platelets towards clinical application and the further industrial production.

13:40 – 13:51

GENERATION, CHARACTERIZATION AND TRANSPLANTATION IN A PRECLINICAL MODEL OF HUMAN EMBRYONIC STEM CELL-DERIVED RETINAL PIGMENT EPITHELIAL CELLS LACKING HUMAN LEUKOCYTE ANTIGEN-1 AND -2

Petrus-Reurer, Sandra[1], Winblad, Nerges[2], Gorchs, Laia[3], Chrobok, Michael[4], Wagner, Arnika Kathleen[4], Bartuma, Hammurabi[5], André, Helder[5], Lardner, Emma[5], Aronsson, Monica[5], Westman, Sofie[5], Alici, Evren[4], Kaipe, Helen[6], Kvanta, Anders[5] and Lanner, Fredrik[2]

[1]Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, [2]Clinical Sciences, Intervention and Technology, Karolinska Institutet, Stockholm, Sweden, [3]Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden, [4]Medicine Huddinge, Center for Hematology and Regenerative Medicine, Karolinska Institutet, Stockholm, Sweden, [5]Clinical Neuroscience, Section for Ophtalmology and Vision, Karolinska Institutet, St. Erik Eye Hospital, Stockholm, Sweden, [6]Laboratory Medicine; Clinical Immunology and Transfusion Medicine, Karolinska Institutet, Stockholm, Sweden

Allogeneic human embryonic stem cell (hESC)-derived retinal pigment epithelial (RPE) cells could serve to replace lost tissue in geographic atrophy (GA), the dry advanced form of age-related macular degeneration (AMD). Here we describe a strategy to avoid allogenic mismatched graft immunorejection by the establishment of a beta-2 microglobulin (B2M) knock-out hESC (hESCB2M-/-:CIITA+/+) and a B2M and class-II major histocompatibility complex transactivator (CIITA) double knock-out hESC (hESCB2M-/-;CIITA-/-) lines that can be further differentiated into hESC-RPEB2M-/-;CIITA+/+ and hESC-RPEB2M-/-;CIITA-/-. Derivation of the edited hESC-RPE lines was carried out in xe-

no-free and fully defined conditions using human recombinant laminin-521. Interferon (IFN)-gamma ELISA was performed after co-culture with purified CD8+ and CD4+ T-cells both under stimulatory and non-stimulatory conditions. Chromium release cytotoxicity assay was assessed after co-culture with freshly isolated and interleukin (IL)-2-activated NK cells. Suspensions of differentiated hESC-RPE were transplanted subretinally into the large-eyed rabbit model. Following rejection of transplanted cells, immune cell presence was analyzed by immunohistochemistry and the existence of human-specific antibodies in serum was evaluated by flow cytometry. hESC-RPEB2M-/-;CIITA+/+ and hESC-RPEB2M-/-;CIITA-/- lacked surface human leukocyte antigen-I (HLA-I), or HLA-I and surface human leukocyte antigen-II (HLA-II), respectively, and preserved key properties of native RPE cells. In addition, hESC-RPEB2M-/-;CIITA-/- showed minimal activation of both CD8+ and CD4+ T-cells (whereas hESC-RPEB2M-/-;CIITA+/+ still activated CD4+ T-cells) but retained NK-cell cytotoxicity compared to hESC-RPEB2M+/+;CIITA+/+. After subretinal transplantation in a large-eyed preclinical model without immunosuppression, both hESC-RPEB2M-/-;CIITA+/+ and hESC-RPEB2M-/-;CIITA-/- showed reduced and delayed donor cell rejection. In conclusion, we generated cell lines that lack surface HLA-I and HLA-II with reduced T-cell response together with decreased rejection in a preclinical rabbit model. This emerges as a first step to overcome host-donor mismatch in non-autologous cell-based treatment for AMD.

13:51 – 14:02

PRECISION BRAIN HEALTH: ANSWER ALS IS A POPULATION BASED MULTI-OMICS PROGRAM TO IDENTIFY ALS SUBGROUPS, BIOMARKERS AND DRUGGABLE PATHWAYS USING IPSC TECHNOLOGY

Svendsen, Clive[1], Thompson, Leslie[2], Fraenkel, Ernest[3], Finkbeiner, Steve[4], Van Eyk, Jennifer[5], Cudkowicz, Merit[6], Berry, James[6], Maragakis, Nicholas[7], Sherman, Alex[8], Thompson, Terri[2], Baxi, Emily[7] and Rothstein, Jeffrey[7]

[1]Regenerative Medicine Institute, Cedars-Sinai, Los Angeles, CA, USA, [2]Psychiatry/Neurobiology and Behavior, University California, Irvine, CA, USA, [3]Biological Engineering, Massachusetts Institute of Technology, Boston, MA, USA, [4]Taube/Koret Center for Neurodegenerative Disease Research at Gladstone, J. David Gladstone Institutes, San Francisco, CA, USA, [5]Biomedical Sciences, Cedars-Sinai Medical Center, Los Angeles, CA, USA, [6]Neurology, Massachusetts General Hospital, Boston, MA, USA, [7]Neurology, Johns Hopkins University, Baltimore, MD, USA, [8]Neurological Clinical Research Institute, Massachusetts General Hospital, Boston, MA, USA

Answer ALS is a comprehensive multi-omics approach to ALS to ascertain, at a population level, the clinical-molecular subtypes of ALS. Over 1000 participants, including 100 matched controls, were recruited at 8 national ALS centers and followed longitudinally over one year. Whole genome sequencing was conducted on all participants. In addition, a smartphone-based system was employed to collect deep clinical data including fine motor activity, speech, breathing and linguistics/cognition. In collaboration with IBM Research, speech analysis reveals a strong correlation between clinical progression indices and speech. In parallel, blood-derived iPS cells from ALS patients and controls were used to generate motor neurons which were then subjected to multi-omic analytics including: RNA transcriptomics, epigenomics, proteomics, high content imaging and longitudinal high throughput single cell analyses. From the 1050 participants enrolled to date, > 400 whole genomes have been sequenced and > 400 iPS cell lines generated. Integrated clinical and biological signatures are now being generated using bioinformatics and computational biology to establish patterns that may lead to a better understanding of the underlying mechanisms of disease. Early multi-omics analyses of a trial subset of >130 sporadic and familial ALS and control iPS motor neuron cell lines were used to determine if biological subgroups could be identified. Definite subgrouping was apparent in an initial subset of ~30 patients and appears to be influenced by co-analyses of clinical and biological data sets. C9 patients were found have a prominent defect in nuclear transport, chromatin remodeling and RNA metabolism. For some subgroups, antisense oligonucleotides targeting relevant pathway s could mitigate molecular injury- reverting cells towards control patient profiles. Relevant pathways and molecular targets are being verified in post mortem brain tissue as well as fly models. These studies demonstrate distinct, reliably identifiable subgroups among sporadic and familial ALS patients and the great utility in iPS based approaches to disease pathophysiology and therapy discovery. Open access to early datasets is being instituted (data.answerals.org) and iPS lines, paired with relevant clinical profiles, are available for request.

Funding Source: The Robert Packard Center for ALS Research at Johns Hopkins; The Answer ALS Foundation; ALS Finding A Cure; ALSA; MDA

14:02 – 14:13

PATIENT-DERIVED TUMOR INFILTRATING LYMPHOCYTES CAN BE REPROGRAMMED AND DIFFERENTIATED TO CANCER ANTIGEN SPECIFIC T CELLS

Good, Meghan L.[1], Tamaoki, Naritaka[1], Maeda, Takuya[1], Islam, SM Rafiqul[1], Bosch-Marce, Marta[1], Kruhlak, Michael[2], Pack, Svetlana[3], Bedanova, Nicole[3], Malekzadeh, Parisa[1], Yoseph, Rami[1], Liu, Chengyu[4], Hanada, Kenichi[1], Rosenberg, Steven[1], Vizcardo, Raul[1] and Restifo, Nicholas[1]

[1]Surgery Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [2]Experimental Immunology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [3]Experimental Pathology Laboratory, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA, [4]Transgenic Core, Division of Intramural Research, National Heart Lung and Blood Institute, National Institutes of Health, Bethesda, MD, USA

Adoptive T Cell Transfer (ACT) using cancer antigen specific T cells can be effective for some patients with advanced cancer, but responses may be limited by the transfer of terminally differentiated effector cells. Induced Pluripotent Stem Cells (iPSC)

could provide a limitless source for the in vitro generation of antigen specific T cells. When T cells are reprogrammed to iPSC and redifferentiated to T cell lineage, the iPSC and their progeny retain the same T cell receptor (TCR) gene rearrangement as the original T cell. Therefore, reprogramming tumor infiltrating lymphocytes (TIL) with cancer-antigen specific TCR could generate iPSC-derived T cells for use in ACT. However, T cell-derived iPSC are typically generated from a T cell clone and cancer antigen specific TCR have not previously been identified in iPSC generated by reprogramming bulk TIL (TIL-iPSC). To determine whether TIL-iPSC inherit cancer antigen specific TCR and preserve specificity after differentiation, we reprogrammed TIL to iPSC, differentiated TIL-iPSC to immature T cells using OP9-DLL1 co-culture system, and assessed activation by co-culture with peptide pulsed antigen presenting cells (APC). Using a T cell line and heterogeneous TIL from the infusion bags of several patients, we could reprogram cancer antigen specific T cells to iPSC, which retained rearranged TCR against mutant peptides. TIL-iPSC generated from mutant GBAS reactive T cells were differentiated to CD34+CD43+ hematopoietic progenitors and subsequently CD4-CD8- double negative (DN) and CD4+CD8+ double positive (DP) T cells. TIL-iPSC-derived immature T cells demonstrated antigen-specific upregulation of the activation marker 4-1BB. TIL-iPSC were then generated from the infusion bag of a patient with regression of metastatic colorectal cancer following ACT and differentiated to DN and DP T cells, which are now being tested for antigen-specific activation. We have demonstrated that iPSC with cancer antigen specific TCR can be obtained through reprogramming of heterogeneous TIL, and patient-derived TIL-iPSC can be differentiated to immature T cells which show antigen specific upregulation of 4-1BB. The ability of TIL-iPSC derived T cells to retain antigen specificity is pivotal for the future application of TIL-iPSC derived T cell products in cell-based therapies.

Funding Source: This research was supported by the Intramural Research Program of the US National Cancer Institute and the NIH Center for Regenerative Medicine.

14:13 – 14:24

DEVELOPMENT OF A HUMAN INDUCED PLURIPOTENT STEM CELL-DERIVED PHOTORECEPTOR REPLACEMENT THERAPY FOR INHERITED RETINAL DEGENERATIVE DISEASES

Chase, Lucas[1], Phillips, Joe[2], Shelley, Brandon[1], Wallace, Kyle[1], Dias, Andrew[1], Meline, Benjamin[1], Sternfeld, Matthew[1], Phillips, Jenny[1], Fenn, Marisa[1], Berndt, Erich[1], Jager, Lindsey[4], Ludwig, Allison[3], Nilles, Kelsy[3], Stuedemann, Sara[3], Mack, Amanda[4], Cliff, Carter[1]and Gamm, David[5]

[1]Ocular Cell Therapy, Opsis Therapeutics / Fujifilm-Cellular Dynamics, Inc., Madison, WI, USA, [2]McPherson Eye Research Institute, Waisman Center, University of Wisconsin, Madison, WI, USA, [3]Waisman Center, University of Wisconsin, Madison, WI, USA, [4]iPSC Reprogramming Technologies, Fujifilm-Cellular Dynamics, Inc., Madison, WI, USA, [5]Ophthalmology and Visual Sciences, McPherson Eye Research Institute, Waisman Center, University of Wisconsin, Madison, WI, USA

Built upon the landmark discoveries of human embryonic stem cells (hESC) and induced pluripotent stem cells (hiPSC), the field of regenerative medicine has made significant strides both in terms of drug discovery and cell-based therapies. Photoreceptors are the light-sensing cells of the retina, and ultimately the gatekeepers of vision. In retinal degenerative diseases such as retinitis pigmentosa, photoreceptor dysfunction and death leads to vision loss and ultimately blindness. To address the unmet need for retinal cell replacement, we are developing an allogeneic hiPSC-based cell manufacturing platform for retinal cell types including retinal pigment epithelium (iRPE) and photoreceptor precursor cells (iPRP). To enable these developments, optimized protocols, reagents and processes were established ranging from iPSC reprogramming, retinal differentiation, scale-up culture, cell purification, quality control assays and transplantation techniques. To specifically test the therapeutic potential of highly purified iPRP as a cell replacement therapy for inherited retinal diseases (IRD), we have performed subretinal transplantation studies in an immunocompromised rat model of photoreceptor degeneration (Foxn1/S334ter-3). Over time, transplanted photoreceptors reform an outer nuclear layer, assume more mature rod and cone phenotypes, produce the appropriate synaptic machinery and integrate with the host retina. In addition, as a result of protocol and process improvements, long-term photoreceptor grafts show minimal off-target cells, absence of cell proliferation and lack of ectopic cell migration. To enable a more broadly applicable photoreceptor replacement therapy across a spectrum of IRD patients (rod and cone disorders), the process was further optimized to yield an approximately equal ratio of rods vs. cones and thus enable both replacement strategies. This work represents progress towards a next generation of ocular therapies with a focus on replacing the cells lost during disease with authentic iPSC-derived photoreceptors.

14:24 – 14:35

LONG-TERM IMMUNOPROTECTION AND FUNCTIONAL SURVIVAL OF HUMAN STEM CELL-DERIVED BETA CELLS MICROENCAPSULATED IN ALGINATE WITH CXCL12 IN A HEALTHY NON-HUMAN PRIMATE WITHOUT SYSTEMIC IMMUNOSUPPRESSION

Alagpulinsa, David A.[1], Sobell, Don[2], Engquist, Elise[3], Pop, Ramona[3], Veres, Adrian[3], Shulmister, Rachel[2], Okewunmi, Jeffrey[2], Lei, Ji[4], Markmann, James[4], Melton, Douglas[3] and Poznansky, Mark[2]

[1]Vaccine and Immunotherapy Center, Massachusetts General Hospital, Charlestown, MA, USA, [2]Vaccine and Immunotherapy Center, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA, [3]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [4]Department of Surgery, Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Human stem cell-derived insulin-producing β cells (SC-βcells) represent a practical source for islet replacement to achieve a functional cure for type 1 diabetes. SC-β cells encapsulated in various biomaterials to avoid systemic immunosuppression has

only been shown in rodent models to restore long-term glycemic control. Translation of these approaches in large animals and humans is often problematic due to a robust foreign body response and pericapsular fibrotic overgrowth. We recently reported that SC-β cells alginate-encapsulated with the immunomodulatory and pro-survival chemokine, CXCL12, can restore long-term glycemic correction without systemic immunosuppression in immunocompetent mice. Here, we report long-term functional survival of SC-β cells alginate-microencapsulated with CXCL12 in a non-human primate up to six months without immunosuppression. Microencapsulated SC-β cells were transplanted into the great omentum of a non-diabetic NHP and a cohort of the microcapsules transplanted intraperitoneally in parallel in immunocompetent C57BL/6 diabetic mice. We tracked biochemical, immunologic and hematologic parameters, blood glucose levels, serum C-peptide levels in the NHP over a six-month period. Biopsies of the transplanted microcapsules were recovered at 1, 3 and at 6 months post-transplantation to analyze the survival, functionality and the local immune responses to the microencapsulated cells. The blood glucose levels of the NHP remained stable within normal range throughout the study period without hypoglycemic incidence, while normoglycemia was restored in all transplanted diabetic mice throughout the six-month period. Non-random plasma C-peptide levels of the NHP remained relatively stable (~200 pM to 700 pM). Recovered SC-β cells at 1, 3- and 6-months post-transplantation were glucose-response, with glucose-stimulated insulin secretion indices ranging from 1.33 to 2.31. Majority of microcapsules recovered from the recipient omental sac at all time points were free-floating and had no fibrotic overgrowth. Downstream analysis using RNA sequencing and immunohistochemistry of the differentiation and cell mediated and humoral immune response profiling are ongoing. These preliminary findings have laid the groundwork for ongoing pilot studies in diabetic NHPs.

Funding Source: JDRF

14:35 – 14:46

DEVELOPMENT OF A HUMAN ESC-DERIVED INHIBITORY INTERNEURON CELLULAR THERAPEUTIC TO TREAT REFRACTORY EPILEPSY AND NEUROPATHIC PAIN

Nicholas, Cory R.[1], Bershteyn, Marina[2], Broer, Sonja[3], Chien, China[3], Fuentealba, Luis[3], Havlicek, Steven[2], Kriks, Sonja[2], Lee, Seonok[4], Maury, Yves[2], Nethercott, Hubert[2], Parekh, Mansi[3], Salter, Naomi[4], Spatazza, Julien[3], Wang, Xidao[3], Watson, Michael[4], Priest, Catherine[3], Rubenstein, John[5], Alvarez-Buylla, Arturo[6] and Kriegstein, Arnold[7]

[1]Neurona Therapeutics, San Francisco, CA, USA, [2]Discovery Research, Neurona Therapeutics, South San Francisco, CA, USA, [3]Preclinical Development, Neurona Therapeutics, South San Francisco, CA, USA, [4]Process Sciences, Neurona Therapeutics, South San Francisco, CA, USA, [5]Psychiatry, University of California, San Francisco, CA, USA, [6]Neurological Surgery, University of California, San Francisco, CA, USA, [7]Neurology, University of California, San Francisco, CA, USA

Imbalanced activity of neural circuits is a feature of multiple neurological disorders. Inhibitory interneuron dysfunction and/or depletion can contribute to neural hyperactivity in the affected central nervous system. We are developing a cryopreserved allogeneic cellular therapeutic comprised of clinical-grade human cortical-type GABAergic interneurons to rebalance local neuronal activity and treat chronic, drug-resistant focal epilepsies and neuropathic pain. A combinatorial screening approach identified an animal component-free manufacturing method using small molecules to reproducibly derive post-mitotic interneurons from human embryonic stem cells (hESCs) with >85% efficiency. The interneurons express markers of a medial ganglionic eminence (MGE)-type cortical lineage, including LHX6, MAF, and MAFB. Furthermore, the cortical-type interneurons appropriately down regulate NKX2.1 and do not express markers of other neural lineages. Single-cell RNA sequencing analysis demonstrates a homogeneous composition of hESC-derived interneurons with a similar profile to primary human fetal cortical interneurons. Following transplantation into the rodent brain or spinal cord, the hESC-derived interneurons functionally integrate, mature, and persist for more than one year post-injection. Moreover, the transplanted human interneurons significantly suppress seizure frequency and duration in two preclinical rodent models of chronic temporal lobe epilepsy and alleviate allodynia in two models of chronic neuropathic pain. These results support further preclinical development of the hESC-derived interneuron therapeutic candidate toward potential first in-human clinical trials.

Funding Source: This research was made possible in part by a grant from the California Institute for Regenerative Medicine (Grant Number DISC2-10525).

14:46 – 15:06

BIO-ENGINEERED HESC-DERIVED RETINAL PIGMENTED EPITHELIAL CELL IMPLANT FOR AGE-RELATED MACULAR DEGENERATION

Humayun, Mark, Kashani, Amir**,** Lebkowski, Jane**,** Clegg, Dennis**,** Hinton, David**,** Zhu, Dan Hong**,** Thomas, Biju**,** Pennington, Britney and Mitra, Debbie

Roski Eye Institute, Keck Medicine of USC, Los Angeles, CA, USA

Age-related macular degeneration (AMD) is the leading cause of blindness in elderly patients in western countries. Anti-vascular endothelial growth factors have helped treat neovascular AMD but there are no treatments for advanced atrophic AMD with geographic atrophy (GA). Degeneration of the retinal pigment epithelium (RPE) is seen early in the disease and later becomes absent altogether. As a potential therapeutic intervention for GA, a bioengineered implant was developed consisting of pluripotent stem cell-derived RPE cells polarized on an ultrathin parylene membrane which has the diffusion properties of the native Bruch's membrane. An open-label, FDA cleared, phase 1/2a study is underway to assess the safety and activity of the bioengineered subretinal implant in subjects with vision loss from GA. Key inclusion criteria included diagnosis of NNAMD with GA, pseudophakic status, best-corrected visual acuity of 20/200 or worse (cohort1) or 20/80 to 20/400 (cohort 2) and age 55-85 years. A single investigational implant has been surgically delivered to the area

of RPE loss in the worse eye of each subject. Surgical delivery involved pars plana vitrectomy, subretinal dissection and implantation of the implant using a custom insertion device. Patients have been administered a 60-day course of tacrolimus immunosuppression in the peri-implantation period. The primary outcome measure is safety at 1-year post-implant. Secondary endpoints include assessment of best corrected visual acuity, microperimetry based fixation testing and optical coherence tomography (OCT). Immunological monitoring is being conducted to assess the development of antibody mediated immune responses to HLA antigens on the allogeneic implanted RPE cells. Subjects are being followed with multiple visits throughout the first year and with annual visits during years 2-5. To date, 15 subjects have successfully received the implant. OCT demonstrated an appropriately placed CPCB-RPE1 implant in the subretinal space of GA in all cases. Preliminary results from the demonstrate the feasibility, activity and safety of the implant will be presented. Support for this program has been obtained from the California Institute of Regenerative Medicine and from Santen Pharmaceutical Co, Ltd.

SATURDAY, 29 JUNE, 13:15 – 15:15

CONCURRENT IVB: DEVELOPMENTAL PRINCIPLES FOR STEM CELLS

Concourse F, Level One

13:20 – 13:40

EPIGENETIC REGULATION IN EARLY EMBRYO DEVELOPMENT AND SOMATIC CELL REPROGRAMMING

Gao, Shaorong

Tongji University, Shanghai, China

Epigenetic reprogramming plays important roles in creating a totipotent embryo from terminally differentiated gametes, and as well as in reprogramming of somatic cells to totipotent/pluripotent state. In this talk, I'll briefly summarize the recent progress that we achieved in understanding the mechanism of epigenetic reprogramming in normal embryo development and somatic cell reprogramming. In particular, the regulation and role of histone modifications and DNA methylation in early embryo development and somatic cell reprogramming will be discussed.

13:40 – 13:51

UNDERSTANDING AREA SPECIFIC CELL TYPES IN THE DEVELOPING HUMAN CORTEX

Bhaduri, Aparna[1], Andrews, Madeline[2], Eze, Ugomma[2], Kriegstein, Arnold[2], Nowakowski, Tomasz[3] and Sandoval Espinosa, Carmen[2]

[1]Regeneration Medicine, Neurology, University of California, San Francisco, CA, USA, [2]Regeneration Medicine, University of California, San Francisco, CA, USA, [3]Anatomy, University of California, San Francisco, CA, USA

The human brain is composed of diverse cell types across brain regions that enable unique capabilities. Within the brain, the cerebral cortex is responsible for a number of cognitive functions and sensory integration, with distinct cortical regions controlling a variety of tasks including motion, vision, speech, and judgment. Recent work exploring the cell types of two distinct cortical regions in the human and mouse suggests that excitatory neurons are area specific and emerge during developmental stages of peak neurogenesis. However, further characterization of cortical arealization is required to understand whether gradients, sharp boundaries, or some combination of patterns describes the areal distribution of neurons and other cortical cell types. Importantly, accurate modeling of cortical development and understanding biological constraints for any attempts at stem cell therapies requires characterizing when neuroepithelia or radial glia transition from a uniform population into areal specific progenitors, and the degree to which they are committed to an areal fate. In order to comprehensively characterize the areal diversity of cell types during human development, we performed single-cell sequencing of a variety of cortical regions and sub-cortical structures from 20 intact first and second trimester brain samples. With over a million cells, we identify hundreds of cells types including temporal and area specific neurons, interneurons and radial glia populations, as well as a number of subtypes from each of these classes that are expressed across most cortical areas. Additionally, we find a small number of subpopulations of neuroepithelial cells and identify several key pathways that may regulate the switch from neuroepithelia to radial glia identity. Together, these datasets suggest a model of both area restricted progenitor populations as well as radial glia cell types that are observed across cortical regions, suggesting an orchestrated interplay of fate determination that gives rise to the required cell diversity of the human cerebral cortex.

Funding Source: This work is funded by the NIH BRAIN Initiative U01MH114825 as well as the NIH NINDS F32NS103266

13:51 – 14:02

DISTINCT STAGE DEPENDENT REQUIREMENTS FOR RUNX1 AND GROUP F SOX GENES DURING HUMAN HAEMATOPOIESIS

Bruveris, Freya F.[1], Ng, Elizabeth[1], Leitoguinho, Ana Rita[1], Motazedian, Ali[2], Vlahos, Katerina[3], Sourris, Koula[3], McDonald, Penelope[4], Davidson, Nadia[5], Oshlack, Alicia[5], Stanley, Edouard[2] and Elefanty, Andrew[1]

[1]Blood Development, Murdoch Childrens Research Institute, Melbourne, Australia, [2]Immune Development, Murdoch Children's Research Institute, Melbourne, Australia, [3]iPS Core Facility, Murdoch Children's Research Institute, Melbourne, Australia, [4]Kidney Development, Murdoch Children's Research Institute, Melbourne, Australia, [5]Bioinformatics, Murdoch Children's Research Institute, Melbourne, Australia

We modeled human haematopoiesis using in vitro differentiation of human pluripotent stem cell (hPSCs) reporter lines, following endothelial (SOX17) and haematopoietic (RUNX1C) development. The blast colony forming cell (BL-CFC) assay, that mimics extra-embryonic yolk sac haematopoiesis, revealed that SOX17-

CD34+CD43- endothelial-like cells were the major source of haematopoietic progeny while SOX17+CD34+CD43- cells mostly formed endothelium. Deletion of RUNX1 permitted a single wave of erythropoiesis that was GFI1/1B-dependent. Conversely, deletion of SOX17 or all Group F SOX genes did not influence formation of BL-CFCs, or their endothelial or haematopoietic progeny. Differentiation of GROUP F SOX- deficient cell lines towards an intra-embryonic fate revealed severe defects in vascular patterning and reduced haemogenic capacity of the endothelium, partially mediated by reduced NOTCH signaling and recapitulated by inhibiting γ-secretase. Our data indicate distinct haemogenic and endothelial precursors in differentiating hPSCs and characterise the requirements for RUNX1 and SOX genes during extra- and intra-embryonic human haematopoiesis.

14:02 – 14:13

CELL FATE DETERMINATION OF ENDOCRINE PROGENITORS IN MURINE AND HUMAN PANCREATIC DEVELOPMENT

Sneddon, Julie B.[1], Wong, Daniel[2], Byrnes, Lauren[2], Peixoto, Gabriel[2], Bouza, Jacquelyn[2] and McMullen, Reed[2]

[1]Diabetes Center, Broad Stem Cell Center, Department of Anatomy, University of California, San Francisco, CA, USA, [2]Diabetes Center, University of California, San Francisco, CA, USA

The mammalian pancreas arises through a series of coordinated events, including specification, proliferation, differentiation, and maturation. Despite substantial progress in understanding some of the signaling events underlying these processes, a global view of the timing and dynamics of these processes in the developing pancreas was not previously possible. Utilizing a combination of single-cell RNA-sequencing, immunohistochemistry, in situ hybridization, and genetic lineage tracing, we have constructed a transcriptional atlas of the developing pancreas. This atlas serves as a guidebook for endocrine development, identifying novel intermediate progenitor states and lineage relationships, and characterizing cellular dynamics across developmental time. We have verified the existence of novel endocrine cell states in mouse and human fetal tissue and during the directed differentiation of human embryonic stem cells towards a pancreatic beta cell fate. Furthermore, our data suggest that in contrast to the previous models, lineage allocation of hormone-expressing cells occurs at a novel intermediate endocrine progenitor cell stage that we have identified, marked by the expression of the transcription factor Fev. Lastly, by combining the directed differentiation of human pluripotent stem cells to the pancreatic beta cell lineage, along with CRISPR/Cas9 gene editing, we have now built a platform for modeling and manipulating the novel candidate lineage regulators found in this study. Deeper knowledge of these lineage decisions may substantially improve directed differentiation efforts to efficiently generate functional beta cells for cellular replacement therapy for people with diabetes. This study establishes a roadmap of pancreatic development and highlights the power of combining single-cell transcriptomic information with in vivo lineage tracing and genome editing to understanding lineage dynamics in developing organs.

Funding Source: We gratefully acknowledge funding from the Treadwell Foundation and from the UCSF Program for Breakthrough Biomedical Research (PBBR), which is partially funded by the Sandler Foundation.

14:13 – 14:24

X CHROMOSOME DYNAMICS FROM PREIMPLANTATION HUMAN EMBRYOS TO DEVELOPING PRIMORDIAL GERM CELLS

Chitiashvili, Tsotne[1], Dror, Iris[1], Liebscher, Simone[2], Schenke-Layland, Katja[2], Plath, Kathrin[1] and Clark, Amander[3]

[1]Department of Biological Chemistry, University of California, Los Angeles, CA, USA, [2]Department of Women's Health, Research Institute for Women's Health, Eberhard Karls University Tuebingen, Germany, [3]Molecular Cell and Developmental Biology Department, University of California, Los Angeles, CA, USA

Dosage compensation of genes on the X chromosome is one of the most important epigenetic events in female mammalian development. Although the mouse has served as the primary model to study the regulation of X chromosome dosage compensation during pre- and post-implantation development and in stem cell differentiation, it is now appreciated that these mechanisms are not fully conserved during human development. For instance, the mechanism of dosage compensation and remodeling of the epigenetic state of the X chromosome differ between human and mouse pre-implantation embryos and pluripotent stem cells. This raises the question of how X-chromosome dosage is regulated in human female primordial germ cells (hPGCs) - since in the mouse PGCs have a similar epigenetic state of the X as pluripotent cells. Thus, it is unclear whether hPGCs remodel the X-chromosome similar to pre-implantation human embryos or whether they follow the dynamics of the mouse. To address this, we took an unbiased approach and sequenced ~50,000 single cells from ten human fetal gonads including ~2100 prenatal human germline cells. We show that X-linked genes are biallelically expressed and that their dosage is higher in female relative to male hPGCs, from as early as 7 weeks of human development. Over time of PGC development female X-linked gene dosage drops. Additionally, we show that the active X chr's in female hPGCs are coated with the lncRNAs XACT and XIST, demonstrating that hPGCs share X chromosome regulatory mechanisms with human pre-implantation embryos. Finally, we analyzed hPG-like cells (hPGCLCs) generated from primed human pluripotent stem cells (hPSCs) and show that hPGCLCs inherit a similar X-state as the starting hPSCs, suggesting that hPGCLCs are either epigenetically younger than hPGCs of the 7-week embryo or that the X status in primed hPSCs yields patterns of incorrect X state in hPGCLCs. Overall, our work suggests that similar mechanisms of X chromosome regulation occur in hPGCs and human pre-implantation embryos and that hPGCLCs do not yet accurately recapitulate the epigenetic status of the X-chromosome in hPGCs in vivo. Our data show that the X state will be a unique readout for staging proper hPGC establishment from hPSCs, and strengthen

the notion that the pluripotent and germ cell states are similar in their epigenetic regulation.

14:24 – 14:35

PROPERTY OF EMBRYONIC HUMAN OLIGODENDROCYTE PRECURSOR CELLS AND MECHANISM OF HUMAN WHITE MATTER EXPANSION

Huang, Wei, Bhaduri, Aparna, Velmeshev, Dmitry and Kriegstein, Arnold

Eli and Edythe Broad Center of Regeneration Medicine and Stem Cell Research, University of California, San Francisco, CA, USA

One of the most prominent features of the human brain is the fabulous size of the cerebral cortex. Previous studies showed that both oRGs and IPCs play important roles in the human neurogenesis and grey matter expansion. But the mechanism of the human oligodendrocyte genesis and white matter expansion remain largely unknown. Here by single-cell RNA-seq of live human cortical cells and IHC on fixed human brain slices in the late 2nd trimester, we find evidences for local generation of OPCs in the developing cortex. Moreover, we find lineage-committed IPCs (O-IPCs) that produce OPCs in the human cortex. We also reconstruct the developmental trajectory of oligodendrocyte genesis and interpret the lineage relationship between neurogenesis and gliogenesis. Further study on cultured brain slices indicates that both O-IPCs and OPCs in the embryonic human brain undergo multiple rounds of division and act as transit amplifier to increase the progenitor cell pool, which might contribute to the white matter expansion. And one of the marker genes of OPCs, PCDH15, is required for the dispersion of OPCs after cell division.

14:35 – 14:46

THE YAP/TEAD TRANSCRIPTION FACTOR COMPLEX CONTROLS A SELF-RENEWAL PROGRAM IN THE SENSORY PROGENITORS OF THE MOUSE ORGAN OF CORTI

Gnedeva, Ksenia[1], Wang, Xizi[1], McGovern, Melissa[2], Barton, Matthew[3], Llamas, Juan[1], Yu, Haoze[1], Tao, Litao[1], Trecek, Talon[1], Monroe, Tanner[4], Makmura, Welly[1], Martin, James[4], Warchol, Mark[5] Groves, Andy[2], and Segil, Neil[1]

[1]Regenerative Medicine and Stem Cell Research, Keck School of Medicine University of Southern California, Los Angeles, CA, USA, [2]Stem Cells, Regeneration and Tissue Repair, Baylor College of Medicine, Baylor, TX, USA, [3]Audiology and Communication Sciences, Washington University School of Medicine, St. Louis, MO, USA, [4]Molecular Physiology and Biophysics, Baylor College of Medicine, Baylor, TX, USA, [5]Department of Otolaryngology-Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO, USA

In the developing organ of Corti, establishment of a prosensory domain requires a spatio-temporal separation of cell-cycle exit and fate determination, making it a unique system to dissect the molecular events that control a switch from self-renewal to terminal differentiation. Using single cell RNA-sequencing we identified two distinct populations corresponding to the actively cycling and cell-cycle arrested sensory progenitors, and assessed gene expression changes and changes in chromatin accessibility (ATAC-seq) to understand the molecular basis for this transition. Within the differentially regulated open chromatin associated with self-renewing progenitors, the binding motif for Tead transcription factors was highly enriched. Although we found that Tead transcription factors are continuously expressed in the sensory domain of the cochlear duct, their co-activator, and the target of Hippo signaling - Yap1 - is degraded coinciding spatially and temporally with the characteristic wave of progenitor cell-cycle exit. Conditional loss of Yap in the inner ear results in great reduction of the sensory organ size, likely resulting from a premature cell-cycle exit. Progenitor cell differentiation, nevertheless, is unaffected in the absence of Yap, as hair cells and supporting cells are specified normally. We also show that constitutive activation of Yap signaling prevents progenitor cell-cycle exit, and results in loss of differentiation and overgrowth of the sensory epithelia. Finally, we demonstrate a role for Yap/Tead signaling during regeneration in the neonatal inner ear. We show that after hair cell damage, nuclear accumulation of Yap is triggered in proliferating supporting cells; while overexpression of a dominant negative peptide, that prevents Yap/Tead interaction, abolishes this regenerative response. Collectively our data suggest the Yap/Tead transcription factor complex directly control a progenitor self-renewal gene network in the nascent inner ear sensory organs. This leads to the hypothesis that growth of the organ of Corti during development, as well as regeneration of hair cells, may be constrained by physical forces impinging on the sensory epithelia, and signaled through the Hippo pathway.

Funding Source: National Institute of Deafness and Communication Disorders (1R21DC016984-01)

14:46 – 15:06

BUILDING MUSCLES: FROM SOMITES TO MUSCULAR DYSTROPHIES

Pourquié, Olivier

Harvard University/Brigham and Women's Hospital, Boston, MA, USA

Skeletal muscles of the body arise from segmented embryonic structures called somites. The segmental or metameric organization of somites is established early in embryogenesis when pairs of embryonic segments are rhythmically produced by the presomitic mesoderm (PSM). The tempo of somite formation is controlled by a molecular oscillator known as the segmentation clock. While this oscillator has been well characterized in model organisms, whether a similar oscillator exists in humans remains unknown. We have previously shown that human embryonic stem (ES) cells or induced pluripotent stem (iPS) cells can differentiate in vitro into PSM upon activation of the Wnt signaling pathway combined with BMP inhibition. We show that these human PSM cells exhibit Notch and YAP-dependent oscillations of the cyclic gene HES7 with a 5-hour period. Single cell RNA-sequencing comparison of the differentiating iPS cells with mouse PSM re-

veals that human PSM cells follow a similar differentiation path and exhibit a remarkably coordinated differentiation sequence. When these PSM-like cells are allowed to develop further in vitro, they produce striated, millimeter-long muscle fibers together with satellite-like cells. We will present the cellular and molecular characterization and the regenerative potential of these human PAX7+ satellite-like cells produced in vitro. We have also used human isogenic iPS lines differentiated to a myogenic fate to establish an in vitro model of Duchenne Muscular Dystrophy recapitulating several key features of this pathology.

SATURDAY, 29 JUNE, 13:15 – 15:15

CONCURRENT IVC: STEM CELL METABOLISM

Room 502, Level Two

13:20 – 13:40

METABOLIC UNDERPINNINGS OF TOTIPOTENCY

Brickman, Joshua M.[1], Bone, Robert**,** Riveiro, Alba**,** Heckenback, Indra**,** Trusina, Ala**,** Morgani, Sophie**[2],** Lowndes, Molly**,** Nielson, Michael**,** Sulek , Karolina**,** Mann, Matthias**,** Dall, Morten and Treebak, Jonas

[1]University of Copenhagen, Denmark, [2]Memorial Sloan Kettering Cancer Center, New York, NY, USA

Embryonic stem cells (ESCs) are immortal cell lines derived from the peri-implantation mammalian embryo. They are generally characterized as pluriptotent, able to contribute to the embryonic, but not extra-embryonic lineages. We have previously shown that we could isolate single ESCs that are totipotent, able to colonize the embryonic, and both extra-embryonic lineages. Totipotent ESCs arise under distinct conditions and we could identify them based on the simultaneous expression of pluripotency factors, and extra-embryonic transcripts as reported by a particularly sensitive fluorescent reporter for the primitive endoderm maker, Hhex. Based on transcriptomic and proteomic analysis of ESCs in different conditions that could give rise to totipotent cells, we identified metabolic regulators, in particular lipid metabolism, as a unique signature of this state. Here we discuss how this altered metabolic activity is translated into enhanced functional potency. Common to all conditions that promoted totipotency, in addition to direct assessment of Hhex positive fractions, was higher rates of oxidative phosphorylation (OXPHOS). Moreover, the stimulation of increased OXPHOS in conventional conditions for pluripotent culture, resulted in increased co-expression of pluripotent factors and extra-embryonic RNA alongside an enhanced capacity of these cells to contribute to both embryonic and extra-embryonic lineages. Using these cultures with increased OXPHOS as a model, we have characterized the signaling, metabolomic and transcriptomic changes associated with the enhanced potency of these cells and have used machine learning to link changing metabolism to specific pathways associated with early embryonic development.

13:40 – 13:51

LIPID DEPRIVATION INDUCES A STABLE NAÏVE-TO-PRIMED INTERMEDIATE STATE OF PLURIPOTENCY IN HUMAN PSC

Cornacchia, Daniela[1], Zhang, Chao[2], Zimmer, Bastian[3], Chung, Sun Young[3], Fan, Yujie[3], Soliman, Mohamed[3], Tchieu, Jason[3], Chambers, Stuart[3], Shah, Hardik[4], Paull, Daniel[5], Konrad, Csaba[6], Vincendeau, Michelle[3], Noggle, Scott[7], Manfredi, Giovanni[6], Finley, Lydia[3], Cross, Justin[4], Betel, Doron[2] and Studer, Lorenz[3]

[1]Center for Stem Cell Biology, Sloan Kettering Institute for Cancer Research, New York, NY, USA, [2]Institute for Computational Biomedicine, Weill Cornell Medicine, New York, NY, USA, [3]Center for Stem Cell Biology, Sloan Kettering Institute, New York, NY, USA, [4]Cancer Metabolism Center, Sloan Kettering Institute, New York, NY, USA, [5]New York Stem Cell Foundation Global Stem Cell Array, New York Stem Cell Foundation, New York, NY, USA, [6]Brain and Mind Research Institute, Weill Cornell Medicine, New York, NY, USA, [7]New York Stem Cell Foundation, New York, NY, USA

Current challenges in capturing naïve human pluripotent stem cells (hPSC) suggest that the regulation of the naïve-to-primed pluripotency transition in humans remains incompletely understood. Here, we report on the unexpected finding that hPSC culture in chemically defined Essential8™ medium (E8) induces a naïve-to-primed intermediate state of pluripotency characterized by increased expression of core pluripotency markers and key naïve markers, a naïve mitochondrial and bioenergetic profile as well as naïve-to-primed intermediate epigenomic traits, high clonogenicity and enhanced neuroectodermal differentiation. Transcriptionally, E8-hPSC are marked by activated lipid biosynthesis and suppressed MAPK/TGFβ gene expression. Paradoxically, ERK signaling in E8 hPSC is endogenously suppressed, despite high levels of exogenous FGF2. Naïve-to-primed intermediate traits and ERK inhibition in E8-hPSC are dependent on lipid-free culture conditions and are rapidly lost upon lipid exposure. Short-term pharmacological ERK inhibition restores intermediate features even in presence of lipids. Finally, we identify de novo lipogenesis and suppressed MAPK/TGFβ expression as a common transcriptional signature of E8-hPSC and the human pre-implantation epiblast in vivo. These findings implicate exogenous lipid availability in the regulation of the human naïve-to-primed transition and define E8-hPSC as a stable naïve-to-primed intermediary pluripotent state.

13:51 – 14:02

A NOVEL INSULIN-INDEPENDENT GLUCOSE LOWERING ACTIVITY

Rivera-Feliciano, Jose[1], Rosado-Olivieri, Edwin[1], Kunz, Timothy[1] and Melton, Douglas[2]

[1]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [2]Stem Cell and Regenerative Biology, Harvard University and HHMI, Cambridge, MA, USA

To address the widespread incidence of diabetes, our lab developed a protocol to direct the differentiation of human embryonic or induced pluripotent stem cells into functional, insulin expressing beta-cells. These Stem Cell-derived beta-cells (SC-beta) can be used to study beta-cell development, function, and physiology, and they have the potential to treat diabetes by cell transplantation. To identify novel secreted and transmembrane proteins, we developed a technique called Endoplasmic Reticulum Sequencing (ER-seq) that enriches RNAs of secreted/transmembrane proteins by physically isolating actively translating ribosomes at the surface of the endoplasmic reticulum. We applied the ER-seq method to SC-beta cells and sequenced the associated mRNA to find novel hormones that regulate glucose metabolism. Using this method, we identified an uncharacterized protein coding gene, which we called ERseq08. ERseq08 mRNA and protein is most abundant in the beta cells of mice and humans. Delivery of plasmid DNA expressing ERseq08 into mouse liver, via hydrodynamic tail vein injection, reduces blood glucose levels in glucose tolerance tests. Surprisingly, it does so independent of insulin action as it lowers blood glucose in the presence of the potent insulin receptor antagonist, S961. Additionally, ERseq08 can lower blood glucose levels in a beta-cell ablation model--Streptozotocin treated mice. In mice, ERseq08 lowers blood glucose in a glucose dependent manner without causing hypoglycemia. While it is well known that pancreatic beta cells make insulin, this new finding with ERseq08 may represent a second system by which beta-cells regulate glucose metabolism. This discovery has the potential to impact the development of new therapeutics for all diabetics and could complement or replace some of the major drugs used as the current standard of care in diabetes treatments.

14:02 – 14:13

ISOCITRATE DEHYDROGENASE 1 MAINTAINS QUIESCENCE OF MURINE HAIR FOLLICLE STEM CELLS

Ambrus, Aaron M[1], Jelinek, David[1], Gallagher, Elizabeth[1], Lemons, Johanna[2], Guinn, Emily[1] and Coller, Hilary[1]

[1]Molecular, Cell, and Developmental Biology, University of California, Los Angeles, CA, USA, [2]Chemistry, Princeton University, Princeton, NJ, USA

Our skin serves as a barrier to protect us from pathogens, extreme temperatures and ultraviolet radiation. Hair is an important appendage of skin that enhances this protection. Residing in the dermis layer of the skin, the hair follicle houses the hair and controls its growth. Hair follicle stem cells are located in a niche known as the bulge. These bulge stem cells are quiescent during the hair follicles resting stage, telogen. During the transition from telogen to anagen, a subset of these quiescent bulge stem cells will re-enter the cell cycle and move downward, proliferating rapidly. These proliferating cells will then terminally differentiate, giving rise to all of the cell types required to form a new hair. There is a growing realization of the importance of metabolic pathways in cell cycle control. Based on findings in proliferating and quiescent cells in culture, we used in situ metabolic activity assays to monitor the activity of metabolic enzymes in mouse skin. We found that Isocitrate Dehydrogenase (IDH) activity is high in the bulge stem cells of mouse skin. This high level of IDH activity was rapidly lost when quiescent stem cells were induced to proliferate during the anagen phase of the hair follicle cycle to produce transit-amplifying cells. Thus, we hypothesized that IDH activity may be required to maintain bulge stem cells in a quiescent state. To test this, we treated mouse skin with IDH inhibitors and observed an increase in proliferation within the skin, including the stem cells. We then evaluated the impact of IDH1 deletion on two in vivo models in which we could study quiescence to proliferation transitions: hair growth and wound healing. With regard to hair growth, we found that mice deficient for IDH progressed more rapidly through their hair follicle cycle than control mice. With respect to wound healing, we found that IDH1-mutant mice initially healed their wounds more rapidly compared to control mice. Taken together, our results demonstrate IDH1 inactivation leads to a hyper-proliferative phenotype, suggesting that IDH maintains hair follicle stem cell quiescence. Our results suggest IDH as a new metabolic control point, which may suggest strategies for hair growth therapy and may have implications for treatment of disorders characterized by depletion of critical cell populations.

Funding Source: National Center for Advancing Translational Sciences UCLA CTSI Grant UL1TR000124. Jonsson Comprehensive Cancer Center Impact Grant NIH R01 PIs Lowry and Christofk 1 R01 AR070245-01A1

14:13 – 14:24

MAPPING AND PHARMACOLOGIC TARGETING OF METABOLIC PATHWAYS TO REJUVENATE AGED MUSCLE STEM CELLS

Raval, Manmeet H, Cheng, Pin-Chung and Rodgers, Joseph

Stem Cell Biology and Regenerative Medicine, University of Southern California, Los Angeles, CA, USA

Age-associated decline in healing capacity is attributable to loss of stem cell regenerative function. Skeletal muscle stem cells (MuSCs) or satellite cells are tissue resident stem cells required for skeletal muscle repair and regeneration. Injury initiates a cascade in which tissue resident MuSCs “activate”. Activated MuSCs commit to the cell cycle and undergo division, proliferation, and differentiation to ultimately regenerate muscle. We and others have shown that MuSC activation slows with aging and this correlates with impaired healing. Importantly, our previous work has shown that increasing the speed of MuSC activation is sufficient to improve the speed and efficiency of tissue repair. Suggesting that MuSC activation is a target to design therapies to improve healing. However, the molecular and cellular mechanism that regulates MuSC activation was unknown. Here, we show that the metabolic properties of MuSCs directly control the speed of their activation. We used primary MuSCs isolated from mouse models of aging (juvenile, adult and old), to map metabolic function (oxidative phosphorylation) and cell cycle activation (G0 to G1 transition) kinetics. Using Seahorse flux analyzer, we found that freshly isolated MuSCs from old animals display a significantly lower basal oxidative metabolic rates compared to MuSCs from juvenile and adult animals. We also found that old MuSCs take significantly longer time to undergo G0 to G1 transition (measured by pRB immunostaining) as compared to juvenile and adult MuSCs. Interestingly, we found that culturing old MuSCs with

pharmacologic modulators of metabolism, to increase metabolic substrate flux into the mitochondria, was sufficient to increase G0 to G1 transition speed and activation speed to the levels of adult MuSCs. Similarly, decreasing metabolic substrate flux to the mitochondria in juvenile MuSCs was sufficient to slow their activation speed to the level of old MuSCs. Overall, these results indicate a direct relationship between MuSC mitochondrial metabolic flux, G0 to G1 transition kinetics, and activation speed, suggesting that changes in metabolic flux underlie age-associated defects in MuSCs activation and muscle regenerative functions.

Funding Source: NIH/NIA (AG041764) and The Donald E. and Delia B. Baxter Foundation to J.T.R.

14:24 – 14:35

NON-OXIDATIVE BRANCH OF PENTOSE PHOSPHATE PATHWAY IS IMPORTANT FOR NEURAL DIFFERENTIATION OF HUMAN INDUCED PLURIPOTENT STEM CELLS

Gu, Wen[1], Lowry, William[2], Plath, Kathrin[3] and DeBerardinis, Ralph[1]

[1]Children's Research Institute/ Howard Hughes Medical Institute, University of Texas Southwestern Medical Center, Dallas, TX, USA, [2]Molecular, Cell, and Developmental Biology, University of California, Los Angeles, CA, USA, [3]Biological Chemistry, University of California, Los Angeles, CA, USA

Metabolism changes drastically during cellular specification, and the dysregulation of which may lead to inborn errors of metabolism in patients, currently a handful of which could be detected by newborn screening in the clinic. To understand the role of metabolic regulation during neural differentiation, we derived induced pluripotent stem cells (iPSCs) from consented patients with or without known neurological symptoms, such as early-onset encephalopathy, and then differentiated these cells into neural progenitor cells (NPCs) and neuron-like cells. We first conducted mass spectrometry-based metabolomics experiments, and identified that the levels of pentose phosphate pathway (PPP) metabolites were changed in NPCs compared with isogenic fibroblasts and iPSCs. Consistently, mRNA level of a particular PPP gene, TKTL1 (Transketolase Like 1), was upregulated in neural lineages among a panel of cell lines and patient tissues. To determine whether and how NPCs utilize glucose for PPP activities, we cultured cells with 13C-glucose and performed metabolic flux analysis. We detected increased glycolytic flux through the non-oxidative branch of PPP in NPCs, and the labeling pattern of erythrose, pentose, and sedoheptulose phosphates is consistent with increased transketolase activities in NPCs. To determine the functional consequences of TKTL1 deficiency during neural specification, we generated TKTL1 knockout NPCs with CRISPR/Cas9, and differentiated these cells together with their wildtype counterparts into neuron-like cells. We found that TKTL1 loss-of-function disrupts the non-oxidative PPP flux, induces metabolic stress, and affects differentiation potential of NPCs into neuron-like cells. To further understand the mechanism by which TKTL1 deficiency affects neural differentiation, we examined the metabolic flux in nucleotide and NAD+ biosynthesis pathways, and found that the ribose units derived from PPP are important for the biosynthesis of purines, pyrimidines, and NAD+ in NPCs, indicating that increased biosynthesis of these macromolecules might be required for neural differentiation. Together, our findings demonstrate that a previously lesser studied enzyme, TKTL1, is important for non-oxidative PPP activity and plays a functional role in regulating neuronal differentiation.

14:35 – 14:46

REPROGRAMMING HEMATOPOIETIC STEM CELL FUNCTION VIA MODULATION OF MITOCHONDRIAL ACTIVITY

Girotra, Mukul[1], Rincon-Restrepo, Marcela[1], Oggier, Aurelien[2], Coukos, George[1], Naveiras, Olaia[2], Rezzi, Serge[3] and Vannini, Nicola[1]

[1]Ludwig Institute for Cancer Research, University of Lausanne, Epalinges, Switzerland, [2]SV-ISREC, École Polytechnique Fédérale de Lausanne, Switzerland, [3]Nestlé Institute of Health Sciences SA, Lausanne, Switzerland

A fine balance of quiescence, self-renewal and differentiation is key to preserve the hematopoietic stem cell (HSC) pool, and maintain lifelong production of all mature blood cells. In recent years cellular metabolism has emerged as a crucial regulator of HSC fate. HSCs differ from their committed progeny by relying primarily on anaerobic glycolysis rather than mitochondrial oxidative phosphorylation for energy production. However, whether this change in the metabolic program is the cause or a consequence of the unique function of HSCs remains unknown. We previously demonstrated that modulation of mitochondrial metabolism influences HSC fate, by chemically uncoupling the electron transport chain we were able to maintain HSC function in culture conditions that normally induce rapid differentiation.Moreover, we demonstrated that modulation of mitochondrial activity in ex-vivo cultured human HSCs, via NAD+ boosting agent Nicotinamide Riboside (NR), results in better long-term blood production in serially transplanted humanized mice. Strikingly, in vivo administration of NR dramatically improves survival and accelerates blood recovery in HSC-transplanted mice. Here we proceeded to carry out a screen, using mitochondrial activity as readout, to identify metabolic modulators that enhance HSC activity and function. We found two novel candidates, a natural compound and a vitamin precursor, that modulate mitochondrial activity in both mouse and human HSCs, and resulted in enhanced HSC function post bone-marrow transplantation. Interestingly, we found that these candidates mediate their effects partially via inducing mitophagy, supporting recent studies highlighting the role of mitophagy as a key driver of HSC function. Moreover, our preliminary analysis reveals that they mediate similar effects in aged human HSCs, making them ideal candidates to revert age-associated myeloid bias in human patients. Our data thus reveal a causal relationship between mitochondrial metabolism, mitophagy and fate choice in HSCs, and also provide a valuable tool to identify optimal ex vivo conditions for HSC expansion and improve the outcome for patients suffering from bone marrow insufficiency.

14:46 – 15:06

ADAPTIVE METABOLIC PROGRAMMING PROMOTES LIVER CANCER CELL PROLIFERATION

Han, Weiping

Singapore Bioimaging Consortium, Singapore

Metabolic state is a key determinant of cell fate and proliferation. Unlike stem cells, which must conform to programmed pathways to achieve defined fates, cancer cells adopt specific metabolic states through adaptive metabolic programming to meet the cellular requirements for their uncontrolled proliferation. Such metabolic states for cancer cells result from the complex interplay of genetic mutations, epigenetic deregulation, and metabolic reprogramming. It is hoped that understanding the functional integration of the signaling pathways relevant to liver cancer with the altered metabolic network will reveal novel approaches to cancer therapy. We choose to focus on liver cancer because it is a leading cause of cancer-related death worldwide and there is very limited treatment option available. Considering that tumors display profound and highly adaptive changes in cellular metabolism, we used a comprehensive 'multi-omics' approach across multiple rodent models of HCC, and studied metabolic pathways and enzymes that may be directed in potential therapeutic development.

SATURDAY, 29 JUNE, 13:15 – 15:15

CONCURRENT IVD: MECHANISMS OF TRANSDIFFERENTIATION

Room 408A, Level Two

13:20 – 13:40

DISSECTING CELL PLASTICITY, ONE CELL AT A TIME

Graf, Thomas, Francesconi, Mirko**,** Di Stefano, Buno and Lehner, Ben

Center for Genomic Regulation, Barcelona, Spain

Based on the low frequencies of transcription factor (TF)-induced reprogramming of somatic cells into iPS cells typically observed, Yamanaka introduced the 'elite' cell model. Indeed, certain types of blood cell progenitors, such as GMPs, qualify as 'elite' cells as their reprogramming efficiency exceeds 25%, while many other cell types are nearly resistant. This raises the question as to whether 'elite' cells are generally plastic, i.e., whether they are also highly susceptible to TF-induced transdifferentiation. Alternatively, there might be different types of 'elite' cells, such as cells prone to reprogramming and others biased for transdifferentiation. We have investigated this question using a single cell approach with pre-B cells induced to convert either into macrophages or iPS cells. Transdifferentiation was induced by the sustained exposure of the cells to C/EBPa, while reprogramming into iPS cells was achieved by a pulse of C/EBPa followed by the Yamanaka factor cocktail OSKM. Although both protocols yielded single cell trajectories consistent with deterministic processes we observed an asynchrony in the speed by which the cells acquire a new fate. We traced this asynchrony to a heterogeneity in the starting pre-B cell population, with large pre-B cells reprogramming rapidly and efficiently into iPS cells and more slowly into macrophages. In contrast, small pre-B cells transdifferentiated rapidly into macrophages but were largely resistant to reprogramming. These differences correlated most strongly with the level of Myc in the starting population, with large pre-B cells being Myc high and small pre-B cells being Myc low. Our data suggest that cells can exhibit different types of plasticity and raise the possibility that TF-induced cell reprogramming and transdifferentiation obey different rules.

13:40 – 13:51

SINGLE-CELL BASED COMPUTATIONAL APPROACH TO IDENTIFY CELL SUBPOPULATION IDENTITY TRANSCRIPTIONAL CORE: APPLICATIONS TO CELLULAR CONVERSION

del Sol, Antonio[1], Okawa, Satoshi[2], Ravichandran, Srikanth[2] and Arenas, Ernest[3]

[1]LCSB, University of Luxembourg, Belvaux, Luxembourg, [2]LCSB, University of Luxembourg, Esch-Alzette, Luxembourg, [3]Molecular Biophysics and Biochemistry, Karolinska Institutet, Stockholm, Sweden

Single-cell RNA sequencing allows defining molecularly distinct cell subpopulations. However, the identification of specific sets of transcription factors (TFs) that define the identity of these subpopulations remains a challenge. Here we propose that subpopulation identity emerges from the synergistic activity of multiple TFs. Based on this concept, we develop a computational platform (TransSyn) for identifying synergistic transcriptional cores that determine cell subpopulation identities. TransSyn leverages single-cell RNA-seq data, and performs a dynamic search for an optimal synergistic transcriptional core using an information theoretic measure of synergy. A large-scale TransSyn analysis identifies transcriptional cores for 186 subpopulations, and predicts identity conversion TFs between 3786 pairs of cell subpopulations. Finally, TransSyn predictions enable experimental conversion of human hindbrain neuroepithelial cells into medial floor plate midbrain progenitors, capable of rapidly differentiating into dopaminergic neurons. Thus, TransSyn can facilitate designing strategies for conversion of cell subpopulation identities with potential applications in regenerative medicine.

Funding Source: FNR CORE grant (C15/BM/10397420) IRP Grant (R-AGR-3227-11)

13:51 – 14:02

CAMP/EPAC1/RAP1 AXIS PLAYS AN ESSENTIAL ROLE IN ETV2-INDUCED ENDOTHELIAL REPROGRAMMING

Kim, Da-Hyun, Kim, Jae-Jun, Choi, Soon Won and Kang, Kyung-Sun

Adult Stem Cell Research Center and Research Institute for Veterinary Science, Seoul National University, Seoul, Korea

Although the generation of ETV2-induced endothelial cells (iECs) from human fibroblasts serves as a novel therapeutic strategy in regenerative medicine, the process is inefficient, resulting in incomplete iEC angiogenesis. Therefore, we employed high-throughput sequencing and identified molecular mechanisms underlying ETV2-mediated endothelial transdifferentiation to efficiently produce iECs retaining appropriate functionality in long-term culture. We revealed that the majority of ETV2 targets in human fibroblasts are related to vasculature development and signaling transduction pathways including Rap1 signaling. From a screening of signaling pathway modulators, we confirmed that forskolin facilitated efficient and rapid iEC reprogramming via activation of cAMP/EPAC1/Rap1 axis. Remarkably, the iECs obtained via cAMP signaling activation showed superior angiogenesis in vitro. Moreover, these cells could form aligned endothelium along the vascular lumen ex vivo when seeded into decellularized liver matrix scaffold. Overall, our study provided evidence that cAMP downstream effectors are required for the efficient generation of iECs with angiogenesis potential.

14:02 – 14:13

THE NOVEL LNCRNA LNC-NR2F1 IS PRO-NEUROGENIC AND MUTATED IN HUMAN NEURODEVELOPMENTAL DISORDERS

Ang, Cheen Euong[1], Chang, Howard[2] and Wernig, Marius[3]

[1]Stem Cell Biology, Stanford University, Stanford, CA, USA, [2]Dermatology, Stanford University, Stanford, CA, USA, [3]Pathology, Stanford University, Stanford, CA, USA

Long noncoding RNAs (lncRNAs) are important in the establishment and maintenance of cellular identity and have been found to be involved in disease progression. Despite that, little is known about the roles of lncRNAs in neurogenesis. Adult cerebral cortex comprises of two main populations of neurons: excitatory projection neurons and inhibitory interneurons. Most cortical interneurons originate from progenitors residing primarily in ventral telencephalon which migrate tangentially to reach their final positions in the developing cortex. Given the role of GABA as the primary inhibitory neurotransmitter in the cortex, deviations from the usual ratio of excitatory and inhibitory neuron is suspected to be the cause of many neuropsychiatric diseases. Thus, studies on the development and function of inhibitory neurons are highly warranted. To investigate how coding and lncRNAs change their expressions during tangential migration from ganglionic eminences into the cortex, we decided to perform RNAseq for inhibitory progenitor and migratory cells at E13.5. Using a lncRNA discovery pipeline reveals that there are 11102 differentially expressed lncRNAs among MGE/LGE/Cortex Gad67GFP populations. Integrating excitatory neuronal datasets from Calegari and Arlotta group revealed that 170 of those are enriched in the inhibitory progenitors and migratory cells. Next, we were interested in seeing whether the same lncRNAs are enriched in induced fibroblasts to neurons (iN) reprogramming. We discovered that iN reprogramming upregulates a subset of lncRNAs which are conserved in mouse and human brain development. Overexpression of those lncRNA candidates in MEF is sufficient to promote iN maturation. Overlapping the candidates with the database of copy number variation morbidity map of patients with neurodevelopmental delay showed recurrent focal genomic mutations affecting one lncRNA candidate (ncE). Finally, we located a triad family where ncE is the only transcript disrupted and only the father and the son inherited the truncated ncE display neurocognitive deficits. Summing up, this shows how the integration of candidates obtained from sufficiency screen done on the induced neuron platform with human genomic and mouse RNAseq data provides an exquisite insight into the effect of lncRNA in human neurogenesis.

14:13 – 14:24

UNVEILING REPROGRAMMING ROADBLOCK AND ESSENTIAL GENES VIA A CRISPR/CAS9-MEDIATED GENOME-WIDE KNOCKOUT SCREEN

Kaji, Keisuke[1], Beniazza, Meryam[1], Kaemena, Daniel[1] and Yusa, Kosuke[2]

[1]MRC Centre for Regenerative Medicine, University of Edinburgh, UK, [2]Cellular Genetics, Wellcome Trust Sanger Institute, Cambridge, UK

The generation of induced pluripotent stem cells (iPSCs) by overexpression of Oct4, Sox2, Klf4 and c-Myc in 2006 transformed the classical view of the cellular epigenetic landscape. However, even now only ~1% of starting cells can reach pluripotency and little is known which genes are the cause of this low efficiency and which genes are necessary for pluripotency induction. In order to illuminate reprogramming mechanisms further, we have performed CRISPR/Cas9-mediated genome-wide knockout screening during reprogramming of mouse embryonic fibroblasts (MEFs) with a lentiviral gRNA library containing 90,000 gRNAs. This screen unveiled 16 novel reprogramming roadblock genes, of which knockout of 8 enhances reprogramming efficiency >4-fold, in addition to previously reported roadblock genes, p53, p21, Men1, Dotl1, Gtf2i, Jun. None of them seem to be involved in replicative senescence. Among them, knockout of Zfp266, Zc3h10 and Men1 exhibit accelerated reprogramming kinetics, similar to that previously reported for Dot1l. In addition, we have also identified 16 genes essential for iPSC generation but not for ES cell self-renewal/clonogenicity or MEF proliferation. Excitingly, 9 of these essential genes enhanced reprogramming when overexpressed together with Yamanaka factors, including a poorly characterized putative transcription repressor Hic2. Overexpression of Hic2 enhanced reprogramming of both MEFs and neural stem cells about 10-fold and dramatically accelerated reprogramming kinetics. Removal of Hic2 N-terminal BTB/POZ domain abolished the enhancement effect indicating protein-protein interaction through this domain is critical for Hic2 to contribute to pluripotency induction. This dataset serves as a valuable resource for

better understanding molecular mechanisms of iPSC generation and the fundamental principles of how to convert cellular identities more efficiently and faithfully.

Funding Source: This work is supported by the MRC senior non-clinical fellowship.

14:24 – 14:35

SINGLE-CELL MAPPING OF LINEAGE AND IDENTITY IN DIRECT REPROGRAMMING

Morris, Samantha, Biddy, Brent, Kong, Wenjun, Guo, Chuner, Kamimoto, Kenji and Waye, Sarah

Department of Developmental Biology, Washington University in St Louis, MO, USA

Direct lineage reprogramming involves the remarkable conversion of cellular identity. Single-cell technologies aid in deconstructing the considerable heterogeneity in transcriptional states that typically arise during lineage conversion. However, lineage relationships are lost during cell processing, complicating trajectory reconstruction. Here, we present 'CellTagging', a combinatorial cell indexing methodology, permitting the parallel capture of clonal history and cell identity, where sequential rounds of cell labeling enable the construction of multi-level lineage trees. CellTagging and longitudinal tracking of fibroblast to induced endoderm progenitor (iEP) reprogramming reveals two distinct trajectories: one leading to successfully reprogrammed cells, and one leading to a 'dead-end' state, paths determined in the earliest stages of reprogramming. We find that the expression of a putative methyltransferase, Mettl7a1, is associated with the successful reprogramming trajectory, where its addition to the reprogramming cocktail increases the yield of iEPs. To dissect the gene regulatory logic underlying these distinct trajectories in further detail, we apply a novel approach to record transcription factor binding in the earliest stages of fate conversion, linking these initial events to reprogramming outcome. Together, these results demonstrate the utility of our lineage tracing method to reveal the molecular mechanisms underlying direct reprogramming.

Funding Source: NIH grants R01-GM126112, R21-HG009750; P30-DK052574; SVCF, Chan Zuckerberg Initiative Grants HCA-A-1704-01646 and HCA2-A-1708-02799; The Children's Discovery Institute MI-II-2016-544; Vallee Scholar Award.

14:35 – 14:46

INNATE IMMUNE SIGNALLING AND WNT SIGNALLING FUNCTION SEQUENTIALLY IN HEPATOCYTE REPROGRAMMING

Li, Lu[1], Lin, Ping[2], Zhu, Wencheng[1], Gao, Yun[3], Li, Weiping[1], Mao, Yunuo[3], Li, Hong[2], Tang, Fuchou[3], Li, Yixue[2] and Hui, Lijian[1]

[1]State Key Laboratory of Cell Biology, Shanghai Institute of Biochemistry and Cell Biology, Shanghai, China, [2]Chinese Academy of Sciences Key Laboratory of Computational Biology, CAS-MPG Partner Institute for Computational Biology, Shanghai, China, [3]Department of Obstetrics and Gynecology, Peking University, Beijing, China

The liver possesses a high regenerative capacity under injury conditions. Lineage tracing experiments have shown that following injury hepatocytes undergo reprogramming to hepatic progenitor-like cells (HPC), which express both hepatocyte marker HNF4a and progenitor marker Sox9. Remarkably, Sox9+HNF4a+ HPCs can give rise to both hepatocytes and biliary cells. However, injury-induced cellular reprogramming occurs mainly in hepatocytes around portal vein. Dissecting the molecular dynamics underlying reprogramming would greatly facilitate the development of new strategies to promote liver regeneration. Here we performed single-cell RNA sequencing (scRNA-seq) of 624 individual cells spanning the reprogramming stages during DDC-induced injury. Through reconstructing the reprogramming trajectory and identifying sequential molecular events, we revealed a two-step mechanism for the full reprogramming process. Notch, YAP and innate immune signalling are early activated molecular events, whereas WNT and FGF signalling are activated in the late stage of reprogramming. Moreover, we found that macrophage depletion inhibited DDC-induced hepatocyte reprogramming, whereas activation of WNT signalling greatly promoted it. Collectively, our work provides key insights into the crucial features of the in vivo reprogramming process and can assist in the development of new treatments for endogenous repair after liver injuries.

14:46 – 15:06

DIRECT LINEAGE REPROGRAMMING FOR CELL THERAPY AND MODELING DISEASE

Kim, Jongpil

Dongguk University, Seoul, Korea

Recent advances in direct lineage reprogramming have garnered considerable interest for human disease modelling and cell replacement strategies. Recently, we reported that electromagnetized gold nanoparticles facilitate an efficient direct lineage reprogramming into induced dopamine neurons which provide a proof of principle for lineage conversion as a potentially viable and safe therapeutic strategy for the treatment of Parkinson disease. Moreover, we have reported the generation of induced neuron-based model of sporadic Alzheimer's disease, and used this system to explore the pathogenic mechanisms resulting from the sporadic Alzheimer's disease risk factor APOE 3/4. These results demonstrate in proof of principle the utility of induced neuron-based modelling of Alzheimer's disease for therapeutic discovery. Finally, I will discuss the recent updates on the in vivo gene targeting using Cas9 nanocomplexes as a novel therapeutic agent for Alzheimer's disease.

SATURDAY, 29 JUNE, 13:15 – 15:15

CONCURRENT IVE: TOOLS TO INTERROGATE STEM CELLS

Room 408B, Level Two

13:20 – 13:40

SPATIAL GENOMICS: TRANSCRIPTOME PROFILING IN SITU BY RNA SEQFISH+

Cai, Long

California Institute of Technology, Pasadena, CA, USA

Imaging the transcriptome in situ with high accuracy has been a major challenge in single cell biology, particularly hindered by the limits of optical resolution and the density of transcripts in single cells. We developed seqFISH+, that can image the mRNAs for 10,000 genes in single cells with high accuracy and sub-diffraction-limit resolution, in the mouse brain cortex, subventricular zone, and the olfactory bulb, using a standard confocal microscope. The transcriptome level profiling of seqFISH+ allows unbiased identification of cell classes and their spatial organization in tissues. In addition, seqFISH+ reveals subcellular mRNA localization patterns in cells and ligand-receptor pairs across neighboring cells. This technology demonstrates the ability to generate spatial cell atlases and to perform discovery-driven studies of biological processes in situ.

13:40 – 13:51

SPATIALLY-RESOLVED SINGLE CELL ANALYSIS OF BONE MARROW MICRO-DOMAINS IN STEADY STATE AND DISEASE

Haase, Christa[1], Gustafsson, Karin[2], Yeh, Shu-Chi[1], Mei, Shenglin[3], Milosevic, Jelena[2], Sykes, David[2], Kharchenko, Peter[3], Scadden, David[4] and Lin, Charles[1]

[1]Wellman Center for Photomedicine, Massachusetts General Hospital, Boston, MA, USA, [2]Center for Regenerative Medicine, Massachusetts General Hospital, Boston, MA, USA, [3]Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA, [4]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA

The function and state of a cell is strongly affected by the interaction with its cellular micro-environment. Single-cell RNA (scRNA-seq) sequencing is an important tool for studying such interactions, identifying molecular pathways that are activated and revealing the composition of heterogeneous tissue samples. It can help to elucidate mechanisms regulating hematopoietic stem and progenitor cell quiescence and differentiation as well as malignant transformation and proliferation. However, most approaches for obtaining single-cell samples rely on tissue homogenization, resulting in an almost complete loss of spatial information. We have developed an experimental methodology for obtaining single cell gene expression data of cells isolated from defined anatomic locations of the calvarial bone marrow. It relies on precise femtosecond laser etching of bone to create a microchannel, through which a micropipette is inserted to aspirate several thousand cells for parallel scRNA-seq. The procedure is carried out under image guidance, using video-rate intravital multi-photon microscopy to identify and extract cells from specific target locations. This experimental platform, integrable into any multiphoton microscope, defines a new technique for spatially-resolved single-cell analysis. We present here a study of cells isolated from such BM micro-domains in steady state and disease, showing the potential heterogeneity in bone marrow microenvironment for leukemia engraftment and maintenance.

13:51 – 14:02

RECONSTRUCTION OF DEVELOPMENTAL LANDSCAPES AND TRAJECTORIES FROM INTEGRATIVE ANALYSIS OF LARGE-SCALE SINGLE-CELL DATA

Shu, Jian[1,2], Tabaka, Marcin[1,2], Berube, Peter[1,2], Lee, Lia[1,2], Subramanian, Vidya[1], Schiebinger, Geoffrey[1], Cleary, Brian[1], Solomon, Aryeh[1,2], Markoulaki, Stella[2], Hochedlinger, Konrad[3], Regev, Aviv[1,4], Jaenisch, Rudolf[2] and Lander, Eric[1]

[1]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [2]Whitehead Institute, Cambridge, MA, USA, [3]Harvard University, Cambridge, MA, USA, [4]MIT, Cambridge, MA, USA

Understanding the molecular programs that guide cell fate transition during development is a major goal of modern biology. Here, we developed novel experimental and computational methods for studying developmental time course single-cell data to infer ancestor-descendant fates and model the regulatory programs that underlie them. We demonstrated the power of these methods by applying them to around 1,000,000 scRNA-seq, scATAC-seq, and spatial transcriptomic profiles collected during 1) reprogramming of fibroblasts to pluripotency by the Yamanaka factors; 2) by different reprogramming cocktails; 3) reprogramming of fibroblasts to totipotency by a new cocktail; 4) mouse embryonic development from the pluripotent state to terminally differentiated state focusing on extraembryonic lineage development. We constructed high-resolution maps of mouse embryonic development and different reprogramming strategies that uncovers universal mechanisms of successful reprogramming; discovers new cell fates; predicts the origin and fate of any cell class; suggests cell-cell interactions, and implicates regulatory models in particular trajectories in development and reprogramming. Our approach provides the first large-scale, high resolution roadmaps of normal mouse embryonic development and reprogramming to pluripotency and totipotency using various reprogramming cocktails. It also provides a general framework for studying cell fate conversions in natural and induced settings.

14:02 – 14:13

NEW SINGLE CELL TOOLS TO ADVANCE REGENERATIVE MEDICINE

Bonaguidi, Michael, Bay, Maxwell, Peng, Lei, Zhang, Naibo and Zadeh, Arman

Stem Cell Biology and Regenerative Medicine, University of Southern California, Los Angeles, CA, USA

A fundamental goal in regenerative medicine is finding the root cause of stem cell dysfunction to guide the development of restorative therapies. Aging is a main driver of endogenous stem cell decline, however identifying and treating the underlying molecular networks remain unknown. Here, we introduce new data science algorithms entitled "Revealing Origins and Ontological Targets (ROOT)". ROOT organizes and analyzes the order of molecular events, identifies potential causes of disorder, and prioritizes clinically approved small molecules for intervention. We have implemented ROOT to assess single-cell transcriptomic data extracted from young and older mouse neural stem cells (NSCs). Trajectory reconstruction and heuristic algorithms identified age-related gene networks in quiescent NSCs. Remarkably, age-related metabolic, and cell signaling networks are conserved across hematopoietic, muscle and epidermal stem cells. ROOT's computational drug discovery then matched seven clinically relevant drugs predicted to overcome age-related NSC dysfunction. Importantly, three of the compounds mobilized endogenous NSCs in middle-aged mice to increase neural stem cell number and initiate neurogenesis. Our results provide proof-of-principle validation of ROOT's ability for drug discovery compared to current benchmarks. This unbiased approach has the potential to accelerate the success and reduce the cost of scientific discovery, drug repurposing and personalized medicine.

Funding Source: NS080913 from NIH, Whittier Foundation, Baxter Foundation

14:13 – 14:24

TRANSPLANTABLE NANO CELLULAR MATRICES FOR SCALED-UP CULTURE OF HUMAN ES/IPS CELLS

Kamei, Kenichiro

Institute for Integrated Cell-Material Sciences, Kyoto University, Japan

Human pluripotent stem cells (hPSCs) hold great potential for industrial and clinical applications. To cure patients who have serious diseases in large tissues (e.g., heart and liver), large quantities of quality-controlled hPSCs must be prepared for further differentiation procedures for targeted tissue cells and better transplanted cell engraftments at the curing area in a patient. However, the use of traditional two-dimensional (2D) culture systems (i.e., culture dishes, multi-well plates or flasks) to generate high quality and large quantity hPSCs is not realistic due to the requested huge space and medium as well as too labor-intensive procedures. For this purpose, it is necessary to establish 3D culture systems to allow for an increase in the number of cells per unit volume. Although the numbers of 3D hPSC culture systems have been reported, they also showed a number of drawbacks, such as insufficient cell growth, unexpected cell differentiation, scalability, and hydrodymanic shear stress. To address these issues, we develop a new type of extracellular matrix (ECM) enabling efficient promotion of hPSC self-renewal and prevention of undesired differentiation during culture. Nanofibers have unique advantages over conventional ECMs for increasing interaction with cells, and can be fabricated with defined materials. Thus, nanofiber matrices would be suitable for good manufacture's practice. However, since nanofibers are mechanically fragile, it is difficult to apply for establishing 3D cell culture system with them alone. Therefore, we introduce a microfiber matrix as a backbone to improve mechanical stability; we named this "Fiber-on-Fiber" matrix. This matrix allows hPSC expansion at a much higher density than conventional culture dishes with the same amount of culture medium, while maintaining pluripotency, robust proliferation, and normal karyotype. Moreover, due to the mechanically stability, hPSCs on biodegradable FF matrices grafted into animals differentiated into all three germ layers without any cytotoxic effects on both transplanted cells and host animals. Thus, we conclude that our FF matrices could serve as an alternative cellular matrix enabling a whole array of hPSC applications from stable culture to cell transplantation.

Funding Source: Japan Society for the Promotion of Science (JSPS)

14:24 – 14:35

SINGLECELLNET: A COMPUTATIONAL TOOL TO ASSESS THE FIDELITY OF CELL FATE ENGINEERING AND TO AID CELL ATLASES

Tan, Yuqi[1] and Cahan, Patrick[2]

[1]Molecular Biology and Genetics, Johns Hopkins School of Medicine, Baltimore, MD, USA, [2]Biomedical Engineering, Johns Hopkins University, Baltimore, MD, USA

Single cell RNA-Seq has emerged as a powerful tool in diverse applications, ranging from determining the cell-type composition of tissues to uncovering the regulators of developmental programs. A near-universal step in the analysis of single cell RNA-Seq data is to hypothesize the identity of each cell. Often, this is achieved by finding cells that express combinations of marker genes that had previously been implicated as being cell-type specific, an approach that is not quantitative and does not explicitly take advantage of other single cell RNA-Seq studies. Here, we describe our tool, SingleCellNet (SCN), which addresses these issues and enables the classification of query single cell RNA-Seq data in comparison to reference single cell RNA-Seq data. SCN had markedly superior performance as compared to other methods in 19 out of 21 training-validation datasets (by mean-AUPRC). Unlike currently used projection-based single cell RNA-Seq analysis methods, SCN does not rely on the assumption that there are shared cell types between the reference and the query datasets. We also demonstrated that SCN can determine the identity of previously unidentified cell types in a heterogeneous complex tissue and it can comprehensively assess the identity and fidelity of engineered cells. Furthermore, SCN code is open-source (available on GitHub), extensively documented, and actively supported. To broaden its availability, SCN can be executed as a code capsule via Code Ocean. As more data across

developmental time points are accrued, we anticipate that SCN will provide a means to quantify not only the identity, but also the stage of development and maturation of engineered cells.

Funding Source: This work was supported by the National Institutes of Health under grant R35GM124725 to PC the Biochemistry, Cellular, and Molecular Biology Program T32 Training grant T32GM007445 to YT.

14:35 – 14:46

TARGETING OF HEPATOCYTE SUBPOPULATION CONTRIBUTING TO POST-NATAL LIVER GROWTH IS CRUCIAL FOR MAINTENANCE OF TRANSGENE EXPRESSION IN LIVER-DIRECTED GENE THERAPY

Milani, Michela[1], Starinieri, Francesco[2], Canepari, Cesare[2], Liu, Tongyao[3], Moalli, Federica[4], Ambrosi, Gioia[4], Feo, Alessandro[2], Aloia, Luigi[5], Plati, Tiziana[1], Biffi, Mauro[1], Covino, Cesare[6], Nichols, Timothy[7], Huch, Meritxell[5], Iannacone, Matteo[4], Peters, Robert[3], Cantore, Alessio[1] and Naldini, Luigi[1]

[1]Regenerative Medicine, San Raffaele Telethon Institute for Gene Therapy, Milano, Italy, [2]Regenerative Medicine, Vita-Salute San Raffaele University, Milan, Italy, [3]Bioverativ Inc., Waltham, MA, USA, [4]Dynamics of Immune Responses, IRCCS Ospedale San Raffaele, Milan, Italy, [5]Department of Physiology, Development and Neuroscience, The Gurdon Institute, Cambridge, UK, [6]Advanced Light and Electron Microscopy BioImaging Center, IRCCS Ospedale San Raffaele, Milan, Italy, [7]Department of Pathology and Laboratory Medicine, University of North Carolina, Chapel Hill, NC, USA

Liver-directed gene therapy with adeno-associated viral (AAV) vectors delivering a clotting factor transgene into hepatocytes has shown successful results in adults with hemophilia. However, because AAV vectors do not actively integrate into the host cell genome, they are diluted upon cell division during liver growth, thus challenging their proficient use in pediatric patients. In contrast, lentiviral vectors (LV) integrate into the target cell chromatin and are maintained as cells divide. We developed LV that achieve stable and therapeutic levels of coagulation factor IX (FIX) transgene expression in the liver of adult mice, dogs and non-human primates, after intravenous (i.v.) delivery. We then set out to evaluate the fate of LV-modified liver cells during growth. We administered increasing doses of LV expressing marker genes (GFP or luciferase) under the control of hepatocyte-specific expression cassettes i.v. to newborn mice. Exploiting 3D imaging of cleared livers and bioluminescence, we show that transduced hepatocytes are maintained over time and proliferate locally. Unexpectedly, we observed an initial, promoter-independent, decrease in transgene expression due to dilution of transduced hepatocytes, followed by stable maintenance sustained by LV-targeted hepatocyte expansion, suggesting different growth phases supported by different cell populations within the mouse liver. We administered LV-FIX to 2-week old mice, right before the observed decrease in transgene expression, and showed 3-fold higher FIX output compared to newborn, suggesting targeting of the new hepatocyte subpopulation contributing to liver growth at that time. Ongoing studies are underway to investigate the nature of transduced hepatocytes at the different time points. We are also investigating the clonal composition of hepatocytes during post-natal liver growth, in Alb-Cre/Rosa26-confetti mice. In addition, we show in vivo transduction of bile duct cells able to generate LV-positive liver organoids in vitro. Our work will inform about the extent and mechanism underlying long-term maintenance of LV-transduced hepatocytes, provide a rationale for application of LV-mediated liver gene therapy to pediatric patients and may shed light on the role of different cell populations involved in post-natal liver growth.

14:46 – 15:06

SUPER-RESOLUTION IMAGING OF CHROMATIN IN REPROGRAMMING AND DIFFERENTIATION

Lakadamyali, Melike

University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA, USA

Nucleosomes help structure chromosomes by compacting DNA into fibers. Chromatin organization plays an important role for regulating gene expression; however, due to the nanometer length scales involved, it has been very difficult to visualize chromatin fibers in vivo. Using super-resolution microscopy, quantitative analysis and simulations, we have been gaining new insights into chromatin organization at nanometer length scales in intact nuclei. For example, we found that nucleosomes assemble into heterogeneous groups of varying sizes, which we named "clutches," in analogy with "egg clutches". Clutch organization is highly cell specific and I will give various examples of this specificity in the context of stem cell differentiation and somatic cell reprogramming. Overall, our results reveal how the chromatin fiber is formed at nanoscale level and link chromatin fiber architecture to cell state.

SATURDAY, 29 JUNE, 16:00 – 18:45

PLENARY VII: BASICS AND TRANSLATION: NEURAL ECTODERM

West Hall B, Level One

Sponsored by BlueRock Therapeutics

16:05 – 16:25

ISSCR TOBIAS AWARD LECTURE: TARGETING CHROMATIN TO REVERSE LEUKEMIA STEM CELL GENE EXPRESSION

Armstrong, Scott

Department of Pediatric Oncology, Dana-Farber Cancer Institute, and Division of Hematology/Oncology, Boston Children's Hospital, Harvard Medical School/The Broad Institute of MIT and Harvard, Boston, MA, USA

Leukemia causing oncogenes such as MLL-rearrangements and NPM1 mutations induce self-renewal in myeloid progenitors as a

critical step during leukemia stem cell development. During this process, inappropriate expression of stem-cell associated genes such as the homeotic (HOX) genes and MEIS1 is activated in myeloid progenitors. HOX/MEIS1 expression is also found in up to 40% of cases of Acute Myelogenous Leukemia (AML) suggesting that reversal of this gene expression might provide therapeutic benefit. Recent studies from our group and others have defined the chromatin associated protein complexes that maintain this aberrant gene expression and thus defined new potential therapeutic opportunities to target leukemia stem cell associated gene expression programs. Multiple groups and pharma/biotech companies have now developed small molecule inhibitors of chromatin associated proteins. Some of these small molecule enzymatic inhibitors have recently entered early phase trials and have shown reversal of HOX/MEIS1 expression and some complete clinical responses. Another approach to target chromatin associated complexes is to block critical protein-protein interactions. An example is inhibition of the MLL1-Menin interaction, an approach that has also been shown to reverse stem cell-associated gene expression. We have recently developed potent and selective MENIN-MLL1 interaction inhibitors that are effective in vitro and in vivo. Structure-based design yielded the potent, highly selective and orally-bioavailable small molecule inhibitor VTP-50469. We have used mouse models of MLL-rearranged or NPM1c mutant AML, to show that leukemia development is preceded by a period of myeloid progenitor self-renewal. This pre-malignant progenitor self-renewal can be reversed, and AML development can be prevented by treatment with the VTP-50469. VTP-50469 also eradicates NPM1c mutant or MLL-rearranged human AML in patient derived xenograft models. These studies suggest it may be possible to prevent AML development in high-risk populations by targeting chromatin associated complexes to reverse pre-leukemic self-renewal and that the same approaches can treat fully developed MLL-rearranged or NPM1 mutant AML. These studies support rapid translation of this approach to clinical trials.

16:25 – 16:45

ERNEST MCCULLOCH MEMORIAL LECTURE: BUILDING AND REPAIRING THE HUMAN BRAIN USING PLURIPOTENT STEM CELLS

Studer, Lorenz

Memorial Sloan Kettering Cancer Center, New York, NY, USA

Human pluripotent stem cells (PSCs) present a powerful tool for studying development and disease and for developing cell-based therapies in regenerative medicine. Our group has developed strategies to coax human PSCs into a myriad of specific cell types of the central and peripheral nervous system. Those strategies are based on insights from developmental biology which guide the rationale design of stem cell differentiation technologies in 2D and 3D. I will discuss some of the emerging strategies to address remaining bottlenecks in human PSC research such as the derivation of late-born cell types, the establishment of 3D cultures with appropriate topographical organization or challenges related human PSC-based disease modeling. Furthermore, I will present an update on our work geared towards the translation of hPSC technology in regenerative medicine, in particular the development of a dopamine neuron replacement therapy for Parkinson's disease (PD). I will review some of the many hurdles that needed to be overcome towards starting a human clinical trial. Those range from biological questions about the optimal cell source and stage to manufacturing issues, regulatory questions, medical and surgical considerations. I will also present some of the next generation developments that go beyond our initial phase I study such as use of universal cell technology and further improvements in purifying and defining a most optimal cell product for both safety and efficacy. We are excited that this technology is now at the verge of clinical entry and may pave the way for other hPSC-based cell products and disease targets in the future.

16:45 – 17:05

COORDINATION BETWEEN STOCHASTIC AND DETERMINISTIC CHOICES IN THE DROSOPHILA OPTIC LOBES

Desplan, Claude

New York University, New York, NY, USA

The Drosophila compound eye is composed of ~800 ommatidia (unit eyes) that contain photoreceptors R1-R6 specialized in motion vision and R7 and R8 involved in the detection of color or polarized ligh. Depending on the pair of rhodopsins expressed in R7 and R8, 3 subtypes of ommatidia can be distinguished: 70% are 'yellow' type and express UV-sensitive Rh4 in R7 and green-Rh6 in R8. 30% are 'pale' type and expresses UV-Rh3 in R7 and blue-Rh5 in R8. A third type at the Dorsal Rim Area is involved in polarized light detection for navigation. Yellow and pale ommatidia are randomly distributed in the retina and their expression is controlled by the stochastic expression of the transcription factor Spineless (Ss) in yellow R7. In the absence of Ss, ommatidia are pale. R7 and R8 project to the medulla part of the optic lobe where they form the color vision circuit that sent information to higher processing centers. At least 100 types of medulla neurons process color and motion inputs by extracting visual information. They are organized in 800 columns corresponding to the 800 ommatidia in the retina. Neural stem cells that produce medulla neurons sequentially express six transcription factors in a temporal manner: Each of the ~800 neuroblast sequentially produces about 25 neurons that emerge from the series of temporal windows. These 'Uni-columnar neurons' have a 1:1 stoichiometry photoreceptors. The less numerous 'multi-columnar' neurons have larger receptor fields and are present at a lower stoichiometry; they emerge from the same neural stem cells but are produced by neuroblasts in distinct sub-regions of the medulla. Therefore, the generation of the many medulla cell types involves a very deterministic pattern integrating temporal and spatial information. How does his very hard-wired pathway accommodate the stochastic input of R7 and R8 cells? I will describe how yellow R7s produce Dpr11, a cell adhesion molecule that recognizes specifically DIPγ on the surface of Dm8, R7's neuronal targets. Two types of Dm8 (DIPγ+ or -) are produced in excess but only those that connect to their stochastically produced cognate yellow (DIPγ+) or pale R7s (DIPγ-) do survive. This allows stochastically generated visual information to be propagated down into two different circuits to process different wavelengths of light.

17:05 – 17:25

DRIVING AND DEFINING NEURONAL DIVERSITY USING REPROGRAMMING

Baldwin, Kristin

Scripps Research Institute, La Jolla, CA, USA

Neuron comprise a conspicuously diverse yet clearly recognizable cell type. Diversity among neurons contributes to the variation in cognition and behaviors that characterize different species and to the selective vulnerabilities that underlie most neurologic diseases. Historically neurons have been divided into subtypes based on their morphology, anatomic location, patterns of connectivity or electric excitability or expression of particular marker genes. However, new techniques for genomic and transcriptional profiling of individual neurons from mouse and human brains have uncovered new axes of neuronal diversity with relevance for human brain development and disease. We will describe new aspects of neuronal genomic, transcriptional and functional diversity that we have uncovered using cloning and whole genome sequencing, direct reprogramming with transcription factors and interspecies brain chimeras. Results will be discussed regarding their relevance to basic mechanisms of brain development and evolution, and with respect to mechanisms underlying selective vulnerabilities in neurologic diseases such as autism, addiction and Alzheimer's disease.

17:25 – 17:36

REGULATION OF GENES UNDERLYING SCHIZOPHRENIA RISK BY 22Q11.2 IN HUMAN NEURONS

Nehme, Ralda[1], Pietilainen, Olli[1], Ganna, Andrea[1], Trehan, Aditi[1], Tegtmeyer, Matthew[1], Hawes, Derek[1], Herring, Amanda[1], Daly, Mark[1], Barrett, Lindy[1], Palotie, Aarno[1] and Eggan, Kevin[1,2]

[1]Stanley Center, Broad Institute of Harvard and MIT and Harvard University, Cambridge, MA, USA, [2]Harvard Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA

Deletion of chromosomal region 22q11.2 confers a substantial risk for neurodevelopmental and psychiatric disorders, including schizophrenia, intellectual disability, and autism. Despite its high prevalence, how 22q11.2 deletion mediates these phenotypes remains unresolved. While mouse studies have recapitulated a subset of the phenotypes observed in patients, human models are needed to recapitulate neuropsychiatric phenotypes. However, previous studies utilizing human induced pluripotent stem cell (hiPSC)-derived neuronal models have relied on a small number of biological replicates, and are thus sensitive to stochastic changes compounded by genetic heterogeneity and experimental variance. Here, we have generated iPSCs from a large number of control donors and donors with 22q11.2 deletion, and now have an unprecedented sample set of 51 individuals. This enabled us to execute a well powered study and detect meaningful changes in RNA abundance. Further, we engineered hPSCs with 22q11.2 deletion to validate results in an isogenic setting. We then coupled these resources with a highly efficient neuronal differentiation scheme to generate excitatory, patterned induced neurons (hpiNs) at large scale, and analyzed cells at three stages: stem cells, progenitors, and neurons, from all lines, in triplicates. RNA sequencing data from both our case/control and isogenic cohorts revealed that deletion of 22q11.2 alters the expression of genes both within (cis) and outside (trans) the deletion region. Furthermore, trans-regulated genes were cell-type specific. Importantly, linkage disequilibrium (LD) score regression analysis revealed a significant enrichment of trans-regulated genes for schizophrenia polygenic risk, specifically in neurons. These results showed, for the first time, that 22q11.2 regulates genes underlying schizophrenia risk in human neurons, and underscored cell-type specific mechanisms of the 22q11.2 deletion. We conclude that 22q11.2 regulates the expression of both cis and trans genes to mediate psychiatric phenotypes. These findings provide novel mechanistic insights on how a rare copy number variant collaborates with risk genes in a cell-type specific manner to alter transcriptional landscape and mediate neuropsychiatric phenotypes.

17:36 – 17:47

RECONSTRUCTION OF THE HUMAN BLOOD-BRAIN BARRIER IN VITRO REVEALS THE PATHOGENIC MECHANISMS OF APOE4 IN CEREBRAL AMYLOID ANGIOPATHY

Blanchard, Joel W., Bula, Michael and Tsai, Li-Huei

Picower Institute for Learning and Memory, Massachusetts Institute of Technology, Cambridge, MA, USA

The majority of Alzheimer's disease patients and 20–40% of non-demented elderly experience amyloid deposits along their cerebral vasculature, a condition known as cerebral amyloid angiopathy (CAA). CAA impairs the function of the blood-brain barrier (BBB) leading to ischemia, hemorrhages, and accelerated cognitive dysfunction. The APOE4 allele is the strongest known risk factor for CAA and sporadic Alzheimer's disease (AD), however, the pathogenic mechanisms underlying this predisposition are unknown. Using human iPSC-derived cells we recreate the human BBB in vitro generating a highly tractable model that recapitulates key anatomical and physiological properties of the BBB. Similar to the human brain BBB, we find that amyloid accumulates on our in vitro BBB (iBBB) and both APOE4 homozygous and heterozygous iBBBs exhibit significantly more amyloid accumulation than APOE3/3 iBBBs. We then used reciprocal isogenic iPSC-derived iBBBs to dissect the mechanisms underlying APOE4 risk for CAA. Through combinatorial experiments we pinpoint the causal cells through which APOE4 predisposes CAA. This revealed that APOE4 causes cell type-specific dysregulation of APOE gene expression. We identify the pathways underlying APOE dysregulation and find that inhibiting these pathways with FDA-approved drugs returns APOE expression in APOE4 iBBBs to equivalent levels seen in APOE3 iBBBs. And remarkably, the identified drugs prevent the build-up of amyloid in APOE4 iBBBs. Collectively, this work establishes a human model of the BBB, defines a mechanism through which APOE4 predisposes amyloid

deposition, and uncovers new therapeutic opportunities for CAA and potentially AD.

Funding Source: This work was supported by The Robert A. and Renee E. Belfer Family Foundation, Cure Alzheimer's Foundation, NIH 1-U54-HG008097-03 to L.H.T and Glenn Foundation for Medical Research and American Federation for Aging Research to J.W.B.

17:47 – 18:07

STEM CELLS IN THE ADULT HUMAN RETINAL PIGMENT EPITHELIUM AND THEIR THERAPEUTIC POTENTIAL

Temple, Sally

Neural Stem Cell Institute, Rensselaer, NY, USA

The retinal pigment epithelium (RPE) is a central nervous system tissue specialized to support the neural retina and is essential for vision. Degeneration of the RPE can lead to blinding conditions such as age-related macular degeneration (AMD), a highly prevalent, neurodegenerative disease. We previously showed that the adult human retina contains a rare population of cells capable of being activated to a stem cell state after exposure to mitogens in culture. Starting with cadaver eyes donated to eye banks, the RPE layer is extracted and retinal pigment epithelial stem cells (RPESCs) are activated, efficiently expanding in culture to produce over a billion cells per single donor. This is currently being done under GMP conditions in preparation for a clinical trial. RPESC-derived RPE cells are similar to native RPE and are effective at preventing vision loss in the Royal College of Surgeons rat. Importantly, a particular stage of RPESC is most efficacious to preserve vision: neither very early proliferating RPESCs nor mature RPE cells are as effective as an intermediate RPESC-RPE cell stage. In this regard, RPESC-RPE are similar to other stem cell products applied to degenerative neural conditions in exhibiting stage-dependent efficacy. We have identified a novel long non-coding RNA that tracks with potency of the product. RPESC-RPE have potential as a transplantable therapeutic cell to counter RPE cell loss due to diseases such as AMD. Additionally, as this unique cell can be obtained from the human retina throughout adulthood, even from nonagenarians and patients with AMD, an exciting possibility is to produce activated RPESCs in vivo to promote endogenous repair for degenerative retinal conditions.

18:17 – 18:37

RECENT PROGRESS IN IPS CELL RESEARCH AND APPLICATION

Yamanaka, Shinya

Gladstone Institutes, San Francisco, CA, USA and Center for IPS Cell Research and Application, Kyoto University, Kyoto, Japan

Induced pluripotent stem cells (iPSCs) can proliferate almost indefinitely and differentiate into multiple lineages, giving them wide medical application. As a result, they are being used for new cell-based therapies, disease models and drug development around the world. In 2014, the world's first clinical study using iPSCs began for the treatment of age-related macular degeneration (AMD). iPSCs can be used for regenerative medicine to restore organ function. To push these efforts, we are proceeding with an iPSC stock project in which clinical-grade iPSC clones are being established from "super" donors with homologous HLA haplotypes, which are associated with decreased immune response and therefore less risk of transplant rejection. In 2015, we started distributing an iPSC stock clone to organizations in Japan, and clinical study using the iPSC stock began for AMD patients in 2017. Additionally, clinical trial for Parkinson's disease started using the iPSC stock-originated neurons in August, 2018 and the surgery to transplant dopaminergic progenitors into the patient's brain was conducted at Kyoto University Hospital. Most recently, clinical study of cell therapy for spinal cord injury led by Keio University, which neural progenitor cells derived from the iPSC stock are transplanted has been just approved by the agency in 2019. Other applications of iPSCs include drug screening, toxicity studies and the elucidation of disease mechanisms using disease-specific iPSCs from patients with intractable diseases. 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 or to establish personalized medicine. We reported a new drug screening system using iPSCs derived from fibrodysplasia ossificans progressiva (FOP) patients, revealing one drug candidate, Rapamycin. Based on these findings, we have achieved to initiate a clinical trial to treat FOP patients in 2017. Over the past decade iPSCs research made a great progress. However, there are still various hurdles to be overcome, iPSC-based science is certainly moving forward for delivering innovative therapeutic options to the patients with intractable diseases.

PRESENTER INDEX

Y

Z

Upgrade Your Human Cell Culture

www.promocell.com

Complete solutions for culturing and assaying

Primary Human Cells, Cancer Cells, and Stem & Blood Cells

Meet us
ISSCR booth #320

Test your cell culture knowledge at our booth and win a **FREE** Stem Cell plush toy from GIANTMicrobes®

At PromoCell we offer a complete portfolio of products for culturing and assaying human stem cells.

With personalized support by PhD Scientists and product customization at hand, we are your best stem cell research partner.

PromoCell

STEMCELL™
TECHNOLOGIES

THE NEW STANDARD FOR hPSC MAINTENANCE

Raise the bar with new stabilized mTeSR™ Plus medium.

Visit STEMCELL Technologies at **Booth #615** to learn about adding mTeSR™ Plus to your lab. You can also win prizes and explore other applications, including culturing organoids, genome editing, and more.

www.stemcell.com/why-mtesrplus