ISSCR 2015

ANNUAL MEETING

STOCKHOLM | SWEDEN

24-27 JUNE

Stockholmsmässan

An Unveiling of
Stem Cell Innovation

FINAL PROGRAM

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Co-Sponsored By: WiRM

Stem Cell Expansion Simplicity, Performance, and Purity

CORNING

With the next generation of rLaminin 521 (Human) pre-coated surfaces exclusively from Corning Life Sciences

Visit booth #B07:10 to learn more about Corning® PureCoat™ rLaminin-521 (Human) cultureware, an animal-free, cGMP manufactured pre-coated recombinant Laminin 521 platform that reduces steps in your workflow, **streamlines** culture **scale-up,** and **reduces process-related risk**.

For more information on applications that are ideal for Corning PureCoat rLaminin-521 (Human) cultureware, attend our innovation showcase presentation or visit our technical posters.

Corning rLaminin-521 (Human) joins Corning Life Sciences' line of advanced cell culture surfaces, extracellular matrices, scalable vessel platforms, microcarriers, and cell culture media, providing innovative solutions for stem cell research. Visit **www.corning.com/lifesciences** to learn more.

ISSCR Innovation Showcase

"Stem cell culture, differentiation, and scale-up – novel technologies enabling research and cell processing applications"

Date: Friday, June 26
Times: 11:30 a.m. to 12:30 p.m.
Location: Victoria Hall

Karolinska Institutet

Dear Friends,

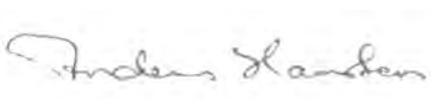
On behalf of Karolinska Institutet and the Wallenberg Institute for Regenerative Medicine (WIRM), we are delighted to welcome you to the 13th Annual Meeting of the International Society for Stem Cell Research (ISSCR).

Since its start, ISSCR has not only steadfastly promoted the highest level of quality in research and ethics, but also fostered a true international spirit transmitting that stem cell research is a global effort where progress is made not only in many research areas but also in many countries. This is, indeed, reflected in the annual meetings, which are held in various parts of the world. This year, we are proud that Stockholm is the host.

Karolinska Institutet and WIRM are honoured to welcome you to our vibrant stem cell research community, which has grown rapidly over the last few years. We also bid you welcome to the beautiful city of Stockholm, and hope that you over the next several days will enjoy both first-class science and the scenic "Venice of the North".

We sincerely hope that you will experience a productive meeting and have an enjoyable time!

Yours sincerely,



Anders Hamsten
Vice-Chancellor
Karolinska Institutet

Urban Lendahl
Director
Wallenberg Institute
for Regenerative Medicine

INTERNATIONAL 2015 SYMPOSIA

SUZHOU CHINA 2015

19-22 OCTOBER

Stem Cells:

BASIC BIOLOGY TO DISEASE THERAPIES

FEATURED SPEAKERS

Austin Smith, PhD, FRS
Cambridge Stem Cell Institute, University of Cambridge, UK

Sally Temple, PhD
Neural Stem Cell Institute, USA

JOIN STEM CELL SCIENCE LEADERS IN EXPLORING the latest exciting directions of stem cell research including new techniques in genome editing that are moving the field to new understandings of disease and toward therapeutic applications. Opportunities for short talks selected from abstracts and numerous networking events round out the program. Topics include:

- Genome Editing
- Lineage: Endoderm
- Lineage: Mesoderm
- Pluripotent Cells
- Road to the Clinic

REGISTER NOW

Visit www.**isscr.org/suzhou-2015** to register and submit an abstract.

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

CSH Asia 冷泉港·亚洲 Cold Spring Harbor Asia

Stockholms stad

City of Stockholm

A Message from the Mayor

I'd like to welcome all attendants of the ISSCR 13th Annual Meeting 2015 to the City of Stockholm, the Capital of Scandinavia. Stockholm is a city dedicated to sustainable growth, health and science, and we are very proud to be able to host such an important gathering as your conference.

Today Stockholm is one of the fastest growing cities in Europe. With a population of well-educated and innovative citizens the businesses in the fields of Life Science and ICT are developing fast. Many companies and individuals strive to establish themselves in our city, and are very welcome. We know that we can offer a stable society where it is easy to fit in and establish yourself. With open minds and hearts the Stockholmers welcomes the challenges of a global and competitive world and we like to believe that we are well-equipped and able to face them.

Stem cell research is very much in focus when we all hope for better health and treatments for ailments still plaguing humanity. I wish you the very best of luck with your endeavours and I hope that your time in Stockholm will be fruitful and useful for your research – to the benefit of us all.

But Stockholm is not only a city of businesses and research. I certainly hope that you all are able to find some time to experience our cultural heritage, the beauty of a city on water, and our splendid and internationally renowned cuisine, amongst all other things that Stockholm has to offer.

You are truly welcome to Stockholm!

Karin Wanngård
Mayor of Stockholm

MEETING SUPPORTERS

Co-Sponsor

The Wallenberg Institute for Regenerative Medicine (WIRM) is a Research Institute financed by a research grant from Knut och Alice Wallenbergs Stiftelse. The aim of WIRM is to advance research on the blood system at Karolinska Institutet, both during normal hematopoietic development and in disease. This is accomplished by recruitment of leading international expertise, both at the senior level and at the level of new junior group leaders. WIRM also builds new important research infrastructure for stem cell research and regenerative medicine, ranging from a state-of-the-art FACS facility to supporting core facilities for cellular reprogramming/iPS, GMP production of clinical grade cells, transgenic mouse technology, zebrafish and live cell imaging.

Gold

Silver

Boehringer Ingelheim
Burroughs Wellcome Fund
Centre for Commercialization of Regenerative Medicine (CCRM)
Lonza
Mesoblast
Novo Nordisk Foundation
Ontario Institute for Regenerative Medicine (OIRM)

Bronze

Fluidigm Corporation
GE Healthcare Life Sciences
Harvard Stem Cell Institute
Massachusetts General Hospital Center for Regenerative Medicine
Nature Publishing Group
Stem Cell Program at Boston Children's Hospital
Stemgent, part of the ReproCELL Group
SwedenBio
Takeda Pharmaceuticals International, Inc.

Contributors

Cell Therapy Catapult

TABLE OF CONTENTS

GENERAL INFORMATION

REGISTRATION AND BADGE PICKUP

Pick up your attendee name badge in the registration area (Stockholmsmässan Exhibition and Convention Center, Hall B Foyer) during posted hours. Bring your confirmation email for faster badge retrieval at the self-check-in kiosks. Name badges are required for admission to all sessions, social events and the Exhibition Hall. Badges may be picked up during the following times:

Tuesday, 23 June, 2015 | 14:00 – 18:00
Wednesday, 24 June, 2015 | 7:30 – 20:00
Thursday, 25 June, 2015 | 8:15 – 18:30
Friday, 26 June, 2015 | 8:15 – 18:30
Saturday, 27 June, 2015 | 8:15 – 18:30

For hotel matters, please visit the housing assistance desk in the registration area Tuesday and Wednesday during registration hours.

MEDIA OFFICE

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

Wednesday, 24 June, 2015 | 8:00 – 16:00
Thursday, 25 June, 2015 | 8:00 – 16:00
Friday, 26 June, 2015 | 9:00 – 16:00
Saturday, 27 June, 2015 | 9:00 – 12:00

MEDIA PANELS
Thursday, 25 June, 2015 | 11:30 – 12:30
Friday, 26 June, 2015 | 11:30 – 12:30

SPEAKER READY ROOM

Speakers are welcome to review their uploaded presentations in the Speaker Ready Room during the following times:

Wednesday, 24 June, 2015 | 8:00 – 19:00
Thursday, 25 June, 2015 | 8:00 – 19:00
Friday, 26 June, 2015 | 8:00 – 19:00
Saturday, 27 June, 2015 | 8:00 – 16:30

LOST AND FOUND

Please bring found items to the registration area (Stockholmsmässan, Hall B Foyer). If you lost an item, stop by during registration hours for assistance.

STOCKHOLM CONVENTION BUREAU DELEGATE SERVICES

Visit the Stockholm Convention Bureau's hospitality desk at the Stockholmsmässan by the main West Entrance to plan your dining, activities, and tours.

Wednesday, 24 June, 2015 | 8:00 – 17:00
Thursday, 25 June, 2015 | 8:00 – 17:00
Friday, 26 June, 2015 | 8:00 – 17:00
Saturday, 27 June, 2015 | 8:00 – 15:00

MESSAGE CENTER

Post messages for friends and colleagues using the message board in ISSCR Central located in the Exhibition Hall (Stockholmsmässan, Hall B). Please note we are unable to page meeting delegates.

JOB OPPORTUNITIES
Need a job? Need to hire? Post resumes and employment opportunities on the designated board in ISSCR Central located in the Exhibition Hall (Stockholmsmässan, Hall B).

THINGS YOU SHOULD KNOW

RECORDINGS PROHIBITED
Still photography, video and/or audio taping of the sessions, presentations and posters at the ISSCR 2015 Annual Meeting is strictly prohibited. Intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation.

SMOKING
Smoking is prohibited in the Stockholmsmässan.

INTERNET ACCESS
Enjoy complimentary Wi-Fi throughout the Stockholmsmässan thanks to our supporter BioLamina.
To connect to the Wi-Fi:
1. Enable your wireless and search for open networks
2. Connect to the network called ISSCR2015
3. Open a web browser
4. You will be redirected to the landing page

ISSCR 2015 MOBILE APP
Have the ISSCR 2015 schedule in the palm of your hand thanks to our supporter AstraZeneca. Download the free ISSCR 2015 Mobile App from the Apple Store or Google Play to your smart phone and/or tablet 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
- Sync the app across all of your devices with Multi-Device Sync
- Receive important real-time communications from ISSCR
- Build a personalized schedule
- Bookmark exhibitors
- Rate the sessions you attend and comment on them, too
- Find attendees and connect with your colleagues through Friends
- Stay in-the-know and join in on social media with #ISSCR2015

GENERAL INFORMATION

Downloading the mobile app is easy! Simply go to the App Store or Google Play and search for "ISSCR 2015." For all other web-enabled devices, including tablets, Blackberry and Windows phones enter m.core-apps.com/isscr2015 into your browser to be automatically directed to the proper download version for your mobile device.

COAT CHECK

For your convenience, you may leave coats and bags in the designated zone near the Stockholmsmässan's West Entrance by the Victoria Hall room.

Wednesday, 24 June, 2015 | 8:30 – 21:00
Thursday, 25 June, 2015 | 8:30 – 20:30
Friday, 26 June, 2015 | 8:30 – 20:30
Saturday, 27 June, 2015 | 8:30 – 19:00

MOTHERS' ROOM

Room K3, near the Stockholmsmässan's Hall K Foyer in Level 1, is a private room available Wednesday, 24 June through Saturday, 27 June 8:00 – 17:00. If you require access outside these hours, please visit the registration area.

MEETING ROOMS

Sign up for first-come, first-served ISSCR ad hoc meetings in rooms K11-K13 located in the Stockholmsmässan, Hall K, Level 2. Sign-up sheets are posted outside each room listing available time slots for each day. Informal seating areas are also available throughout the Stockholmsmässan and Meet-Up Hubs in the Exhibition Hall.

PARKING

Parking is available at the Stockholmsmässan for 120 SEK daily or 40 SEK per hour. The parking fee in the Stockholmsmässan's outdoor parking lot is 100 SEK daily or 35 SEK per hour. The pay stations accept credit cards.

STOCKHOLMSMÄSSAN EXHIBITION AND CONVENTION CENTER

RESTAURANTS AND CAFÉS

There are many dining options in the Stockholmsmässan.

	Tuesday, 23 June	Wednesday, 24 June	Thursday, 25 June	Friday, 26 June	Saturday, 27 June
Flavour Kitchen		11:00-14:00	11:00-14:00	11:00-14:00	11:00-14:00
Flavour Bar	9:00-17:00	9:00-18:00	9:00-18:00	9:00-18:00	9:00-18:00
The Garden		11:00-14:00	11:00-14:00	11:00-14:00	11:00-14:00
Caffè Galleria		11:00-15.00	11:00-15.00	11:00-15:00	11:00-14:00

ISSCR MOBILE APP INFORMATION

HAVEN'T DOWNLOADED THE ISSCR 2015 MOBILE APP YET?

IT'S EASY, TRY ANY OF THESE THREE METHODS:

SEARCH the App Store and Google Play for "ISSCR 2015" . SCAN this OR code

For all other web-enabled devices including tablets, Blackberry and Windows phones enter "m.core-apps.com/isscr2015" into your browser and be automatically directed to the proper download version for your device.

Check out all of the mobile app features:

- Build a personalized schedule and bookmark exhibitors
- Search for scientific content, presenters, exhibitors and events
- Sync the app across all of your devices with

Multi-Device Sync

- Rate the sessions you attend and comment on them, too
- Browse through floor plans of the Exhibition Hall and the Convention Center

The ISSCR 2015 mobile app is supported by

AstraZeneca

ISSCR LEADERSHIP

BOARD OF DIRECTORS

OFFICERS

PRESIDENT
Rudolf Jaenisch
Whitehead Institute for Biomedical Research, USA

PRESIDENT ELECT
Sean J. Morrison
UT Southwestern Medical Center, USA

VICE PRESIDENT
Sally Temple
Neural Stem Cell Institute, USA

CLERK
George Q. Daley
Boston Children's Hospital, USA

TREASURER
Haifan Lin
Yale University School of Medicine, USA

PAST PRESIDENT
Janet Rossant
The Hospital for Sick Children Research Institute, Canada

DIRECTORS

Timothy Allsopp
Neusentis Regenerative Medicine, United Kingdom

Arturo Alvarez-Buylla
University of California San Francisco, USA

Nissim Benvenisty
Hebrew University, Israel

Hans C. Clevers
Hubrecht Institute, Netherlands

Hongkui Deng
Peking University, China

Connie J. Eaves
Terry Fox Lab BC Cancer Agency, Canada

Urban Lendahl
Karolinska Institutet, Sweden

Christine L. Mummery
Leiden University Medical Center, Netherlands

Hideyuki Okano
Keio University, School of Medicine, Japan

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

David T. Scadden
Massachusetts General Hospital and Harvard University, USA

Austin G. Smith
Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute, United Kingdom

Deepak Srivastava
Gladstone Institutes, USA

Elly Tanaka
DFG Research Center for Regenerative Therapies, Technische Universitaet Dresden, Germany

Amy Wagers
Joslin Diabetes Center, USA

Shinya Yamanaka
Center for iPS Cell Research and Application, Japan

EX OFFICIO MEMBERS

Elaine Fuchs
Rockefeller University, USA

Fred H. Gage
Salk Institute for Biological Studies, USA

Leonard I. Zon
Boston Children's Hospital, USA

ANNUAL MEETING PROGRAM COMMITTEE

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

Joshua M. Brickman
University of Copenhagen, Denmark

Anne Brunet
Stanford University School of Medicine, USA

Jacob Hanna
Weizmann Institute of Science, Israel

Gordon M. Keller
McEwen Centre for Regenerative Medicine, University Health Network, Canada

Urban Lendahl
Karolinska Institute, Sweden

Olle Lindvall
University of Lund, Sweden

Christine L. Mummery
Leiden University Medical Center, Netherlands

Charles Murry
University of Washington, USA

Hideyuki Okano
Keio University, School of Medicine, Japan

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

Austin G. Smith
Wellcome Trust-Medical Research Council Cambridge Stem Cell Institute, United Kingdom

Fiona M. Watt
Centre for Stem Cells and Regenerative Medicine, United Kingdom

Marius Wernig
Stanford University, USA

Owen N. Witte
University of California, Los Angeles/Howard Hughes Medical Institute, USA

Qi Zhou
Institute of Zoology, Chinese Academy of Sciences, China

Mark Zimmerman
Janssen, Pharmaceutical Companies of Johnson and Johnson, USA

EX OFFICIO MEMBER

Rudolf Jaenisch
Whitehead Institute for Biomedical Research, USA

COMMITTEES AND TASKFORCES

AUDIT
Allen C. Eaves, *Chair*
Valerie Horsley
Freda D. Miller
Martin F. Pera

AWARDS
John E. Dick, *Chair*
John B. Gurdon
Olle Lindvall
Jane E. Visvader

CLINICAL TRANSLATION
Armand Keating, *Chair*
Koichi Akashi
Benjamin Alman
Peter Coffey
Michele De Luca
Robert J. Deans
Connie J. Eaves
Catriona H.M. Jamieson
Robert Lanza
Richard T. Lee
Maria T. Millan
Charles Murry
Duanqing Pei
Fernando Pitossi
Mahendra Rao
David T. Scadden
Lorenz Studer
John W. Thomas
Daniel J. Weiss

ISSCR COMMITTEES

CLOSER LOOK WEBSITE REVIEW TASKFORCE

Megan Munsie, *Chair*
Clare Blackburn
Corey S. Cutler
Lawrence S.B. Goldstein
Nipan Israsena
Fernando Pitossi
Douglas A. Sipp

COMMUNIATIONS TASKFORCE

Shinya Yamanaka, *Chair*
Leonard I. Zon, *Chair*
Urban Lendahl
Sean J. Morrison
Janet Rossant
Deepak Srivastava
Sally Temple
Rudolf Jaenisch, *Ex Officio*

ETHICS AND PUBLIC POLICY

Jonathan Kimmelman, *Chair*
Aida I.A. Al-Aqeel
Timothy Caulfield
Lawrence S.B. Goldstein
Insoo Hyun
Kazuto Kato
Jason S. Robert
Beth Roxland
Jeremy Sugarman
Giuseppe Testa

FINANCE

Haifan Lin, *Chair*
Gregory A. Bonfiglio
Daniel Marshak
Sean J. Morrison
Sally Temple
David A. Westman

GUIDELINES UPDATE TASKFORCE

Steering Committee
Jonathan Kimmelman, *Chair*
Nissim Benvenisty
Timothy Caulfield
George Q. Daley
Helen E. Heslop
Insoo Hyun
Charles Murry
Douglas A. Sipp
Lorenz Studer
Jeremy Sugarman

Members
Jane F. Apperley
Roger A. Barker
Paolo Bianco
Annelien L Bredenoord
Christopher K. Breuer
Marcelle Cedars
Joyce Frey-Vasconcells
Ying Jin
Richard T. Lee
Christopher McCabe
Megan Munsie
Steven Piantadosi
Mahendra Rao
Masayo Takahashi
Mark Zimmerman

INDUSTRY

Timothy Allsopp, *Chair*
Jiwen Zhang, *Chair*
Asano Asami-Odaka
Joydeep Basu
Lauren Drowley
Julie Holder
Johan Hyllner
Ravi Jagasia
Anish Sen Majumdar
Chris Mason
Michael H. May
John D. McNeish
Kristian Tryggvason
Mark Zimmerman
Claudia Zylberberg

INTERNATIONAL AFFAIRS

Nissim Benvenisty, *Chair*
Andrew G. Elefanty, *Chair*
Salvador Aznar-Benitah
Cédric Blanpain
Hongkui Deng
Dieter Egli
Yukiko Gotoh
Ronald D. McKay
Lygia Pereira
Giuseppe Testa

JUNIOR INVESTIGATORS

Valentina Greco, *Chair*
Akitsu Hotta, *Chair*
Andrea Ditadi
Helmuth Gehart
Garrett Heffner
Keisuke Kaji
Esteban Orlando Mazzoni
Sarita Panula
Sacha Prashad
Keiyo Takubo
Julia Tischler

LEGISLATIVE EDUCATIONAL INITIATIVE

George Q. Daley, *Chair*
Lawrence S.B. Goldstein, *Chair*
Sean J. Morrison, *Chair*
Elena Cattaneo
R. Alta Charo
Jonathan Kimmelman
Alan O. Trounson
Shinya Yamanaka
Rudolf Jaenisch, *Ex Officio*

MEMBERSHIP

Martin F. Pera, *Chair*
Amander T. Clark
Outi Hovatta
Dan S. Kaufman
Linheng Li
Malin Parmar
Douglas A. Sipp
Elly Tanaka

NOMINATING
Janet Rossant, *Chair*
Nissim Benvenisty
Rudolf Jaenisch
Urban Lendahl
Haifan Lin
Sean J. Morrison
David T. Scadden
Sally Temple
Shinya Yamanaka

PUBLICATIONS
Arnold R. Kriegstein, *Chair*
Lior Gepstein
Konrad Hochedlinger
Haifan Lin
Christine L. Mummery
Huck Hui Ng
Hans R. Schöler
Joanna Wysocka
Leonard I. Zon

STRATEGIC OVERSIGHT
George Q. Daley, *Chair*
Nissim Benvenisty
Hideyuki Okano
Kathrin Plath
Elly Tanaka

ISSCR ABSTRACT REVIEWERS

Gregor B. Adams
Karen Adelman
Koichi Akashi
Warren S. Alexander
Robin Ali
Timothy Allsopp
Ernest Arenas
Sophie Astrof
Laure Bally-Cuif
Allison Bardin
Milena Bellin
Sean Bendall
Nissim Benvenisty
Paolo Bianco
Dominique Bonnet
Michael Brand
Annelien L. Bredenoord
Kristen J. Brennand
Christopher K. Breuer
Vania Broccoli
Jeremy Brockes
Oliver Brüestle
Michael Buszczak
Alexandra Capela
Stuart M. Chambers
Tao Cheng
Neil C. Chi
Eric Chiao
Susana Chuva de Sousa Lopes
Michael Clarke
Hans C. Clevers
Paul Coffer
Peter Coffey
Alan Colman
Bruce R. Conklin
Chad Cowan
Kevin D'Amour
Francesco Dazzi
Benjamin Dekel
Hongkui Deng
Chris N. Denning
Fiona Doetsch
Daniela Drummond-Barbosa
Elaine Dzierzak
Andrew G. Elefanty
Nicola Elvassore
Grigori N. Enikolopov
Anna Falk
Anne C. Ferguson-Smith
Willem E. Fibbe
Camilla Forsberg
Paul S. Frenette
Michaela Frye
Hironobu Fujiwara
Fred Gage
Shaorong Gao
Niels Geijsen
Lior Gepstein
Penney Gilbert
Richard J. Gilbertson
Joseph Gold
Steven A. Goldman
Azadeh Golipour
Berthold Gottgens
Magdalena Götz
Thomas Graf
Valentina Greco
May Griffith
Shukry Habib
Anna-Katerina Hadjantonakis
Petra Hajkova
Sian Harding
David Hay
Kristian Helin
Brigid L. Hogan
Valerie Horsley
Ya-Chieh Hsu
Lijian Hui
Natalia B. Ivanova
Kim B. Jensen
Weizhi Ji
Ying Jin
Naihe Jing
Jeffrey Karp
Dan S. Kaufman
David Kent
Carla Kim
Arnold R. Kriegstein
Michael Kyba
Michael Laflamme
François Lallemend
Fredrik Lanner
Tsvee Lapidot
Jonas Larsson
Katarina Le Blanc
Ruth Lehmann
Ross Levine
Qing Li
Melissa H. Little
Pentao Liu
Cristina Lo Celso
William Lowry

ISSCR ABSTRACT REVIEWERS

Jun Lu
Graziano Martello
Zubin Master
Erika L. Matunis
John D. McNeish
Alexander Meissner
Eran Meshorer
Hanna Mikkola
Jennifer L. Moody
Klaas Mulder
Kiran Musunuru
Shyh-Chang Ng
Emi Nishimura
Trista E. North
M. Cristina Nostro
Todd Nystul
Carmel Maureen O'Brien
Hideyuki Okano
Tamer T. Onder
Eirini Papapetrou
In-Hyun Park
Malin Parmar
Robert Passier
Thomas Perlmann
Kathrin Plath
Raymond Poot
Louise Purton
April Pyle
Shahin Rafii
Emma Rawlins
Bruno Reversade
Pamela G. Robey
Bernardus Antonius Roelen
Lee Rubin
Michael A. Rudnicki
Hannele Ruohola-Baker
Maike Sander
Henrik Semb
Yufang Shi
Paul Simmons
András Simon
Hongjun Song
Frank Staal
William L. Stanford
John Stingl
Stephen Strom
Lorenz Studer
Jeremy Sugarman
Atsushi Suzuki
Viviane Tabar
Yasuhiko Tabata
Takashi Tada
Elly Tanaka
Fuchou Tang
Ana Isabel Teixeira
Derk ten Berge
Paul J. Tesar
Giuseppe Testa
Fabian Theis
Emily Titus
David Traver
Alan O. Trounson
Ann Tsukamoto
Leigh Turner
Michael Underhill
Jane E. Visvader
Amy Wagers
Carol B. Ware
Paul Whiting
Ian Wilmut
Andrew Xiao
Yasuhiro Yamada
Yukiko Yamashita
Fanyi Zeng
Kang Zhang
Xiaoqing Zhang
Qiao Zhou
Hao Zhu
Jianhong Zhu
Leonard I. Zon
Thomas P. Zwaka

PRESIDENTIAL SYMPOSIUM - MANIPULATING STEM CELLS IN DEVELOPMENT AND DISEASE

FRED H. GAGE

Salk Institute For Biological Studies, USA

Fred H. Gage, a professor in the Laboratory of Genetics, joined the Salk Institute in 1995. Dr. Gage's work concentrates on the adult central nervous system and unexpected plasticity and adaptability to environmental stimulation that remains throughout the life of all mammals. In addition, he models human neurological and psychiatric disease in vitro using human stem cells. Finally his lab studies the genomic mosaicism that exists in the brain as a result of mobile elements that are active during neurogenesis. Prior to joining Salk, Dr. Gage was a professor of neuroscience at the University of California, San Diego. He is a Fellow of the American Association for the Advancement of Science, a member of the National Academy of Sciences, the Institute of Medicine, the American Philosophical Society and the American Academy of Arts and Sciences and a foreign member of the European Molecular Biology Organization. Dr. Gage served as president of the Society for Neuroscience (2002), and president of the International Society for Stem Cell Research (2011-2012).

JÜRGEN KNOBLICH

IMBA- Institute of Molecular Biotechnology, Austria

Jürgen Knoblich is a Senior Scientist and Deputy Scientific Director of IMBA-Institute of Molecular Biotechnology in Austria. He completed his PhD in the laboratory of Christian Lehner at the Friedrich Miescher Institute of the Max Planck Society in Tübingen. After a postdoctoral period in the laboratory of Yuh Nung Jan at the University of California, San Francisco he joined the Institute of the Max Planck Society in 1997 as a junior group-leader. In 2004, he moved to IMBA where he is now senior scientist and deputy director. The Knoblich lab uses Drosophila and mouse genetics as well as 3D culture models derived from human ES or iPS cells, to identify the molecular mechanisms that control asymmetric cell division and the balance between proliferation and differentiation in neural stem cell lineages.

SHINYA YAMANAKA

Kyoto University, Japan and University of California, San Francisco, USA

Shinya Yamanaka is a professor and the director of the Center for iPS Cell Research and Application (CiRA) at Kyoto University and a senior investigator at the Gladstone Institute of Cardiovascular Disease in San Francisco. Born in Osaka in 1962, he received his MD from Kobe University and his PhD from Osaka City University. After working as a postdoctoral fellow at Gladstone between 1993 and 1996, he took up an assistant professorship at Osaka City University in 1996 and an associate professorship at the Nara Institute of Science and Technology in 1999. Moving to Kyoto University in 2004, he reported in 2006 that his team succeeded in generating induced pluripotent stem (iPS) cells. For this discovery, Dr. Yamanaka received the 2012 Novel Prize in Physiology or Medicine.

FEATURED SPEAKERS

ANNE McLAREN MEMORIAL LECTURE

JEANNIE T. LEE

Howard Hughes Medical Institute, Harvard Medical School, and Massachusetts General Hospital, USA

Jeannie T. Lee is an Investigator of the Howard Hughes Medical Institute and professor of Genetics at Harvard Medical School. Dr. Lee specializes in the study of epigenetic regulation by long noncoding RNAs using X-chromosome inactivation as a model system. For her work on RNA-mediated chromatin change, Dr. Lee became the recipient of the 2010 Molecular Biology Prize from the National Academy of Sciences, USA. Dr. Lee is a Fellow of the American Association for the Advancement of Science, has been named a Distinguished Graduate Awardee of the University of Pennsylvania School of Medicine and has served on the Board of Directors of the Genetics Society of America. Dr. Lee began her work on epigenetic regulation at the Whitehead Institute/MIT with Rudolf Jaenisch and served as chief resident of clinical pathology at the Massachusetts General Hospital. As a young investigator, she received the Basil O'Connor Scholar Award from the March of Dimes and the Pew Scholars Award. In 2011, she co-founded RaNA Therapeutics to use the potential of long noncoding RNAs to treat disease.

ERNEST McCULLOCH MEMORIAL LECTURE

HIROMITSU NAKAUCHI

University of Tokyo, Japan and Stanford University, USA

After obtaining his MD and PhD degrees in Japan, Hiro Nakauchi went to Stanford University for post-doctoral position and isolated CD8 genes. After coming back to Japan, he started working on hematopoietic stem cells in his laboratory in RIKEN. In 1994, he became a professor of Immunology in the University of Tsukuba where he determined the phenotype of mouse hematopoietic stem cells and established an in vivo clonal analysis system. In 2002, he became a professor of Stem Cell Therapy in the Institute of Medical Science at the University of Tokyo (IMSUT). In 2008, he was appointed as a director of newly established Center for Stem Cell Biology and Regenerative Medicine in IMSUT. Recently, he began a new lab at the Institute of Stem Cell Biology and Regenerative Medicine, Stanford University. Goals of his work are to clarify the mechanism of stem cell self-renewal and to contribute to cell and gene therapy and regenerative medicine.

JOIN US IN HONORING THE RECIPIENTS OF THE 2015 ISSCR AWARDS

McEwen Award for Innovation
Presidential Symposium, Wednesday, 24 June

Supported by the McEwen Centre for Regenerative Medicine

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

IRVING WEISSMAN, ***Stanford School of Medicine, USA,*** and **HANS CLEVERS**, ***Hubrecht Institute, Netherlands,*** are the recipients of the 2015 McEwen Award for Innovation in recognition of their long-standing contributions to the field and their identification, prospective purification and characterization of somatic tissue-associated stem cells and advancement of their research findings toward clinical applications.

Join us for the 2015 award presentation which will take place during the Presidential Symposium on the afternoon of Wednesday, 24 June.

ISSCR Public Service Award
Presidential Symposium, Wednesday, 24 June

Supported by past and present members of the ISSCR board of directors

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

The 2015 ISSCR Public Service Award is presented to **ALAN TROUNSON**, ***MIMR-PHI Institute of Medical Research, Australia,*** in recognition of his service as a visible and effective spokesperson for the field on an international level. Dr. Trounson is renowned for his pioneering work in in vitro fertilization and other reproductive technologies, and was an early researcher and advocate for the use of human embryonic stem cells in medical research.

Join us for the 2015 award presentation which will take place during the Presidential Symposium on the afternoon of Wednesday, 24 June.

JOIN US IN HONORING THE RECIPIENTS OF THE 2015 ISSCR AWARDS

ISSCR-BD Biosciences Outstanding Young Investigator Award
Plenary VI: IMMUNOLOGY AND STEM CELLS, Saturday

Supported by BD Biosciences

The ISSCR-BD Biosciences Outstanding Young Investigator Award recognizes the exceptional achievements of an investigator in the early part of his or her independent career in stem cell research.

PAUL TESAR, ***Case Western Reserve University School of Medicine, USA,*** is the recipient of the seventh annual Outstanding Young Investigator Award. Dr. Tesar's studies have shaped the global understanding of both pluripotent stem cell and oligodendrocyte biology.

Join us for the 2015 award presentation which will take place during Plenary Session VI in the morning of Saturday, 27 June.

CONGRATULATIONS TO THE 2015 TRAVEL AWARD RECIPIENTS

PROUDLY SUPPORTED BY THE ISSCR

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Wassim Abou-Kheir
Melih Acar
Cantas Alev
Ana Amaral
Mariana Amorós
Cheen Euong Ang
Yen-Sin Ang
Christopher Antos
Amruta Barhanpurkar
Ori Bar-Nur
Karim Ben M'Barek
Ivan Carcamo-Orive
Diogo Castro
Kathryn Cheah
Ya-Wen Chen
Huan-Chieh Cho
Henia Darr
Andrea Ditadi
Carmen Dominguez-Brauer
Diana Dou
Mariane Fráguas
Layla Galindo
Shay Geula
Rajesh Gunage
Robert Hesse
Sara Howden
Yue Huang
Justin Ichida
David Kent
Satish Khurana
Agnete Kirkeby
Yuki Komurasaki
Larissa Langhi
Qian Yi Lee
Hongqing Liang
Alexander Lin
Troy Lund
Vrisha Madhuri
Zubin Master
Shannon McKinney-Freeman
Kenji Miki
Peter Nagy
Xavier Nissan
Takaaki Noguchi
Il-Hoan Oh
Hyemin Oh
Heather O'Leary
Sarita Panula
Phetcharat Phanthong
Stephanie Protze
Yoach Rais
Enrique Ros
Tyson Ruetz
Ido Sagi
Christina Schreck
Nikoletta Smyrni
Frank Soldner
Tian Tian
Olof Torper
Ras Trokovic
Aline Urban-Paffaro
Alexandra Van Keymeulen
Sandra Varum
Roman Vasyliev
Graham Walmsley
Yuan Wang
Uri Weissbein
Yasong Wu
Mitsutoshi Yamada
Huangtian Yang
Huijuan Yang
Atilgan Yilmaz
Bo Zhao
Daniel Zingg
Luis Zurkirchen

PROUDLY SUPPORTED BY THE BEIHAO STEM CELL AND REGENERATIVE MEDICINE TRANSLATIONAL RESEARCH INSTITUTE, CHINA

Rene Adam
Zhengwen An
Brian Ballios
Patrick Brauer
Chih-Chiang Chen
Jean-Pierre Etchegaray
Zhengliang Gao
Maneesha Inamdar
Ying Jin
Julien Legrand
Yu-Tsen Lin
Zhaoyu Lin
Pentao Liu
Hiroko Nobuta
Ursula Nosi
Duygu Payzin
Martyna Popis
Alexey Ruzov
Tammy Ryan
Hayami Sugiyama
Man Tong
Tudorita Tumbar
Kim Vanuytsel
Ami Watanabe
On Tik Wong
Chenlin Zhou

FOCUS SESSIONS

Wednesday, 24 June

8:30-12:30*

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

BIOTECHNOLOGY ENTREPRENEURIALISM: HOW SCIENTIFIC DISCOVERIES TRANSLATE INTO A BUSINESS OPPORTUNITY OR 'SO YOU WANT TO SPIN OUT A COMPANY!'

Room K1

8:30 - 12:30

Organized by: the ISSCR Industry Committee

Are you contemplating launching a start-up? Gain first-hand knowledge on how to develop a business case and pitch your idea. What are the expectations of venture capitalist and pharma when considering a new opportunity? What does the new company look like and how does it function? Don't miss this great opportunity to network with your peers and representatives from industry, academia and biopharma as well as successful entrepreneurs to discuss their personal experiences and view to expand your vision of novel funding models to help accelerate your research profile while potentially forging new collaborations.

8:30-08:40	**Introductory remarks: John D. McNeish,** *GlaxoSmithKline, ISSCR Industry Committee, USA and* **Mark Zimmerman**, *PhD, Janssen Research and Development LLC, ISSCR Industry Committee, USA*
8:40-10:40	**Part I. Case Studies** Academic to start-up experience **Kenneth R. Chien,** *Karolinska Institutet / Wallenberg-Karolinska CardioVascular Initiative, Moderna Therapeutics, Sweden* **Allen C. Eaves,** *STEMCELL Technologies Inc, Canada* **Hans S. Keirstead,** *NeoStem Oncology, USA* Venture capital perspective **Robert Millman, JD,** *CEO and Co-Founder, Semma Therapeutics, USA* Large biotechnology to startup experience **Thomas J. Livelli,** *Promega Corporation, USA*
10:40-11:00	**Break / Networking**
11:00-12:30	**Part II. Interactive Panel Discussion and Audience Discussion** **Kenneth R. Chien,** *Karolinska Institutet / Wallenberg-Karolinska CardioVascular Initiative, Moderna Therapeutics, Sweden* **Allen C. Eaves,** *STEMCELL Technologies Inc, Canada* **Hans S. Keirstead,** *NeoStem Oncology, USA* **Annika Espander,** *Asperia AB, Sweden* **Hans S. Keirstead,** *NeoStem Oncology, USA* **Thomas J. Livelli,** *Promega Corporation, USA* **Robert Millman,** *Semma Therapeutics, USA*

STEM CELL ENGINEERING

Room A2

8:30 - 12:30

Organized by: Kevin Healy, *University of California, Berkeley, USA* and **Todd McDevitt,** *Gladstone Institute, University of California San Francisco, USA*

Human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs) are unique and important sources for stem cell technologies. Due to their ability to differentiate into a variety of different cell populations, hESCs and hiPSCs are important sources for cell replacement therapies, tissue engineering strategies, and drug development and toxicity assessment. In the last decade, there have been numerous studies that demonstrate proof-of-concept for stem cell-based strategies to encourage the functional regeneration of tissues damaged by injury or disease. Furthermore, a number of groups have exploited hESCs and hiPSCs, differentiated into specific cells types (e.g., cardiomyocytes, hepatocytes) for drug screening and toxicity testing. New technologies are needed to address bottlenecks in exploiting stem cells for these emerging technologies. This Focus Session will expose attendees to novel engineering approaches in biomanufacturing, pro-survival systems for stem cell transplantation, and microphysiological systems (i.e., organs-on-a-chip). This session will appeal to attendees interested in clinical translation of stem cells and those interested in using these cells for drug screening regimens by allowing a pre-clinical drug 'design and test' workflow to identify efficacious and low toxicity drugs and drug combinations on various organs.

HUMANITY IN A DISH

Room A4

8:30 - 12:30

Organized by Chad A. Cowan, *Harvard University, USA*

Genome-wide association studies have identified many common genetic variants that influence human health and disease. In this focus session we will bring together experts in stem cell biology and human genomics to discuss recent progress and challenges in developing cell based functional genomic assays at scale for common diseases in cohort studies, as well as highlight iPSC resources available for genomic research. There will be two sessions:

1) **COREdinates: Stem Cell Core Facilities Group:** Highlighting the roles that core facilities play in cell therapies and disease modeling applications, including the production and banking of iPSC cohorts.
   Session Chair: Mark Tomishima, *Memorial Sloan Kettering Cancer Center, USA*

8:30 - 8:50 Overview of COREdinates and preclinical development work for Parkinson's consortia
Mark Tomishima, *Memorial Sloan Kettering Cancer Center, USA*

8:50 - 9:10 Essential 8™ Medium: New application horizons for culturing human pluripotent stem cells (hPSCs)
Roland Leathers, *Thermo Fisher Scientific, USA*

HUMANITY IN A DISH (continued)

Room A4

9:10 - 9:50 Are all iPSCs created equal? A comparison of iPSCs from different source tissue
Jennifer Moore, *RUCDR, USA*

9:30 - 9:30 Taming the beast; 5S practice applied to large scale iPSC production
Chris Kirton, *Sanger Institute, United Kingdom*

9:50 – 10:10 Realizing the potential: Ensuring accessibility of cell line and data resources
Tenneille Ludwig, *WiCell, USA*

2) **The Functional Annotation of Human Genetic Variants:** highlighting ongoing efforts in several labs to use large cohorts of iPSCs and genome editing to functionally characterize human genetic variants associated with common disease.
Session Chair: Cashell Jaquish, *NHLBI, USA*

10:10 - 10:30 The UK Human Induced Pluripotent Stem Cells Initiative (HIPSCI): Up date and application to metabolic disorders
Ludovic Vallier, *University of Cambridge, United Kingdom*

10:30 - 10:50 Directing iPSC to specific lineages
Mohan C Vemuri, *Thermo Fisher Scientific, USA*

10:50 - 11:10 Phenotypic similarities between iPSC derived endothelial cells and native pulmonary artery
Marlene Rabinovitch, *Stanford University, USA*

11:10 - 11:30 Generation of a cohort of human iPSC and iPSC-derived cardiomyocytes from 222 individuals to study the role of human variants in cardiac phenotypes
Kelly Frazer, *University of California San Diego, USA*

11:30 - 11:50 The Influence of donor age on genetic and epigenetic characteristics of iPSCs
Kristin Baldwin, *Scripps Research Institute, USA*

11:50 – 12:10 Using iPSC-derived cardiomyocytes for biomarker and drug development
Ulrich Broeckel, *Medical College Wisconsin, USA*

12:10 – 12:30 iPSC-based modeling of blood-born disease: clinical trials in a test tube
George Murphy, *Boston University, USA*

CRITICAL CHALLENGES INVOLVED IN MAKING LARGE SCALE HUMAN IPSC RESOURCES AVAILABLE TO A GLOBAL COMMUNITY

Room A6

8:30 - 12:30

Organized by Michael Sheldon, *RUCDR Infinite Biologics, Rutgers University, USA*
The session will address the major issues associated with ongoing international initiatives for large scale production of collections of iPSC lines. Topics for discussion will include the scientific applications of large collections, establishment of reference lines and standards for quality control, the challenges faced in distributing iPSCs across borders, and the role of funding agencies in support and coordination of large collections. An important thematic emphasis will be on the necessity for standardization and cooperation among the groups in this field from the earliest days. There will be two sessions:

1) **Quality Control and Characterization:** data requirements for iPSCs that are accepted by repositories for distribution, identifying a set of characterization assays that should be performed, how best to deal with documenting genomic stability and pluripotency, and repository logistics (sample handling, storage and distribution).

The central role of biorepositories in the iPSC field
Michael Sheldon, *RUCDR Infinite Biologics, USA*

Genetic stability of human pluripotent stem cells
Peter Andrews, *International Stem Cell Initiative (ISCI)/Sheffield, United Kingdom*

Procurement, banking, testing and supply of hPSCs for both research and clinical application experiences of the UK Stem Cell Bank and a consensus from the International Stem Cell Banking Initiative.
Glyn Stacey, *National Institute for Biological Standards and Control (NIBSC), United Kingdom*

The European Bank for induced pluripotent Stem Cells approach to cell line characterisation
Tim Allsopp, *European Bank for induced pluripotent Stem Cells (EBISC) / Pfizer, United Kingdom*

Standardized reagents to support iPS cell generation, validation, and banking
Erik Hadley, *STEMCELL Technologies, Canada*

2) **Informatics and Global Coordination:** harmonizing the various collections of hiPSCs around the world, working towards the creation of single (or centralized) portal(s) which allow us to search all of the iPSC repositories worldwide for a particular line, improving public awareness of the existence of these collections and how they can be accessed. Additionally, the important issues of intellectual property and regulatory hurdles to their dissemination, both to the academic and industrial communities, will be addressed.

hESCreg: Pluripotent stem cell registries for data comprehension and comparison
Andreas Kurtz, *Human Embryonic Stem Cell Registry (hESCreg), Germany*

Developing a single point of truth for iPSC information: An open- sourced, semantic web approach
Richard Pearse, *Eagle I, USA*

Standards for IPSC data storage and distribution
Ian Streeter, *European Molecular Biology Laboratory - European Bioinformatics Institute, United Kingdom*

IP and ethics consideration in stem cell distribution
Emmanuelle Astoul, *Wellcome Trust Sanger Institute, United Kingdom*

Challenges and opportunities in resource and data integration: an NIH perspective
David Panchision, *National Institute of Mental Health, USA*

MEET-UP SESSIONS

Meet-ups are opportunities for attendees to gather at a designated space and time to hold informal conversations around a shared topic or interest.

STEM CELL SCIENCE IN STOCKHOLM

Thursday, 25 June
12:15-13:00
Exhibition Hall Meet-up Hub 1

The Stockholm region holds an exceptional environment that brings great potential for fueling groundbreaking advances in the field of regenerative therapeutics. 'Stockholm - Center of Excellence Stem Cells' welcomes you to meet invited experts expanding their views regarding how to maximize your potential for discovery, development of therapeutic applications and commercial opportunities. Become part of the stem cell cluster in Stockholm, today!

MEET THE EDITORS OF STEM CELL REPORTS

Thursday, 25 June
15:15-16:00
Exhibition 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 you are interested in around open-access, scientific publishing. Hear more about what the journal means for the ISSCR now and heading into its third year.

GERMAN STEM CELL NETWORK

Thursday, 25 June
15:15-16:00
Exhibition Hall Meet-up Hub 2

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

LET'S TALK: 'A CLOSER LOOK'

Friday, 26 June
15:15-16:00
Exhibition Hall Meet-up Hub 1

The ISSCR's 'A Closer Look at Stem Cells' website has been reconfigured and re-launched. Join us to learn more about this invaluable source for reliable information and resources linking the broader community with the vibrant stem cell research sector. Through expanded content, including disease- and condition-specific information, improved visuals and dynamic content, this website builds on the existing ISSCR resources to inform the community of the state of progress and the field. Importantly, the content empowers those researching health care options to make smart decisions through an understanding of clinical translation and stem cell science.

CONTINUE THE CONVERSATION: INTERNATIONAL SOCIETIES AND NETWORKS

Friday, 26 June
15:15-16:00
Exhibition Hall Meet-up Hub 2

Join the ISSCR International Affairs Committee and representatives from international societies and networks for a discussion on how to foster communication and strengthen ties with each other and the ISSCR.

EARLY CAREER GROUP LEADER EVENT

HOW TO BUILD A SUCCESSFUL LAB: LEARNING FROM THE EXPERTS

Wednesday, 24 June
11:25-12:45
East Gallery

oirm Ontario Institute for Regenerative Medicine

Advance registration is required.
Supported by the Ontario Institute for Regenerative Medicine

The ISSCR board of directors invites early-career group leaders to join them for table-level conversations followed by a group discussion on the balance between investing in your people and in yourself to achieve the ultimate goal of moving science forward, publishing and obtaining grants.

JUNIOR INVESTIGATOR EVENTS

Attend networking and career-building sessions designed specifically for trainee members. Advance registration for these events is required.

MEET THE EXPERTS NETWORKING LUNCHES

Thursday, 25 June
11:30-13:00
East Gallery

Takeda

Supported by Takeda Pharmaceuticals

Friday, 26 June
11:30-13:00
East Gallery

Boston Children's Hospital Stem Cell Program · HSCI HARVARD STEM CELL INSTITUTE · CRM MGH CENTER FOR REGENERATIVE MEDICINE

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

These popular networking events provide the opportunity for junior investigators to meet stem cell leaders in a casual setting. Enjoy lunch and discussion with peers and an expert in the field. Experts will come from a variety of settings including industry, publishing, and academic research centers.

SPECIAL EVENTS

JUNIOR INVESTIGATOR SOCIAL NIGHT

Thursday, 25 June
21:00-24:00
München Bryggeriet
Torkel Knutssonsgatan 2, Stockholm

Supported by Karolinska Institutet

Always a highlight of the meeting, the Junior Investigator Social Night is where young investigators from around the world meet, mingle, dance and socialize. This fun-filled night of entertainment will take place at München Bryggeriet (Munich Brewery), located in the heart of Stockholm.

Advance registration is required. ISSCR annual meeting badge and photo ID required for entry.

CAREER PANEL: STRATEGIES FOR SUCCESS IN PUBLISHING –TRICKS OF THE TRADE

Saturday, 27 June
11:30-13:00
East Gallery

Presented by the ISSCR Junior Investigators Committee

Are you a graduate student or postdoc in the midst of writing your first paper and wondering which journal would be the best fit? Looking to maximize the visibility and impact of your research? Join our panel of experts to learn some tricks of the trade for getting your research results published and read. We will discuss strategies on how to be accepted in prestigious journals, scientific integrity, and the future of scientific publications. Don't miss this opportunity to have an in-depth look at the inner workings of scientific publishing.

PANELISTS

Hans C. Clevers, *Hubrecht Institute/University Medical Centre Utrecht and president of the Royal Netherlands Academy of Arts and Sciences, Netherlands*

Esteban O. Mazzoni, PhD, *assistant professor of biology, New York University, USA*

Christine Mummery, *Leiden University Medical Center and editor-in-chief of the ISSCR journal Stem Cell Reports, Netherlands*

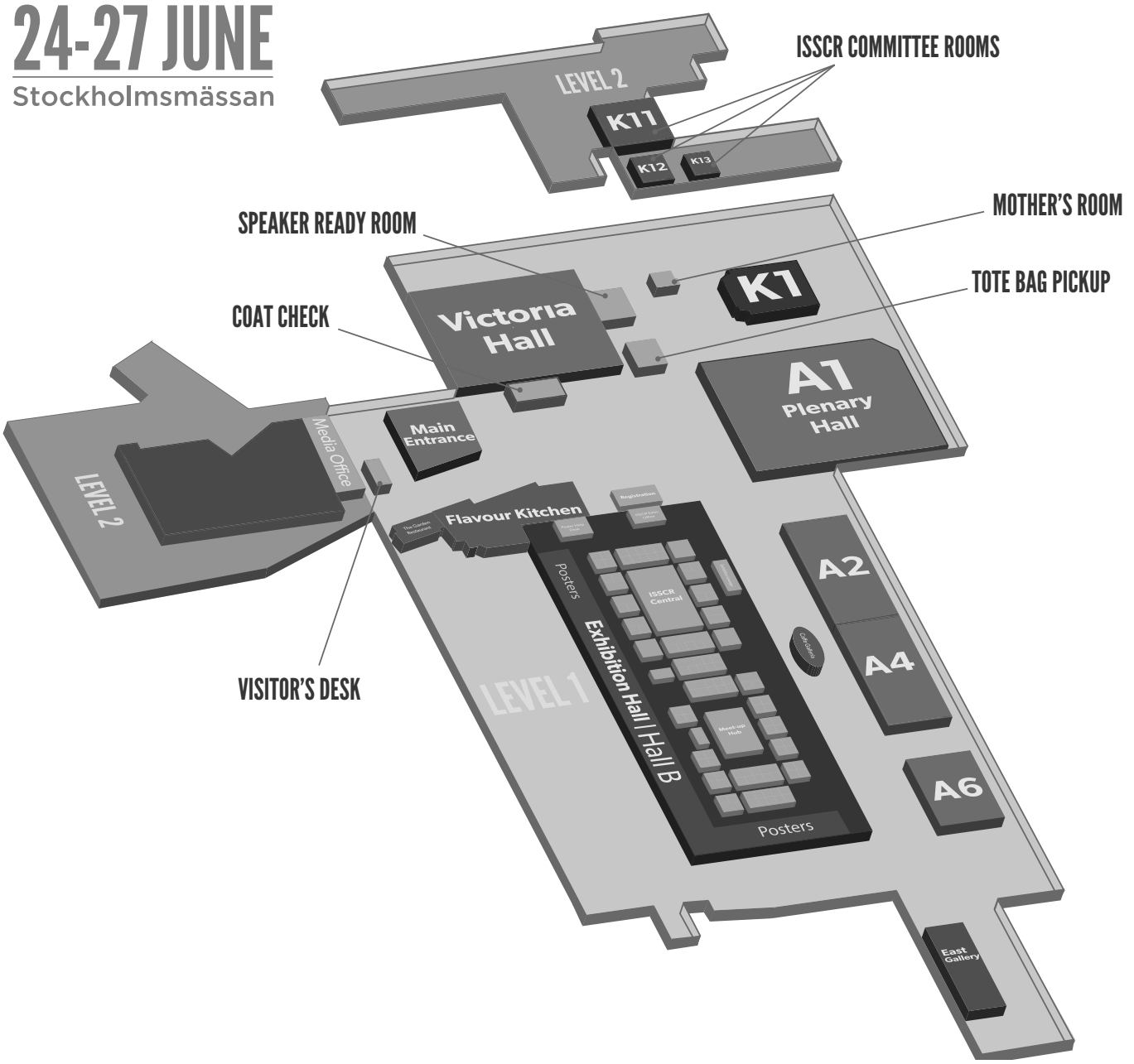
Deborah Sweet, *publishing director, Cell Press and editor-in-chief of Cell Stem Cell, USA*

Nathalie Le Bot, *senior editor, Nature, United Kingdom*

MODERATOR

Andrea Ditadi, *McEwen Centre for Regenerative Medicine and ISSCR Junior Investigators Committee, Canada*

ISSCR 2015
ANNUAL MEETING
STOCKHOLM | SWEDEN
24-27 JUNE
Stockholmsmässan



PROGRAM SCHEDULE

TUESDAY, 23 JUNE

14:00 - 18:00	REGISTRATION	Hall B Foyer

WEDNESDAY, 24 JUNE

7:30 - 20:00	REGISTRATION	Hall B Foyer
8:30 - 12:30	FOCUS SESSIONS	
	STEM CELL ENGINEERING *Presented by:* ***Kevin Healy,*** *University of California, Berkeley, USA and* ***Todd McDevitt,*** *Gladstone Institute, University of California San Francisco, USA*	Room A2
	HUMANITY IN A DISH *Presented by:* ***Chad Cowan,*** *Harvard University, USA*	Room A4
	CRITICAL CHALLENGES INVOLVED IN MAKING LARGE SCALE HUMAN IPSC RESOURCES AVAILABLE TO A GLOBAL COMMUNITY *Presented by:* ***Michael Sheldon,*** *RUCDR Infinite Biologics, USA*	Room A6
	BIOTECHNOLOGY ENTREPRENEURIALISM-HOW SCIENTIFIC DISCOVERIES TRANSLATE INTO A BUSINESS OPPORTUNITY OR SO YOU WANT TO SPIN OUT A COMPANY! *Presented by:* ***The ISSCR Industry Committee***	Room K1
11:25-12:45	EARLY CAREER GROUP LEADER LUNCHEON (Advance registration required)	East Gallery
13:00 - 15:15	PRESIDENTIAL SYMPOSIUM: MANIPULATING STEM CELLS IN DEVELOPMENT AND DISEASE *Supported by: Janssen Research & Development, LLC* **Chair: Rudolf Jaenisch,** *Whitehead Institute for Biomedical Research and MIT, USA*	Plenary Hall A1
13:00 - 13:10	WELCOME REMARKS	
13:10 - 13:20	PRESIDENT'S ADDRESS: **Rudolf Jaenisch,** *Whitehead Institute for Biomedical Research and MIT, USA*	
13:20 - 13:30	PRESENTATION OF THE MCEWEN AWARD FOR INNOVATION TO IRVING WEISSMAN AND HANS CLEVERS	
13:30 - 13:40	PRESENTATION OF THE ISSCR PUBLIC SERVICE AWARD TO ALAN TROUNSON	
13:40 - 14:00	**Fred H. Gage** Salk Institute for Biological Studies, USA SOMATIC MOSAICISM AND GENOMIC DIVERSITY	
14:00 - 14:20	**Jürgen Knoblich** *IMBA-Institute of Molecular Biotechnology, Austria* MODELING HUMAN BRAIN DEVELOPMENT AND DISEASE IN 3D CULTURE	
14:20 - 14:40	**Shinya Yamanaka** Center for iPS Cell Research and Application, Japan RECENT PROGRESS IN IPS CELL APPLICATION	

WEDNESDAY, 24 JUNE (continued)

14:40 - 15:10	**THE ANNE McLAREN MEMORIAL LECTURE:** **Jeannie T. Lee** *Massachusetts General Hospital and Harvard Medical School, USA* REGULATORY INTERACTIONS BETWEEN EPIGENETIC COMPLEXES AND THEIR RNA INTERACTOMES	
15:15 - 16:00	**REFRESHMENT BREAK**	Exhibition Hall B
15:15 - 20:30	**ISSCR EXHIBITION HALL OPEN**	Exhibition Hall B
16:00 - 18:05	**PLENARY II: REGENERATION AND ENGRAFTMENT** **Chair: Elaine Fuchs,** *Rockefeller University, USA*	Plenary Hall A1
16:00 - 16:20	**Jonas Frisen** *Karolinska Institutet, Sweden* ADULT NEUROGENESIS IN HUMANS	
16:25 - 16:45	**Kari K. Alitalo** *University of Helsinki, Finland* TARGETING ENDOTHELIAL GROWTH FACTOR PATHWAYS IN CANCER AND CARDIOVASCULAR DISEASE	
16:50 - 17:10	**Elly Tanaka** *DFG Research Center for Regenerative Therapies, Technische Universitaet Dresden, Germany* MOLECULAR CIRCUITRY CONTROLLING REGENERATION OF A PATTERNED LIMB	
17:15 - 17:25	**Poster Teasers**	
17:25 - 18:00	**THE ERNEST McCULLOCH MEMORIAL LECTURE:** **Hiromitsu Nakauchi** *University of Tokyo, Japan and Stanford University School of Medicine, USA* "STEM CELL NICHE" - FROM CELLS TO ORGANS AND BEYOND	
18:05 - 20:30	**OPENING RECEPTION** *Supported by: Wallenberg Institute for Regenerative Medicine (WIRM)*	Exhibition Hall B
18:30 - 20:30	**POSTER PRESENTATION I** ODD numbered posters presented 18:30 to 19:30 EVEN numbered posters presented 19:30 to 20:30	Exhibition Hall B

PROGRAM SCHEDULE

THURSDAY, 25 JUNE

8:15 - 18:30	**REGISTRATION**	Hall B Foyer
8:15 - 9:00	**MORNING COFFEE AND TEA**	Plenary Hall Foyer
9:00 - 11:20	**PLENARY III: DISEASE MODELING** *Supported by Burroughs Wellcome Fund* **Chair: Janet Rossant,** *The Hospital for Sick Children Research Institute, Canada*	Plenary Hall A1
9:00 - 9:20	**Carla Kim** *Boston Children's Hospital Stem Cell Program, USA* LUNG STEM CELL APPROACHES TO UNDERSTANDING DIFFERENTIATION, DISEASE AND THERAPY	
9:25 - 9:45	**Hans Clevers** *Hubrecht Institute, Netherlands* LGR5 STEM CELLS IN SELF-RENEWAL AND CANCER	
9:50 - 10:00	**Poster Teasers**	
10:00 - 10:20	**Nissim Benvenisty** *Hebrew University, Israel* MODELING EPIGENETIC DISORDERS USING HUMAN PLURIPOTENT STEM CELLS	
10:25 - 10:45	**Erika Sasaki** *Advanced Research Center, Keio University, Central Institute for Experimental Animals, Japan* TRANSGENIC MARMOSETS FOR MODELING HUMAN DISEASES AND DEVELOPING NEW REGENERATIVE THERAPIES	
10:50 - 11:10	**Steven A. Goldman** *University of Copenhagen, Denmark and University of Rochester Medical Center USA* HUMAN GLIAL PROGENITOR CELL-BASED TREATMENT AND MODELING OF NEUROLOGICAL DISEASE	
11:00 - 20:00	**ISSCR EXHIBITION HALL OPEN**	Exhibition Hall B
11:20 - 13:15	**LUNCH BREAK ON YOUR OWN**	
11:30 - 12:30	**INNOVATION SHOWCASES** **IRVINE SCIENTIFIC** Optimizing Ex Vivo Expansion, Differentiation and DMSO-Free Cryopreservation of Mesenchymal Stem/ StromalCells **Cyndi Kwan,** *Irvine Scientific* **Jessie H.-T. Ni,** *Irvine Scientific*	Room A2

THURSDAY, 25 JUNE (continued)

11:30 - 12:30	**INNOVATION SHOWCASES**	
	LONZA Smart Technologies for Advancing Stem Cell Research and Discoveries **Minh Hong,** *Lonza* **Pollyanna Goh,** *Queen Mary University of London* **Behnam Ahamadian,** *Lonza* **Richard L. Gieseck III,** *University of Cambridge, United Kingdom*	Room A4
	FLUIDIGM CORPORATION Bridging the Gap Between Cell Biology, Genomics, and Single-Cell Analysis **Adam Gracze,** *University of North Carolina, Chapel Hill, USA* **Candia Brown,** *Fluidigm*	Room A6
	STEMGENT, part of the ReproCELL Group Derivation of Clinically Relevant iPS Cell Lines from Human Blood-Derived Endothelial Progenitor Cells Using Self-Replicative RNA **Sarah Eminli-Meissner,** *Stemgent*	Room K1
	BIOLOGICAL INDUSTRIES An Innovative Serum-Free, Xeno-Free, Culture System for Expansion and Differentiation of Clinical Grade Human Mesenchymal Stem Cells **David Fiorentini,** *Biological Industries*	Victoria Hall
11:30 - 13:00	**MEET THE EXPERTS NETWORKING LUNCH** (Junior Investigator event; advance registration required) *Supported by: Takeda Pharmaceuticals International, Inc.*	East Gallery
12:15 - 13:00	**MEET-UPS** STEM CELL SCIENCE IN STOCKHOLM	Meet-up Hub 1
	WANT TO HEAR MORE ABOUT THE FIRST "EUROPEAN BANK FOR INDUCED PLURIPOTENT STEM CELLS"(EBiSC)?	Meet-up Hub 2
13:15 - 15:10	**CONCURRENT IA: NEURAL STEM CELLS AND DIFFERENTIATION** *Supported by: StemCells, Inc.* **Chair: Arturo Alvarez-Buylla,** *University of California, San Francisco, USA*	Room A2
13:25 - 13:45	**Magdalena Götz** *Institute of Stem Cell Research, Helmholtz Zentrum Muenchen, Germany* MECHANISMS OF ENDOGENOUS AND FORCED NEURONAL REPAIR	
13:50 - 14:02	**Stavros Taraviras** *Medical School, University of Patras, Greece* NEW PLAYERS CONTROLLING RADIAL GLIAL CELLS COMMITMENT AND DIFFERENTIATION TO EPENDYMAL CELLS	
14:05 - 14:17	**Moa Stenudd** *Karolinska Institutet, Sweden* SPINAL CORD EPENDYMAL CELLS ARE FUNCTIONALLY HETEROGENEOUS WITH RESTRICTED PROGENITOR CELLS AND STEM CELLS	

THURSDAY, 25 JUNE (continued)

13:15 - 15:10	**CONCURRENT IA: NEURAL STEM CELLS AND DIFFERENTIATION** (continued)	Room A2
14:20 - 14:32	**Diogo S. Castro** *Instituto Gulbenkian de Ciencia, Portugal* ASCL1/MASH1 COORDINATELY REGULATES GENE EXPRESSION AND THE CHROMATIN LANDSCAPE DURING NEUROGENESIS	
14:35 - 14:47	**Boaz P. Levi** *Allen Institute for Brain Science, USA* TRANSCRIPTOMIC CHARACTERIZATION OF SINGLE FIXED HUMAN RADIAL GLIAL PROGENITORS	
14:50 - 15:02	**Yechiel Elkabetz** *Tel-Aviv University, Israel* CONSECUTIVE BUILDING BLOCKS OF HUMAN NEURAL STEM CELL ONTOGENY DERIVED FROM PLURIPOTENT STEM CELLS: FUNDAMENTALS AND IMPLICATIONS	
13:15 - 15:10	**CONCURRENT IB: HEMATOPOIESIS** **Chair: George Q. Daley,** *Boston Children's Hospital, USA*	Room A4
13:25 - 13:45	**Hanna Mikkola** *University of California, Los Angeles, USA* TRANSCRIPTIONAL CONTROL OF HEMOGENIC ENDOTHELIUM FATE	
13:50 - 14:02	**Trista E. North** *Beth Israel Deaconess Medical Center, Harvard Medical School, USA* THE SEROTONERGIC NERVOUS SYSTEM REGULATES HEMATOPOIETIC STEM CELL PRODUCTION VIA THE HYPOTHALAMIC-PITUITARY-INTERRENAL AXIS	
14:05 - 14:17	**Heather Ann O'Leary** *Indiana University School of Medicine, USA* EXTRA PHYSIOLOGIC OXYGEN SHOCK/STRESS (EPHOSS) BLUNTS HEMATOPOIETIC STEM CELL PHENOTYPE/FUNCTION VIA REACTIVE OXYGEN SPECIES AND THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE	
14:20 - 14:32	**Eva M. Fast** *Harvard University, USA* REPROGRAMMING SHORT TERM BLOOD STEM CELLS TO A LONG TERM FATE BY PROSTAGLANDIN E2	
14:35 - 14:47	**Salemiz Sandoval** *University of California, Los Angeles, USA* THE OPPOSING ROLES OF LET-7C AND MIR-125 IN HUMAN HEMATOPOIETIC STEM CELL MAINTENANCE AND PROLIFERATION	
14:50 - 15:02	**Peter Geon Kim** *Boston Children's Hospital, USA* INTERFERON SIGNALING PROMOTES MATURATION OF AGM HSCS	

THURSDAY, JUNE 25 (continued)

13:15 - 15:10 **CONCURRENT IC: CONTROL AND INDUCTION OF PLURIPOTENCY** Victoria Hall
Chair: Hongkui Deng, *Peking University, China*

13:25 - 13:45 **Bing Lim**
Genome Institute of Singapore and Merck Research Lab, Singapore and Stanford University School of Medicine, USA
DIRECT REPROGRAMMING TO SOMATIC PROGENITOR CELLS: LINEAGE COMMITMENT REVISITED

13:50 - 14:02 **Ying Zhang**
Institute of Zoology, Chinese Academy of Sciences, China
M6A RNA METHYLATION IS REGULATED BY MICRORNAS AND PROMOTES REPROGRAMMING TO PLURIPOTENCY

14:05 - 14:17 **Kaloyan M. Tsanov**
Harvard Medical School, USA
LIN28 PHOSPHORYLATION COUPLES SIGNALING TO THE POST-TRANSCRIPTIONAL CONTROL OF PLURIPOTENCY

14:20 - 14:32 **Jennifer A. Mitchell**
University of Toronto, Canada
KLF4 NUCLEAR EXPORT REQUIRES ERK ACTIVATION AND INITIATES EXIT FROM NAIVE PLURIPOTENCY

14:35 - 14:47 **Joel W. Blanchard**
The Scripps Research Institute, USA
UNCOVERING NOVEL MECHANISMS AND INDUCERS OF PLURIPOTENCY VIA COMBINATORIAL ANTIBODY SCREENING

14:50 - 15:02 **Cynthia Bamdad**
Minerva Biotechnologies, USA
A PRIMITIVE GROWTH FACTOR IS SUFFICIENT TO INDUCE STABLE NAÏVE STATE HUMAN PLU RIPOTENCY VIA A LIF- AND FGF-INDEPENDENT PATHWAY; REPROGRAMMING IN THIS NOVEL GROWTH FACTOR CONFERS SUPERIOR DIFFERENTIATION

13:15 - 15:10 **CONCURRENT ID: SINGLE CELL BIOLOGY** Room A6
Supported by: Fluidigm Corporation
Chair: Fred H. Gage, The Salk Institute for Biological Studies, USA

13:25 - 13:45 **Fuchou Tang**
Peking University, China
DISSECTING GENE REGULATION NETWORK IN HUMAN EARLY EMBRYOS AT SINGLE-CELL AND SINGLE-BASE RESOLUTION

13:50 - 14:02 **Stefan Semrau**
Whitehead Institute for Biomedical Research, USA
EARLY LINEAGE BIFURCATION DURING DIFFERENTIATION OF EMBRYONIC STEM CELLS REVEALED BY SINGLE-CELL TRANSCRIPTOMICS

14:05 - 14:17 **Lakshmi Sandhow**
Karolinska Institutet, Sweden
EARLY B-CELL FACTOR 2 IDENTIFIES MESENCHYMAL STEM CELLS IN MOUSE SKIN TISSUE

THURSDAY, 25 JUNE (continued)

13:15 - 15:10	**CONCURRENT ID: SINGLE CELL BIOLOGY** (continued)	Room A6
14:20 - 14:32	**Victoria Moignard** *University of Cambridge, United Kingdom* DECODING THE REGULATORY NETWORK FOR BLOOD DEVELOPMENT FROM SINGLE-CELL GENE EXPRESSION MEASUREMENTS	
14:35 - 14:47	**Cole Trapnell** *University of Washington, USA* DEFECTS IN MYOGENIC TRANSDIFFERENTIATION REVEALED BY ALIGNMENT OF SINGLE-CELL PSEUDOTIME SERIES EXPERIMENTS	
14:50 - 15:02	**Nigel Kee** *Ludwig Institute for Cancer Research, Karolinska Institutet, Sweden* SINGLE CELL RNA SEQUENCING UNCOVERS CLOSE RELATIONSHIP BETWEEN DOPAMINE AND SUBTHALAMIC NUCLEUS NEURON LINEAGES	
13:15 - 15:10	**CONCURRENT IE: GERMLINE AND RNA BIOLOGY** **Chair: Kathrin Plath,** *University of California, Los Angeles School of Medicine, USA*	Room K1
13:25 - 13:45	**Haifan Lin** *Yale University School of Medicine, USA* UNITING MAJOR CONSTITUENTS OF THE GENOME: THE ROLE OF PIRNAS IN THE GERMLINE	
13:50 - 14:02	**Wei Jiang** *Boston Children's Hospital, USA* LNCRNA DEANR1 REGULATES HUMAN ENDODERM DIFFERENTIATION BY FACILITATING FOXA2 ACTIVATION	
14:05 - 14:17	**Alexey Ruzov** *University of Nottingham, United Kingdom* REARRANGEMENT OF CARBOXYLCYTOSINE PATTERNS INITIATES GENOME REPROGRAMMING DURING SPERMIOGENESIS	
14:20 - 14:32	**Bernard A. Roelen** *Utrecht University, Netherlands* PIWIL3 AND PIRNAS IN MAMMALIAN OOCYTES	
14:35 - 14:47	**Shay Geula** *Weizmann Institute of Science, Israel* GENETIC DISSECTION OF M6A RNA METHYLATION FUNCTION AND ROLE IN EARLY MAMMALIAN DEVELOPMENT	
14:50 - 15:02	**Henia Darr** *Ichan School of Medicine at Mount Sinai, USA* IDENTIFICATION OF TRANSLATIONAL NETWORKS ORCHESTRATING PLURIPOTENT CELL FATE THROUGH EIF4E REGULATION	
15:10 - 16:00	**REFRESHMENT BREAK**	Exhibition Hall B
15:15 - 16:00	**MEET-UPS**	
	MEET THE EDITORS OF STEM CELL REPORTS	Meet-up Hub 1
	GERMAN STEM CELL NETWORK	Meet-up Hub 2

THURSDAY, 25 JUNE (continued)

16:00 - 17:55 **CONCURRENT IIA: DISEASE MODELING** Victoria Hall
Chair: David Scadden, *Massachusetts General Hospital and Harvard Stem Cell Institute, USA*

16:10 - 16:30 **Hideyuki Okano**
Keio University School of Medicine, Japan
MODELING OF HUMAN NEUROLOGICAL / PSYCHIATRIC DISORDERS USING IPSC TECHNOLOGY AND TRANSGENIC NON-HUMAN PRIMATES

16:35 - 16:47 **Dalit Ben-Yosef**
Tel-Aviv Sourasky Medical Center and Tel-Aviv University, Israel
MOLECULAR AND FUNCTIONAL DEFICIENCIES IN FRAGILE X NEURONS DERIVED FROM HUMAN EMBRYONIC STEM CELLS

16:50 - 17:02 **Lindy Barrett**
Broad Institute, USA
UNBIASED INTERROGATION OF POLYGENIC BRAIN DISORDERS USING STEM CELL MODELS

17:05 - 17:17 **Xavier Nissan**
CECS I-Stem, France
DRUG SCREENING ON HUTCHINSON GILFORD PROGERIA USING PLURIPOTENT STEM CELLS REVEALS NEW PHARMACOLOGICAL MODULATORS OF PRELAMIN A FARNESYLATION

17:20 - 17:32 **Yen-Sin Ang**
Gladstone Institutes and University of California, San Francisco, USA
MODELING GATA4 HAPLOINSUFFICIENCY USING IPS-DERIVED CARDIOMYOCYTES REVEALS GENOME-WIDE INTERACTION WITH TBX5 AND HISTONE MODIFIERS NECESSARY FOR CARDIAC LINEAGE COMMITMENT AND FUNCTION

17:35 - 17:47 **Frank Soldner**
Whitehead Institute for Biomedical Research, USA
CONNECTING GENOTYPE TO DISEASE PHENOTYPE: DISSECTING THE EFFECT OF PARKINSON'S DISEASE ASSOCIATED RISK VARIANTS ON GENE EXPRESSION

16:00 - 17:55 **CONCURRENT IIB: STEM CELL REGULATORY NETWORKS AND MODELS** Room A2
Supported by: Stemgent, part of the ReproCELL Group
Chair: Austin G. Smith, *Wellcome Trust - Medical Research Council Cambridge Stem Cell Institute, United Kingdom*

16:10 - 16:30 **Joanna Wysocka**
Stanford University School of Medicine, USA
ON PECULIARITIES OF BEING A HUMAN: USING STEM CELLS TO STUDY HUMAN EVOLUTION AND HUMAN-SPECIFIC ASPECTS OF DEVELOPMENTAL GENE REGULATION

16:35 - 16:47 **Rene Christian Adam**
The Rockefeller University, USA
COUPLING PIONEER FACTORS AND SUPER-ENHANCERS TO GOVERN STEM CELL PLASTICITY AND LINEAGE CHOICE

THURSDAY, 25 JUNE (continued)

16:00 - 17:55 **CONCURRENT IIB: STEM CELL REGULATORY NETWORKS AND MODELS** (continued) Room A2

16:50 - 17:02 **Deanne J Whitworth**
University of Queensland, Australia
PLATYPUS INDUCED PLURIPOTENT STEM CELLS REVEAL THAT ACQUISITION OF SOX2 RESPONSIVENESS FACILITATED EXPANSION OF THE PLURIPOTENCY NETWORK DURING MAMMALIAN EVOLUTION

17:05 - 17:17 **Daniel Klimmeck**
German Cancer Research Center (DKFZ), Germany
IDENTIFICATION OF REGULATORY NETWORKS IN HSCS AND THEIR IMMEDIATE PROGENY VIA INTEGRATED PROTEOME, TRANSCRIPTOME, AND DNA METHYLOME ANALYSIS

17:20 - 17:32 **Pablo Navarro**
Institut Pasteur, France
MITOTIC INHERITANCE OF THE PLURIPOTENCY NETWORK ACTIVITY

17:35 - 17:47 **Micha Drukker**
Helmholtz Center Munich, Germany
THE CURIOUS CASE OF TROPHOBLAST DIFFERENTIATION FROM HUMAN PLURIPOTENT STEM CELLS

16:00 - 17:55 **CONCURRENT IIC: RELATIONSHIPS AND CLONALITY** Room A4
Chair: Sean Morrison, *Children's Research Institute at UT Southwestern, USA*

16:10 - 16:30 **Thomas P. Zwaka**
Icahn School of Medicine at Mount Sinai, USA
CELL COMPETITION IN PLURIPOTENT STEM CELLS

16:35 - 16:47 **Graham G. Walmsley**
Stanford University School of Medicine, USA
CHARACTERIZATION AND THERAPEUTIC MODULATION OF A DERMAL LINEAGE WITH INTRINSIC FIBROGENIC POTENTIAL

16:50 - 17:02 **Brian G. Ballios**
University of Toronto, Canada
INDUCTION OF ROD PHOTORECEPTOR-SPECIFIC PROGENITORS FROM ADULT MOUSE RETINAL STEM CELLS

17:05 - 17:17 **Arianna Baggiolini**
University of Zurich, Switzerland
GENETIC LINEAGE TRACING DEMONSTRATES MULTIPOTENCY OF PREMIGRATORY AND MIGRATORY NEURAL CREST CELLS IN VIVO

17:20 - 17:32 **Chee Jia Chin**
University of California, Los Angeles, USA
A QUANTITATIVE FRAMEWORK FOR INTERROGATING LINEAGE POTENTIAL VIA GENETIC TAGGING IN HIGHLY COMPLEX CELL POPULATIONS

THURSDAY, 25 JUNE (continued)

16:00 - 17:55	**CONCURRENT IIC: RELATIONSHIPS AND CLONALITY** (continued)	Room A4
17:35 - 17:47	**Andrea Ditadi** *McEwen Centre for Regenerative Medicine, Canada* THE HUMAN DEFINITIVE HEMOGENIC ENDOTHELIUM GENERATING MULTIPOTENT HEMATOPOIETIC PROGENITORS REPRESENTS A DISTINCT LINEAGE FROM ARTERIAL VASCULAR ENDOTHELIUM	
16:00 - 17:55	**CONCURRENT IID: STEM CELLS IN MODEL ORGANISMS** **Chair: Leonard I. Zon,** *Boston Children's Hospital, USA*	Room A6
16:10 - 16:30	**David Traver** *University of California, San Diego, USA* DECODING THE MOLECULAR CUES THAT REGULATE HSC SPECIFICATION	
16:35 - 16:47	**Rajesh Dattaram Gunage** *The National Centre for Biological Sciences – Tata Institute of Fundamental Research, India* NEW NICHE AND NOVEL STEM CELL DURING DEVELOPMENT OF DROSOPHILA MUSCULATURE	
16:50 - 17:02	**Valentina Greco** *Yale Medical School, USA* MESENCHYMAL INDUCED CELL DEATH AND EPITHELIAL PHAGOCYTOSIS REGULATE THE HAIR FOLLICLE STEM CELL POOL	
17:05 - 17:17	**Alexander Lin** *University of Toronto, Canada* YORKIE MEDIATES A SIZE SENSING MECHANISM DURING PLANARIAN REGENERATION	
17:20 - 17:32	**Christopher Antos** *DFG Research Center for Regenerative Therapies Dresden, Technische Universitaet Dresden, Germany* THE CALCINEURIN CONTROLS PROPORTIONAL GROWTH OF ZEBRAFISH REGENERATING FINS	
17:35 - 17:47	**Robert Hesse** *University of California, San Francisco, USA* MAMMALIAN ARF SUPPRESSES VERTEBRATE EPIMORPHIC REGENERATION	
16:00 - 17:55	**CONCURRENT IIE: CELL ADHESION, MOTILITY AND MIGRATION** **Chair: Elly Tanaka,** *DFG Research Center for Regenerative Therapies, Technische Universitaet Dresden, Germany*	Room K1
16:10 - 16:30	**Anna-Katerina Hadjantonakis** *Sloan-Kettering Institute for Cancer Research, USA* GUTS AND GASTRULATION: LIVE IMAGING CELL DYNAMICS TO INTERROGATE MORPHOGENESIS IN THE EARLY MAMMALIAN EMBRYO	

THURSDAY, 25 JUNE (continued)

16:00 - 17:55	**CONCURRENT IIE: CELL ADHESION, MOTILITY AND MIGRATION** (continued)	Room K1
16:35 - 16:47	**Troy C. Lund** *University of Minnesota, USA* SPECIFIC INHIBITION OF HEMATOPOIETIC CELL MIGRATION TO ADIPOGENIC MARROW - "NO PLACE TO HOME"	
16:50 - 17:02	**Layla Testa Galindo** *Federal University of São Paulo, Brazil* CHONDROITIN SULFATE BLOCKS NEURAL STEM CELL ENTRANCE INTO A BRAIN INJURY SITE THROUGH THE NOGO RECEPTOR AND RHOA/ROCK ACTIVATION	
17:05 - 17:17	**Enrique A Ros** *Universidad de los Andes, Chile* RAPID ASSESSMENT OF DIRECTED MIGRATION: A NOVEL MICROFLUIDIC-BASED 3D POTENCY TEST FOR COMBINATORIAL SCREENING OF STEM CELLS	
17:20 - 17:32	**Cantas Alev** *RIKEN Center for Developmental Biology, Japan* TRANSCRIPTOME ANALYSIS OF THE AVIAN PRIMITIVE STREAK REVEALS NOVEL MARKERS INVOLVED IN MESENDODERM DIFFERENTIATION OF HUMAN PLURIPOTENT STEM CELLS	
17:35 - 17:47	**Riina Harjumäki** *University of Helsinki, Finland* SILICA BIOREPLICATION PROVIDES NEW INSIGHTS INTO THREE-DIMENSIONAL STEM CELL SPHEROIDS	
18:00 - 20:00	**POSTER PRESENTATION II and RECEPTION** ODD numbered posters presented 18:00 to 19:00 EVEN numbered posters presented 19:00 to 20:00 *Reception supported by: Lonza*	Exhibition Hall B
21:00 - 00:00	**JUNIOR INVESTIGATOR SOCIAL NIGHT** (Junior Investigator event; advance registration required) *Supported by: Karolinska Institutet*	Münchenbryggeriet (Munich Brewery)

FRIDAY, 26 JUNE

8:15 - 18:30	REGISTRATION	Hall B Foyer
8:15 - 9:00	MORNING COFFEE AND TEA	Plenary Hall Foyer
9:00 - 11:20	PLENARY IV: PLURIPOTENCY AND MECHANISMS OF REPROGRAMMING **Chair: Shinya Yamanaka,** *Center for iPS Cell Research and Application, Japan*	Plenary Hall A1
9:00 - 9:25	ISSCR BUSINESS MEETING	
9:25 - 9:45	**Konrad Hochedlinger** *Howard Hughes Medical Institute and Harvard Medical School, USA* THE HISTONE CHAPERONE CAF-1 SAFEGUARDS SOMATIC CELL IDENTITY DURING TRANSCRIPTION FACTOR-INDUCED REPROGRAMMING	
9:50 - 10:10	**Amanda G. Fisher** *Imperial College London, United Kingdom* TITLE NOT AVAILABLE	
10:15 - 10:20	POSTER TEASERS	
10:25 - 10:45	**Austin G. Smith** *Wellcome Trust - Medical Research Council Stem Cell Institute, University of Cambridge, United Kingdom* PROGRESSION FROM THE EMBRYONIC STEM CELL GROUND STATE	
10:50 - 11:10	**Duanqing Pei** *Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, China* CELL FATE DECISIONS DURING SOMATIC CELL REPROGRAMMING	
11:00 - 20:00	ISSCR EXHIBITION HALL OPEN	Exhibition Hall B
11:20 - 13:15	LUNCH BREAK ON YOUR OWN	
11:30 - 12:30	INNOVATION SHOWCASES **Thermo Fisher Scientific** 11:30-12:00 Rapid and Quantitative Assessment of Human Pluripotent Cell Differentiation Potential **Alexander Meissner,** *Harvard Stem Cell Institute* 12:00 - 12:30 Developing a Patient-Derived Cardiac Disease Modeling Platform to Accelerate Early Stage Drug Discovery for Heart Disease **Andrew Lee,** *Stem Cell Theranostics, Inc.*	Room A2

FRIDAY, 26 JUNE (continued)

AJINOMOTO — Room A4

11:30 - 12:30

Culture Systems for The Safe Amplification and in Vitro Organogenesis of Human Pluripotent Cells
Tariq Enver, *University College London Cancer Institute*
Peter Andrews, *The University of Sheffield, Center for Stem Cell Biology*
Takanori Takebe, *Yokohama City University Graduate School of Medicine*

STEMCELL TECHNOLOGIES — Room A6

11:30 - 12:00

Methods and Culture Reagents to Maintain a Spectrum of Human Pluripotent Stem Cell States from Naïve-Like to Primed

Wing Chang, *STEMCELL Technologies*

12:00 - 12:30

Integrated Workflow for Reproducibly Modeling Neurological Disease Using Neuronal Subtypes and Astrocytes Derived from Human Pluripotent Stem Cells

Vivian Lee, *STEMCELL Technologies*

Xianmin Zeng, *XCell Science Inc. and Buck Institute*

CORNING — Victoria Hall

11:30 - 12:30

Stem Cell Culture, Differentiation and Scale-Up – Novel Technologies Enabling Research and Cell Processing Applications

Paula Flaherty, *Corning*

Deepa Saxena, *Corning*

BIO-TECHNE — Room K1

11:30 - 12:30

Standardized Stem Cell Differentiation: From Kits to Individualized Protocols

Joy Aho, *Bio-Techne*

11:30 - 13:00 — MEET THE EXPERTS NETWORKING LUNCH — East Gallery

Supported by: Boston Children's Hospital Stem Cell Program, MGH Center for Regenerative Medicine, and Harvard Stem Cell Institute

(Junior Investigator event; advance registration required)

13:15 - 15:10 — CONCURRENT IIIA: NEURAL DEGENERATION — Room A2

Chair: Sally Temple, *Neural Stem Cell Institute, USA*

13:25 - 13:45 — **Kevin C. Eggan**
Harvard University, USA
NEW IDEAS ABOUT ALS FROM STUDIES OF STEM CELL-DERIVED MOTOR NEURONS

FRIDAY, 26 JUNE (continued)

13:50 - 14:02 **Sol M. Reyna**
University of California, San Diego, USA
IPSC-DERIVED NEURONS WITH PS1 DE9 MUTATIONS HAVE REDUCED TRANSCYTOSIS DUE TO CALCIUM DYSREGULATION

14:05 - 14:17 **Justin K. Ichida**
University of Southern California, USA
THE LOSS OF C9ORF72 PROTEIN FUNCTION CAUSES THE DEGENERATION OF ALS PATIENT-DERIVED MOTOR NEURONS

14:20 - 14:32 **Hidetoshi Sakurai**
Center for iPS Cell Research and Application (CiRA), Kyoto University, Japan
ENGRAFTABLE MUSCLE STEM CELLS ARE GENERATED FROM HUMAN IPS CELLS WITHOUT MYOGENIC TRANSGENE INDUCTION

14:35 - 14:47 **Laura K. Hamilton**
Université de Montreal, Canada
ELEVATED OLEIC ACID LEVELS WITHIN THE FOREBRAIN STEM CELL NICHE SUPPRESS NEURAL STEM CELL ACTIVATION IN ALZHEIMER'S DISEASE

14:50 - 15:02 **Jacqueline P. Robbins**
King's College London, United Kingdom
THE AMYLOID CASCADE IN IPSC-DERIVED HUMAN CORTICAL NEURONS

13:15 - 15:10 **CONCURRENT IIIB: STEM CELLS AND CANCER** Room K1
Chair: Amy Wagers, *Harvard University, USA*

13:25 - 13:45 **Yasuhiro Yamada**
Center for iPS Cell Research & Application , Kyoto University, Japan
CANCER CELL REPROGRAMMING UNVEILS STABLE MAINTENANCE OF CANCER CELL IDENTITY THROUGH KEY ONCOGENIC SIGNALS

13:50 - 14:02 **Alexandra Van Keymeulen**
Université Libre de Bruxelles (ULB), Belgium
REACTIVATION OF MULTIPOTENCY BY ONCOGENIC PIK3CA INDUCES BREAST TUMOR HETEROGENEITY

14:05 - 14:17 **Hanna Sabelström**
University of California, San Francisco, USA
SOX9 AS A DOWN-STREAM TARGET IN RAS/MEK-DRIVEN PEDIATRIC GLIOMA

14:20 - 14:32 **Daniel Zingg**
University of Zurich, Switzerland
THE EPIGENETIC MODIFIER EZH2 CONTROLS MELANOMA METASTASIS THROUGH SILENCING OF TUMOR SUPPRESSIVE METABOLIC NETWORKS

FRIDAY, 26 JUNE (continued)

13:15 - 15:10 **CONCURRENT IIIB: STEM CELLS AND CANCER (continued)**

14:35 - 14:47 **Maria Anna Zipeto**
University of California, San Diego, USA
TARGETED REVERSAL OF INFLAMMATORY CYTOKINE DRIVEN ADAR1 LET-7 FAMILY EDITING IN CANCER STEM CELLS

14:50 - 15:02 **Catherin Niemann**
University of Cologne, Germany
INTERFERENCE WITH STEM CELL-SPECIFIC SURVEILLANCE MECHANISMS RESULTS IN SKIN TUMOUR INITIATION

13:15 - 15:10 **CONCURRENT IIIC: TRANSDIFFERENTIATION AND REPROGRAMMING** Victoria Hall
Chair: Timothy Allsopp, *Neusentis Regenerative Medicine, United Kingdom*

13:25 - 13:45 **Thomas Graf**
Center for Genomic Regulation, Spain
C/EBP ALPHA CREATES AN ELITE CELL STATE IN B CELLS

13:50 - 14:02 **Christophe Heinrich**
Grenoble Institute of Neurosciences-INSERM U 836, France
SOX2-INDUCED CONVERSION OF NG2 GLIA INTO NEURONS IN THE ADULT CEREBRAL CORTEX FOLLOWING ACUTE INVASIVE INJURY

14:05 - 14:17 **Yoach Rais**
Weizmann Institute of Science, Israel
HIGH-RESOLUTION MAPPING OF REPROGRAMMING EPIGENETICS FOLLOWING IDENTIFICATION OF MBD3/NURD COMPONENT GATAD2A AS A KEY TARGET FOR ACHIEVING DETERMINISTIC PLURIPOTENCY INDUCTION

14:20 - 14:32 **Ori Bar-Nur**
Harvard University, USA
PLURIPOTENCY FACTOR-INDUCED LINEAGE CONVERSION INVOLVES A TRANSIENT PASSAGE THROUGH AN IPS CELL STAGE

14:35 - 14:47 **Qian Yi Lee**
Stanford University, USA
UNRAVELLING THE DYNAMICS OF REPROGRAMMING OF FIBROBLASTS INTO NEURONS

14:50 - 15:02 **Tyson Joel Ruetz**
Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, United Kingdom
IDENTIFICATION OF A POTENT SIGNALLING PATHWAY THAT ORCHESTRATES BOTH REPROGRAMMING AND TRANSDIFFERENTIATION

FRIDAY, 26 JUNE (continued)

13:15 - 15:10 **CONCURRENT IIID: PANCREAS, LIVER, LUNG, INTESTINE** Room A6

Supported by: Novo Nordisk Foundation

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

13:25 - 13:45 **Henrik Semb**
Danish Stem Cell Center, Denmark
HOW TO MAKE BETA CELLS FOR CELL THERAPY IN DIABETES

13:50 - 14:02 **Valerie Gouon-Evans**
Icahn School of Medicine at Mount Sinai, USA
IDENTIFICATION OF AN ENDODERM-DERIVED KDR+ PROGENITOR WITH A BI-POTENT LIVER AND ENDOTHELIAL FATE

14:05 - 14:17 **Zhong-Dong Shi**
Sloan Kettering Institute, USA
GENOME EDITING IN HUMAN PLURIPOTENT STEM CELLS REVEALS DISTINCT AND OVERLAPPING ROLES OF GATA6 AND GATA4 IN HUMAN ENDODERM AND PANCREAS DEVELOPMENT

14:20 - 14:32 **Ya-Wen Chen**
Columbia University, USA
MODELING HUMAN BRANCHING MORPHOGENESIS USING HUMAN EMBRYONIC STEM CELLS IN VIVO

14:35 - 14:47 **Carmen Dominguez-Brauer**
Ontario Cancer Institute, Canada
DEFINING THE ROLE OF MULE IN INTESTINAL CANCER

14:50 - 15:02 **Katherine A. Benson**
Boston University School of Medicine, USA
HUMAN PLURIPOTENT STEM CELL MODELING OF AIRWAY EPITHELIAL DIFFERENTIATION

13:15 - 15:10 **CONCURRENT IIIE: EPITHELIAL AND MESENCHYMAL STEM CELLS** Room A4

Supported by: GE Healthcare Life Sciences

Chair: Andras Simon, *Karolinska Institutet, Sweden*

13:25 - 13:45 **Shahin Rafii**
Weill Cornell Medical College, USA
PLURIPOTENT-INDEPENDENT REGENERATION OF STABLE ORGANS ENABLED BY VASCULAR NICHE INDUCTION

13:50 - 14:02 **Alicia M. Farin**
Cedars-Sinai Medical Center, USA
P53 CONTROLS AIRWAY EPITHELIAL PROGENITOR CELL SELF-RENEWAL AND DIFFERENTIATION

FRIDAY, 26 JUNE (continued)

13:15 - 15:10	**CONCURRENT IIIE: EPITHELIAL AND MESENCHYMAL STEM CELLS (continued)**	Room A4
14:05 - 14:17	**Christine Anne Wells** *The University of Queensland, Australia* A MOLECULAR CLASSIFICATION OF MESENCHYMAL STEM CELLS	
14:20 - 14:32	**Denise Gay** *INSERM UMR 967, France* ROLES FOR MACROPHAGES IN WOUND-INDUCED HAIR FOLLICLE NEOGENESIS	
14:35 - 14:47	**Hiroaki Sugiyama** *Tokyo Women's Medical University, Japan* CELL-SHEET BASED STEM CELL THERAPY FOR OCULAR SURFACE	
14:50 - 15:02	**Violaine K. Harris** *Tisch MS Research Center of New York, USA* FDA-APPROVED PHASE I CLINICAL TRIAL INVESTIGATING INTRATHECAL MESENCHYMAL STEM CELL-DERIVED NEURAL PROGENITORS (MSC-NP) IN MULTIPLE SCLEROSIS: AN INTERIM ANALYSIS	
15:10 - 16:00	**REFRESHMENT BREAK**	Exhibition Hall B
15:15 - 16:00	**MEET-UPS**	
	LET'S TALK: A CLOSER LOOK WEBSITE	Meet-up Hub 1
	CONTINUE THE CONVERSATION: ISSCR INTERNATIONAL SOCIETIES AND NETWORKS	Meet-up Hub 2
16:00 - 17:55	**PLENARY V: THERAPY WITH STEM CELLS** *Supported by: Boehringer Ingelheim* **Chair: Hideyuki Okano,** *Keio University School of Medicine, Japan*	Plenary Hall A1
16:00 - 16:20	**Stephen Huhn** *StemCells, Inc., USA* CLINICAL TRANSLATION OF NEURAL STEM CELL TRANSPLANTATION: EMERGING SAFETY AND PRELIMINARY EFFICACY WITH HUMAN CENTRAL NERVOUS SYSTEM STEM CELLS, HUCNS-SC	
16:25 - 16:45	**Douglas A. Melton** *Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, USA* GENERATING FUNCTIONAL HUMAN BETA CELLS FROM STEM CELLS	
16:50 - 17:00	PATIENT ADVOCATE ADDRESS: **Marcus Storch,** *Tobias Foundation, Sweden* LAUNCHING A PRIVATE INITIATIVE IN A MONOPOLIZED HEALTH CARE SYSTEM: MY STORY BEHIND THE CREATION OF THE TOBIAS REGISTRY AND THE TOBIAS FOUNDATION	

FRIDAY, 26 JUNE (continued)

17:00 - 17:20	**Allan Robins** *ViaCyte, Inc., USA* DEVELOPMENT OF AN ENCAPSULATED STEM CELL THERAPY FOR DIABETES	
17:25 - 17:45	**Katarina Le Blanc** *Karolinska Institutet, Sweden* BRINGING MESENCHYMAL STEM CELLS INTO THE CLINIC	
18:00 - 20:00	**POSTER PRESENTATION III AND RECEPTION** ODD numbered posters presented 18:00 to 19:00 EVEN numbered posters presented 19:00 to 20:00	Exhibition Hall B

SATURDAY, 27 JUNE

8:15 - 18:30	**REGISTRATION**	Hall B Foyer
8:15 - 9:00	**MORNING COFFE AND TEA**	Plenary Hall Foyer
9:00 - 11:20	**PLENARY VI: IMMUNOLOGY AND STEM CELLS** *Supported by: Mesoblast* **Chair: Connie Eaves,** *Terry Fox Laboratory BC Cancer Agency, Canada*	Plenary Hall A1
9:00 - 9:20	**Carl H. June** *University of Pennsylvania School of Medicine, USA* ADOPTIVE T CELL THERAPY WITH ENGINEERED T CELLS	
9:25 - 9:45	**Patrick Aubourg** *Hôpital Bicêtre, France* HEMATOPOIETIC STEM CELL GENE THERAPY WITH LENTIVIRAL VECTOR IN 4 PATIENTS WITH CEREBRAL X-LINKED ADRENOLEUKODYSTROPHY: LONG-TERM OUTCOME	
9:50 - 10:10	**Juan Carlos Zúñiga-Pflücker** *University of Toronto, Canada* FROM STEM CELLS TO T CELLS, IN VITRO APPLICATIONS AND IN VIVO IMPLICATIONS	
10:10 - 10:30	**John Ioannidis** *Stanford University School of Medicine, USA* REPRODUCIBLE RESEARCH: CRISIS OR OPPORTUNITY?	

SATURDAY, 27 JUNE (continued)

10:40 - 11:15	**ISSCR-BD BIOSCIENCES OUTSTANDING YOUNG INVESTIGATOR AWARD PRESENTATION AND LECTURE** **Paul J. Tesar** *Case Western Reserve University, USA* PLURIPOTENT STEM CELL TECHNOLOGIES FOR UNDERSTANDING OLIGODENDROCYTE DEVELOPMENT AND DISEASE	
11:00 - 16:00	**ISSCR EXHIBITION HALL OPEN**	Exhibition Hall B
11:20 - 13:00	**LUNCH BREAK ON YOUR OWN**	
11:30 - 13:00	**JUNIOR INVESTIGATOR CAREER PANEL LUNCH** **STRATEGIES FOR SUCCESS IN PUBLISHING: TRICKS OF THE TRADE** (Junior Investigator event; advance registration required)	East Gallery
12:00 - 12:30	**INNOVATION SHOWCASES**	
	BD BIOSCIENCES Flow Cytometric Applications for Determining the Quality of Stem Cell Cultures **Nil Emre,** *BD Biosciences*	Room A2
	MERCK MILLIPORE From Research to GMP Manufacturing: A Guide to Translating Your Process **Julie Murrell,** *EMD Millipore*	Room A4
	MILTENYI BIOTECH Towards Clinical Workflows for Generating iPSCs and Functional Derivatives **Sebastian Knöbel,** *Miltenyi Biotec*	Room A6
	UNION BIOMETRICA Large Particle Flow Cytometry for Cells and Cell Clusters in Stem Cell Research **Rock Pulak,** *Union Biometrica*	Victoria Hall
	MERCK MILLIPORE Live Cell Analysis of Cancer Stem Cell Heterogeneity Based on Intracellular Biomarkers and Fluorescent Labelling of ALDHpos Cells **Vi Chu,** *EMD Millipore* **Victor Koong,** *EMD Millipore*	Room K1
13:15 - 15:10	**CONCURRENT IVA: ROAD TO THE CLINIC** **Chair: Deepak Srivastava,** *Gladstone Institutes, USA*	Room A4
13:25 - 13:45	**Robin Ali** *University College London, United Kingdom* RETINAL REPAIR THROUGH TRANSPLANTATION OF PHOTORECEPTORS	

SATURDAY, 27 JUNE (continued)

13:50 - 14:02 **Farid Boulad**
Memorial Sloan Kettering Cancer Center, USA
FIRST US PHASE I CLINICAL TRIAL OF GLOBIN GENE TRANSFER FOR THE TREATMENT OF BETA-THALASSEMIA MAJOR

14:05 - 14:17 **Mitsutoshi Yamada**
The New York Stem Cell Foundation Research Institute, USA
MITOCHONDRIAL COMPETITION AFTER NUCLEAR TRANSFER IN HUMAN OOCYTES

14:20 - 14:32 **Zubin Master**
Albany Medical College, USA
THE MORAL RESPONSIBILITIES OF ACADEMIC RESEARCH INSTITUTIONS TO SAFEGUARD THE INTEGRITY OF RESEARCH

14:35 - 14:47 **Klaus Zweckberger**
Department of Neurosurgery, University of Heidelberg, Germany
COMBINED TREATMENT OF SELF-ASSEMBLING PEPTIDES AND NEURAL PRECURSOR CELLS AFTER EXPERIMENTAL CERVICAL SPINAL CORD INJURY

14:50 - 15:02 **Sara Emily Howden**
Murdoch Children's Research Institute, Australia
SIMULTANEOUS REPROGRAMMING AND GENE CORRECTION OF PATIENT FIBROBLASTS

13:15 - 15:10 **CONCURRENT IVB: EPIGENETICS** Room A6
Chair: Haifan Lin, *Yale University School of Medicine, USA*

13:25 - 13:45 **Karen Adelman**
National Institute of Environmental Health Sciences, USA
PAUSING OF RNA POLYMERASE II REGULATES MAMMALIAN DEVELOPMENTAL POTENTIAL THROUGH CONTROL OF SIGNALING NETWORKS

13:50 - 14:02 **Iñigo Narvaiza**
The Salk Institute for Biological Studies, USA
COMPARATIVE EPIGENOMIC ANALYSIS OF REGULATORY ELEMENTS IN HUMAN AND CHIMPANZEE STEM CELLS

14:05 - 14:17 **Tahsin Stefan Barakat**
University of Edinburgh, MRC Centre for Regenerative Medicine, United Kingdom
STABLE X CHROMOSOME REACTIVATION IN FEMALE HUMAN INDUCED PLURIPOTENT STEM CELLS

14:20 - 14:32 **Tudorita Tumbar**
Cornell University, USA
SIGNALING COUPLES HAIR FOLLICLE STEM CELL QUIESCENCE WITH CHROMATIN STATES ASSOCIATED WITH PLASTICITY

SATURDAY, 27 JUNE (continued)

13:15 - 15:10	**CONCURRENT IVB: EPIGENETICS (continued)**	Room A6
14:35 - 14:47	**Yonatan Stelzer** *Whitehead Institute for Biomedical Research, USA* A NOVEL DNA METHYLATION REPORTER FOR REAL TIME TRACING OF EPIGENETIC CHANGES DURING DEVELOPMENT AND REPROGRAMMING, AT SINGLE CELL RESOLUTION	
14:50 - 15:02	**Juliane Schmidt** *Friedrich Miescher Institute for Biomedical Research, Switzerland* REGULATION OF MAMMALIAN DNA METHYLATION BY TRANSCRIPTION FACTOR BINDING	

13:15 - 15:10	**CONCURRENT IVC: MODELING DISEASE WITH IPSCS** **Chair: Nissim Benvenisty,** *Hebrew University, Israel*	Room A2
13:25 - 13:45	**Chad Cowan** *Harvard Stem Cell and Regenerative Biology, Harvard University, USA* ELUCIDATING METABOLIC DISEASE MECHANISMS USING HUMAN PLURIPOTENT STEM CELLS	
13:50 - 14:02	**Mingxia Gu** *Stanford School of Medicine, USA* PATIENT-SPECIFIC IPSC DERIVED ENDOTHELIAL CELLS UNCOVER MECHANISMS RELATED TO PENETRANCE OF A BMPR2 MUTATION IN CAUSING PULMONARY ARTERIAL HYPERTENSION	
14:05 - 14:17	**Junya Toguchida** *Institute for Frontier Medical Sciences, Kyoto University, Japan* ENHANCED CHONDROGENESIS OF INDUCED PLURIPOTENT STEM CELLS FROM PATIENTS WITH NEONATAL-ONSET MULTISYSTEM INFLAMMATORY DISEASE OCCURS VIA THE CASPASE 1-INDEPENDENT CAMP/PKA/CREB PATHWAY	
14:20 - 14:32	**Zhifen Chen** *Technical University of Munich, Germany* OPTICAL ACTION POTENTIAL RECORDING: A TOOL FOR CARDIAC DISEASE MODELING AND HIGH-THROUGHPUT DRUG SCREENING IN HIPSC-DERIVED CARDIOMYOCYTES	
14:35 - 14:47	**Josh Chenoweth** *Lieber Institute for Brain Development, USA* THERAPEUTIC STRATEGIES THAT TARGET GENETIC RISK FOR PSYCHIATRIC DISORDERS	
14:50 - 15:02	**Kim Vanuytsel** *Boston University School of Medicine, USA* INDUCED PLURIPOTENT STEM CELL (IPSC) MODELING REVEALS A ROLE FOR GROWTH DIFFERENTIATION FACTORS (GDFS) IN THE ETIOLOGY OF **B**-THALASSEMIA	

SATURDAY, 27 JUNE (continued)

13:15 - 15:10 **CONCURRENT IVD: TISSUE ENGINEERING; ORGAN DEVELOPMENT AND REGENERATION** — Victoria Hall

Chair: Thomas Perlmann, *Karolinska Institutet, Sweden*

13:25 - 13:45 **Christopher S. Chen**
Boston University and Harvard University, USA
FORCES, FORM, AND ENGINEERING CELL AND TISSUE FUNCTION

13:50 - 14:02 **Michael Brand**
TU Dresden, BIOTEC/CRTD, Germany
REGENERATION OF THE ADULT ZEBRAFISH BRAIN: THE ROLE OF LINEAGE CONVERSION

14:05 - 14:17 **Johnny Kim**
Max Planck Institute for Heart and Lung Research, Germany
FUNCTIONAL SYSTEMS ANALYSIS OF THE ADULT MUSCLE STEM CELL IDENTIFIES CRUCIAL REGULATORS OF MUSCLE REGENERATION

14:20 - 14:32 **Agnete Kirkeby**
Lund University, Sweden
MODELING HUMAN NEURAL TUBE ANATOMY THROUGH CULTURING OF STEM CELLS UNDER MICROFLUIDIC GRADIENTS

14:35 - 14:47 **Ruth Tevlin**
Stanford University, USA
IMPAIRMENT IN FRACTURE HEALING IN A MOUSE MODEL OF TYPE 2 DIABETES IS DRIVEN BY SKELETAL STEM CELL NICHE DYSREGULATION

14:50 - 15:02 **Iwan Jones**
Umeå University, Sweden
HUMAN EMBRYONIC STEM CELL DERIVED NEURAL CREST CELLS FOR PERIPHERAL NERVE REPAIR

13:15 - 15:10 **CONCURRENT IVE: STEM CELL NICHE** — Room K1

Chair: Hans C. Clevers, *Hubrecht Institute, Netherlands*

13:25 - 13:45 **Cristina Lo Celso**
Imperial College London, United Kingdom
PLASTIC INTERACTIONS BETWEEN NORMAL AND MALIGNANT HAEMATOPOIETIC CELLS AND THEIR BONE MARROW NICHES

13:50 - 14:02 **Christina Schreck**
Klinikum rechts der Isar der Technical University Munich, Germany
WNT5A EXPRESSED BY THE NICHE IS REQUIRED TO MAINTAIN MIGRATORY PROPERTIES OF HEMATOPOIETIC STEM CELLS THROUGH THE PLANAR CELL POLARITY PATHWAY

SATURDAY, JUNE 27 (continued)

13:15 - 15:10	**CONCURRENT IVE: STEM CELL NICHE (continued)**	Room K1
14:05 - 14:17	**Owen J. Tamplin** *Boston Children's Hospital, USA* COLONIZATION OF A HEMATOPOIETIC STEM CELL NICHE REVEALED BY LIGHTSHEET LIVE IMAGING OF THE ZEBRAFISH KIDNEY MARROW	
14:20 - 14:32	**Melih Acar** *UT Southwestern Medical Center, USA* DEEP IMAGING OF BONE MARROW SHOWS NON-DIVIDING HEMATOPOIETIC STEM CELLS ARE PERISINUSOIDAL	
14:35 - 14:47	**Shannon L. McKinney-Freeman** *St. Jude Children's Research Hospital, USA* FUNCTIONAL SCREEN IDENTIFIES NOVEL REGULATORS OF MURINE HEMATOPOIETIC STEM CELL ENGRAFTMENT	
14:50 - 15:02	**Il-Hoan Oh** *Catholic University of Korea, Medical School, Korea* MICROENVIRONMENTAL REMODELING AS A PARAMETER AND PROGNOSTIC FACTOR OF HETEROGENEOUS LEUKEMOGENESIS IN ACUTE MYELOID LEUKEMIA	
15:10 - 16:00	**REFRESHMENT BREAK**	Exhibition Hall B
16:00 - 18:20	**PLENARY VII: MAKING TISSUES AND ORGANS** **Chair: Gordon Keller,** *McEwen Centre for Regenerative Medicine, University Health Network, Canada*	Plenary Hall A1
16:00 - 16:10	President-elect address: **Sean J. Morrison,** *UT Southwestern Medical Center, USA*	
16:15 - 16:35	**Deepak Srivastava** *Gladstone Institutes, USA* CELLULAR REPROGRAMMING APPROACHES FOR CARDIOVASCULAR DISEASE	
16:40 - 17:00	**Amy Wagers** *Joslin Diabetes Center, Harvard University, Cambridge, MA, USA* LOCAL AND SYSTEMIC REGULATORS OF AGING PHENOTYPES IN MAMMALIAN TISSUES	
17:05 - 17:25	**Masayo Takahashi** *RIKEN Center for Developmental Biology, Japan* RETINAL CELL THERAPY USING IPS CELLS	
17:30 - 18:05	KEYNOTE LECTURE: **Robert Langer** *Massachusetts Institute of Technology, USA* NEW MATERIALS AND TISSUE ENGINEERING	
18:10 - 18:20	Closing Remarks	

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

Read about the latest research, breakthroughs, and ISSCR news with our two monthly e-newsletters!

The PULSE e-newsletter

Stay up-to-date on ISSCR news, the latest stem cell research news, scientific and industrial meetings, and more through The Pulse.

This monthly online publication has become a valuable resource for ISSCR members and the field for vetted, topical information.

ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

MEMBER News

Read about important ISSCR news, explore the Job Board, listen to the upcoming Stem Cell Podcast episodes, and more through the ISSCR exclusive Member News.

This monthly publication keeps members up-to-date on everything ISSCR-related, including our monthly Member Spotlight. You are automatically signed up to receive the Member News when you join or renew your membership with the ISSCR.

www.isscr.org

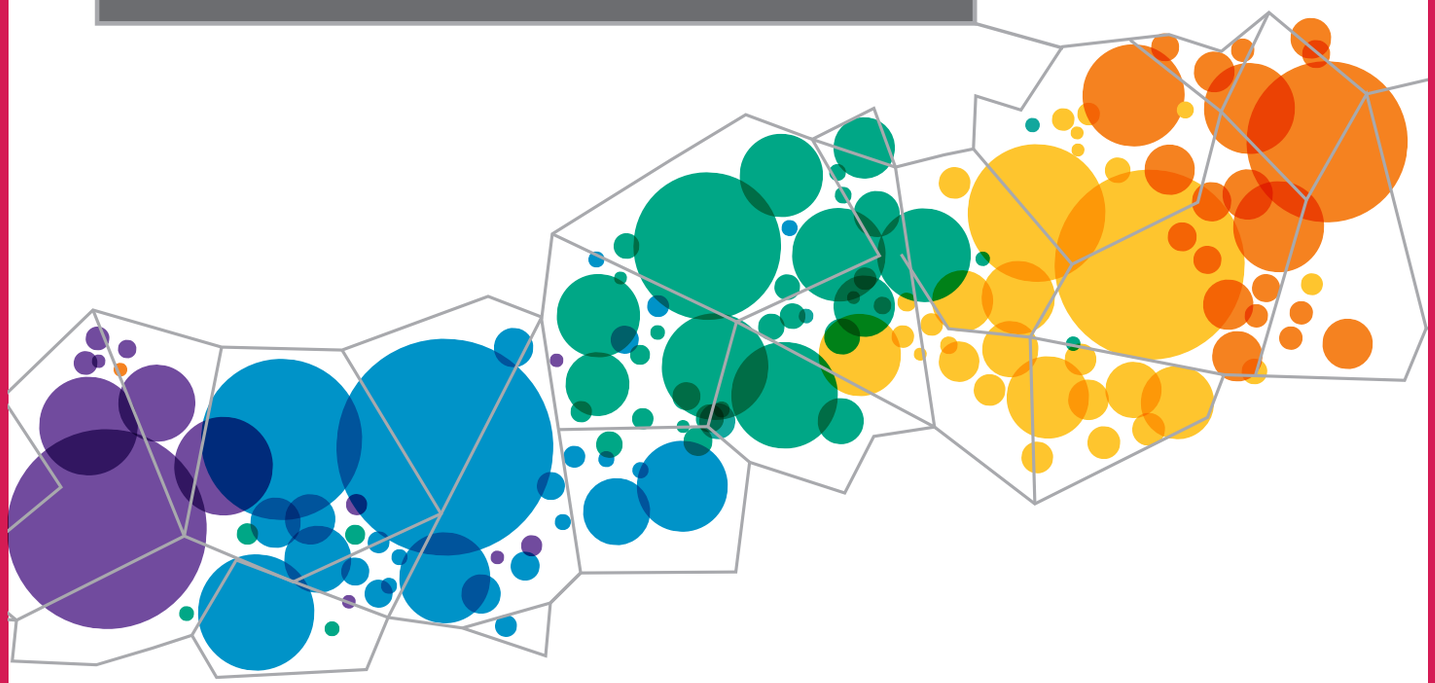
ISSCR INTERNATIONAL SOCIETY FOR STEM CELL RESEARCH

WWW.ISSCR.ORG

INTERNATIONAL 2016 SYMPOSIA

Save the Dates

for our 2016 International Symposia series:



DRESDEN
GERMANY
1-3 FEBRUARY

KYOTO
JAPAN
22-24 MARCH

FLORENCE
ITALY
18-20 OCTOBER

WEDNESDAY, 24 JUNE, 13:00 – 15:15

PRESIDENTIAL SYMPOSIUM: STEM CELLS, DEVELOPMENT AND DISEASE

PLENARY HALL A1

Supported by: Janssen Research & Development, LLC

SOMATIC MOSAICISM AND GENOMIC DIVERSITY

Gage, Fred H.

Laboratory of Genetics, Salk Institute for Biological Studies, La Jolla, CA, USA

The first part of the talk will focus on a recent model of human aging and the potential molecular signature that may reveal unexpected vulnerability in neuronal substructures. In the second part of the talk I will focus on the recent finding that LINE-1 (Long Interspersed Nucleotide Elements-1 or L1) retroelements are active in somatic neuronal progenitor cells (NPCs) providing an additional mechanism for neuronal diversification. Together with their relatives including Alus, retroelement sequences constitute nearly 50% of the mammalian genome with L1 elements alone representing 20%. The fact that L1 can retrotranspose in a defined window of neuronal differentiation, changing the genetic information in single neurons in random manner, allows the brain to develop in distinctly different ways. This characteristic of variety and flexibility may contribute to the uniqueness of an individual brain. Finally, we characterized induced pluripotent stem cells (iPSC) derived from somatic cells from humans, bonobos and chimpanzees. IPSC-derived mature neurons from all species were able to express basic properties of functioning neurons, but non-human primates' cells have a different gene expression profile and behave differently when compared to human cells. Some of these changes reveal a potential role for retroelement activity in human evolution.

MODELING HUMAN BRAIN DEVELOPMENT AND DISEASE IN 3D CULTURE

Lancaster, Madeline, Renner, Magdalena, Knoblich, Jürgen

IMBA-Institute of Molecular Biotechnology, Vienna, Austria

The human brain is highly unique in size and complexity. While many of its characteristics have been successfully studied in model organisms, recent experiments have emphasized unique features that cannot easily be modeled in animals. We have therefore developed a 3D organoid culture system derived from human pluripotent stem cells that recapitulates many aspects of human brain development. These cerebral organoids are capable of generating several brain regions including a well-organized cerebral cortex. Furthermore, human cerebral organoids display stem cell properties and progenitor zone organization that show characteristics specific to humans. Finally, we use both RNAi and patient specific iPS cells to model microcephaly, a human neurodevelopmental disorder that has been difficult to recapitulate in mice. This approach reveals premature neuronal differentiation with loss of the microcephaly protein CDK5RAP2, a defect that could explain the disease phenotype. Our data demonstrate an in vitro approach that recapitulates development of even this most complex organ, which can be used to gain insights into disease mechanisms.

RECENT PROGRESS IN IPS CELL APPLICATION

Yamanaka, Shinya

Center for iPS Cell Research and Application, Kyoto, Japan

Induced pluripotent stem cells (iPSCs) can proliferate almost indefinitely and differentiate into multiple lineages. These properties have made them invaluable tools for cell-based therapies, disease models and drug discovery. In fact, despite being a recent technology, the evolution of iPSCs is arguably without precedent in the medical sciences. We have been optimizing iPSC technologies for regenerative medicine by reducing the risk of tumorigenicity while maintaining iPSC induction at high efficiency. In 2014, the world's first clinical study using iPSCs was announced. Here, iPSC-derived RPE (retinal pigment epithelium) sheets were transplanted to treat age-related macular degeneration. Studies have also shown the benefits of iPSC-based treatments on other disorders, giving expectation that iPSC-based regenerative medicine will be widely used in the near future. We expect to commence clinical research using iPSCs for Parkinson's disease and thrombocytopenia in the next few years, but first must gauge the safety of the cells being transplanted. To further promote iPSC-based cell therapy, we have initiated an iPSC stock project in which iPSC clones are being established from donors with homologous HLA haplotype. Such clones should decrease the immune response and therefore lower the risk of transplant rejection. Other applications of iPSCs include drug screening, toxicity studies and the elucidation of disease mechanisms. In addition, iPSCs may have preventative measures, as they make it possible to predict the patient condition and provide a preemptive therapeutic approach to protect against the onset of disease or to establish personalized medicine. Moreover, accumulating evidence is demonstrating the benefits of iPSCs in drug repositioning or better assessing drug candidates that have been categorized as false-positive or false-negative based on conventional testing methods.

ANNE McLAREN MEMORIAL LECTURE

REGULATORY INTERACTIONS BETWEEN EPIGENETIC COMPLEXES AND THEIR RNA INTERACTOMES

Lee, Jeannie T.

Howard Hughes Medical Institute, Department of Molecular Biology, Massachusetts General Hospital, Boston, MA, USA, and Department of Genetics, Harvard Medical School, Boston, MA, USA

It has become increasingly clear that chromatin regulatory complexes associate with long noncoding RNA. Some, such as Polycomb repressive complex 2 (PRC2) and CTCF, have very large RNA interactomes. How is the specificity of interaction achieved and what are the consequences of interaction with RNA? The inactive X chromosome serves as an excellent model by which to investigate such questions. My presentation will focus on what we have learned about regulatory interactions between long noncoding RNA and specific chromatin factors that are important to the process of X-chromosome inactivation.

WEDNESDAY, 24 JUNE, 16:00 - 18:05

PLENARY II: REGENERATION AND ENGRAFTMENT

PLENARY HALL A1

ADULT NEUROGENESIS IN HUMANS

Frisen, Jonas

Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden

In most mammals, neurons are added throughout life in the hippocampus and olfactory bulb. The generation of new neurons in the adult brain serves to maintain a pool of neurons with unique properties, present for a limited time after their birth, which enable specific types of neural processing. Whether adult neurogenesis has decreased with evolution, and the possible extent of this process in humans, has long been a topic of debate. We have used histochemical and carbon dating approaches to assess the distribution and extent of adult neurogenesis in humans. Hippocampal neurons are generated throughout life in humans, with a turnover rate comparable in middle aged humans and mice. A larger subpopulation of hippocampal neurons is continuously exchanged in humans compared to mice and there is a smaller relative decline in neurogenesis during aging in humans compared to mice. Humans appear unique among mammals in that olfactory bulb neurons are as old as the individual, and there is no detectable adult olfactory bulb neurogenesis. Moreover, whereas there normally is little neurogenesis in the adult striatum in most mammals, this is an area relatively enriched in neuroblasts in the adult human brain, and where there is continuous generation of interneurons. Adult born striatal neurons are selectively depleted in patients with Huntington's disease. There is a unique pattern of adult neurogenesis in humans. We are currently exploring how this process is affected in diverse types of human pathology.

TARGETING ENDOTHELIAL GROWTH FACTOR PATHWAYS IN CANCER AND CARDIOVASCULAR DISEASE

Alitalo, Kari K.

Translational Cancer Biology Program and Wihuri Research Institute, University of Helsinki, Helsinki, Finland

During embryonic development, the blood vasculature develops from embryonic mesoderm via the migration and assembly of endothelial progenitor cells, a process called vasculogenesis. The embryonic blood vasculature then expands via angiogenesis, vessel remodelling and functional specialisation, giving rise to a second vascular system, the lymphatic vasculature. Our understanding of the cellular and molecular mechanisms underlying the formation and morphogenesis of the developing vasculature has progressed significantly in recent years, and this knowledge can now be used for therapeutic manipulation of the vascular system. Anti-angiogenic drugs are used in the treatment of cancer patients, but most patients are either refractory or eventually acquire resistance to anti-angiogenic therapeutics. A combination of angiogenesis inhibitors based on solid knowledge of the major interacting angiogenesis signaling pathways could significantly advance the efficacy of the tumor therapy. The opposite idea of pro-angiogenic therapy in cardiovascular disease is to grow new functional blood vessels and thus restore blood flow to ischemic tissue. Several attempts have been made to stimulate angiogenesis and arteriogenesis in tissue ischemia, with limited success. One of the obstacles has been the property of vascular endothelial growth factor to promote vascular permeability, which can be therapeutically targeted in a variety of disease models by using angiopoietins. The growth of lymphatic vessels, lymphangiogenesis, regulates a number of pathological processes including tissue inflammation and tumor dissemination but is insufficient in patients suffering from lymphedema, a debilitating condition characterized by chronic tissue edema and impaired immunity. Lymphangiogenic growth factors provide possibilities to treat these diseases. Increased understanding of vascular growth factor biology should facilitate development of therapeutics also for cardiovascular and regenerative medicine.

MOLECULAR CIRCUITRY CONTROLLING REGENERATION OF A PATTERNED LIMB

Tanaka, Elly

DFG Research Center for Regenerative Therapies, Technische Universität Dresden, Dresden, Germany

Salamander limb regeneration is an outstanding paradigm for regeneration complex patterned, multi-tissue structures. In this system our work and the work of others indicate that connective tissue cells harbor critical information about their position in the limb, and this positional memory is used during regeneration to elicit limb outgrowth and formation of the appropriate, missing portion. How these cells know their position in the limb, and what to form after amputation are essential questions to understand. Classical experiments have shown that interaction of anterior specified and posterior specified tissue is required for limb outgrowth. We have delineated the molecular circuitry underlying the interaction of anterior and posterior cells that is required to integrate growth and patterning to elicit regeneration of a fully patterned limb.

POSTER TEASERS

W-1358
IDENTIFICATION OF CRITICAL FUNCTIONS OF DISC1 IN MAJOR MENTAL ILLNESS

Srikanth, Priya, Muratore, Christina, Selkoe, Dennis, **Young-Pearse, Tracy L.**

Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

W-1028
HETEROGENOUS EXPRESSION OF IMMUNOMODULATORY MOLECULES BY ACTIVATED HUMAN BONE MARROW-DERIVED MESENCHYMAL STROMAL CELLS

Schepers, Koen, Wiekmeijer, Anna-Sophia, Sakamoto, Yuichi, Ji, Yu, Schrama, Ellen, Roelofs, Helene, Fibbe, Willem

Immunohematology and Blood Transfusion, LUMC, Leiden, Netherlands

W-1380
ESTABLISHMENT IN CULTURE OF MOUSE EXPANDED POTENTIAL STEM CELLS

Ryan, David, Wang, Wei, Tsang, Jason, Yang, Jian, **Liu, Pentao**

Wellcome Trust Sanger Institute, Cambridge, United Kingdom

W-1347
CORRECTED MUTATION BY GENE TARGETING IN PATIENT-DERIVED IPS CELLS RESCUES DISEASE PHENOTYPES AND IDENTIFIES A CANDIDATE PHARMACOLOGICAL INTERVENTION

Nobuta, Hiroko[1], Yang, Nan[2], Ng, Yi Han[2], Marro, Samuele[2], Rowitch, David H.[1], Wernig, Marius[2]

[1]University of California, San Francisco, San Francisco, CA, USA, [2]Stanford University, Stanford, CA, USA

W-1375
IN VITRO DIFFERENTIATION OF HUMAN EMBRYONIC STEM CELLS INTO OVARIAN FOLLICLE-LIKE CELLS

Kee, Kehkooi[1], Jung, Dajung[1], Li, Lin[1], Xiong, Jie[1], Qin, Xunsi[2], Chen, Shunfeng[2], Luo, Mengyuan[1], Peng, Jia[3], Matzuk, Martin M.[3], Shen, Wei[2]

[1]Tsinghua University School of Medicine, Beijing, China, [2]Key Laboratory of Animal Reproduction and Germplasm Enhancement in Universities of Shandong, Qingdao Agricultural University, Qingtao, China, [3]Centers for Drug Discovery and Reproductive Medicine, Baylor College of Medicine, Houston, TX, USA

ERNEST McCULLOCH MEMORIAL LECTURE

STEM CELL NICHE - FROM CELLS TO ORGANS AND BEYOND

Nakauchi, Hiromitsu[1,2,3]

[1]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA, [2]Division of Stem Cell Therapy, Center for Stem Cell Biology and Regeneration Medicine, The Institute of Medical Science, The University of Tokyo, Japan, [3]Japan Science Technology Agency, ERATO, Nakauchi Stem Cell and Organ Regeneration Project, Japan

Hematopoietic stem cells (HSCs) are the best studied stem cells. They have played a flagship role in stem cell biology, providing a number of conceptual ideas and models. Among them is the concept of the "niche", a special bone-marrow microenvironment that by exchanging cues regulates stem-cell fate (self-renewal, differentiation, hibernation, and proliferation). The HSC niche also plays an important role in HSC transplantation (HSCT). Successful engraftment of donor HSCs critically depends on myeloablative pretreatment to empty the niche, such as high-dose irradiation or chemotherapy. While HSCT can be life-saving, myeloablation causes many treatment-associated deaths

and secondary complications. Recently we discovered in mice that one of the essential amino acids is indispensable for proliferation and survival of HSCs. Dietary restriction of this amino acid alone drastically reduced HSC numbers, emptied the BM niche, and promoted engraftment of donor HSCs without myeloablation. Since human HSCs also require this same amino acid, these findings raise the possibility that dietary restriction of this amino acid alone may permit novel non-myeloablative pre-treatment in HSCT. The concept of the stem-cell niche was further extended to generation of organs. We postulated that an "organ niche" exists in a developing animal and that this niche was empty when development of an organ is genetically disabled. This organ niche, we reasoned, should be compensated developmentally by blastocyst complementation using wild-type pluripotent stem cells. We provided proof of principle of organogenesis from xenogeneic pluripotent stem cells (PSCs) in an embryo unable to form a specific organ, demonstrating in mouse the generation of functionally normal rat pancreas by injecting rat PSCs into Pdx1-/- (pancreatogenesis-disabled) mouse embryos. This principle has held in large animals such as pigs. When pancreatogenesis-disabled pig embryos were complemented with blastomeres from wild-type pig embryos to produce chimeric pigs, the chimeras had normal pancreata and survived to adulthood. Demonstration of generation of a functional organ from PSCs in pigs is a very important step toward generation of human cells, tissues, and organs from individual patients' own PSCs. Analogy with the HSC niche, postulating the embryonal "organ niche", has proved intellectually useful. To extend the analogy to tumor biology, postulating a "leukemic/cancer stem cell niche", may not be too far-fetched. To define the precise components and mechanisms of the HSC niche, and to develop ways to manipulate them, seem likely to be valuable in hematologic medicine. Definition and manipulation of their counterparts in various embryonal niches and malignancy niches may be valuable in regenerative medicine and tumor therapy. The next few years' work in these areas, extending and précising our knowledge of "the niche", thus offers exciting promise.

THURSDAY, 25 JUNE, 9:00 - 11:20

PLENARY III: DISEASE MODELING

PLENARY HALL A1

Supported by Burroughs Wellcome Fund

LUNG STEM CELL APPROACHES TO UNDERSTANDING DIFFERENTIATION, DISEASE AND THERAPY

Kim, Carla

Boston Children's Hospital Stem Cell Program, Boston, MA, USA

Homeostasis in the normal lung and epithelial repair in the injured lung involve the stimulation of region-specific stem/progenitor cell populations that reside in distinct niches. In the distal lung, tissue regeneration and repair is carried out by epithelial stem/progenitorpopulations, including bronchioalveolar stem cells (BASCs), bronchiolar club (Clara) cells, alveolar type II cells (AT2 cells) and alveolar progenitors. These multipotent stem cells repair epithelial cell injury, yet it is unknown howstem cells are instructed to selectively replace the injured lineage. We developed clonal three-dimensional (3D) co-culture techniques with endothelial cells and distal lung stem cells to probe the instructive mechanisms. Single bronchioalveolar stem cells (BASCs) had bronchiolar and alveolar differentiation potential in lung endothelial cell co-cultures. Using these systems, we have discovered a new BMP-NFATc1/calcineurin/TSP1 pathway in lung endothelial cells that drives alveolar lineage-specific BASC differentiation. Discovery of this pathway points to methods to direct the derivation of specific lung epithelial lineages from multipotent cells. These findings elucidate a pathway that may be a critical target in lung diseases and lung cancer and provide new tools to understand the mechanisms of respiratory diseases at the single cell level. More detailed insight into how this pathway regulates differentiation will be discussed.

LGR5 STEM CELLS IN SELF-RENEWAL AND CANCER

Clevers, Hans

Royal Netherlands Academy of Arts and Sciences and University Medical Centre, Hubrecht Institute, Utrecht, Netherlands

The intestinal epithelium is the most rapidly self-renewing tissue in adult mammals. We originally defined Lgr5 as a Wnt target gene, transcribed in colon cancer cells. Two knock-in alleles revealed exclusive expression of Lgr5 in cycling, columnar cells at the crypt base. Using lineage

tracing experiments in adult mice, we found that these Lgr5+ve crypt base columnar cells (CBC) generated all epithelial lineages throughout life, implying that they represent the stem cell of the small intestine and colon. Lgr5 was subsequently found to represent an exquisitely specific and almost 'generic' marker for stem cells, including in hair follicles, kidney, liver, mammary gland, inner ear, tongue and stomach epithelium. Single sorted Lgr5+ve stem cells can initiate ever-expanding crypt-villus organoids, or so called 'mini-guts' in 3D culture. The technology is based on the observation that Lgr5 is the receptor for a potent stem cell growth factor, R-spondin. Similar 3D cultures systems have been developed for the Lgr5+ve stem cells of stomach, liver, pancreas and kidney. Intestinal cancer is initiated by Wnt pathway-activating mutations in genes such as APC. As in most cancers, the cell of origin has remained elusive. Deletion of APC in stem cells, but not in other crypt cells results in progressively growing neoplasia, identifying the stem cell as the cell-of-origin of adenomas. Moreover, a stem cell/progenitor cell hierarchy is maintained in early stem cell-derived adenomas, lending support to the "cancer stem cell"-concept.

POSTER TEASERS

T-1035

REGULATION OF STEM TO PROGENITOR TRANSITION IN THE MESENCHYME STEM CELL NICHE

An, Zhengwen, Sharpe, Paul

King's College London, London, United Kingdom

T-1094

HEMATOPOIETIC STEM CELLS DEVELOP IN THE ABSENCE OF ENDOTHELIAL CADHERIN 5

Anderson, Heidi[1], Patch, Taylor[1], Reddy, Pavankumar N.G.[2], Hagedorn, Elliottt J.[2], Kim, Peter G.[2], Chen, Michael J.[2], Bauer, Daniel E.[2], Frye, Maike[3], Vestweber, Dietmar[3], Paw, Barry[1], Zon, Leonard [1,4], Orkin, Stuart H.[5], Daley, George Q.[2], Shah, Dhvanit Indravadan[1]

[1]Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, [2]Pediatrics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, [3]Max Planck Institute for Molecular Biomedicine, Muenster, Germany, [4]Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, [5]Dana Farber Cancer Institute, Harvard Medical School, Boston, MA, USA

T-1312

CRYOPRESERVED DOPAMINE NEURONS DERIVED FROM HUMAN IPSC MAINTAIN MIDBRAIN LINEAGE AFTER TRANSPLANTATION IN ANIMAL MODELS OF PARKINSON'S DISEASE

Wakeman, Dustin R.[1], Hiller, Benjamin M.[1], Marmion, David J.[1], McMahon, Christopher W.[2], Kordower, Jeffrey H.[1]

[1]Neurological Sciences, Rush University, Chicago, IL, USA, [2]Cellular Dynamics International, Madison, WI, USA

T-1260

IN VIVO REPROGRAMMING OF STRIATAL NG2 GLIA INTO FUNCTIONAL NEURONS THAT INTEGRATE INTO LOCAL HOST CIRCUITRY

Torper, Olof Anders, Ottosson, Daniella Rylander, Lau, Shong, Grealish, Shane, Parmar, Malin

Developmental and Restorative Neurobiology, Lund University, Lund, Sweden

T-1191

SMEK1/2 IS A NUCLEAR CHAPERONE FOR CLEAVED WNT RECEPTOR RYK, A NOVEL NON-CANONICAL WNT SIGNALING PATHWAY REGULATING NEURAL CELL FATE DETERMINATION

Chang, Wen-Hsuan[1], Choi, Si Ho[2], Gao, Fan[1], Moon, Byoung San[1], Lu, Wange[3], Lyu, Jungmook[4]

[1]Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, University of Southern California, Los Angeles, CA, USA, [2]Dongnam Institute of Radiological and Medical Sciences, Busan, Korea, [3]The Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, University of Southern California, Los Angeles, CA, USA, [4]Department of Ophthalmology and Visual Science, College of Medicine, Catholic Institute for Visual Science, Seoul, Korea

MODELING EPIGENETIC DISORDERS USING HUMAN PLURIPOTENT STEM CELLS

Benvenisty, Nissim

Hebrew University, Jerusalem, Israel

Human pluripotent stem cells hold the promise to change the way we model human genetic and epigenetic disorders. Parental imprinting is a form of epigenetic regulation by which genes are expressed exclusively according to their parent-of-origin. In humans, aberrations of imprinted genes are linked with several diseases, developmental disorders and malignancies. To analyze the role of parental imprinting in human embryogenesis, we generated parthenogenetic

human induced pluripotent stem (iPS) cells, having only maternal chromosomes. By comparing the gene expression profile of parthenogenetic and normal pluripotent stem cells, we have identified multiple novel imprinted genes, and uncovered their potential targets. In addition, in vitro and in vivo differentiation assays were conducted to examine the developmental potential of these cells. To uncover the epigenetic landscape of parthenogenesis we mapped global DNA methylation levels in these cells. Our study identified multiple imprinted differentially methylated regions (iDMRs). These include iDMRs in loci associated with human disorders, and a novel class of intergenic iDMRs. By differentiating human parthenogenetic iPS cells into different cell types and combining DNA methylation with a 5' RNA sequencing methodology, we were able to identify tissue- and isoform-dependent imprinted genes in a genome-wide manner. We demonstrate that nearly half of all imprinted genes express both biallelic and monoallelic isoforms that are controlled by tissue-specific alternative promoters. The major genetic disorder that involves loss of expression of paternally imprinted genes is Prader-Willi syndrome (PWS). To model PWS in humans we generated patient-derived iPS cells, and studied molecular aspects of this disease. Unexpectedly, our analysis uncovered up-regulation of maternally imprinted genes residing on chromosome 14. Such crosstalk between two imprinted regions suggests a more complex regulation of imprinting than previously appreciated. Our results emphasize the usefulness of human pluripotent stem cells in studying human epigenetic disorders, and particularly in modeling imprinting diseases.

TRANSGENIC MARMOSETS FOR MODELING HUMAN DISEASES AND DEVELOPING NEW REGENERATIVE THERAPIES

Sasaki, Erika

Advanced Research Center, Keio University, Tokyo, Japan

Several stem cell lines have been established in the last decade, including human iPS and mesenchymal stem cells, and these stem cells have been used to develop new regenerative medicines. These new therapies are offering much hope by promising to greatly extend the number and range of patients who could benefit from transplants. Before these stem cell therapies can be used clinically, their short- and long-term safety and efficacy must be examined thoroughly. However, in vivo experiments are inappropriate for assessing the safety and efficacy of stem cells or stem-cell-derived tissue transplantation from an ethical standpoint. Therefore, preclinical studies using animal models, including non-human primates, are essential. To assess the safety and efficacy of stem cell therapies, we are attempting to establish a non-human primate experimental animal system for regenerative medicine using the common marmoset (Callithrix jacchus). The common marmoset is useful in biomedical research. It is an anthropoid primate that routinely ovulates multiple oocytes per ovarian cycle, has a relatively short gestation period, and reaches sexual maturity at around 1.5 years of age. Additionally, several reproductive techniques have been established for the common marmoset, such as ovarian cycle synchronization and efficient protocols for superovulation and in vitro fertilization. These features enable studies of reproductive biology and the development of genetically modified primates. Using these biological characteristics, several transgenic human disease marmosets with germline transmission of the transgene have been established. With the success of these transgenic marmosets, research into human disease, physiology, and the development of drug therapies is expected to increase. Furthermore, recently developed genome-editing technologies have accelerated the production of genetically modified human disease models in non-human primates. These transgenic marmosets will provide powerful preclinical models for studies in regenerative medicine.

HUMAN GLIAL PROGENITOR CELL-BASED TREATMENT AND MODELING OF NEUROLOGICAL DISEASE

Goldman, Steven A.

University of Copenhagen, Copenhagen , Denmark and University of Rochester Medical Center, Rochester, NY, USA

The most abundant precursor cells of the adult human brain are glial progenitor cells, which can give rise to both astrocytes and oligodendrocytes. As a result, diseases of glial cells may provide readily accessible targets for cell-based therapies. The myelin diseases, which involve the loss or dysfunction of oligodendrocytes in the brain and spinal cord, are among the most prevalent and disabling conditions in neurology, and may be particularly appropriate targets for progenitor cell-based therapy. This talk will focus on the potential utility of human glial and oligodendrocyte progenitor cell transplantation as a means of treating both congenital and acquired diseases of myelin. It will cover potential sources of both tissue and stem cell-derived glial progenitor cells, as well as the use of human iPSC-derived glial progenitors in myelin repair, and the potential limitations on the clinical use of each. The talk will also include a description of the glial chimeric mice that result from the neonatal implantation of human glial progenitors into the mouse brain. In these mice, the human glial progenitors out-compete their murine counterparts to eventually dominate the glial population of the recipient brains. Human glial chimerization has

significant effects on neurophysiology and behavior, which suggest the importance of human-specific glial attributes to neural network function, and thus the potential for glial contributions to human-specific neurodegenerative and psychiatric disorders. By generating human glial chimeric mice using hiPSC-derived glial progenitors, we may now investigate the phenotype-selective role of glia in human brain disease, by producing patient-derived and disease-specific human glial chimeras. These mice provide us a new model system within which to study not only the myelin disorders, but the entire range of human neurological and neuropsychiatric diseases in which glia may causally participate.

THURSDAY, 25 JUNE, 13:15 - 15:10

CONCURRENT IA: NEURAL STEM CELLS AND DIFFERENTIATION

ROOM A2

Supported by StemCells, Inc.

MECHANISMS OF ENDOGENOUS AND FORCED NEURONAL REPAIR

Götz, Magdalena, Ninkovic, Jovica, Gascon, Sergio, Murenu, Elisa, Sirko, Lana, Masserdotti, Giacomo

Institute of Stem Cell Research, Helmholtz Zentrum Muenchen, Neuherberg/Munich, Germany

I will present the first live in vivo imaging of adult neural stem cells in vivo and report on how they divide normally and after regenerative injury in the adult zebrafish brain. This analysis allowed us identifying several mechanisms by which adult neural stem cells enhance the neuronal output after brain injury. I will then turn towards the mammalian brain and discuss possible mechanisms why cells with neural stem cell potential that dedifferentiate within the injury site fail to generate neurons - based on transcriptome analysis comparing endogenous neural stem cells and reactive astrocytes. I will then move towards approaches overcoming this block in neurogenesis and present new mechanistic insights into novel pathways allowing to successfully instruct the generation of rather mature neurons after traumatic brain injury with very high efficiency in vivo.

NEW PLAYERS CONTROLLING RADIAL GLIAL CELLS COMMITMENT AND DIFFERENTIATION TO EPENDYMAL CELLS

Kyrousi, Christina[1], Arbi, Marina[2], Lalioti, Marilena[1], Founta, Konstantina[1], Skavatsou, Eleni1, Pilz, Gregor[3], Goetz, Magdalena[3], Lygerou, Zoi[2], Taraviras, Stavros[1]

[1]Department of Physiology, Medical School, University of Patras, Patras, Greece, [2]Department of Biology, Medical School, University of Patras, Patras, Greece, [3]Institute of Stem Cell Research, Neuherberg, Germany

Radial glial cells (RGs) are the main neural stem cell population in the developing cortex. At the early stages of neurogenesis they perform self-renewal divisions in order to expand their number. During middle and late neurogenesis radial glial cells perform differentiating divisions generating neurons and glial cells that colonize the developing cortex. A small subpopulation of RGs, named late radial glial cells, contributes to the generation of adult neural stem cells and multiciliated ependymal cells, which reside in the subependymal zone at lateral walls of the adult cortex. The molecular pathways governing radial glial cells fate commitment and differentiation decisions are poorly understood. Towards understanding the mechanisms that control neural stem cells fate decisions we investigate the in vivo role of Idas (MCIDAS) and Lynkeas, two novel proteins sharing homology with Geminin. Idas was recently shown to regulate the expression of genes required for multiciliated cell formation in Xenopus skin and kidney cells. Our analysis showed that Idas and Lynkeas are the earliest known marker of radial glial cells committed to the ependymal cell lineage in the developing mouse brain. RGs upon Idas or Lynkeas overexpression loss their neural stem cells characteristics and prematurely differentiated into multiciliated ependymal cells, while inactivation experiments resulted in blockage of multiciliated ependymal cells generation. We have also shown that Idas and Lynkeas act upstream of known transcription factors essential for the commitment and differentiation of RGs towards ependymal cells, while they are negatively regulated by Notch pathway. Our results show that Idas and Lynkeas are key players for radial glial cells fate commitment and differentiation to multiciliated ependymal cells.

SPINAL CORD EPENDYMAL CELLS ARE FUNCTIONALLY HETEROGENEOUS WITH RESTRICTED PROGENITOR CELLS AND STEM CELLS

Stenudd, Moa[1], Sabelström, Hanna[1], Ståhl, Fredrik[1], Göritz, Christian[1], Basak, Onur[2], Clevers, Hans[2], Brismar, Hjalmar[3], Barnabé-Heider, Fanie[4], Frisén, Jonas[1]

[1]Department of Cell and Molecular Biology, Karolinska Institutet, Stockholm, Sweden, [2]Hubrecht Institute for Developmental Biology & Stem Cell Research, Utrecht, Netherlands, [3]Science for Life Laboratory, Karolinska Institutet, Stockholm, Sweden, [4]Department of Neuroscience, Karolinska Institutet, Stockholm, Sweden

The neural stem cells in the adult spinal cord are ependymal cells. After spinal cord injury, ependymal cells are activated and generate more than half of the astrocytes in the forming glial scar and a small fraction of remyelinating oligodendrocytes. We recently showed that the ependymal cell contribution to the glial scar is essential to regain tissue integrity and limits neuronal loss after spinal cord injury. These findings identified ependymal cells as an interesting target for manipulating the cellular response to spinal cord injury to preserve or regain function. Several studies have shown that ependymal cells are heterogeneous in morphology and protein expression, but there is limited evidence of functional heterogeneity and no previous reports of ependymal cell subpopulations with neural stem cell properties. Pinpointing the exact identity of the neural stem cells within the ependymal cell population is important to develop therapies that modulate the endogenous neural stem cell response to spinal cord injury. We have assessed stem cell properties of functionally separate subpopulations of ependymal cells using genetic fate mapping. We characterized a subpopulation of restricted progenitor cells that are recombined in Glast-CreER mice. We show that Glast-CreER recombined ependymal cells proliferate under physiological conditions, display limited self-renewal in vitro, and do not generate migrating or differentiating progeny in vivo after spinal cord injury. We also characterized a subpopulation of ependymal cells with neural stem cell properties in Troy-CreER mice. Troy-CreER recombined ependymal cells display extensive self-renewal in vitro. They have a low proliferative rate in the intact spinal cord, but they increase their proliferation and generate both scar-forming astrocytes and remyelinating oligodendrocytes in vivo after spinal cord injury. In summary, we show that the neural stem cell potential of the adult spinal cord is contained within a subpopulation of ependymal cells, while other ependymal cells are restricted progenitor cells. Ependymal cells with neural stem cell properties may pose an interesting target for modulating the endogenous neural stem cell response to spinal cord injury.

ASCL1/MASH1 COORDINATELY REGULATES GENE EXPRESSION AND THE CHROMATIN LANDSCAPE DURING NEUROGENESIS

Castro, Diogo S.[1], Raposo, Alexandre A S F[1], Vasconcelos, Francisca F.[1], Drechsel, Daniela[2], Berninger, Benedikt[3], Buckley, Noel J.[4], Guillemot, François[2]

[1]Instituto Gulbenkian de Ciencia, Oeiras, Portugal, [2]MRC National Institute for Medical Research, London, United Kingdom, [3]Institute of Physiological Chemistry, University Medical Center Johannes Gutenberg University Mainz, Mainz, Germany, [4]Department of Psychiatry, University of Oxford, Oxford, United Kingdom

The generation of new neurons in the embryonic nervous system requires a number of precisely orchestrated steps, whereby proliferating neural progenitors become committed to the neuronal fate, exit cell cycle and undergo a complex program of migration and differentiation. Proneural transcription factors of the bHLH family, such as Ascl1/Mash1, are pivotal regulators of the neurogenic process. Ascl1 is expressed in proliferating neural/stem progenitors in the germinal layers of the developing brain and spinal cord regions, where it promotes sequentially the proliferation and differentiation of progenitors towards a neuronal program. Previous studies have shown that this occurs via the concomitant regulation of distinct transcriptional targets of Ascl1. However, what determines which subsets of genes are regulated by Ascl1 in proliferating versus differentiating progenitors remains poorly understood. Here we used a cellular model of neurogenesis to investigate how Ascl1 activity is restricted by, and impacts the chromatin landscape when promoting the differentiation of adherent cultures of neural stem/progenitor cells. By combining expression profiling with genome-wide mapping of Ascl1 binding sites (ChIP-seq), and DNAse I hypersensitivity sites (DNAse-seq), we found that: i) Ascl1 binding occurs mostly at distal enhancers and is associated with activation of gene transcription; ii) Accessibility of Ascl1 to its binding sites remains largely unchanged in proliferating and differentiating progenitors, as judged by the binding profile of overexpressed Ascl1 in both conditions; iii) In a subset of its target sites, Ascl1 binds to regions of closed chromatin in proliferating cells, promoting chromatin accessibility and the appearance of new regions of open-chromatin; and iv) New regions of open-chromatin are associated with genes expressed "de novo" during differentiation. Overall, our study suggests that access of Ascl1 to chromatin in proliferating cells is not a major impediment for activation of differentiation target genes. In addition, it reveals a novel function of Ascl1 in promoting chromatin accessibility during neurogenesis, linking the chromatin landscape at Ascl1 target regions with the temporal progression of its transcriptional program along the neuronal lineage.

TRANSCRIPTOMIC CHARACTERIZATION OF SINGLE FIXED HUMAN RADIAL GLIAL PROGENITORS

Levi, Boaz P.[1], Thomsen, Elliot R.[1], Mich, John K.[1], Yao, Zizhen[1], Hodge, Rebecca D.[1], Doyle, Adele[2], Jang, Sumin[3], Nelson, Angelique M.[1], Shapovalova, Nadiya V.[1], Ramanathan, Sharad[1]

[1]Allen Institute for Brain Science, Seattle, WA, USA, [2]University of California, Santa Barbara, Santa Barbara, CA, USA, [3]Harvard University, Cambridge, MA, USA

Our neocortex is involved in higher order cerebral functions that make us uniquely human. The diversity of the progenitor radial glial cells (RGs) populating the germinal zone of a developing human neocortex has been distinguished only by position, behavior and morphology. We do not have molecular markers that identify the different progenitor cell types and hence know very little about the genetic pathways control their development, fate and function. To determine expression patterns that distinguish the diversity of human RGs we developed a new Fixed Single Cell RNA-Seq (FSC-Seq) method for transcriptome profiling single fixed, stained, and sorted cells. We validated FSC-Seq using human embryonic stem cells (hESCs) and demonstrate genome-wide transcriptomic data from live single cells is nearly identical to that from fixed single cells. We applied FSC-Seq to enrich and profile primary single human radial glial (RG) and intermediate progenitor cells (IPCs)-the majority of progenitors in the germinal zones of the developing human neocortex. By analyzing the gene expression patterns, we shows that RGs can be separated into ventricle zone (VZ)-restricted RGs (vRGs) and outer subventricular zone-localized RGs (oRG) based on the reciprocal expression of several genes, and these molecular markers point to a mechanism for molecular control of the lineage and function of oRG cells. Our findings provide an important step towards a molecular understanding of the lineage and function of the recently-evolved human neocortical progenitors including oRGs. Furthermore, we show FSC-Seq is a powerful method for profiling precise populations of single cells from complex biological tissue to understand their development.

CONSECUTIVE BUILDING BLOCKS OF HUMAN NEURAL STEM CELL ONTOGENY DERIVED FROM PLURIPOTENT STEM CELLS: FUNDAMENTALS AND IMPLICATIONS

Elkabetz, Yechiel[1], Edri, Reuven[2], Yaffe, Yakey[1], Ziller, Michael J.[3], Mutukula, Naresh[2], Volkman, Rotem[2], Masheko-Polotov, Diana[2], Ziv, Omer[2], Zaritsky, Assaf[4], Federman-Gross, Aya[2], Meissner, Alexander[3]

[1]Tel-Aviv University, Tel-Aviv, Israel, [2]Cell and Developmental Biology, Tel-Aviv University, Tel-Aviv, Israel, [3]Department of Stem Cell and Regenerative Biology, Broad Institute of MIT and Harvard, Cambridge, MA, USA, [4]Department of Cell Biology, UT Southwestern Medical Center, Dallas, TX, USA

Modeling key cell fate decisions and heterogeneity in neural progenitors is fundamental for revealing origin of diverse lineages, identifying molecular forces regulating distinct potencies, and generating homogeneous neural stem cell (NSC) populations for regenerative medicine. Here we report our recent progress in developing such approaches and their implications. We isolated consecutive neural progenitors derived from human PSCs differentiated along cortical development based on their Notch activation state. We first isolated Notch active CNS neuroepithelial cells exhibiting high proliferation and broad potential. These successively yield early and mid cerebral neurogenic radial glia followed by gliogenic radial glia, together recapitulating hallmarks of NSC ontogeny, cortical lamination and glial transformation in Notch dependent manner. We used isolated stages as modules to identify forces driving cell fate transitions. We employed gene expression analysis and epigenetic profiling combined with computational approaches to infer key regulators progressively remodeling the epigenetic landscape, and followed by shRNA functional validation. This allowed uncovering a core gene regulatory network of stably expressed transcription factors that dynamically interacts with stage specific factors to regulate cortical NSC fate transition. We further identified dynamics of pathway activation during this process and developed a streamlined and robust protocol for efficient cortical cell fate conversion from naïve and primed PSCs using small molecules. Finally, we found that transition through neurogenic phases in our experimental paradigm is characterized by extensive remodeling also of neural rosette formation, radial organization, and interkinetic nuclear and centriole migration dynamics, which all correlate with progressive changes in neurogenic NSC capacity in vitro. We hence developed a quantitative live imaging framework combined with reporters for these organelles to objectively measure these features during corticogenesis in vitro and further used these reporters to isolate distinct NSCs based on their chosen cell fate immediately following their division, allowing new cellular and molecular insights into cell fate decision of NSCs during human corticogenesis in vitro.

THURSDAY, 25 JUNE, 13:15 - 15:10

CONCURRENT IB: HEMATOPOIESIS

ROOM A4

TRANSCRIPTIONAL CONTROL OF HEMOGENIC ENDOTHELIUM FATE

Mikkola, Hanna

Broad Stem Cell Research Center, University of California, Los Angeles, Los Angeles, CA, USA

Hematopoietic stem/progenitor cells (HS/PC) emerge from hemogenic endothelium during embryogenesis. The mechanisms that provide hemogenic competence in endothelium during specific developmental window have been unknown. We showed that lack of bHLH factor Scl prevents HS/PC specification in the endothelium, which becomes misspecified to cardiac fate. Ectopic cardiomyogenesis was also observed in endocardium and cushion mesenchymal cells in SclKO hearts. We showed that Scl dictates the hematopoietic vs. cardiac fate choice by binding to enhancers of key hematopoietic and cardiac transcription factors. Scl is not a pioneer factor, but exploits epigenetically primed state that was acquired at the enhancers in mesoderm. We hypothesized that Scl binding in hematopoietic enhancers converts them to fully active state, but in cardiac enhancers prevents their activation by cardiac factors. ATAC sequencing confirmed that mesoderm transition to hemogenic endothelium is accompanied by Scl dependent chromatin opening in hematopoietic enhancers, while cardiac enhancers remain closed and lose the primed epigenetic state. ATAC sequencing of endothelial precursors in hemogenic tissues and the heart in vivo documented that the extinction of hemogenic and cardiogenic potential in endothelium is accompanied by closed chromatin state in Scl regulated enhancers. In contrast, the cushion mesenchymal cells in the heart display open chromatin in cardiac enhancers until later in development, which parallels the timing of Scl requirement for cardiac repression. These data imply that primed epigenetic state followed by opening or closure of chromatin at cardiovascular enhancers indicates the readily available fate options. Our data suggest that Scl controls gene expression by recruiting Pol2 to primed enhancers and regulating enhancer RNAs. These data provide a model of how bHLH factors exploit and modify the epigenetic landscape to control mutually exclusive fate decisions during development.

THE SEROTONERGIC NERVOUS SYSTEM REGULATES HEMATOPOIETIC STEM CELL PRODUCTION VIA THE HYPOTHALAMIC-PITUITARY-INTERRENAL AXIS

Kwan, Wanda[1], Cortes, Mauricio[1], Goessling, Wolfram[2], **North, Trista E.**[1]

[1]Department of Pathology, Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA, [2]Department of Genetics, Brigham and Women's Hospital, Boston, MA, USA

There is increasing evidence that neuronal signals contribute to hematopoietic stem and progenitor cell (HSPC) production and maintenance; however, the mechanism(s) and necessity for brain-mediated HSPC and/or niche regulation is unclear. Serotonin (5HT), a neurotransmitter in the brain and a hormone in the periphery, was identified in a screen for HSPC modulators in zebrafish. Exposure to 5HT or fluoxetine (5HT reuptake inhibitor) increased HSPC formation in the aorta-gonad-mesonephros (AGM) region as shown by runx1/cmyb in situ hybridization, and confirmed by FACS and qRT-PCR analysis ($p<0.05$). The stimulatory effect of 5HT was seen both during HSPC niche formation, as well as when AGM HSPCs emerge and expand. Peripheral and neuronal 5HT are synthesized by tryptophan hydroxylase 1 (TPH1) and TPH2, respectively. Chemical inhibition of these rate-limiting enzymes decreased HSPC numbers; morpholino (MO) mediated-knockdown of tph2 likewise diminished HSPC production ($p<0.05$), which was rescued by exogenous 5HT; these effects were confirmed via an inducible tph2-ablation model. While the sympathetic nervous system (SNS) can contribute to HSPC emergence and mobilization, the effect of 5HT was independent of SNS function as shown using 6-OHDA-induced sympathetic nerve lesions. 5HT activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to cortisol production and activation of glucocorticoid receptor (GR) to mediate peripheral responses. Gene expression of corticotropin-releasing hormone receptor (crh), pro-opiomelanocortin (pomc) and nr3c1 (GR), as well as total cortisol level, was increased in 5HT-treated embryos ($p<0.05$). In contrast, MO-knockdown of tph2 decreased cortisol production ($p<0.05$). As GRs are expressed on HSPCs and in the niche, these data suggest neuronal 5HT regulates HSCs through the hypothalamic-pituitary-interrenal (HPI) axis (teleost HPA axis counterpart) and peripheral cortisol production. Consistent with this hypothesis, GR agonists increased embryonic HSPC production, while MO-knockdown of GR and analysis of GR mutants revealed drastic reductions in HSPCs and rag2+ lymphoid progenitors. Collectively, our data highlight a novel mechanism of neural regulation of HSPC induction and expansion via the serotonergic system and HPI stress response pathway.

EXTRA PHYSIOLOGIC OXYGEN SHOCK/STRESS (EPHOSS) BLUNTS HEMATOPOIETIC STEM CELL PHENOTYPE/FUNCTION VIA REACTIVE OXYGEN SPECIES AND THE MITOCHONDRIAL PERMEABILITY TRANSITION PORE

O'Leary, Heather Ann[1], Mantel, Charlie[1], Huang, Xin Xin[1], Chitteti, Brahmanandra R.[1], Cooper, Scott[1], Srour, Edward F.[1], Haas, David M.[2], Broxmeyer, Hal E.[1]

[1]Microbiology and Immunology, Indiana University School of Medicine, Indianapolis, IN, USA, [2]Obstetrics and Gynecology, Indiana University School of Medicine, Indianapolis, IN, USA

Hematopoietic stem cells (HSC) reside in hypoxic niches (~1-4% O2), however, HSC studies are consistently performed using cells isolated in ambient air (~20% O2), regardless of subsequent processing in low oxygen tension. By collecting/processing stem cells in physiologically native conditions of hypoxia, where all procedures are performed inside a hypoxic chamber, we demonstrate that brief exposure of mouse bone marrow (BM) or human cord blood (CB) cells to ambient oxygen decreases recovery of phenotypic, and functional, self-renewing long-term repopulating HSC and concomitantly increases numbers of progenitor cells, a phenomenon we term Extra Physiologic Oxygen Shock/Stress (EPHOSS). Up to 5 fold greater numbers of long-term (LT)-HSCs (murine BM or human CB) are recovered from cells harvested in 3% O2 compared to those harvested in air, or even those harvested in 3% O2 and then exposed to air as little as 15 minutes before analysis. Competitive transplant experiments were completed at 3% O2 using a custom mouse respirator, and revealed an increase in mouse bone marrow competitive repopulating units (CRUs) when BM is harvested, and retained, in hypoxic conditions compared to air in primary recipients. This suggests that true numbers of HSCs, as well as the transplantation potency of BM and CB, have been consistently underestimated due to rapid initiation of differentiation of LT-HSCs in ambient air (EPHOSS). Mechanistically, we link mitochondrial function/ mitochondrial permeability transition pore (MPTP), ROS and cyclophilin D to EPHOSS. Genetic or pharmacological suppression of cyclophilin D function [CypD -/- mice or collecting cells in Cyclosporin A (CSA), respectively] protects phenotypic, functional, and transplantable HSCs from enhanced ROS levels and EPHOSS during collection in air. Limiting dilution analysis transplants show at least an average of 3-5 fold increase in phenotypic, functional, and transplantable mouse BM and human CB LT-HSCs. Collectively, this suggests that EPHOSS results in irreversible ROS induced differentiation signals during air harvest, due to mitochondrial permeability transition pore (MPTP) opening. Therefore, pharmacological mitigation of EPHOSS (using CSA) during HSC collections may be clinically advantageous for enhancement of patient transplantation.

REPROGRAMMING SHORT TERM BLOOD STEM CELLS TO A LONG TERM FATE BY PROSTAGLANDIN E2

Fast, Eva M.[1], Durand, Ellen M.[2], Binder, Vera[2], Maher, Rebecca[2], Sporrij, Audrey[1], Ojeaburu, Leslie[1], Yang, Song[2], Zhou, Yi[2], Zon, Leonard I.[2]

[1]Department of Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [2]Stem Cell Program and Division of Hematology/Oncology, Howard Hughes Medical Institute, Boston Children's Hospital, Boston, MA, USA

Hematopoietic stem cells (HSCs) have remarkable regenerative capabilities, a feature that can be exploited during hematopoietic stem cell transplantation. Our lab has previously shown a beneficial effect of Prostaglandin E2 (PGE2) on HSC self-renewal. In an ongoing clinical trial this drug is showing promising results for umbilical cord blood (UCB) transplantation. To further define how PGE2 affects HSC self-renewal we determined which HSC subpopulation functionally responds to PGE2 in a transplantation setting. Mouse long-term (LT)-HSCs, short-term (ST)-HSCs and multipotent progenitors (MPPs) were isolated by FACS and exposed to the drug ex vivo before transplantation. We assessed engraftment potential by a competitive repopulation assay using peripheral blood chimerism as a readout. Traditionally, ST-HSCs and LT-HSCs are defined as being able to both engraft equally well but ST-HSCs tend to exhaust after 2-3 months. Remarkably, in our experiments, a two-hour pulse of PGE2 was sufficient to extend peripheral blood contribution of ST-HSCs for up to one year. This long term effect persisted in competitive secondary transplants. On a molecular level PGE2 mainly signals through the transcription factor CREB. Using ChIP-Seq in human CD34+ cells we mapped genome wide binding sites of phospho-CREB in CD34+ cells after PGE2 treatment. Our bioinformatic analysis suggests that 77% of regions specifically bound by pCREB in this context are located in intronic or intergenic portions of the genome. To correlate these potential enhancers with gene expression, we performed RNAseq and integrated it with preexisting microarray experiments in human CD34+ UCB cells. Gene set enrichment analysis (GSEA) indicated that PGE2 increases a quiescence gene signature containing several chemokines, CREM and PTGS2. Together our results imply that PGE2 triggers a functional conversion of mouse ST-HSCs to long term self-renewing HSCs. Through CREB, PGE2 activates a quiescence program in human CD34+ cells and a similar mechanism might also prevent mouse ST-HSCs from exhausting. These results are relevant to human UBC transplantations where PGE2 could affect a "ST-HSC-like" population. Furthermore future genetic studies aiming to functionally analyze gene sets affected by PGE2 will enrich basic understanding of HSC self-renewal.

THE OPPOSING ROLES OF LET-7C AND MIR-125 IN HUMAN HEMATOPOIETIC STEM CELL MAINTENANCE AND PROLIFERATION

Sandoval, Salemiz[1], Parekh, Chintan[2], Zaidi-Merchant, Sania[1], Sedghi, Soudabeh[1], Chin, Chee Jia[1], He, Chong Bin[1], Zhu, Yuhua[1], Kohn, Lisa[3], Rao, Dinesh[1], Crooks, Gay M.[1]

[1]Department of Pathology and Laboratory Medicine, University of California, Los Angeles, Los Angeles, CA, USA, [2]Children's Center for Cancer and Blood Diseases, Children's Hospital, Los Angeles, Los Angeles, CA, USA, [3]David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, CA, USA

In recent years, studies have demonstrated that miRNAs can regulate stem cell function. We have utilized microarray profiling to identify miRNAs that are specifically expressed in human bone marrow (BM) hematopoietic stem cells (HSC). By comparing the miRNA expression profile of HSC to that of early lymphoid progenitors, we identified a cluster of miRNAs (miR-99a/let-7c/miR-125b) that is highly expressed in HSC but almost absent in progenitors and mature cells. To dissect the role of the miRNAs within the cluster we expressed each miRNA in human HSC either individually or as an intact cluster. In vitro differentiation assays showed that expression of let-7c alone in HSC decreased the number and frequency of CD34+ cells and increased myeloid cell output. Let-7c expressing cells also showed markedly reduced proliferative potential in long-term culture initiation cell (LT-CIC) assay. CFSE proliferation assays showed that let-7c expression increased proliferation of CD34neg cells. In contrast, expression of miR-125b alone maintained a high frequency of CD34+ cells in culture and increased LTCIC 30-fold compared to controls. CFSE assay showed that miR-125b expression enhanced the proliferation of CD34+ cells but also maintained a pool of CD34+ cells that proliferated at a lower rate compared to controls. Additionally, miR-125b expressing cells demonstrated increased survival in the presence of staurosporine. Expression of the entire miRNA cluster revealed an intermediate phenotype to that of let-7c and miR-125b expressing cells, with 5-fold increase in LTC-IC over controls, and less significant survival advantage compared to miR-125b alone. Primary and secondary transplant assays of transduced cells demonstrated identical findings to the in vitro and immunophenotypic assays. Let-7c expressing cells failed to engraft in primary transplants, whereas miR-125b expressing cells produced over 100-fold increase in engraftment in primary and secondary transplants compared to controls. Cluster-expressing cells engrafted at intermediate levels in primary and secondary transplants. These data suggest that let-7c functions within the cluster to modulate the proliferative effects of miR-125b in HSC. We are now exploring the transcriptional networks through which let-7c and miR-125b modify the behavior of HSC.

INTERFERON SIGNALING PROMOTES MATURATION OF AGM HSCS

Kim, Peter Geon[1], Ross, Samantha J.[1], Rhee, Catherine[2], Harriss, June V.[2], Tucker, Hayley O.[2], Daley, George Q.[1]

[1]Hematology/Oncology, Boston Children's Hospital, Boston, MA, USA, [2]Department of Molecular Biosciences, The University of Texas at Austin, Austin, TX, USA

In the developing mouse embryo, the first hematopoietic stem cells (HSCs) able to repopulate lethally irradiated adult recipients are detected in the aorta-gonad-mesonephros (AGM) region at embryonic day 11.5 (E11.5). These embryonic hematopoietic stem cells (AGM HSCs) are developmentally immature and undergo further maturation as they transit through the fetal liver to the bone marrow. In contrast to fetal liver or adult HSCs, AGM HSCs have a gene expression signature reminiscent of their endothelial origin, have reduced competitiveness and prefer neonatal recipients over adult recipients. The signaling pathways responsible for the maturation of AGM HSC are currently not well understood. By co-expression gene network analysis we identified that AGM HSCs are relatively deficient in Jak-Stat signaling, notably interferon/Stat1 signaling, compared to fetal liver or adult HSCs. Interferon gamma signaling has recently been identified to have a role in AGM HSC emergence. Here, we show that treatment of AGM HSCs with interferon-alpha enhances long-term hematopoietic engraftment and competitiveness. Additionally, we identify an upstream regulator of interferon/Stat1 signaling, AT-rich interactive domain 3a (Arid3a), which has previously been identified as critical for fetal liver hematopoiesis and B lymphopoiesis. Arid3a KO AGMs are deficient in hematopoietic function, but can be rescued by interferon-alpha treatment. Thus, we have identified an inflammatory signaling cascade that plays a role in normal hematopoietic development. Understanding and appreciating differences between different embryonic HSCs will lead to novel ways to increase the potency of stem cells for therapy.

CONCURRENT IC: CONTROL AND INDUCTION OF PLURIPOTENCY

VICTORIA HALL

DIRECT REPROGRAMMING TO SOMATIC PROGENITOR CELLS: LINEAGE COMMITMENT REVISITED

Cheng, Hui[1], Ang, Heather Yin-Kuan[1], EL Farran, Chadi A[1], Li, Pin[1], Fang, Haitong[1], Liu, Tongming I, Kong, Say Li[1], Lim, Edwin Kok Hao[1], Huber, Tara[1] ,Loh, Kyle M.[2], Loh, Yuin-Han[1], Lim, Bing[1,3]

[1]Genome Institute of Singapore and Institute of Molecular and Cell Biology, Biopolis, Singapore, [2]Stanford Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, CA 94305, USA, [3]Merck Research Lab, Translational Medicine Research Center, Biopolis, Singapore

The transdifferentiation of one cell type to another is an amazing biological phenomenon that speaks to the malleability of the mammalian epigenome. The basic Yamanaka technical strategy underpinning the generation of induced pluripotent stem cells paved the way for the generation of several "induced" lineages such as neuronal and hepatic cells. More recently, hematopoietic stem cells (HSCs) have been induced from either hematopoietic cells (e.g., B lymphocytes) or hemogenic-related cell types (e.g., endothelial cells), and most recently, from completely unrelated cells such as fibroblasts. Each of these approaches use quite different combinations of reprogramming factors, suggesting either the relevance of the starting epigenome or the possibility of multiple alternate Waddington-esque routes to the same lineage. We attempted to reprogram fibroblasts to engraftable hematopoietic progenitors by testing a list of transcriptional factors implicated in hematopoietic development. Our results suggest that a basic minimal combination of key hematopoietic transcriptional factors is critical and sufficient to reinitiate the hematopoietic program. We propose that these factors may be the equivalent of the "lineage commitment" factors that write and orchestrate lineage specification during embryonic hematopoiesis. ChIP-seq analysis of chromatin markers and transcriptional factor binding sites at different time points during reprogramming further revealed the transition of lineages during reprogramming and provided insights into what are some of the molecular pathways recruited for the rewiring of the epigenome. It is likely that following the same principles, transcriptional factors that are known to be crucial for the embryonic development of specific tissue progenitors could be applied for direct conversion of fibroblasts into tissue-specific stem and progenitor cells.

M6A RNA METHYLATION IS REGULATED BY MICRORNAS AND PROMOTES REPROGRAMMING TO PLURIPOTENCY

Zhang, Ying[1], Chen, Tong[2], Hao, Ya-Juan[3], Li, Miao-Miao[3], Wang, Meng[2], Han, Weifang[1], Wu, Yongsheng[3], Lv, Ying[3], Hao, Jie[1], Wang, Libin[1], Li, Ang[3], Yang, Ying[3], Jin, Kang-Xuan[3], Zhao, Xu[3], Li, Yuhuan[1], Ping, Xiao-Li[3], Lai, Wei-Yi[4], Wu, Li-Gang[5], Jiang, Guibin[4], Wang, Hai-Lin[4], Sang, Lisi[1], Wang, Xiu-Jie[2], Yang, Yun-Gui[3], Zhou, Qi[1]

[1]State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China, [2]Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China, [3]Beijing Institute of Genomics, Chinese Academy of Sciences, Beijing, China, [4]Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing, China, [5]Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Beijing, China

N^6-methyladenosine (m^6A) is recently identified as a conserved epitranscriptomic modification of eukaryotic mRNAs, but its features, regulatory mechanisms and functions in cell reprogramming are largely unknown. Here, we report m^6A modification profiles in the mRNA transcriptomes of four cell types with different degrees of pluripotency. Comparative analysis reveals several new features of m^6A, especially gene- and cell type-specific m^6A mRNA modifications. We also show that microRNAs (miRNAs) regulate m^6A modification via a sequence pairing mechanism. Manipulation of miRNA expression or sequences alters m^6A modification levels, through modulating the binding of METTL3 methyltransferase to mRNAs containing miRNA targeting sites. Increased m^6A abundance promotes the reprogramming of mouse embryonic fibroblasts (MEFs) to pluripotent stem cells; conversely, reduced m^6A levels impede reprogramming. Our results therefore uncover a role for miRNAs in regulating m^6A formation of mRNAs, and provide a foundation for future functional studies of m^6A modification in cell reprogramming.

LIN28 PHOSPHORYLATION COUPLES SIGNALING TO THE POST-TRANSCRIPTIONAL CONTROL OF PLURIPOTENCY

Tsanov, Kaloyan M.[1], Kane, Susan[2], Wu, Zhaoting[1], **Seligson, Marc T.[1], Pearson, Daniel S.[1], Powers, John T.[1], Osborne, Jihan K.[1], Gygi, Steven P.[3], Daley, George Q.[1]**

[1]Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, USA, [2]Cell Signaling Technology, Danvers, MA, USA, 3Cell Biology, Harvard Medical School, Boston, MA, USA

Pluripotency requires the precise coordination of dynamic RNA and protein-based regulatory mechanisms, yet how this is achieved at the molecular level remains poorly understood. LIN28/LIN28A, a highly conserved RNA-binding protein, has emerged as a central post-transcriptional regulator of pluripotency, as it blocks the processing of the let-7 miRNA family and directly modulates mRNA translation. Using targeted phosphoproteomics, we detected multiple phosphorylations on LIN28 in pluripotent cells, and identified ERK1/2 as a specific kinase that stabilizes LIN28 post-translationally and thereby regulates its protein levels. Functionally, we have linked this mechanism to the induction of pluripotency via somatic cell reprogramming and the exit from pluripotency upon neural differentiation. Our findings indicate that MAPK/ERK signaling impinges directly on LIN28 to influence the post-transcriptional control of pluripotency, with implications for ground-state pluripotency, development and disease.

KLF4 NUCLEAR EXPORT REQUIRES ERK ACTIVATION AND INITIATES EXIT FROM NAIVE PLURIPOTENCY

Dhaliwal, Navroop K., **Mitchell, Jennifer A.**

Cell and Systems Biology, University of Toronto, Toronto, ON, Canada

In embryonic stem (ES) cells, pluripotency is regulated by an interconnected network of transcription factors including OCT4, SOX2, KLF4 and NANOG which bind in combination to numerous loci throughout the genome. KLF4 is thought to maintain pluripotency by activating Nanog transcription. Although differentiation of ES cells to specific cell types occurs over several days, during which Sox2 and Oct4 expression are maintained, Nanog transcription is reduced within 24 hours. This is similar to the decrease in expression that occurs in the embryo at the transition from the blastocyst to the epiblast. To elucidate the mechanisms through which Nanog is down-regulated as ES cells exit naïve pluripotency we investigated nuclear localisation, gene expression and protein-protein interaction changes during the first 24 hours of pluripotency exit. We observed that whereas NANOG protein levels gradually decrease over the first 24 hours; KLF4 protein becomes more cytoplasmic earlier; after 6 hours, most KLF4 is found in the cytoplasm. During this time SOX2 and OCT4 protein show no change in levels or sub-cellular localization. KLF4 nuclear exit requires ERK activation and occurs through direct contact between ERK, KLF4 and XPO1, a component of the nuclear export machinery. To determine whether or not KLF4 nuclear export is responsible for the decrease in Nanog transcription we inhibited nuclear export using Leptomycin B. Indeed, Nanog expression was maintained when KLF4 nuclear export was inhibited. Surprisingly, at 24 hours KLF4 protein is once again predominantly nuclear. However, KLF4 does not reactivate Nanog transcription potentially due to changes in nuclear protein complexes including reduced interaction of KLF4 with RNAPII. These findings indicate that rapid KLF4 nuclear export initiates the early cascade of gene expression changes that occur within the first 24 hours as ES cells exit naïve pluripotency and commit to a differentiated state.

UNCOVERING NOVEL MECHANISMS AND INDUCERS OF PLURIPOTENCY VIA COMBINATORIAL ANTIBODY SCREENING

Blanchard, Joel W., Xie, Jia, El-Mercharrafie, Nadja, Lerner, Richard A., Baldwin, Kristin K.

The Scripps Research Institute, La Jolla, CA, USA

Development and differentiation proceed by a cascade of events initiated by cell surface signaling. These cell surface events result in signal transduction and ultimately epigenetic modification of the genome. Much progress has been made using combinations of transcription factors to reprogram cells into induced pluripotent stem cells (iPSCs). Thus, we know much about ways to regulate fates by interceding on downstream signaling that primarily acts directly on the genome. However, little attention has been paid to the possibility of initiating reprogramming at the cell surface. We hypothesize that enhancing or replacing nuclear reprogramming factors with antibody based perturbations of cell surface signaling will reveal previously unknown routes pluripotency, and produce iPSCs with less heterogeneity than exists in current lines. To test this hypothesis we developed a screening platform that enables rapid screening of greater than 10^9 unique antibodies that can act as agonists, antagonists or blockers. Antibody targets can rapidly be identified upon discovering a phenotype by extracting the antibody genotype, purifying the target via immunoprecipitation, and subsequent sequencing by mass spectrometry. To demonstrate that these methods comprise an unbiased approach for uncovering novel mechanisms and signaling cascades that influence reprogramming, we performed combinatorial screens to replace Sox2, and Oct4 during the reprogramming of mouse fibroblasts to pluripotency. After screening more than 100 million unique antibodies we identified multiple antibodies that can replace Sox2 or Oct4 during reprogramming. Induced pluripotent cells derived using these antibodies express appropriate pluripotency markers, can be directed to differentiate in vitro, contribute to the inner cell mass of a blastocyst in vivo and yield live chimeric offspring. Using biochemical methods we have identified the target of a Sox2 replacing

antibody. The identified protein has not previously been reported as involved in regulating reprogramming or pluripotency. Through knockdown and expression studies we show that this protein acts to inhibit reprogramming via a novel mechanism. We are currently investigating the role this protein and signaling pathway play in reprogramming efficiency quality and heterogeneity.

A PRIMITIVE GROWTH FACTOR IS SUFFICIENT TO INDUCE STABLE NAÏVE STATE HUMAN PLURIPOTENCY VIA A LIF- AND FGF-INDEPENDENT PATHWAY; REPROGRAMMING IN THIS NOVEL GROWTH FACTOR CONFERS SUPERIOR DIFFERENTIATION

Bamdad, Cynthia[1], Carter, Mark G.[2], Stewart, Andrew K.[2], Smagghe, Benoit J.[3], Lynch, Eileen[2], Bernier, Kyle[3], Rapley, Joseph[4], Keating, Kevin[2], Hatziioannou, Vasilios[4]

[1]Minerva Biotechnologies, Waltham, MA, USA, [2]Stem Cell Group, Minerva Biotechnologies, Waltham, MA, USA, [3]Biochemistry, Minerva Biotechnologies, Waltham, MA, USA, [4]Cancer Biology, Minerva Biotechnologies, Waltham, MA, USA

Scientists have generated human stem cells that mimic mouse naïve cells, but their dependence on the addition of several extrinsic agents, and their propensity to develop abnormal karyotype calls into question their resemblance to a naturally occurring 'naïve' state in humans. Here we report the discovery of a novel cancer-testis antigen that is a stem cell growth factor. This naturally occurring growth factor alone is sufficient to convert human primed state stem cells to a naïve state that is karyotypically stable, without the use of inhibitors, transgenes, LIF or FGF2. In addition, reprogramming somatic cells with transient ectopic expression of OSK or OSKM in the presence of this growth factor, and in the absence of any other growth factor or inhibitor, results in increased efficiency of hiPSC generation. Both hESCs and hiPSCs cultured in this novel growth factor are naïve, have two active X chromosomes, can be passed as single cells, can be clonally expanded and have stable karyotype for more than 30 passages. These naïve cells differentiate down all three germlines as demonstrated by teratoma formation. Further, directed differentiation to cardiomyocytes, neuronal sub-types and mature hepatocytes was superior to that of FGF-grown cells in terms of yield, expression of markers of the desired cell type. In the case of cardiomyocytes, these naïve stem cells had greater strength of contraction, increased beating frequency and synchronized beating for more than 300 days. Transcriptome analysis revealed that a group of genes that are master regulators of differentiation is down-regulated in these naïve stem cells and is regulated by super-enhancers. None of these super-enhancer regulated genes was down-regulated in the other naïve stem cells generated using FGF or LIF based methods. This suggests that in our naïve cells, a master differentiation program is turned off but, upon removal of our novel growth factor, can be rapidly activated to execute a key cell fate decision, such as whether to grow pluripotently or differentiate. RNA SEQ suggests the existence of two naïve states: an early naïve state driven by our novel growth factor, which cannot limit self-replication and a later naïve state regulated by NME1, which limits self-replication when its multimerization state shifts from the active dimer to the inactive hexamer.

THURSDAY, 25 JUNE, 13:15 - 15:10

CONCURRENT ID: SINGLE CELL BIOLOGY

ROOM A6

Supported by Fluidigm Corporation

DISSECTING GENE REGULATION NETWORK IN HUMAN EARLY EMBRYOS AT SINGLE-CELL AND SINGLE-BASE RESOLUTION

Tang, Fuchou

Peking University, Beijing, China

Measuring gene expression in individual cells is crucial for understanding the gene regulatory network controlling human embryonic development. Here we apply single-cell RNA -Seq analysis to human preimplantation embryos, primordial germ cells, and human embryonic stem cells (hESCs). We also systematically profile the DNA methylome of human early embryos from the zygotic stage through to post-implantation. We show that the major wave of genome-wide demethylation is complete at the 2-cell stage, contrary to previous observations in mice. Moreover, the demethylation of the paternal genome is much faster than that of the maternal genome, and by the end of the zygotic stage the genome-wide methylation level in male pronuclei is already lower than that in female pronuclei. Finally, we also show that long interspersed nuclear elements (LINEs) or short interspersed nuclear elements (SINEs) that are evolutionarily young are demethylated to a milder extent compared to older elements in the same family and have higher abundance of transcripts, indicating that early embryos tend to retain higher residual methylation at the evolutionarily younger and more active transposable elements. Our work provides insights of critical features of the transcriptome and DNA methylome landscapes of human early embryos, as well as the functional significance of DNA methylome to regulation of gene expression and repression of transposable elements.

EARLY LINEAGE BIFURCATION DURING DIFFERENTIATION OF EMBRYONIC STEM CELLS REVEALED BY SINGLE-CELL TRANSCRIPTOMICS

Semrau, Stefan[1], Goldmann, Johanna[1], Soumillon, Magali[2], Mikkelsen, Tarjei[2], Jaenisch, Rudolf[1], van Oudenaarden, Alexander[3]

[1]Whitehead Institute for Biomedical Research, Cambridge, MA, USA, [2]Broad Institute of MIT and Harvard, Cambridge, MA, USA, [3]Hubrecht Institute, Utrecht, MA, USA

The development of more efficient and specific in vitro differentiation protocols is hampered by the inherently heterogeneous cellular response to lineage specifying signals. Here, we used our recently developed high throughput single-cell RNA-seq method (SCRB-seq [1]), SMART-seq and single-molecule FISH to quantify the variability in transcriptional states of thousands of individual mouse embryonic stem (mES) cells during differentiation with retinoic acid (RA). After an initial, fast and homogeneous response, transcriptional profiles bifurcated after a 24h delay into an ectoderm-like and an extraembryonic endoderm (XEN)-like state. In contrast to the current belief that cells are initially refractory to lineage specifying signals we also observed that naïve mES cells lose the ability to become XEN-like after only 24h in basal media without RA. By timed MEK inhibition we demonstrated that the MAPK/ERK pathway plays a crucial, time-dependent role for the lineage decision, first promoting differentiation into ectoderm and later (after 24h of RA exposure) into the XEN lineage. A subpopulation of MEK inhibitor treated cells completely failed to differentiate even after prolonged RA exposure. Finally, we developed a minimal, quantitative model, which captures the most important dynamical features of the system. In summary, our study profiled genome-wide transcriptional variability during differentiation and showed that the influence of external signaling input on the lineage decision changes dynamically.

[1] http://biorxiv.org/content/early/2014/03/05/003236

EARLY B-CELL FACTOR 2 IDENTIFIES MESENCHYMAL STEM CELLS IN MOUSE SKIN TISSUE

Sandhow, Lakshmi[1], Xiao, Pingnan[1], Zhang, Yuanyuan[1], Durgaryan, Andranik[1], Kondo, Makoto[1], Dolinska, Monika1, Johansson, Anne-Sofie[1], Kasper, Maria[2], Qian, Hong[1]

[1]Center for Hematology and Regenerative Medicine, Department of Medicine, Karolinska Institutet, Stockholm, Sweden, [2]Department of Biosciences and Nutrition, Karolinska Institutet, Stockholm, Sweden

The rarity of bone marrow (BM) mesenchymal stem cells (MSCs) and the difficulty in obtaining sufficient number of the cells for clinical and research use have led to high priority to isolate MSCs from other tissues. Skin tissue has become an attractive resource for obtaining MSCs due to the ease of harvesting samples and relatively high frequency of MSC-like cells. However, the in vivo cellular identity, functionality and therapeutic potentials of skin MSCs are largely unknown. Consequently, MSCs from skin have been isolated retrospectively based on their plastic adherence, immunophenotype and growth characteristics. We recently reported that mouse BM stromal cells expressing Early B-cell factor 2 (Ebf2) were highly enriched with MSCs. We here found that Ebf2+ cells could be isolated from mouse skin by using multi-color flow cytometry in an Ebf2-EGFP reporter mouse model. The Ebf2+ cells are negative for endothelial cell marker CD31 and hematopoietic cell markers CD45/TER119, but highly express MSC-associated marker SCA1, CD140A and CD51. Single cell colony assay indicated that the frequency of colony-forming unit in fibroblast (CFU-F) reflecting the number of MSCs in the Ebf2+ cells reached as high as 1 in 2. Furthermore, these CFU-Fs displayed the potential to differentiate into osteoblasts and adipocytes. Importantly, skin Ebf2+ cells showed similar capacity in maintaining hematopoietic stem cell activity to that of BM Ebf2+ MSCs in vitro. Most interestingly, in vivo fate-mapping experiment using triple transgenic Ebf2-CreER x Rosa26-tomato x Ebf2-EGFP mice revealed that skin Ebf2+ cells could generate Ebf2- MSC-like cells. Their contributions to skin tissue turn over and wound healing are currently under investigation. Taken together, our data suggested that Ebf2 could identify skin MSCs that displayed similar phenotype and functionality to BM MSCs in mice. The findings provided new knowledge about identity and functionality of skin MSCs.

DECODING THE REGULATORY NETWORK FOR BLOOD DEVELOPMENT FROM SINGLE-CELL GENE EXPRESSION MEASUREMENTS

Moignard, Victoria[1], Woodhouse, Steven[1], Haghverdi, Laleh[2], Lilly, Andrew J.[3], Tanaka, Yosuke[1], Wilkinson, Adam C.[1], Buettner, Florian[2], Macaulay, Iain C.[4], Jawaid, Wajid[1], Diamanti, Evangelia[1], Nishikawa, Shin-Ichi[5], Piterman, Nir[6], Kouskoff, Valerie[3], Theis, Fabian J.[2], Fisher, Jasmin[7], Göttgens, Berthold[1]

[1]Department of Haematology, University of Cambridge, Cambridge, United Kingdom, [2]Institute of Computational Biology, Helmholtz Zentrum München, Neuherberg, Germany, [3]Paterson Institute for Cancer Research, University of Manchester, Manchester, United Kingdom, [4]Sanger Institute-EBI Single Cell Genomics Centre, Wellcome Trust Sanger Institute, Hinxton, Cambridge, United Kingdom, [5]Laboratory for Stem Cell Biology, RIKEN Center for Developmental Biology, Kobe, Japan, [6]Department of Computer Science, University of Leicester, Leicester, United Kingdom, [7]Microsoft Research Cambridge, Cambridge, United Kingdom

The development of mammalian tissues following gastrulation represents one of the most fundamental processes in biology. However, reconstruction of the molecular pathways controlling organ development has been hampered by the difficulty in obtaining sufficient cells for analysis and the lack of methods to resolve embryonic progenitor cells. To address this problem, we devised a strategy to combine gene expression profiling of large numbers of single cells with new computational approaches including the use of diffusion maps for dimensionality reduction and placement of cells in developmental time, and regulatory network synthesis. We applied this approach to blood development, a paradigm of embryonic tissue formation in which increasingly specialised cells are generated from early mesoderm. We mapped the progression of mesoderm towards blood using single cell gene expression analysis of 46 genes in 3,934 cells with blood-forming potential captured from mouse embryos at four time points between E7.0 and E8.5. Reconstruction of the developmental journey at single cell resolution revealed asynchrony of maturation and sequential waves of expression for major regulators. By discretising gene expression into binary states and considering the single gene changes occurring between neighbouring cellular states, we then synthesised a Boolean transcriptional regulatory network model for blood development, identifying known and previously unrecognised regulatory interactions. Model execution recapitulated normal development, while in silico perturbations provided hypotheses about gene function. Using mouse embryo and embryonic stem cell models, we experimentally validated network predictions concerning the role of Hox and Sox factors and Gata1. Our results therefore demonstrate that single-cell analysis of a developing organ coupled with computational approaches can reveal the transcriptional programs that underpin organogenesis and should therefore be a widely applicable approach in the new era of single cell biology.

DEFECTS IN MYOGENIC TRANSDIFFERENTIATION REVEALED BY ALIGNMENT OF SINGLE-CELL PSEUDOTIME SERIES EXPERIMENTS

Cacchiarelli, Davide[1], Qiu, Xiaojie[2], Morse, Michael[2], Grimsby, Jonna[3], Pokharel, Prapti[3], Mikkelsen, Tarjei[3], Rinn, John[1], Trapnell, Cole[2]

[1]Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [2]University of Washington, Seattle, WA, USA, [3]Broad Institute, Cambridge, MA, USA

Reprogramming one cell type into another by forced expression of defined factors has been a subject of intense investigation for much of the past decade. However, even the correct factors may fail to fully and stably reprogram cells at high efficiency, for example because of incomplete silencing of incompatible gene expression programs or inactivity of required signaling pathways. For example, forced expression of MYOD converts human fibroblasts into multinucleated, myotube-like cells. However, the full repertoire of genes required for skeletal muscle contraction are not always activated in reprogrammed cells. Here, we describe a single-cell based strategy for "debugging" reprogramming or transdifferentiation protocols. Recently, we developed an approach based on single-cell RNA-Seq that dramatically increases the temporal resolution of time series gene expression studies. Our algorithm, Monocle, informatically places individual cells in order according to progress through reprogramming, effectively treating each cell as a separate time point. Monocle's ordering of cells in "pseudotime" helps pinpoint key regulators of cell state transitions. However, comparing two related biological processes on this pseudotemporal scale is non-trivial. In order to pinpoint the similarities and differences in gene expression dynamics between related processes, we have developed an algorithm for "aligning" pseudotime series experiments to one another. Alignment of fibroblasts reprogrammed with MYOD against differentiating myoblasts identifies major defects in the induced expression program. The alignment reveals the misregulation of several key signaling pathways and failure to fully silence the fibroblast expression program. Moreover, the timing of expression changes in myoblasts is disrupted, with skeletal muscle genes activated out-of-order in reprogrammed fibroblasts. Finally, we describe ongoing efforts to rescue myogenic

reprogramming based on clues provided by the alignment. We are confident that alignment of single-cell time series experiments will be generally useful for comparing not just differentiation and reprogramming, but also for comparing a wide array of biological processes.

SINGLE CELL RNA SEQUENCING UNCOVERS CLOSE RELATIONSHIP BETWEEN DOPAMINE AND SUBTHALAMIC NUCLEUS NEURON LINEAGES

Kee, Nigel[1], Dahl, Lina[1], Joomardi, Eliza[1], Volakakis, Nickolas[1], Gilberg, Linda[1], Bjorklund, Åsa[2], Storvall, Helena[1], Sandberg, Rickard[1], Perlmann, Thomas[1]

[1]LICR, Stockholm, Sweden, [2]SciLife, Stockholm, Sweden

The extensive neuronal diversity generated from neural stem cells in the mammalian CNS is an impressive feat of development, and also presents a significant challenge to dissect and understand. Ventral midbrain (vMB) dopaminergic neurons are a neuronal subtype that have been rigorously studied, strongly motivated by the interest in engineering stem cells into dopamine neurons for cell replacement in Parkinson's disease. However, classical approaches used to probe vMB neuron diversity and development are hampered by the presence of mixtures of different cell types and maturation stages in whole tissue dissections. To resolve this limitation, we have utilized single-cell RNA-sequencing to reconstruct the differentiation of neuronal lineages in the mouse vMB between embryonic day 10.5 and 13.5. Importantly, the analysis provided a robust genome-wide reconstruction of how neural stem cells expressing the transcription factor Lmx1a transition into postmitotic differentiating neurons. This approach also allowed rapid, comprehensive and unbiased identification of robust gene signatures represented in Lmx1a-expressing neuronal lineages. In vivo validation of one such signature has uncovered an unexpected similarity between developing dopaminergic neurons, and more rostrally developing glutamatergic neurons of the Subthalamic Nucleus. Single-cell RNA-seq thus proves an invaluable technique in successfully interrogating lineage diversity in the developing CNS.

CONCURRENT IE: GERMLINE AND RNA BIOLOGY

ROOM K1

UNITING MAJOR CONSTITUENTS OF THE GENOME: THE ROLE OF PIRNAS IN THE GERMLINE

Lin, Haifan

Yale University School of Medicine, New Haven, CT, USA

The eukaryotic genome has vast intergenic regions containing transposons, pseudogenes, repetitive sequences, and noncoding genes that produce numerous long non-coding RNAs (lncRNAs) and PIWI-interacting RNAs (piRNAs). Yet the functions of the intergenic regions remain largely unknown. In mammals, a unique set of piRNAs, pachytene piRNAs, is abundantly expressed in late spermatocytes and early spermatids. Recently, we showed that piRNAs derived from transposons and pseudogenes mediate the degradation of a large number of mRNAs and lncRNAs in mouse late spermatocytes. In particular, they have a large impact on the lncRNA transcriptome, as a quarter of lncRNAs expressed in late spermatocytes are upregulated in mice deficient in piRNA pathway. Furthermore, our genomic and in vivo functional analyses revealed that retrotransposon sequences are frequently found in the 3' UTR of mRNAs that are targeted by piRNAs for degradation. Similarly, the degradation of spermatogenic cell-specific lncRNAs by piRNAs are mediated by retrotransposon sequences. Moreover, we have shown that pseudogenes regulate mRNA stability via the piRNA pathway. The degradation of mRNAs and lncRNAs by piRNAs requires MIWI and, at least in part, depends on its slicer activity. Together, these findings reveal a highly complex and global RNA regulatory network through which transposons and pseudogenes regulate target mRNA and lncRNA stability via the piRNA pathway to promote meiosis-spermiogenesis transition.

LNCRNA DEANR1 REGULATES HUMAN ENDODERM DIFFERENTIATION BY FACILITATING FOXA2 ACTIVATION

Jiang, Wei, Liu, Yuting, Zhang, Yi

Program in Cellular and Molecular Medicine, Boston Children's Hospital, Boston, MA, USA

Long non-coding RNAs (lncRNAs) are believed to play important roles in regulating diverse biological processes including cell lineage specification. Here we report transcriptome profiling of human endoderm and pancreatic cell lineages using purified cell populations. Analysis of the data sets allowed the identification of hundreds of lncRNAs that exhibit stage-specific expression patterns during endoderm and pancreatic cell lineage differentiation. As a first step in characterizing these lncRNAs, we focus on an endoderm-specific lncRNA DEANR1 (Definitive Endoderm Associated long Non-coding RNA 1) and demonstrate that it plays an crucial role in human endoderm differentiation. Depletion of DEANR1 from human ESCs impairs their endoderm differentiation capacity. In addition, we demonstrate that DEANR1 regulates expression of FOXA2, a transcription factor functional for endoderm differentiation. More importantly, overexpression of FOXA2 is able to rescue defective endoderm differentiation caused by DEANR1 depletion, which supports the notion that FOXA2 is a major DEANR1 target. Mechanistically, DEANR1 interacts with SMAD2/3 and facilitates FOXA2 activation by helping SMAD2/3 recruitment to FOXA2 promoter. Thus, our study thus not only reveals a large set of endoderm and pancreatic beta cell differentiation stage-specific lncRNAs, but also characterizes a novel lncRNA important for endoderm differentiation as well as how it contributes to the differentiation process.

REARRANGEMENT OF CARBOXYLCYTOSINE PATTERNS INITIATES GENOME REPROGRAMMING DURING SPERMIOGENESIS

Ruzov, Alexey, Blythe, Martin, Loose, Matthew

University of Nottingham, Nottingham, United Kingdom

Chromatin of male and female gametes undergoes a number of reprogramming events during the transition from germ cell to embryonic developmental programs in the zygote. This process involves reorganisation of the patterns of 5-methylcytosine (5mC), a DNA modification associated with regulation of gene activity1-4. Notably, both maternal and paternal genomes undergo Tet3-dependent oxidation of 5mC to 5-hydroxymethylcytosine (5hmC), 5-formylcytosine (5fC) and 5-carboxylcytosine (5caC) in one-cell embryos. Although the precise biological function of these oxidised forms of 5mC remain elusive, they may play specific roles in active demethylation and transcriptional regulation. Here we present the results of genome-scale analysis of 5mC/5hmC/5caC distributions in round spermatids and spermatozoa and demonstrate that reprogramming of the paternal genome begins during spermatid maturation. We show that patterns of 5caC genomic distribution are highly dynamic in spermiogenesis. Whereas 5caC is eliminated from LINE1 retroposons and transcriptionally active spermiogenesis-specific genes during spermatid maturation, it is simultaneously accumulated at promoter regions and introns of the genes involved in embryo development. Surprisingly, the elimination of 5caC from LINE1 elements is not associated with their demethylation. Moreover, the genomic regions enriched in 5caC in spermatozoa do not correspond to the loci reported to experience demethylation in the zygote. Our results suggest that embryonic patterns of DNA methylation are prearranged during spermiogenesis and imply a role for 5caC in transcriptional regulation.

PIWIL3 AND PIRNAS IN MAMMALIAN OOCYTES

Roelen, Bernard A.[1], Roovers, Elke F.[2], Rozenkranz, David[3], Mahdipour, Mahdi[4], Han, Chung-Tin[2], He, Nannan[5], Chuva de Sousa Lopes, Susana M.5, van der Westerlaken, Lucette A.[6], Zischler, Hans[3], Butter, Falk[2], Ketting, Rene F.[2]

[1]Farm Animal Health, Utrecht University, Utrecht, Netherlands, [2]Institute of Molecular Biology, Mainz, Germany, [3]Johannes Gutenberg University Mainz, Mainz, Germany, [4]Farm Animal Health, Utrecht University Faculty of Veterinary Medicine, Utrecht, Netherlands, [5]Department of Anatomy and Embryology, Leiden University Medical Center, Leiden, Netherlands, [6]Department of Gynaecology, Leiden University Medical Center, Leiden, Netherlands

The generation of healthy offspring is dependent on the maintenance of healthy compatible germ cells. Particularly the genomic integrity is of importance since genomic errors in sperm cells and oocytes will have resolute consequences for the developing fetus as a whole. In many animal systems, germ cells depend on a system of small 24-30 nucleotide RNAs (piRNAs) and Piwi proteins to counteract transposon activity. In the mouse, 3 genes code for 3 PIWI proteins: PIWIL1 (MIWI), PIWIL2 (MILI) and PIWIL4 (MIWI2). Remarkably, mice that lack either of these proteins exhibit male infertility but the females are fertile. In addition, the majority of small RNAs in mouse oocytes are miRNAs and siRNAs, and this has led to the assumption that piRNAs and PIWI in oocytes have a limited function. Intriguingly, the genomes of most mammalian species, including the human but excluding mice, contain a fourth Piwi paralogue, called PIWIL3.

We sequenced the small RNAs of bovine and human ovaries and detected a high percentage of ~30 nucleotide piRNAs. These piRNAs, bound to PIWIL1, had similar characteristics to those sequenced from testes, including a pronounced ping-pong signal. Only a small percentage (<20%) of both ovary and testis piRNAs corresponded to transposons. Since the majority of cells in the ovary are somatic and most oocytes are in primordial follicles, we also isolated oocytes from antral follicles of bovine ovaries, removed the somatic cumulus cells and sequenced the small RNA populations. Here, less than 1% of the small RNAs were miRNAs and the majority resembled piRNAs with a peak at 26 nucleotides. Remarkably, about 50% of the piRNAs was derived from transposon sequences. Sequencing small RNAs from matured metaphase II stage oocytes revealed a similar pattern while no piRNAs were detected in cumulus cells that surround the oocytes. Most remarkably, 2-4 cell stage embryos obtained after in vitro fertilization of bovine oocytes still contained large numbers of piRNAs. Proteomic analysis bovine oocytes, cumulus cells and testes identified only one of the four piwi paralogues, PIWIL3, in oocytes but not in cumulus cells or testes. In contrast, as expected PIWIL1 and PIWIL2 were detected in bovine testes. Combined these results suggest an unexpected function of PIWIL3 and piRNAs in mammalian oocytes and early embryos.

GENETIC DISSECTION OF M6A RNA METHYLATION FUNCTION AND ROLE IN EARLY MAMMALIAN DEVELOPMENT

Geula, Shay[1], Moshitch-Moshkovitz, Sharon[2], Dominissini, Dan[2], Mansour, Abed AlFatah[1], Rechavi, Gideon[2], Novershtern, Noa1, Hanna, Jacob[1]

[1]*Weizmann Institute of Science, Rehovot, Israel,*
[2]*Chaim Sheba Medical Center, Tel Hashomer, Israel*

The role of epigenetic modifications such as DNA and Histone methylation in regulation of gene expression and cell differentiation has been studied extensively. However, the role of RNA modifications has only started to unveil. N6-methyladenosine (m6A) is the most common mRNA modification found in eukaryotes, marking approximately 30% of all expressed genes. In the last decade, proteins that serve as "writers" (m6A methyltransferase), "erasers" (m6A demethylase) and "readers" (m6A binding proteins) have been discovered, supporting the role of m6A in epigenetic regulation of gene expression. The naïve pluripotent epiblast in the inner cell mass is an important ground state configuration where the epigenetic landscape is reset and prepared for subsequent lineage priming. This process occurs in the pluripotent post-implantation epiblast, afterwards lineage differentiation takes place. While global DNA methylation and histone modification profiling indicated major epigenetic differences between naïve and primed pluripotent states, limited knowledge is available regarding RNA modification level. We have identified Mettl3, an m6A RNA writer, as a critical regulator for terminating naïve pluripotency and enabling cellular commitment to differentiation in vitro and in vivo. We found that Mettl3 Knockout in ESCs is sufficient for complete removal of m6A modifications from their mRNA molecules. Naïve ESCs and the pre-implantation epiblast are viable and present normal pluripotent markers. Yet, they fail to adequately terminate the naïve pluripotent state, and subsequently undergo aberrant priming and early lineage commitment at the post-implantation stage. Our analysis identified m6A as a critical determinant, which destabilizes naïve specific pluripotency genes (e.g. Nanog, Klf2 and Esrrb). m6A restrains transcript stability, therefore safeguards rapid exit from naïve pluripotency. I will present unpublished results on additional aspects of m6A mRNA modification, such as mRNA cellular localization and mRNA secondary structure. Moreover, I will present our analysis on genetic KO models for m6A readers YTHDF1,2 and 3 proteins in pluripotent and differentiated cells. Collectively, our work will help further promote the understanding of mRNA epi-transcriptome in early mammalian development.

IDENTIFICATION OF TRANSLATIONAL NETWORKS ORCHESTRATING PLURIPOTENT CELL FATE THROUGH EIF4E REGULATION

Darr, Henia, Lee, Dung Fang, Schaniel, Christoph, Lemischka, Ihor

Black Family Stem Cell Institute, Ichan School of Medicine at Mount Sinai, New York, NY, USA

Pluripotency research has largely focused on elucidating the transcriptional and epigenetic networks governing self-renewal and pluripotency. However, multiple proteins regulate RNA following its transcription, through translation, until degradation. This is still an unexplored regulatory level of pluripotency. To understand the role of post-transcriptional gene regulation in the pluripotent state, we examined pathways involved in regulating RNA fate and identified numerous RNA binding proteins whose down-regulation impairs mouse embryonic stem cells (ESCs) pluripotency. One of them, Neuroguidin, regulates eIF4E dependent translation initiation. Due to the immense importance of eIF4E regulation in processes such as malignant transformation, development and cell fate determination, the involvement of eIF4E in pluripotency was further investigated. Using OP-Puro to examine translation rate in ESCs, we find that although translation rate is upregulated upon differentiation, this upregulation

is transient, and later in differentiation translation rate is similar to that of ESCs. This is although we do find that ESCs have low levels of eIF4E. We therefore hypothesize that ESCs utilize alternative mechanisms to efficiently translate transcripts such as Myc and Sox2, known to rely on proper levels of eIF4E. To identify such mechanisms, we analyzed additional genes controlling eIF4E activity and found tight dependence of ESCs self-renewal on proper eIF4E regulation. Both genes regulating global levels of eIF4E availability in the cell (such as 4E-bp1) and genes regulating translation of specific transcripts (such as Cpeb) are crucial for maintaining mouse ESCs self-renewal. Analysis of the role of Cpeb is ESCs showed that it binds multiple transcripts involved in pluripotency and self-renewal. Since a Thr171 phosphorylation switches Cpeb from a translational repressor to a translational activator we examined its phosphorylation status in ESCs and found a phosphorylated form, indicating Cpeb activates the translation of its bound transcripts. We therefore suggest that ESCs utilize Cpeb as a mechanism to specifically enhance the translation of certain ES cell transcripts, which otherwise will not be efficiently translated in the eIF4E poor environment.

THURSDAY, 25 JUNE, 16:00 - 17:55

CONCURRENT IIA: DISEASE MODELING

VICTORIA HALL

MODELING OF HUMAN NEUROLOGICAL / PSYCHIATRIC DISORDERS USING IPSC TECHNOLOGY AND TRANSGENIC NON-HUMAN PRIMATES

Okano, Hideyuki

Keio University, School of Medicine, Tokyo, Japan

The induced pluripotent stem cells (iPSCs) technology is attracting attention for their potential to recapitulate the phenotypes of neurological diseases and broaden our understanding of the pathogenesis of many neurological diseases, including those of pediatric and late onset. Since a wide variety of the cells affected in the neurological disorders, the advantages of the iPS technologies would include the fact that cells at various developmental stages can be generated in vitro. We investigated the pathophysiology of various neurological disorder models, which can be subclassified into diseases caused by abnormal gene regulations, those with structural abnormalities of nervous systems, those with abnormal neural functions and those with abnormal gene functions. Through these observations, we conclude that characterization of patient-specific iPS cells could recapitulate the disease process, showing the disease-related accumulation of abnormal deposits, metabolic abnormalities and electrophysiological activities. Thus, iPSC technologies provide an opportunity for preemptive treatments for these diseases. Furthermore, for faithfully modeling the human psychiatric/psychiatric disorders in vivo, we developed transgenic non-human primates (common marmosets) with germline transmission. We generated common marmoset transgenic models of neurodegenrerative diseases, including Parkinson disease, Alzheimer disease and ALS. Furthermore, we could generate knock-out technologies of the common marmoset using genome editing technologies for the generation of transgenic marmoset models of autism and psychiatric disorders.

MOLECULAR AND FUNCTIONAL DEFICIENCIES IN FRAGILE X NEURONS DERIVED FROM HUMAN EMBRYONIC STEM CELLS

Telias, Michael[1], Segal, Menahem[2], Amit, Ami[1], Ben-Yosef, Dalit[1]

[1]Wolfe PGD-SC Lab, Racine IVF Unit, Lis Maternity Hospital, Tel-Aviv Sourasky Medical Center and Tel-Aviv University, Tel-Aviv, Israel, [2]Neurobiology, Weizmann Institute of Science, Rehovot, Israel

Fragile X Syndrome (FXS) is the most common form of inherited cognitive impairment. It is caused by developmental inactivation of the FMR1 gene and its encoded protein FMRP, an mRNA binding protein with pivotal roles in brain development and function. In FXS embryos FMRP is expressed during early embryogenesis and is gradually downregulated at the third trimester of pregnancy. We derived several human embryonic stem cell (hESC) lines from FXS blastocysts, bearing the full CGG expansion mutation and expressing FMR1 at the pluripotent stage and showed that in vitro neural differentiation (IVND) induced complete inactivation of FMR1 in mature neurons. We reported the first successful differentiation of functional neurons from FX-hESCs demonstrating abnormal neurogenesis and aberrant gene expression already during early stages of differentiation, leading to poor neuronal maturation. Human FX neurons fired action potentials but displayed poor synaptic activity. We now explored the molecular mechanisms behind poor and delayed neurogenesis by inducing IVND in three different FX-hESC lines, and by overexpressing FMR1 in FX cells and siRNA-silencing of FMR1 in WT cells. Our results show that, in contrast to fmr1-/- mice, aberrant human embryonic neurogenesis characterizing FX-hESCs is Wnt-independent. Furthermore, we demonstrate that FMRP regulates the repression of SOX2 and the activation of SOX9, which play a key role in neural differentiation, and their aberrant expression in FXS can explain the delayed and abnormal neurogenesis of FX-hESCs. Extensive electrophysiological

analysis of the neurons differentiated from FX-hESCs show that FX neurons can fire single action potentials (APs) but are incapable of firing trains of APs. The APs of FX neurons show reduced amplitude and increased duration. In addition, human FX neurons contain fewer synaptic vesicles and a reduced ability for synaptic release. Notably, synaptic activity in these neurons can be restored by co-culturing the cells with rat neurons, demonstrating critical roles for pre-synaptic mechanisms in FXS pathology. This is the first molecular and electrophysiological analysis of human FX neurons derived in vitro from hESCs demonstrating its value as a convenient vehicle for testing mechanisms of repair in FXS.

UNBIASED INTERROGATION OF POLYGENIC BRAIN DISORDERS USING STEM CELL MODELS

Barrett, Lindy, Manning, Danielle, Bevilacqua, Elizabeth, Dabkowski, Nicole, Herring, Amanda, Bara, Maggie, Ng, Carrie, Moran, Jennifer, Scolnick, Edward, Hyman, Steve, Eggan, Kevin

Broad Institute, Cambridge, MA, USA

Neuropsychiatric and neurodevelopmental disorders, including Schizophrenia (SCZ) and Autism Spectrum Disorder (ASD), have an enormous impact on global health, yet research progress in these areas continues to lag behind other major disease burdens. While many factors contribute to this disparity, inherent genetic complexities have hindered progress in dissecting the underlying pathophysiology. Within the last year, genome-wide analyses have implicated over 100 loci in the etiology of SCZ, the majority of which were previously unknown. In order to understand the phenotypic consequences of emerging human genetic data, we are utilizing state of the art genome-engineering technology, human pluripotent stem cell (hPSC) models and in vitro differentiation. Using CRISPR/Cas9 tools, we have systematically engineered loss-of-function (LoF) mutations in hPSCs for 98 distinct SCZ- and/or ASD- implicated genes. We are now using this extensive library of mutant cell lines to (I) further define CRISPR/Cas9-mediated mutational specificity and efficiency in hPSCs using a powered sample-set, and (II) generate layer II/III excitatory cortical neurons to interrogate molecular, cellular and circuit level phenotypes in relevant populations of human neurons. This project falls at the intersection of neurobiology, stem cell biology and human genetics, and is designed to meet the unique challenges presented by polygenic brain disorders. We believe such rapid, comprehensive and unbiased analyses will provide a critical foundation for understanding basic neurobiological mechanisms, and ultimately aid in the development of better treatments for these devastating conditions.

DRUG SCREENING ON HUTCHINSON GILFORD PROGERIA USING PLURIPOTENT STEM CELLS REVEALS NEW PHARMACOLOGICAL MODULATORS OF PRELAMIN A FARNESYLATION

Nissan, Xavier[1], Blondel, Sophie[1], Egesipe, Anne Laure[1], Ferreira, Lino[2], De Sandre, Annachiara[3], Levy, Nicolas[3], Peschanski, Marc[1]

[1]CECS I-Stem, Evry Cedex, France, [2]Center for Neurosciences and Cell Biology University of Coimbra, Coimbra, Portugal, [3]La Timone Hospital, Marseille, France

Hutchinson Gilford progeria syndrome (HGPS) is a rare genetic disorder causing a systemic accelerated aging in children. To date, all the treatments evaluated in patients are repurposed molecules identified through hypothesis-driven strategies. Another way to identify new chemical entities with a therapeutic potential relies on high throughput screening of compound libraries. Here we report the results of the first high-throughput screening of small molecules performed on a cellular model of this disease. 21,608 small molecules were evaluated on their capacity to inhibit prenylation of prelamin A in mesenchymal stem cells derived from HGPS induced pluripotent stem cells. Results of this drug screening revealed a new class of prenylation inhibitors, named aminopyrimidines, capable of inhibiting prelamin A farnesylation and restoring two of the main in vitro phenotypes associated to this model, namely nuclear shape abnormalities and premature osteoblastic differentiation. Finally, molecular docking and biochemical experiments demonstrated a direct dual inhibition of two of the key enzymes of the prenylation pathway, farnesyl pyrophosphate synthase and farnesyl transferase by mono-aminopyrimidines. Altogether, the present study opens new therapeutic perspectives for the treatment of HGPS by revealing a new family of protein farnesylation inhibitors and may identify new potential treatments for cancers and diseases associated to mutations activating farnesylated proteins, such as those of the RAS family

MODELING GATA4 HAPLOINSUFFICIENCY USING IPS-DERIVED CARDIOMYOCYTES REVEALS GENOME-WIDE INTERACTION WITH TBX5 AND HISTONE MODIFIERS NECESSARY FOR CARDIAC LINEAGE COMMITMENT AND FUNCTION

Ang, Yen-Sin[1], Rivas, Renee[1], Ribeiro, Alexandre[2], Liu, Huey Jiin[1], Spencer, Ian[1], Jang, Gwendolyn[3], Srivas, Rohith[2], Johnson, Jeffrey[3], Li, Molong[1], Huang, Yu[1], Krogan, Nevan[3], Pruitt, Beth[2], Hood, Leroy[4], Synder, Michael[2], Srivastava, Deepak[1]

[1]Gladstone Institutes and University Of California San Francisco, San Francisco, CA, USA, [2]Stanford University, Palo Alto, CA, USA, [3]University Of California San Francisco, San Francisco, CA, USA, [4]Institutes for Systems Biology, Seattle, WA, USA

Precise tuning of gene expression levels by transcription factors is critical for proper lineage commitment, organogenesis, cell growth and tissue function. Heterozygous partial loss-of-function mutations of GATA4--a master regulator of cardiac cell fate determination--cause congenital heart defects and predispose to cardiomyopathy. However, the mechanism by which haploinsufficiency affects transcription and the epigenetic landscape is unknown. Here, we integrated multi-disciplinary approaches including derivation of patient-specific cardiomyocytes (CMs), proteomics, transcriptomics, epigenomics and mechanobiology assays to dissect the molecular mechanisms of GATA4 involved in cardiac lineage commitment and function. Affinity purification of GATA4 from pluripotent stem cell-derived CMs followed by mass spectrometry revealed physical interactions with NuRD-, BAF-, MLL-, HAT-containing protein complexes, suggesting a potential dysregulation of the epigenetic landscape in GATA4 haploinsufficiency. ChIP-seq revealed that GATA4 and its interacting partner, TBX5, co-occupied thousands of loci genome-wide. iPSC-derived CMs made from a human pedigree with GATA4 haploinsufficiency exhibited perturbations to acetylated-H3K27 levels and TBX5 binding at loci normally co-bound by GATA4 and TBX5. GATA4 knockdown in hESC-derived cardiac progenitors and CMs, confirmed putative direct targets of GATA4 and identified novel dose-sensitive targets. These direct gene targets were enriched in pathways representing inflammation, mitochondrial respiration, muscle contraction, cell proliferation and the extracellular matrix. Using bioengineered micropatterns to test mechanobiological functions, we demonstrated changes in contractility and mitochondria function in haploinsufficient CMs, consistent with the transcriptional defects and the cardiomyopathy phenotype observed in GATA4 heterozygous patients. Together, these results uncovered an intimate cooperation between GATA4, TBX5 and epigenetic regulators in directing human cardiac development, provided novel downstream targets and pathways for therapeutic interventions and have broad implications for the understanding of diseases caused by transcription factor haploinsufficiency.

CONNECTING GENOTYPE TO DISEASE PHENOTYPE: DISSECTING THE EFFECT OF PARKINSON'S DISEASE ASSOCIATED RISK VARIANTS ON GENE EXPRESSION

Soldner, Frank[1], Stelzer, Yonatan[1], Shivalila, Chikdu[1], Abraham, Brian J.[1], Barrasa, Inmaculada M.[1], Myers, Richard H.[2], Young, Richard A.[1], Jaenisch, Rudolf[1]

[1]Whitehead Institute for Biomedical Research, Cambridge, MA, USA, [2]Department of Neurology, Boston University School of Medicine, Boston, MA, USA

Genome wide association studies (GWASs) have identified numerous common single-nucleotide polymorphisms (SNPs) associated with human traits and complex diseases, but the vast majority of these variants do not alter protein-coding sequences and have no established biological function or relevance to disease. Using human pluripotent stem cells (hPSCs), we describe an experimental strategy to dissect the function of non-coding disease-associated risk variants based on (i) the prioritization of GWAS-identified risk SNPs in regulatory elements based on genome-scale epigenetic data such as histone modifications, DNase I hypersensitivity and transcription factor binding; (ii) CRISPR/Cas9-mediated genome editing to generate genetically-controlled isogenic hPSCs in which specific disease-associated genetic variants are the sole modified experimental variable; and (iii) the quantitative analysis of cis-acting effects of candidate variants on allele-specific gene expression through deletion or exchange of disease-associated haplotypes. This approach eliminates the system's inherent variables such as in vitro differentiation and results in an internally controlled experimental system, which allows robust and reproducible identification of sequence-specific effects on gene regulation. We apply this genetically controlled experimental system to systematically dissect Parkinson's disease (PD) associated risk variants and identify a common SNP in a non-coding distal enhancer element that regulates the expression of SNCA, a key gene implicated in the pathogenesis of PD. We further provide data suggesting that the transcriptional deregulation of SNCA is mediated by changes in sequence-dependent binding of the brain-specific transcription factors EMX2 and NKX6-1. Thus our data provides a molecular link between GWAS-identified risk variant, altered expression of SNCA and the risk to develop PD. In addition to mechanistic insight, our results have diagnostic and possibly therapeutic implications suggesting that patients with sporadic PD

may benefit from therapies aimed at modulating SNCA expression. Importantly, this work outlines a general experimental paradigm to functionally connect genetic variants with disease relevant phenotypes.

THURSDAY, 25 JUNE, 16:00 - 17:55

CONCURRENT IIB: STEM CELL REGULATORY NETWORKS AND MODELS

ROOM A2

Supported by Stemgent, part of the ReproCELL Group

ON PECULIARITIES OF BEING A HUMAN: USING STEM CELLS TO STUDY HUMAN EVOLUTION AND HUMAN-SPECIFIC ASPECTS OF DEVELOPMENTAL GENE REGULATION

Prescott, Sara L.[1], Srinivasan, Rajini[1], Marchetto, Maria Carolina[2], Narvaisa, Inigo[2], Selleri, Licia[3], Gage, Fred H.[2], Swigut, Tomek[1], Wysocka, Joanna[1, 4]

[1]Department of Chemical and Systems Biology, and Department of Developmental Biology, Stanford University School of Medicine, Stanford, CA, USA, [2]Laboratory of Genetics, The Salk Institute for Biological Studies, La Jolla, CA, USA, [3]Weill Medical College, Cornell University, New York, NY, USA, [4]Institute of Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA.

While studies in model organisms have led to great progress in unveiling the conserved mechanisms of gene regulation, many aspects of development that are unique to humans and other primates remain unexplored, as are regulatory principles underlying emergence of human-specific traits. I will discuss our recent systematic, quantitative analysis of cis-regulatory divergence in the human and chimpanzee neural crest, an embryonic cell population that is most relevant for evolution of human craniofacial form. Our comparative epigenomic approach reveals conserved mechanisms of neural crest gene regulation, as well as principles of enhancer activity change during recent human evolution. Moreover, our studies predict many specific genes, regulatory elements and pathways that shape morphological divergence, and suggests a high overlap between loci that regulate inter- and intra-species variation of the facial shape in humans.

COUPLING PIONEER FACTORS AND SUPER-ENHANCERS TO GOVERN STEM CELL PLASTICITY AND LINEAGE CHOICE

Adam, Rene Christian[1], Yang, Hanseul[1], Rockowitz, Shira[2], Larsen, Samantha[1], Nikolova, Maria[1], Oristian, Daniel[1], Polak, Lisa[1], Kadaja, Meelis[1], Asare, Amma[1], Zheng, Deyou[2], Fuchs, Elaine[1]

[1]The Rockefeller University, New York, NY, USA, [2]Albert Einstein College of Medicine, New York, NY, USA

Adult stem cells (SCs) reside in niches which balance self-renewal with lineage selection and progression during tissue homeostasis. Following injury, culture or transplantation, SCs outside their niche often display fate flexibility, yet the inherent mechanisms remain elusive. Here we show that super-enhancers underlie the identity, lineage commitment and plasticity of adult SCs in vivo. Using hair follicle (HF) as model, we map the global chromatin domains of murine HFSCs and their committed progenitors in their native microenvironments. We show that during lineage progression, super-enhancers and their dense clusters ('epicenters') of transcription factor (TF) binding sites are dynamically remodeled. New fate is acquired by decommissioning old and establishing new super-enhancers and/or epicenters, an auto-regulatory process that abates one master regulator subset while enhancing another. We further examine normal homeostasis and wound-healing where stem cells have exited their niche but have not yet established a new destination. We show that by coupling pioneer factors and super-enhancers, stem cells are able to maintain these transitional states in an ever-changing transcriptional landscape. We provide functional evidence that super-enhancers are dynamic, dense TF-binding platforms that are acutely sensitive to pioneer master regulators whose levels define not only spatial and temporal features of lineage-status, but also stemness, plasticity in transitional states and differentiation.

PLATYPUS INDUCED PLURIPOTENT STEM CELLS REVEAL THAT ACQUISITION OF SOX2 RESPONSIVENESS FACILITATED EXPANSION OF THE PLURIPOTENCY NETWORK DURING MAMMALIAN EVOLUTION

Whitworth, Deanne J.[1], Gauthier, Maely E.[2], Ovchinnikov, Dmitry A.[3], Grimmond, Sean M.[2], Marshall Graves, Jennifer A.[4], Wolvetang, Ernst J.[3]

[1]School of Veterinary Science, University of Queensland, Gatton, Australia, [2]Institute for Molecular Bioscience, University of Queensland, St Lucia, Australia, [3]Australian Institute for Bioengineering and Nanotechnology, University of Queensland, St Lucia, Australia, [4]Research School of Biology, Australian National University, Acton, Australia

During embryonic development all vertebrates transition through a period of pluripotency; however, the mechanisms by which pluripotency has evolved remain unclear. The platypus (Ornithorhynchus anatinus) is an egg-laying monotreme mammal whose ancestors diverged approximately 166 million years ago from the evolutionary pathway that eventually gave rise to both marsupial and eutherian mammals. Consequently, its genome is an extraordinary amalgam of both ancestral reptilian and derived mammalian features. To gain insight into the evolution of mammalian pluripotency we have generated induced pluripotent stem cells (piPSCs) from the platypus. Deep sequencing of the piPSC transcriptome revealed that piPSCs robustly express the core eutherian pluripotency factors OCT4, SOX2 and NANOG. Since SOX2 is not expressed in avian pluripotent stem cells, our data indicate that between 315 million years and 166 million years ago primitive mammals recruited SOX2 into the pluripotency network. Subsequent to the divergence of monotremes around 166 million years ago, the role of SOX2 in eutherian pluripotency has expanded. DAX1/NR0B1 is not expressed in piPSCs and an analysis of the platypus DAX1 promoter revealed the absence of a proximal SOX2-binding DNA motif known to be critical for DAX1 expression in eutherian pluripotent stem cells. Similarly, ESRRB is not expressed by piPSCs and the platypus ESRRB gene lacks two putative SOX2 binding sites within intron 2 which are highly conserved amongst eutherians. Taken together, these data suggest that the acquisition of SOX2 responsiveness by DAX1 and ESRRB has facilitated their recruitment into the pluripotency network of eutherians.

IDENTIFICATION OF REGULATORY NETWORKS IN HSCS AND THEIR IMMEDIATE PROGENY VIA INTEGRATED PROTEOME, TRANSCRIPTOME, AND DNA METHYLOME ANALYSIS

Klimmeck, Daniel[1], Nina, Cabezas-Wallscheid[1], Hansson, Jenny[2], Lipka, Daniel B.[1], Reyes, Alejandro[2], Huber, Wolfgang[2], Milsom, Michael D.[1], Plass, Christoph[1], Krijgsveld, Jeroen[2], Trumpp, Andreas[1]

[1]German Cancer Research Center (DKFZ), Heidelberg, Germany, [2]EMBL, Heidelberg, Germany

Hematopoietic stem cells (HSC) harbor the highest self-renewal capacity and generate a series of multipotent progenitors (MPP) that differentiate into lineage-committed progenitors and subsequently mature cells. To explore essential HSC features, we present integrated quantitative proteome, transcriptome, and methylome analyses of five FACS-sorted HSC and MPP populations (MPP1-4) as previously described in our laboratory From the characterization of more than 6,000 proteins, 27,000 transcripts, and 15,000 differentially methylated regions (DMRs), we identified coordinated changes associated with early differentiation steps. DMRs show continuous gain or loss of methylation during differentiation, and the overall change in DNA methylation correlates inversely with gene expression at key loci. Our data reveal the differential expression landscape of 493 TFs and 682 lncRNAs and highlight specific expression clusters including Wnt and Lin28-Hmga signaling, the imprinted-gene-network, Hox genes, retinoic acid metabolism. We also found an unexpectedly dynamic pattern of transcript isoform regulation, suggesting a critical regulatory role during HSC differentiation, and a cell cycle/DNA repair signature associated with multipotency in MPP2 cells. To address differentiation potential of MPP2-4 we linked our OMICs data with functional reconstitution experiments. We have now expanded this analysis to dormant HSCs identified by label-retaining assays Using single-cell RNA-seq analysis we addressed the heterogeneity within this population and provide first markers and molecular pathways specifically operational in dormant HSCs.

MITOTIC INHERITANCE OF THE PLURIPOTENCY NETWORK ACTIVITY

Navarro, Pablo

Institut Pasteur, Paris, France

The preservation of cell identity relies on the maintenance of gene expression programs through mitosis. Generally, this is mediated by epigenetic systems of repression involving chromatin modifications. However, the invalidation of the main systems of epigenetic repression (Polycomb, CpG methylation, H3K9 methylation) does not dramatically impair ES self-renewal. Hence, pluripotent cells constitute an exception regarding the general mechanism of epigenetic inheritance of gene expression profiles. Whilst chromatin-mediated epigenetic silencing seems not necessary to maintain ES cell identity, ES cells rely on the continuous activity of several pluripotency transcription factors (e.g. Oct4, Sox2, Nanog, Klf4, Esrrb), which genetic abrogation leads to severe self-renewing phenotypes. However, mitosis represents a dramatic event for the cell regarding the interactions established between transcription factors and their binding DNA targets: the high compaction to which the chromatin is subjected during mitosis leads to the general loss of transcription factor binding. Therefore, after each cell division, ES cells need to rapidly re-establish the pluripotency network in order to avoid expression of differentiation genes and maintain their undifferentiated and pluripotent identity: the existence of a memory of gene activation could in this context play a pivotal role. We have hypothesized that some pluripotency regulators may

act as bookmarking factors by remaining bound to critical target genes during mitosis. This would enable the rapid and efficient re-establishment of the network after mitosis such that self-renewal is efficiently preserved. Using imaging and ChIP-Seq approaches we have identified one such pluripotency transcription factor.

THE CURIOUS CASE OF TROPHOBLAST DIFFERENTIATION FROM HUMAN PLURIPOTENT STEM CELLS

Drukker, Micha

Helmholtz Center Munich, Munich, Germany

The emergence of trophoblast-like cells during the course of human pluripotent stem cell (PSC) differentiation is puzzling. This is because trophoblasts are NOT among the known progeny of pluripotent cells in the embryo. By performing genome-scale transcriptional and epigenomic analysis of consecutive trophoblast progenitor stages derived and purified from human PSCs using surface markers CD249 (APA) and SSEA-5, we identified the configuration of a gene activation cascade that establishes the trophoblast fate identity from human PSCs. The cascade consists of activating protein 2 (AP-2) and GATA transcription factors, which are induced directly by TGF-beta signaling in response to BMP4 treatment. These transcription factors subsequently regulate induction of a second layer set of novel and known trophoblast fate promoting genes, including, GCM1, TP63 and a TEAD4 transcription cofactor. We have validated this cascade thorough an siRNA screen. Furthermore, we show that the promoters of the initial genes in the cascade are poised for rapid activation in PSCs (exhibiting H3K4me3/H3K27me3 bivalency). Conversely, the second layer set of genes, which likely finalizes the commitment of the cells to the trophoblast lineage, are repressed by CpG island methylation in human PSCs, and canonical histone repressive modifications are not present in their promoters. We speculate that the "dormancy" of important trophoblast commitment genes in human PSCs represents an attempt of human PSCs to silence a pathway leading to placental development, but this can be overrun by TGF-beta signaling in vitro. This work provides a long-sought mechanistic explanation for trophoblast differentiation from human PSCs, and grounds for understanding epigenetic priming during PSC commitment.

CONCURRENT IIC: RELATIONSHIPS AND CLONALITY

ROOM A4

CELL COMPETITION IN PLURIPOTENT STEM CELLS

Zwaka, Thomas P.

Black Family Stem Cell Institute, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Cell competition represents a radical departure from the established view that embryonic development is simply a matter of following a preprogrammed set of rules. Instead, it is a highly conserved process that promotes the elimination of less fit and potentially dangerous cells during developmental progression. There is abundant evidence to support competition among genetically identical cells in complex organisms. Although we know, for example, that the basis of cell competition is the ability of growing cells to monitor the "fitness" of their neighbors, and is induced by differences in Myc levels and protein synthesis capacity, we are at a loss to understand the subsequent effector mechanisms and pathways. Understanding these molecular relationships might (i) open new perspectives on mammalian embryogenesis and explain why it is so robust; (ii) help us to delineate certain pathologies in which cellular heterogeneity is a dominant feature (especially cancer); (iii) augment clinical purposes by endowing stem cells with competitiveness in a transplantation setting, and (iv) perhaps provide a conceptual substrate for understanding the connection between evolutionary-scale adaptation and developmental processes (adaptive development). To close this developmental knowledge gap, we used forward genetic screens in pluripotent stem cells to uncover a network of genes, including P53 and topoisomerase I (TOP1), that control cell competition in pluripotent cells and the epiblast. A subsequent meta-analysis of the data uncovered a potential master regulator pathway of this cell competition network, EDAR (ectodysplasin receptor, a member of the tumor necrosis factor family), as well as two prime downstream targets, JNK and NFKB. The primary molecular effector mechanism for cell competition is the activation of a canonical immune-related stress response and subsequent phagocytosis of loser cells by winners. We utilized game theory models and found a "zero sum" game at play between cells with biomass preservation. We propose that cell competition permits the selection of the best-fit cells via activation of an ancient stress-related pathway, while, at the same time, maximally preserving resources at this juncture of development.

CHARACTERIZATION AND THERAPEUTIC MODULATION OF A DERMAL LINEAGE WITH INTRINSIC FIBROGENIC POTENTIAL

Walmsley, Graham G., Rinkevich, Yuval, Hu, Michael S., Maan, Zeshaan N., Januszyk, Michael, Duscher, Dominik, Gurtner, Geoffrey C., Lorenz, H. Peter, Longaker, Michael T., Weissman, Irving L.

Stanford University School of Medicine, Stanford, CA, USA

Effective treatment of fibrosis depends upon a mechanistic understanding of its pathogenesis. Fibroblasts remain poorly characterized but are central to the fibrotic response across a range of pathologic states. Using a new murine model, we reveal the presence of multiple embryonic lineages of dermal fibroblasts within the dorsal skin of mice and identify a highly fibrogenic lineage defined by embryonic expression of Engrailed-1 (En1). En1-derived fibroblasts were traced using En1-Cre; ROSA26-mTmG transgenic mice. Flow cytometry, transplantation methodologies, and small molecule-based inhibition allowed for identification of En1 lineage-specific surface markers. En1-derived fibroblasts were selectively ablated during wound healing using transgenic mice. En1-derived fibroblasts were found to be responsible for the majority of connective tissue deposition during dermal development, wound healing, radiation-induced fibrosis, and cancer stroma formation in the dorsal skin. Lineage-specific cell ablation using localized administration of diphtheria toxin (DT) led to significantly reduced scar formation (*$p<0.01$) following excisional wounding and significantly reduced melanoma growth (*$p<0.01$). Tensile strength testing of DT-treated and control wounds revealed that although scar formation was significantly reduced in DT-treated as compared to control wounds, tensile strength was not significantly affected. Furthermore, we identified CD26/DPP4 as a surface marker that allows for the isolation of this fibrogenic scar-forming lineage and demonstrated that small molecule-based inhibition of CD26/DPP4 leads to significantly reduced scar formation (*$p<0.001$) during excisional wound healing. In conclusion, we have identified multiple lineages of fibroblasts in the dorsal skin. Among these, we have characterized a single lineage responsible for the fibrotic response to injury in the dorsal skin of mice and demonstrated that targeted inhibition of this lineage results in reduced scar formation with no effect on the structural integrity of the healed skin. These results hold promise for the development of therapeutic approaches to fibrotic disease, wound healing, and cancer progression in humans.

INDUCTION OF ROD PHOTORECEPTOR-SPECIFIC PROGENITORS FROM ADULT MOUSE RETINAL STEM CELLS

Ballios, Brian G.[1], Khalili, Saeed[2], Donaldson, Laura[3], van der Kooy, Derek[2]

[1]Faculty of Medicine, University of Toronto, Toronto, ON, Canada, [2]Molecular Genetics, University of Toronto, Toronto, ON, Canada, [3]Division of Ophthalmology, McMaster University, Hamilton, ON, Canada

Adult retinal stem cell (RSCs) derived from the ciliary epithelium (CE) of mice can give rise to all retinal cell types. Taurine, retinoic acid and FGF2/heparin (T+RA+FH) added to differentiating clonal RSC colonies increases the number of rods to 90% of all progeny; RSC progeny produce 10% rods when differentiated in 1%FBS+FH (pan-retinal conditions). We hypothesized that T/RA acts on RSC progeny in an instructive, rather than permissive, manner to bias photoreceptor differentiation through the enrichment of rod-specific progenitors. RSCs were clonally isolated from the CE of 4-6 week old mice. We used limiting dilutions (<1 clone / well) of a fluorescent retroviral construct to label individual progenitor clones in vitro. In addition, single cell sorting isolated non-pigmented and pigmented cells in wells, which were then treated with T/RA for 28 d. Survival, clone size, and phenotype were assessed by immunocytochemistry. Clonal retroviral labeling revealed enrichment in the percentage of rod-only clones between 1%FBS (13%) to T/RA (over 70%), without affecting clone size or overall cell survival. This strongly argues against selective survival of rod progenitors or differential survival of post-mitotic rods within a clone. In 1%FBS, clones derived from single non-pigmented progenitors were distributed between non-rod and mixed clones, with a minority of rod-only clones (100% Rhodopsin-positive; n=4 of 28 clones). Clones derived from pigmented cells in 1%FBS never gave rise to rod-only clones. In T+RA conditions, all clones derived from non-pigmented progenitors (n=34) were rod-only clones, while those derived from pigmented progenitors (n=47 of 48) were almost all no-rod clones. Of note, one rod-only clone (the largest) was derived from a single pigmented cell in T+RA conditions, suggesting potential neural lineage plasticity in a very early, pigmented progenitor. Survival rates of non-pigmented cell derived clones were similar in T+RA and 1%FBS. This study marks an important step in the characterization of a rod-specific progenitor - no markers exist and literature is divided on their existence in vivo. Our study suggests a critical role for exogenous signals in early lineage decisions, instructing the commitment of undifferentiated progeny to fate-restricted retinal progenitors.

GENETIC LINEAGE TRACING DEMONSTRATES MULTIPOTENCY OF PREMIGRATORY AND MIGRATORY NEURAL CREST CELLS IN VIVO

Baggiolini, Arianna[1], Varum, Sandra[1], Mateos, José María[2], Bettosini, Damiano[1], John, Nessy[1], Ziegler, Urs[2], Dimou, Leda[3], Clevers, Hans[4], Furrer, Reinhard[5], Sommer, Lukas[1]

[1]Institute of Anatomy, University of Zurich, Zurich, Switzerland, [2]Center for Microscopy and Image Analysis, University of Zurich, Zurich, Switzerland, [3]Department of Physiological Genomics, Ludwig Maximilian University of Munich, Munich, Germany, [4]Hubrecht Institute, KNAW and University Medical Center Utrecht, Utrecht, Netherlands, [5]Institute of Mathematics, University of Zurich, Zurich, Switzerland

The neural crest (NC) belongs to the lineages with the broadest developmental potential, generating cell types as diverse as peripheral neurons, myelinating Schwann cells, and pigment cells, among others. However, there is a long-standing controversy as to whether individual NC cells in vivo are multipotent, or whether the NC is comprised of a heterogeneous mixture of lineage-restricted progenitors. Here, we performed in vivo fate mapping of single trunk NC cells both at premigratory and migratory stages using the R26R-Confetti mouse model. We combined quantitative analysis with definitive markers of differentiation to show that the NC population consists of only few fate-restricted cells, while the majority of NC cells are multipotent. Moreover, multipotency is maintained in migratory NC cells even after their emergence from the dorsal neural tube. Thus, our findings definitively show, for the first time, that both premigratory and migrating NC cells in the mouse are multipotent in vivo.

A QUANTITATIVE FRAMEWORK FOR INTERROGATING LINEAGE POTENTIAL VIA GENETIC TAGGING IN HIGHLY COMPLEX CELL POPULATIONS

Chin, Chee Jia[1], Cooper, Aaron[2], Lill, Georgia R.[2], Evseenko, Denis[3], Zhu, Yuhua[1], He, Chong Bin[1], Casero, David[1], Pellegrini, Matteo[4], Kohn, Donald B.[2], Crooks, Gay M.[1]

[1]Department of Pathology and Laboratory Medicine, David Geffen School of Medicine (DGSOM), University of California, Los Angeles, CA, USA, [2]Department of Microbiology, Immunology and Molecular Genetics, University of California, Los Angeles, CA, USA, [3]Department of Orthopedic Surgery, Orthopedic Hospital Research Center, DGSOM, University of California, Los Angeles, CA, USA, [4]Department of Molecular, Cell, and Developmental Biology, University of California, Los Angeles, CA, USA

Human PSC cultures differentiate into all three germ layers through a regulated series of stages that resemble normal embryogenesis. Understanding how each of the lineages are developmentally inter-related in the PSC system will inform strategies for efficient production of many specialized cell types from PSC. We have applied lentiviral marking followed by vector integration site analysis (VISA) with high-throughput sequencing (HTS) to robustly define the developmental relationships of three mesodermal lineages, hematopoietic, endothelial and mesenchymal, as they emerge from human embryonic mesoderm. In contrast to other studies that have used VISA to track differentiation of stem cells in which self-renewing clones become dominant over time, we have developed this technique to map the fate of rapidly dividing, transient population of progenitors during PSC differentiation. These studies were made possible by our ability to target a human embryonic mesoderm progenitor (hEMP) population that represents the earliest defined stage of mesoderm commitment from PSC. Lentiviral transduction of these CD326-CD56+ hEMP and HTS of their hematopoietic, mesenchymal and endothelial progeny demonstrated marking of a tripotent population with limited self-renewal and early bifurcation of the hematopoietic and mesenchymal lineages. Our bioinformatics analyses uncovered the critical influence of sampling on the interpretation of shared integration sites among highly complex populations. We present a quantitative framework to estimate and overcome the impact of sampling, an important issue for the accurate interpretation all such high complexity data sets which attempt to address questions of clonality. Through rigorous application of control populations in the analysis, we demonstrated that lentiviral integration site analysis could track a dynamic process of lineage fate decisions in polyclonal populations with heterogeneous or unknown composition. The new approach described in our study can be applied to other clonal analyses that involve HTS as a high-resolution output to fully explore the clonal repertoire amongst a diversely labeled starting population.

THE HUMAN DEFINITIVE HEMOGENIC ENDOTHELIUM GENERATING MULTIPOTENT HEMATOPOIETIC PROGENITORS REPRESENTS A DISTINCT LINEAGE FROM ARTERIAL VASCULAR ENDOTHELIUM

Ditadi, Andrea[1], Sturgeon, Christopher[1], Tober, Joanna[2], Awong, Geneve[1], Kennedy, Marion[1], Phillips, Amanda[2], Azzola, Lisa[3], Ng, Elizabeth[3], Stanley, Edouard[3], French, Deborah[4], Cheng, Xin[4], Gadue, Paul[4], Elefanty, Andrew[3], Keller, Gordon[1]

[1]McEwen Centre for Regenerative Medicine, Toronto, ON, Canada, [2]University of Pennsylvania, Philadelphia, PA, USA, [3]Murdoch Children's Research Institute, Victoria, Australia, [4]Children's Hospital of Philadelphia, Philadelphia, PA, USA

The generation of hematopoietic stem cells (HSCs) from human pluripotent stem cells (hPSCs) has been hampered by a lack of understanding of the key steps that lead to their formation in vivo. Embryonic hematopoiesis is complex as it consists of two distinct programs, primitive and definitive, that differ in their developmental potential. HSCs are generated only during the definitive stage in a Notch-dependent manner and arise from a progenitor population known as hemogenic endothelium (HE), through a process commonly referred to as the endothelial-to-hematopoietic transition (EHT). As HE is associated with major arteries in the embryo, it has generally been assumed that these progenitors represent a subpopulation of arterial vascular endothelium (VE). Here we present clear evidence that hPSC-derived HE and arterial and venous VE represent separate lineages that can be distinguished based on expression of the surface markers CD34, CD73 and CD184. We demonstrate at a clonal level that HE is restricted to the CD34+CD73-CD184- fraction of day 8 embryoid bodies (EBs) and show that under defined conditions these progenitors undergo NOTCH-dependent EHT to generate lymphoid, myeloid and erythroid progeny. Arterial and venous VE progenitors, by contrast, segregate to the CD34+CD73medCD184+ and CD34+CD73hiCD184- EB fractions, respectively. Following transplantation into immunocompromised mice, these progenitors maintained their vascular identity and integrated into the host vasculature. Single cell expression analysis of the CD34+CD73medCD184+ and CD34+CD73hiCD184- fractions confirmed the homogeneity of their arterial and venous fates. Additional proof that HE and arterial VE are distinct lineages was provided by studies showing that the CD34+CD73-CD184- population can be segregated based on expression of the arterial marker DLL4 into fractions that contain either HE giving rise to multipotent hematopoietic progenitors (DLL4-), or arterial VE progenitors (DLL4+). Together, these findings provide important new insights into the lineage relationship of human HE and VE and, in doing so, establish a platform for the characterization of this pre-HSC progenitor population and for the identification of the signaling pathways that regulate the development of functional HSCs from it.

THURSDAY, 25 JUNE, 16:00 - 17:55

CONCURRENT IID: STEM CELLS IN MODEL ORGANISMS

ROOM A6

DECODING THE MOLECULAR CUES THAT REGULATE HSC SPECIFICATION

Kobayashi, Isao, Kim, Albert, Melick, Chase, Palazon, Raquel Espin, Clements, Wilson K., Sun, Jingjing, Traver, David

Department of Cellular and Molecular Medicine, Section of Cell and Developmental Biology, University of California, San Diego, San Diego, CA, USA

Hematopoietic stem cells (HSCs) underlie the continued production of blood and immune cell lineages for the lifetime of an organism. In all vertebrate embryos examined, HSCs arise from the unique transdifferentiation of hemogenic endothelium comprising the floor of the dorsal aorta during a brief developmental window. To date, this process has not been replicated in vitro from pluripotent precursors, partly because the full complement of required signaling inputs remains to be determined. Our current efforts are aimed at elucidating the signaling pathways that are required to specify HSCs through aortic endothelial intermediates. Notch signaling plays a key role in the generation of hematopoietic stem cells (HSCs) during vertebrate development, although little is known regarding when, where, and how these events occur. Our current studies demonstrate that Notch signaling is needed iteratively to generate HSC fate, with both environmental and intrinsic requirements. The earliest known requirement is present within the somite to generate the sclerotome, the ventromedial domain of each developing somite. The sclerotome, in turn, is necessary to present Notch ligand to the shared vascular precursors of HSCs as they migrate across the ventral face of the somites. Finally, in a process that is dependent upon proinflammatory signaling, the Notch pathway is utilized again to drive the endothelial to hematopoietic transition of ventral aortic endothelium to HSCs. How these and other signaling inputs are integrated to generate HSC fate will be discussed.

This work is funded by grants from the National Institutes of Health (R01 DK074482), California Institute for Regenerative Medicine (RB4-06158), and American Heart Association (12PILT12860010).

NEW NICHE AND NOVEL STEM CELL DURING DEVELOPMENT OF DROSOPHILA MUSCULATURE

Gunage, Rajesh Dattaram, K., VijayRaghavan

The National Centre for Biological Sciences – Tata Institute of Fundamental Research, Bangalore, India

How myoblasts proliferation are regulated for the formation of muscles of different sizes is an essentially unanswered question. The flight muscles or skeletal muscles of Drosophila develop from adult muscle progenitor (AMP) cells set-aside embryonically. The thoracic segments are all allotted the same small AMP number, while those associated with the wing-disc proliferate extensively to give rise to over 2500 myoblasts, considerably large when compared to other segments. By using various genetic labeling techniques we show an initial symmetric amplification to increase the AMP population and later switch to asymmetric division, forming a stem cell and a differentiated progeny. Notch signaling controls the initial amplification of AMPs, while the switch to asymmetric division additionally requires Wingless (Drosophila Wnt), which regulates Numb expression, an inhibitor of Notch, in the AMP lineage. In both cases, the epidermal tissue of the wing imaginal disc acts as a niche expressing the ligands Serrate and Wingless. In summary, the disc-associated AMPs are a novel muscle stem cell population that orchestrates the early phases of adult flight muscle development. Extending these findings to adult by lineage trace, we show presence of muscle stem cells in mature adult life thus establishing a developmental link to stem cell fate determination.

MESENCHYMAL INDUCED CELL DEATH AND EPITHELIAL PHAGOCYTOSIS REGULATE THE HAIR FOLLICLE STEM CELL POOL

Greco, Valentina, Mesa, Kailin

Yale Medical School, New Haven, CT, USA

Tissue homeostasis is achieved through a balance of cell production (growth) and elimination (regression). Contrary to tissue growth, the cells and molecular signals required for tissue regression remain unknown. To investigate physiological tissue regression, we use the mouse hair follicle, which cycles stereotypically between phases of growth and regression while maintaining a pool of stem cells to perpetuate tissue regeneration3. Here we show by intravital microscopy in live mice4-6 that the regression phase eliminates the majority of the epithelial cells by two distinct mechanisms: terminal differentiation of suprabasal cells and a spatial gradient of apoptosis of basal cells. Furthermore, we demonstrate that basal epithelial cells collectively act as phagocytes to clear dying epithelial neighbors. Through cellular and genetic ablation we show that epithelial cell death is extrinsically induced through TGFβ activation and mesenchymal crosstalk. Strikingly, our data show that regression acts to reduce the stem cell pool as inhibition of regression results in excess basal epithelial cells with regenerative abilities. This study identifies the cellular behaviors and molecular mechanisms of regression that counterbalance growth to maintain tissue homeostasis.

YORKIE MEDIATES A SIZE SENSING MECHANISM DURING PLANARIAN REGENERATION

Lin, Alexander[1], Pearson, Bret[2]

[1]Molecular Genetics, University of Toronto, Toronto, ON, Canada, [2]Program in Developmental and Stem Cell Biology, Hospital for Sick Children, Toronto, ON, Canada

During injury-induced regeneration, adult stem cells (ASCs) must tightly regulate proliferation yet also maintain properly patterned and sized organs and tissues. The mechanisms as to how ASCs are able to achieve this remain largely unknown. To study these processes in vivo, the planarian (Schmidtea mediterranea) is a unique model organism known for its high capacity to regenerate. This ability arises from a large population of ASCs, which have well-characterized gene regulatory networks. However, less understood is how planarian ASCs sustain proper patterning in spite of constant cell turnover. One possibility is the effector of the Hippo tumor suppressor pathway, transcriptional co-factor Yorkie (Yki, vertebrate YAP), which has been demonstrated as a universal regulator in organ size determination across metazoans. We have previously demonstrated that planarians use Yki as a crucial node in controlling stem cell proliferation and patterning. Surprisingly, the loss of yki results in an expansion of the stem cell compartment, with no consequences to self-renewal, differentiation, or cell death. Yki is also important in anterior-posterior axis body patterning by restricting Wnt expression and synergizing with β-catenin to repress head identity. The two defects together: aberrantly expressed patterning molecules and the sustained hyperproliferation, suggest that Yki is required to orchestrate global responses during injury-induced regeneration. Indeed, yki(RNAi) regenerating animals exhibit impaired regeneration as a result of an amplified expression of wound responsive genes. The activin-follistatin signaling pathway is a known regulator for initiating these responses in proportion to the amount of tissue loss. We find that Yki interacts with this signaling cascade and thus, connects Yki to a size-

sensing mechanism following wounding. Finally, the roles for Yki during regeneration are also paralleled in adult homeostasis and can be attributed to an induced injury-like state in yki(RNAi) intact worms. Altogether, this study has uncovered a role for Yki as a size-sensing regulator to balance ASC proliferation, and body patterning through an interaction with Wnt/β-catenin signaling.

THE CALCINEURIN CONTROLS PROPORTIONAL GROWTH OF ZEBRAFISH REGENERATING FINS

Kujawski, Satu[1], Lin, Weilin[2], Wagner, Michael[3], El-Armouche, Ali[3], Zhang, Yixin[2], Antos, Christopher[1]

[1]DFG-Center for Regenerative Therapies Dresden, Technische Universität Dresden, Dresden, Germany, [2]B CUBE Center for Moleclar Bioengineering, Technische Universität Dresden, Dresden, Germany, [3]Institute of Pharmacology and Toxicology, Technische Universität Dresden, Dresden, Germany

Animals that regenerate organs and appendages control the growth of stem and progenitor cells to reform lost structures to the same dimensions as the original structures. This proportional regeneration involves coordinating rapid allometric (disproportional) growth with the restoration of isometric (proportional) cell proliferation once the correct tissue dimensions are reached. It is unknown what executes this coordinated control. We show that the calcium-dependent phosphatase calcineurin regulates this control. Calcineurin inhibition results in continued allometric outgrowth of regenerating fins beyond their original dimensions. Congruent with these results, calcineurin activity is low when the rate of progenitor cell proliferation is highest, and its activity increases as the regeneration rate decreases. Furthermore, inhibition of calcineurin in uninjured adult fins switches isometric growth into allometric growth, demonstrating that calcineurin regulates appendage allometry. Previous results show that the rate of regenerative outgrowth is controlled by position along the proximodistal axis, but it is unknown what this positional control is. Our growth rate measurements and morphometric analysis of proximodistal asymmetry indicate that calcineurin inhibition shifts fin regeneration from a distal isometric growth program to an allometric proximal program. This shift is associated with the promotion of retinoic acid signaling, a signal transduction mechanism that affects positional information along the proximodistal axis. Furthermore, we provide evidence that calcineurin regulates potassium conductance via a potassium leak channel that has been shown to promote allometric growth. In summary, we identified a calcineurin-mediated mechanism that operates as a molecular switch between distal isometric growth and proximal allometric growth.

MAMMALIAN ARF SUPPRESSES VERTEBRATE EPIMORPHIC REGENERATION

Hesse, Robert, Kouklis, Gayle, Evason, Kimberly, Ahituv, Nadav, Pomerantz, Jason

University of California San Francisco, San Francisco, CA, USA

Evolution of tumor suppressors, and their relationship to proliferation and differentiation suggests that species-specific tumor suppressor repertoires may influence regenerative capacity. To directly test that premise we "humanized" the zebrafish p53 pathway by introducing regulatory and coding sequences of the human tumor suppressor ARF into the zebrafish genome which does not normally contain an ARF ortholog, and then examined epimorphic fin regeneration. Remarkably, ARF was dormant throughout development and in uninjured or lacerated fish, but was expressed after amputation in the blastema during epimorphic regeneration. This context-dependent expression of ARF effectively abolished fin regeneration and also suppressed experimentally induced liver tumorigenesis, but did not interfere with other physiological functions. ARF intracellular functions were conserved in zebrafish where mitogenic signaling resulted in binding of zebrafish E2F to the human ARF promoter and activation of ARF-dependent p53 functions during regeneration but not development. These findings identify distinct tumor suppressor responses to developmental versus regenerative proliferation, and point to a similarity between tumorigenesis and regeneration. This example of antagonistic pleiotropy in which the ARF tumor suppressor evolved regeneration suppressor characteristics implies that approaches to induce epimorphic regeneration clinically would need to disrupt ARF-p53 axis activation.

THURSDAY, 25 JUNE, 16:00 - 17:55

CONCURRENT IIE: CELL ADHESION, MOTILITY AND MIGRATION

ROOM K1

GUTS AND GASTRULATION: LIVE IMAGING CELL DYNAMICS TO INTERROGATE MORPHOGENESIS IN THE EARLY MAMMALIAN EMBRYO

Hadjantonakis, Anna-Katerina

Developmental Biology Program, Sloan-Kettering Institute for Cancer Research, New York, NY, USA

Gastrulation is a paradigm for the coupling of cell fate specification and tissue morphogenesis. In the mouse embryo, gastrulation transforms a cup-shaped structure comprising two tissue layers (epiblast and visceral endoderm), into one comprising three tissue layers

(epiblast, mesoderm and gut endoderm). I will discuss our studies investigating how the gut endoderm, the precursor tissue of the respiratory and digestive tracts and associated organs, emerges. By using approaches such as live cell imaging combined with the analysis of mutants in which gut endoderm morphogenesis is perturbed, we are developing a mechanistic understanding of the cell behaviors regulating this process. Our data suggest that morphogenesis of gut endoderm involves dynamic widespread intercalation between two cell populations, pluripotent epiblast-derived definitive endoderm and so-called extra-embryonic visceral endoderm. This morphogenetic event results in the formation of an epithelium on the surface of the embryo, comprising cells of two distinct origins. Definitive endoderm progenitors execute a stereotypical sequence of cell behaviors. They likely undergo at least a partial epithelial-to-mesenchymal-transition (EMT) at the primitive streak, where they are specified. They then migrate within, or aligned with, the mesenchymal 'wings' of mesoderm. Finally, they intercalate into the overlying visceral endoderm epithelium, and in doing so undergo an MET (mesenchymal-to-epithelial-transition).

SPECIFIC INHIBITION OF HEMATOPOIETIC CELL MIGRATION TO ADIPOGENIC MARROW - "NO PLACE TO HOME"

Kramer, Ashley, Stadem, Paul, Lehrke, Michale, Lund, Troy C.

University of Minnesota, Minneapolis, MN, USA

The hematopoietic cell niche serves to maintain hematopoiesis and recruit cells after hematopoietic cell transplant. The determinants of homing and engraftment after transplant are incompletely understood, but are often mediated by small chemokines from the "niche" cells. We determined the transcriptome of both zebrafish and mouse niche cells and found several small candidate proteins that were radiation inducible. Specifically, dermatopontin (DPT) was highly expressed in adipocytes (10-fold versus endothelial cells and 7.5-fold versus osteocytes, ANOVA $p = 0.02$). Immunohistochemistry (IHC) and ELISA confirmed that DPT expression was predominately localized to adipocyte-rich regions of the marrow. After radiation, DPT was increased 20-fold in the bone marrow as shown by RT-PCR ($p < 0.01$). Homing assays in DPT pre-treated irradiated mice showed a 90% reduction ($n = 12$, $p = 0.02$) and a 40% reduction ($n = 6$, $p < 0.05$) in whole marrow and lin-sca1+kit+ cells that migrated to the marrow 20 hours post-transplant, respectively. This reduction in homing translated to decreases in short- and long-term multilineage engraftment. The murine tibia has both adipocyte rich and adipocyte poor regions with the former recruiting 2-fold fewer donor hematopoietic cells versus adipocyte poor regions at 20 hours after adoptive transfer in irradiated recipients ($n = 9$, $p < 0.05$). Colony forming unit assays and apoptosis assays of LSK cells revealed no toxic effects of DPT on hematopoietic cells suggesting a specific defect in cell migration. Adhesion assays showed a 25% decrease in the number of hematopoietic cells that adhered to DPT coated plates ($n=6$, $p = 0.01$), and IHC revealed that DPT binds to the inner endothelial surface of the vascular after myeloablative conditioning. We performed CFU assays of circulating cells 20 hours after adoptive transfer and found that DPT led to an increased number of circulating CFU (149 v 83 CFU/ml, $p=0.002$) indicating that transplanted cells remained in circulation instead of efficiently homing to the marrow. These data suggest that DPT retards the ability of hematopoietic cells to adhere and transmigrate across the endothelial barrier during the homing process particularly in regions of increase adiposity making DPT a new and novel regulator of hematopoietic cell trafficking.

CHONDROITIN SULFATE BLOCKS NEURAL STEM CELL ENTRANCE INTO A BRAIN INJURY SITE THROUGH THE NOGO RECEPTOR AND RHOA/ROCK ACTIVATION

Galindo, Layla Testa[1], Vieira-Mundim, Mayara TV[1], Almeida, Maira ES[2], Lamers, Marcelo L.[3], Horwitz, Alan R.[4], Santos, Marinilce F.[2], Porcionatto, Marimélia[1]

[1]Federal University of São Paulo, São Paulo, Brazil, [2]University of São Paulo, São Paulo, Brazil, [3]Federal University of Rio Grande do Sul, Porto Alegre, Brazil, [4]University of Virginia, Charlottesville, VA, USA

Neurogenesis is a key event during central nervous system development and it is sustained in the adult mammalian brain. It is characterized by the generation of neural stem cells (NSC) present in specialized niches such as the subventricular zone (SVZ). In rodents, neuroblasts travel towards the olfactory bulb, where they differentiate and integrate the local circuitry. Injury alters neurogenesis and chemoattractive signals stimulate neuroblasts migration from the SVZ to the injury site in order to regenerate the injured tissue. Traumatic brain injuries (TBI) lead to glial scar formation by reactive astrocytes which produce and secret axonal outgrowth inhibitors. Chondroitin sulfate proteoglycans constitute a well-known class of extracellular matrix molecules secreted and deposited at the glial scar by reactive astrocytes. Our aim was to investigate how chondroitin sulfate (CS) mediates NSC migration in vivo and in vitro. TBI was performed at the motor cortex of adult mice and after 2 weeks brains were fixed and dissected. Immunofluorescence images show that neuroblasts which migrate towards the injury site

are impaired by the presence of CS at the injured area. In vitro experiments performed with NSC cultured as neurospheres suggest that NSC plated on CS migrate a shorter distance than when plated on laminin. Time-lapse, TIRF and kymograph images respectively suggest that CS impairs NSC migration and decreases initial migration speed; induces the formation of big nascent adhesions; alters NSC protrusion dynamics and decreases NSC protrusion speed. FRET images suggest that RhoA is more active when NSC are plated on CS and ROCK inhibition, the main RhoA effector, significantly stimulates NSC migration on both CS and laminin and decreases adhesions size. Furthermore, inhibition of Nogo receptor restored NSC migration on CS substrate in vitro. In conclusion, repair to TBI is challenging mainly due to the glial scar formation and axonal outgrowth inhibition and require the implementation of combined strategies. Neuroblasts migration to the injured site is an endeavor to repair. Here we propose that CS inhibits NSC migration into the glial scar through Nogo receptor activation and RhoA/ROCK signaling pathway.

RAPID ASSESSMENT OF DIRECTED MIGRATION: A NOVEL MICROFLUIDIC-BASED 3D POTENCY TEST FOR COMBINATORIAL SCREENING OF STEM CELLS

Ros, Enrique A.

Medicine Faculty, Universidad de los Andes, Santiago, Chile

While many biological parameters define the therapeutic benefit of stem cells (SC), cell migration (CM) proved to be an important criteria in cell treatments based on systemic delivery approaches. This migration is triggered by gradients of multiples factors secreted from injured tissues, inducing the cell migration to the specific site. Due to this essential role, CM assessment in response to a stable gradient of specific factors could become a revealing potency test for adult SC. The existing methods that evaluate CM have limitations as they fail to present a physiological and stable gradient that mimics the 3D extracellular matrix environment. Here we describe a microfluidic-based fabrication of a migration device capable to display a stable gradient of activating factors relevant to the mobilization of cells through 3D spatially restricted channels. The micro-device consists of a cell loading system that aligns the cells at a starting position, and a series of parallel open top migration channels with walls of factors-laden hydrogels endowed with a cell-adherent bottom. Additionally, we have designed a microfluidic device to obtain a linear gradient of encapsulated factors within the hydrogels based on a fluidic capacitor. The system was validated by using labeled factors visualized by an infrared light. Since, the structural integrity of the channels is essential for their functionality, we created a non-swelling gelatin-based hydrogel capable to encapsulate and release factors while keeping the device channels unscathed. Furthermore, we have tested the linear release of two different molecules, VEGF (22 kDa) and Ovalbumin (43.5 KDa). The measured release at 24 h was of 0.08 % at 37 °C, which correlate with the degradation rate of the hydrogel, suggesting that this release is governed mainly by the degradation rate of the hydrogel and not by the nature of the factor. Finally, we have performed a 12 h migration using adult SC. 2-fold increase in migration was observed in presence of encapsulated VEGF in comparison to the control without factors. An in-house software based on computer vision was developed to calculate the migration distance. The microscale size of the device, rapidity of the assay and controlled release of the factors confer an important advantage for using this technology as a potency test for the screening of SCs.

TRANSCRIPTOME ANALYSIS OF THE AVIAN PRIMITIVE STREAK REVEALS NOVEL MARKERS INVOLVED IN MESENDODERM DIFFERENTIATION OF HUMAN PLURIPOTENT STEM CELLS

Alev, Cantas[1], Wu, Yuping[1], McIntyre, Brendan[2], Bhatia, Mickie[2], Ikeya, Makoto[3], Sheng, Guojun[1]

[1]Laboratory for Early Embryogenesis, RIKEN Center for Developmental Biology, Kobe, Japan, [2]Michael G. DeGroote School of Medicine, McMaster University, Hamilton, ON, Canada, [3]Department of Cell Growth and Differentiation, Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan

The primitive streak of amniotes, of birds and mammals, represents the anatomical correlate of gastrulation, the process during which the three principal germ layers, endoderm, mesoderm and ectoderm emerge from the pluripotent epiblast. Using the chick model and Affymetrix Whole Genome Array-based transcriptome analysis we characterized the spatiotemporally dynamic gene expression profiles of the anterior-posterior and medial-lateral extension of the primitive streak as well as its neighboring epiblast and underlying hypoblast. Besides unraveling an intricate gene expression network present along the axis of the primitive streak, likely involved in the regulation of dorso-ventral patterning of mesoderm, we could also identify multiple novel markers of early mesoderm and endoderm differentiation, including neuropilin 1 (NRP1) and leukemia inhibitory factor receptor (LIFR) expressed selectively in the hypoblast and early endoderm. Utilizing human ES and iPS cells we could further show that NRP1 and LIFR are also viable markers of in vitro endoderm differentiation of human pluripotent stem cells. Using our large scale embryonic transcriptome data sets, we were furthermore able to identify novel

and so far uncharacterized putative pan-mesoderm and EMT markers which are specifically expressed in the avian primitive streak in vivo and tightly regulated during germ-layer formation and differentiation of human pluripotent stem cells in vitro.

SILICA BIOREPLICATION PROVIDES NEW INSIGHTS INTO THREE-DIMENSIONAL STEM CELL SPHEROIDS

Harjumäki, Riina[1], Lou, Yan-Ru[1], Kanninen, Liisa[1], Townson, Jason[2], Kaehr, Bryan[2], Niklander, Johanna[1], Brinker, C. Jeffrey[2], Yliperttula, Marjo[1]

[1]Centre for Drug Research, Division of Pharmaceutical Biosciences, University of Helsinki, Helsinki, Finland, [2]Department of Chemical and Nuclear Engineering, University of New Mexico, Albuquerque, NM, USA

Human pluripotent stem cells (hPSCs), including human embryonic stem cells (hESCs) and human induced pluripotent stem cells (hiPSCs), show great potency in drug research and regenerative medicine. Three-dimensional (3D) cell cultures have proved to maintain better cellular functions and produce more in vivo-like multicellular structures such as spheroids that cannot be obtained in two-dimensional (2D) cell cultures. Although 3D culture is an increasingly used method, little is known about the cell organization in 3D spheroids. To have an in-depth look at the architecture of 3D hPSC, we utilized a silica bioreplication (SBR) process. In this study we show that SBR preserves detailed sub-cellular features of hESCs WA07 and hiPSCs iPS(IMR90)-4 cultured in 3D nanofibrillar cellulose (NFC) hydrogel scaffold and in standard 2D culture. Cells in 3D culture exhibit similar microvillus-coated membranes to those in 2D culture. On the other hand, they are more round and tightly interacting with each other than cells in 2D cultures. SBR also preserves cellular proteins as shown by immunofluorescence staining of cellular markers. This study significantly improves our understanding of stem cell organization at pluripotent stage.

FRIDAY 26 JUNE, 9:00 - 11:20

PLENARY IV: PLURIPOTENCY AND MECHANISMS OF REPROGRAMMING

PLENARY HALL A1

THE HISTONE CHAPERONE CAF-1 SAFEGUARDS SOMATIC CELL IDENTITY DURING TRANSCRIPTION FACTOR-INDUCED REPROGRAMMING

Hochedlinger, Konrad

Howard Hughes Medical Institute and Harvard Medical School, USA

During development, specialized cell lineages are generated through the establishment of cell type-specific transcriptional patterns and epigenetic programs. However, the precise mechanisms and regulators that maintain these specialized cell states remain largely elusive. To identify molecules that safeguard somatic cell identity, we performed two comprehensive RNAi screens targeting known and predicted chromatin regulators during transcription factor-mediated reprogramming of mouse fibroblasts to induced pluripotent stem cells (iPSCs). Remarkably, subunits of the chromatin assembly factor-1 (CAF-1) complex emerged as the most prominent hits from both screens, followed by modulators of lysine sumoylation, DNA methylation and heterochromatin maintenance. Suppression of CAF-1 increased reprogramming efficiencies by several orders of magnitude and generated iPSCs two to three times faster compared to controls without affecting cell proliferation. We demonstrate that suppression of CAF-1 leads to a more accessible chromatin structure specifically at enhancer elements early during reprogramming. These changes were accompanied by increased binding of the reprogramming factor Sox2 to ESC-specific regulatory elements and earlier activation of pluripotency-associated genes. Notably, suppression of CAF-1 also enhanced iPSC formation from blood progenitors as well as the direct conversion of B cells into macrophages and fibroblasts into neurons. Together, our findings reveal the histone chaperone CAF-1 as an unanticipated regulator of somatic cell identity and provide a potential strategy to modulate cellular plasticity in a regenerative setting.

TITLE NOT AVAILABLE

Fisher, Amanda G.

Imperial College London, London, United Kingdom

Abstract not available at time of printing

PROGRESSION FROM THE EMBRYONIC STEM CELL GROUND STATE

Smith, Austin G., Kalkan, Tüzer, Leeb, Martin

Wellcome Trust - Medical Research Council Stem Cell Institute, University of Cambridge, Cambridge, United Kingdom

Naïve pluripotency is the capacity of individual cells to produce all lineages of the mature organism in response to extrinsic cues. In rodents this transient state at the foundation of mammalian development can be captured and propagated in the form of embryonic stem (ES) cells. In the appropriate culture environment ES cells are highly homogeneous and equipotent, and self-renewal is very robust - the ground state. Yet ES cells rapidly enter into multilineage differentiation when released from ground state culture conditions. We are employing both genome-wide screens and candidate approaches to characterise the multiplex molecular machinery that extinguishes the naïve pluripotency programme and enables developmental progression.

POSTER TEASERS

F-1159
STRESS RESPONSES IN MOUSE EPIDERMAL STEM CELLS ARE REGULATED BY NSUN2-MEDIATED RNA METHYLATION

Popis, Martyna, Blanco, Sandra, Frye, Michaela

WT-MRC Cambridge Stem Cell Institute, Cambridge, United Kingdom

F-1509
HIGH-FREQUENCY GENERATION OF TRANSGENIC MICE USING IMPRINTED GENES ENGINEERED ANDROGENETIC HAPLOID EMBRYONIC STEM CELLS

Huang, Yue, Liu, Yufang, Liu, Guang, Zhang, Meili, Sun, Lihong, Wang, Xue

Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China

F-1368
THE HISTONE DEACETYLASE SIRT6 CONTROLS EMBRYONIC STEM CELL FATE VIA TET-DEPENDENT PRODUCTION OF 5-HYDROXYMETHYLCYTOSINE

Etchegaray, Jean-Pierre

MGH Cancer Center-Harvard Medical School, Boston, MA, USA

F-1263
GREATER CHROMOSOMAL STABILITY IN NEURAL CELLS DERIVED BY TRANSDIFFERENTIATION THAN THOSE DERIVED FROM STEM CELLS

Weissbein, Uri[1], Ben-David, Uri[2], Benvenisty, Nissim[1]

[1]*Azrieli Center for Stem Cells and Genetic Research, Department of Genetics, Hebrew University of Jerusalem, Jerusalem, Israel,* [2]*Broad Institute of MIT and Harvard, Cambridge, MA, USA*

F-1191
X-LINKED SEVERE COMBINED IMMUNODEFICIENCY (X-SCID) RAT FOR XENO-TRANSPLANTATION AND FUNCTIONAL EVALUATION

Bumpei, Samata, Jun, Takahashi

Center for iPS Cell Research and Application, Kyoto, Japan

CELL FATE DECISIONS DURING SOMATIC CELL REPROGRAMMING

Pei, Duanqing

Guangzhou Institute of Biomedicine and Health, Chinese Academy of Sciences, Guangzhou, China

Somatic cell reprogramming is emerging as an ideal system for the analysis of mechanisms involved in cell fate decisions. With clearly defined starting cells and the final iPSCs, it has becoming possible to define the molecular events associated with the various fate changes. We initially reported that a mesenchymal to epithelial transition or MET initiates somatic cell reprogramming and have also identified factors critical for this starting step. Subsequently, we refined this mechanism by demonstrating a sequential EMT-MET process for optimal reprogramming. Therefore, the switching between mesenchymal and epithelial fates appears to underlie the cell fate decisions during somatic cell reprogramming. We then focus on the molecular mechanisms that specify the mesenchymal and epithelial fates and factors that can facilitate or inhibit the transitions. We will discuss the newly identified factors for these fate decisions. We believe that a comprehensive analysis for the EMT-MET process may help us better understand not only reprogramming but also other cell fate changes in both normal development and diseases.

FRIDAY 26 JUNE, 13:15 - 15:10

CONCURRENT IIIA: NEURAL DEGENERATION

ROOM A2

NEW IDEAS ABOUT ALS FROM STUDIES OF STEM CELL-DERIVED MOTOR NEURONS

Eggan, Kevin C.

Harvard University, Cambridge, MA, USA

In my laboratory, we pursue two interlocking areas of investigation: the basic biology of stem cell programming and reprogramming, as well as the application of the resulting technologies to studies of the neuromuscular system and the diseases that affect it. A fundamental understanding of how a cell's identity is determined during differentiation and how it can in turn be manipulated experimentally is a central goal of developmental biology, one with substantial ramifications for biomedicine.
We study both the differentiation of embryonic stem cells into the neural lineage and the reprogramming of commonly available differentiated cell types, such as fibroblasts, into either pluripotent stem cells or cells of therapeutic interest, such as spinal motor neurons. To study differentiation and dedifferentiation, we employ a variety of approaches, including stem cell differentiation, nuclear transfer, and defined reprogramming strategies using known transcriptional regulators and novel small-molecule compounds. A number of devastating diseases, including amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA), specifically affect the neuromuscular system. Little is known concerning the molecular pathology underlying these conditions, partly because it has been impossible to access significant quantities of the disease-affected cell, the spinal motor neuron. With recent advances in stem cell and reprogramming biology, we can now produce billions of spinal motor neurons with control and diseased genotypes. We use this new resource to design in vitro disease models for both mechanistic studies and for the discovery of novel small-molecule therapeutics.

IPSC-DERIVED NEURONS WITH PS1 DE9 MUTATIONS HAVE REDUCED TRANSCYTOSIS DUE TO CALCIUM DYSREGULATION

Reyna, Sol M.[1], Woodruff, Grace[1], Santos Chaves, Rodrigo[2], Goldstein, Lawrence LS[1]

[1]University of California San Diego, La Jolla, CA, USA,
[2]University of Sao Paolo, Sao Paolo, Brazil

Mutations in presenilin 1 (PS1) account for the majority of known forms of hereditary Alzheimer's disease (AD), however, beyond the consensus that PS1 mutations alter APP processing, there is little agreement in the field about how PS1 mutations initiate pathogenic events that eventually lead to neurodegeneration. PS1 is a multipass transmembrane protein that acts as the catalytic core of the γ-secretase complex. In addition to the γ-secretase-dependent functions of PS1, there are multiple reports of γ-secretase independent functions including protein sorting and trafficking, proton pump chaperoning, and regulation of cytosolic and lysosomal calcium levels. Our group previously published the generation of an isogenic series induced pluripotent stem cells (iPSCs) with a ΔE9 mutation in the genomic background of Craig Venter. Here, we sought to identify early cellular alterations that precede robust neurodegeneration, by using young neurons derived from iPSCs with and without the ΔE9 mutation. We report that ΔE9 mutations exhibit increased cytosolic calcium levels accompanied by decreased lysosomal and ER calcium levels in a dose-dependent manner. Interestingly, these alterations are not accompanied by changes in lysosomal pH or in the rate of degradation of APP. Furthermore, the calcium dysregulation caused by the PS1 ΔE9 mutant leads to redistribution of Rab11 vesicles and results in reduced endocytosis and axonal transcytosis of select cargo, without affecting bulk endocytosis.

THE LOSS OF C9ORF72 PROTEIN FUNCTION CAUSES THE DEGENERATION OF ALS PATIENT-DERIVED MOTOR NEURONS

Shi, Yingxiao, Lin, Shaoyu, Menendez, Louise, Kisler, Kassandra, Zlokovic, Berislav, Ichida, Justin K.

Stem Cell Biology and Regenerative Medicine, University of Southern California, Los Angeles, CA, USA

A massive expansion of a GGGGCC repeat in an intron of C9orf72 recently emerged as the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), making it a key therapeutic target. However, the neurodegenerative mechanisms underlying C9orf72 ALS/FTD are unclear. Here, we use induced motor neurons (iMNs) generated using transcription factor-mediated reprogramming to show that the loss of C9orf72 protein expression, which results from transcriptional stalling within the repeat expansion, is the major cause of neurodegeneration. Longitudinal tracking showed that C9orf72 patient iMNs undergo accelerated degeneration (3 patients, 3 controls, p=.002) and possess the hallmark pathology of C9orf72 ALS. In contrast, induced dopaminergic neurons from C9orf72 patient iPSCs do not undergo rapid degeneration, suggesting this phenotype is motor neuron specific. Removing the repeat expansion from patient iPSCs using CRISPR/Cas9 editing

fully rescued iMN survival. Thus, C9orf72 iMNs faithfully model ALS disease processes. Similar to postmortem studies, patient-derived iMNs had low C9orf72 protein levels. We found that exogenously restoring C9orf72 expression rescued patient iMN survival. Conversely, knocking out C9orf72 protein expression in control iMNs using CRISPR/Cas9 editing induced rapid degeneration at rates similar to patient iMNs. Thus, the loss C9orf72 protein induces neurodegeneration. C9orf72 shares homology with guanine exchange factors that control endosomal trafficking. Consistent with this function, we found that C9orf72 is localized in endosomes in iMNs. We used a biochemical assay with purified C9orf72 and RAB GTPase proteins to show that C9orf72 acts as a guanine exchange factor for a RAB GTPase that controls the trafficking of early endosomes. The lack of C9orf72 function caused improper endosomal trafficking of glutamate receptors and hyperexcitability in patient and C9orf72-deficient iMNs. This caused excitotoxicity, which induced the rapid neurodegeneration. An FDA-approved drug that suppresses neuronal firing rescued patient iMN survival. Our results from the iMN model indicate that the loss of C9orf72 protein function plays a major role in C9orf72 ALS and provide a clear link between the causal mutation and excitotoxic motor neuron death.

ENGRAFTABLE MUSCLE STEM CELLS ARE GENERATED FROM HUMAN IPS CELLS WITHOUT MYOGENIC TRANSGENE INDUCTION

Sakurai, Hidetoshi[1], Takayama, Satoru[1], Ikeya, Makoto[2], Hotta, Akitsu[3], Zhao, Mingming[1], Takenaka-Ninagawa, Nana[1], Nakasa, Masanori[1], Nakamura, Yumi[1], Sato, Takahiko[4]

[1]Department of Clinical Application, Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan, [2]Department of Cell Growth and Differentiation, Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan, [3]Department of Reprogramming Science, Center for iPS Cell Research and Application (CiRA), Kyoto University, Kyoto, Japan, [4]Kyoto Prefectural University of Medicine, Kyoto, Japan

Cell therapy is one of desired method for treating intractable muscular diseases, such as Duchenne muscular dystrophy (DMD). Skeletal muscle contains a stem cell, called satellite cell, which has remarkable muscle regeneration potential and is considered as a good source of cell therapy. However, the clinical trials of cell therapy using adult satellite cells have never succeeded mainly due to the difficulty of expansion of satellite cells with maintaining their regeneration potentials. Instead of adult satellite cells, generating satellite cells from induced pluripotent stem cells (iPSCs) would have an advantage for application of cell therapy, because of their unlimited proliferation potentials. Although, several procedures for induced engraftable myogenic progenitors have been demonstrated, many of the procedures depend on the induction of myogenic transgene. Here, we demonstrated the effective stepwise differentiation method from human iPSCs to engraftable muscle stem cells without transgene induction. For tracing the first step of myogenic differentiation, we generated Pax3-GFP reporter iPSCs to identify embryonic myogenic progenitors. The Pax3-GFP positive dermomyotome-like population could be induced at over 70% efficiency without expressing neural crest markers. Next, for tracing the commitment of myogenic lineage, we established Myf5-tdTomato reporter iPSCs. The Myf5+ cells could arise from dermomyotome-like population and showed highly myogenic differentiation potential in vitro. Gene expression profile of purified Myf5+ cells demonstrated that the expression of Pax7, a marker of satellite cells, was significantly increased in Myf5+ cells after day70 differentiation. Furthermore, when the Myf5+ cells after day70 differentiation were transplanted to immunodeficient DMD-model mice, the cells could be engrafted in more than one hundred of host myofibers and regenerate the diseased muscles with producing dystrophin. Finally, a part of the engrafted cells settled as a satellite cells in vivo with expressing Pax7. Taken together, we successfully generated the human iPSC-derived muscle stem cells without using transgene induction, which had an advantage for applying the stem cells to cell therapy of muscular diseases.

ELEVATED OLEIC ACID LEVELS WITHIN THE FOREBRAIN STEM CELL NICHE SUPPRESS NEURAL STEM CELL ACTIVATION IN ALZHEIMER'S DISEASE

Hamilton, Laura K.[1], Dufresne, Martin I, Joppe, Sandra E.[1], Petryszyn, Sarah[2], Aumont, Anne[1], Calon, Frederic[2], Furtos, Alexandra[1], Parent, Martin[2], Chaurand, Pierre[1], Fernandes, Karl J.L[1]

[1]Universite de Montreal, Montreal, QC, Canada, [2]Universite Laval, Quebec, QC, Canada

Preservation of stem cell activity within adult tissues is essential for maintaining tissue structure and function. In the brain, neural stem cell (NSC) activity decreases naturally during aging and is dysregulated in models of neurodegenerative diseases, suggesting an involvement in aging- and disease-associated cognitive deficits. Thus, dissecting the mechanisms involved in NSC dysregulation could provide new opportunities for preventive and regenerative therapeutic strategies for neurodegeneration. Interestingly, Alzheimer's disease (AD) is associated with declines in both neurogenesis-regulated cognitive processes

and abnormalities in lipid metabolism. Indeed, lipid accumulations were one of the five original AD-associated tissue pathologies first reported by Alois Alzheimer himself. More recently, links have strengthened between aberrant lipid metabolism and neurodegeneration in AD, while epidemiological studies have demonstrated that AD risk factors include peripheral metabolic conditions such as insulin resistance, obesity and dyslipidemia. However, deeper mechanistic insights into the role of abnormal lipid metabolism in AD have been hindered by the technical complexity involved with localizing, identifying, and determining the biological functions of individual lipid species in the brain. Here, we use a multi-disciplinary strategy to overcome these obstacles. We localize prominent lipid accumulations to ependymal cells of the forebrain NSC niche in both AD patients and the 3xTg-AD mouse model. We identify these AD-associated lipids as 12 specific triglycerides that are particularly enriched with oleic acid side-chains, and show that they likely originate from brain-specific rather than peripheral lipid metabolism defects. Oleic acid elevation was sufficient to recapitulate the AD-associated triglyceride profile and interestingly led to a selective disruption of signalling pathways involved in long-term NSC preservation and an inhibition of NSC expansion and diminished NSC regenerative capacity. Together, our results reveal that lipid metabolism defects originating within a major neurogenic niche can disrupt NSC-mediated regeneration and plasticity in AD. Thus, like many other niche signals, specific fatty acids can influence NSC activity and maintenance.

THE AMYLOID CASCADE IN IPSC-DERIVED HUMAN CORTICAL NEURONS

Robbins, Jacqueline P.[1], Killick, Richard1, Maresca, Marcello[2], Pangalos, Menelas N.[3], Lovestone, Simon[4], Price, Jack[1]

[1]King's College London, London, United Kingdom, [2]AstraZeneca, Mölndal, Sweden, [3]AstraZeneca, Alderley Park, United Kingdom, [4]University of Oxford, Oxford, United Kingdom

Background: Our understanding of the molecular processes underlying Alzheimer's disease (AD) is still limited, hindering the development of effective treatments and highlighting the need for human-specific models. The potential for human induced pluripotent stem cells (iPSCs) to provide a model for AD is an exciting advancement, and has great potential for investigating the mechanisms involved in neurodegeneration. Advances in identifying components of the amyloid cascade are progressing, including the role of the protein clusterin in mediating β-amyloid (Aβ) toxicity. This project aims to investigate the molecular cascade initiated by Aβ previously observed in rodent cells. Mutations in CLU and APOE, major genetic AD risk factors, have been introduced into human induced pluripotent stem cells (iPSCs) by precise genome editing. This will allow us to explore the specific effects of these mutations on neuronal response to Aβ. Methods: iPSCs from a neurotypical male with a APOE ε3/ε3 genotype were differentiated into cortical neurons and treated with Aβ25-35 peptides. CRISPR cas9-mediated gene editing generated a CLU-knockout iPSC line and a knockin APOE line with ε4 genotype. The downstream effect of the Aβ exposure on the cells was measured by a high-throughput cytometry assay, optimised to identify changes in neuronal processes. Western blotting and qPCR assessed changes in protein and gene expression downstream of Aβ. Results: The cell-imaging assay indicated that neuronal processes of the cells degenerate with increasing Aβ concentrations. We also observe that intracellular levels of clusterin are increased in cells treated with Aβ peptides. We are currently testing the phenotype of the CLU knockout cells in order to understand the role of clusterin in AD. Conclusions: We are establishing an isogenic model of sporadic AD with iPSCs of different genotypes, and determining the role of these major AD risk mutations in processing β-amyloid. Evaluating compounds that inhibit this pathway and assessing their effects on phosphorylated tau and cell toxicity in the neuronal cultures will be a key application of this modelling system.

FRIDAY 26 JUNE, 13:15 - 15:10

CONCURRENT IIIB: STEM CELLS AND CANCER

ROOM K1

CANCER CELL REPROGRAMMING UNVEILS STABLE MAINTENANCE OF CANCER CELL IDENTITY THROUGH KEY ONCOGENIC SIGNALS

Yamada, Yasuhiro

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

Cell reprogramming technology has enabled the control of somatic cell identity. One exception is cancer cells, which are generally refractory to reprogramming, suggesting that cancer cell fate is stable. However, how cancer cell identity is stably maintained is poorly understood. Here, using the EWS/ATF1-inducible sarcoma mouse model, we show that EWS/ATF1 expression hampers cell fate conversion in EWS/ATF1-addicted sarcoma cells. By withdrawal of the EWS/

ATF1 expression, the sarcoma cells can be reprogrammed into induced pluripotent stem cells (iPSCs) capable of teratoma formation and chimeric mouse contribution. While EWS/ATF1 expression induces H3K27ac, an active enhancer mark, it simultaneously induces a repressive histone mark, H3K9me3. Upon the transduction of reprogramming transcription factors (TFs), the increased repressive marks by EWS/ATF1 expression are negatively associated with the adjacent transcriptional activation. Furthermore, blockage of oncogene addiction signals in human cancer cell lines facilitates the early stage of TF-mediated reprogramming. These results suggest that the disruption of a strong oncogenic signal leads to epigenetic neutralization, which is associated with flexible transcriptional activity, and permits cell fate conversion of cancer cells. Our results have important implications for understanding the cancer epigenome underlying cancer cell plasticity, which plays a role in the survival and progression of cancer cells.

REACTIVATION OF MULTIPOTENCY BY ONCOGENIC PIK3CA INDUCES BREAST TUMOR HETEROGENEITY

Van Keymeulen, Alexandra[1], Lee, May Yin[1], Ousset, Marielle[1], Rorive, Sandrine[2], Brohée, Sylvain[3], Wuidart, Aline[1], Bouvencourt, Gaelle[1], Giraddi, Rajshekhar R.[1], Dubois, Christine[1], Salmon, Isabelle[2], Sotiriou, Christos[3], Phillips, Wayne A.[4], Blanpain, Cédric[1]

[1]Université Libre de Bruxelles (ULB), Bruxelles, Belgium, [2]Department of Pathology, Erasme Hospital, Université Libre de Bruxelles (ULB), Bruxelles, Belgium, [3]Institut Jules Bordet, Université Libre de Bruxelles (ULB), Bruxelles, Belgium, [4]Surgical Oncology Research Laboratory, Peter MacCallum Cancer Center, Melbourne, Australia

Breast cancer is the most frequent cancer in women and consists of heterogeneous types of tumors that are classified into different histological and molecular subtypes. PIK3CA and p53 are the two most frequently mutated genes and are associated with different types of human breast cancers. The cellular origin and the mechanisms leading to PIK3CA induced tumor heterogeneity remain unknown. Here, we used a genetic approach in mice to define the cellular origin of Pik3ca derived tumors and its impact on tumor heterogeneity. Surprisingly, oncogenic Pik3ca-H1047R expression at a physiological level in basal cells (BCs) induced the formation of luminal ER+PR+ tumors, while its expression in luminal cells (LCs) gave rise luminal ER+PR+ tumors or basal-like ER-PR- tumors. Concomitant deletion of p53 and expression of Pik3ca-H1047R accelerated tumor development and induced more aggressive mammary tumors. Interestingly, expression of Pik3ca-H1047R in unipotent BCs gave rise to the formation of luminal-like cells, while its expression in unipotent LCs gave rise to the formation of basal-like cells, before progressing into invasive tumors. Transcriptional profiling of FACS isolated cells that undergo cell fate transition upon Pik3ca-H1047R expression in unipotent progenitors demonstrated a profound oncogene-induced reprogramming of these newly formed cells and identified gene signatures, characteristic of the different cell fate switches that occur upon Pik3ca-H1047R expression in BC and LCs, which correlated with the cell of origin, tumor type and different clinical outcomes. Altogether our study identifies the cellular origin of Pik3ca-induced tumors and reveals that oncogenic Pik3ca-H1047R activates a multipotent genetic program in normally lineage-restricted populations at the early stage of tumor initiation setting the stage for future intratumoral heterogeneity. These results have important implications for our understanding of the mechanisms controlling tumor heterogeneity and the development of new strategies to block PIK3CA breast cancer initiation.

SOX9 AS A DOWN-STREAM TARGET IN RAS/MEK-DRIVEN PEDIATRIC GLIOMA

Sabelström, Hanna[1], Jandial, Rahul[2], Shchors, Ksenya[3], Masic, Selma[3], Ho, Allen[4], Vandenberg, Scott[5], Nicolaides, Theodore P.[3], Prados, Michael D.[3], James, C. David3, Berger, Mitchel S.3, Evan, Gerard I.3, Snyder, Evan Y.4, Weiss, William A.3, Persson, Anders I.[1]

[1]Department of Neurology, University of California, San Francisco, CA, USA, [2]Division of Neurosurgery, City of Hope Cancer Center and Beckman Research Institute, Los Angeles, CA, USA, [3]Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, CA, USA, [4]Sanford-Burnham Institute for Medical Research, La Jolla, CA, USA, [5]Department of Pathology, University of California, San Diego, La Jolla, CA, USA

Pediatric high-grade gliomas (pHGGs) represent approximately 8-12% of pediatric central nervous system (CNS) tumors and are associated with a dismal prognosis in patients. Genetic alterations in RAS/MEK/PI3K pathways and aberrant overexpression of receptor tyrosine kinases are a hallmark in glioma. We have recently shown that blockade of RAS/MEK, but not RAS/PI3K signaling, in oligodendrocyte progenitor cell (OPC)-derived murine HGGs block self-renewal and induce robust oligodendrocyte differentiation. To study if aberrant RAS/MEK signaling also prevents normal differentiation in astrocyte precursors, we employed a well-established astrocyte-derived HGG (GFAP-HaV12-Ras-LacZ, G-RAS) model. At birth, transgene expression (LacZ) was first identified in discrete regions, including the subventricular zone (SVZ). Expression of the transgene in SVZ neural stem cells (NSCs), but not OLIG2+ cells, resulted in an early postnatal astrocytoma formation and a progressive loss of neurogenesis. Treatment of SVZ

tumorspheres from G-RAS mice and human GBMs, demonstrated that blockade of RAS/MEK, but not RAS/PI3K signaling, induced glial and neuronal differentiation. Treatment of premalignant G-RAS mice with the MEK inhibitor PD325901 completely restored neurogenesis. MEK inhibition in tumorsphere cultures effectively reduced expression of SOX9, a known barrier to neurogenesis. We confirmed that RNA interference of SOX9 induced neuronal differentiation in glioma cells. As one of the target genes of the neuronal determinant miR-124a, we demonstrate that reintroduction of miR-124a in HGG cells block SOX9 expression and induce neuronal differentiation. Our results suggest that a RAS/MEK/miR-124-SOX9 axis in the astrocyte lineage drives pediatric glioma formation.

THE EPIGENETIC MODIFIER EZH2 CONTROLS MELANOMA METASTASIS THROUGH SILENCING OF TUMOR SUPPRESSIVE METABOLIC NETWORKS

Zingg, Daniel[1], Debbache, Julien[1], Schäfer, Simon M.[1], Tuncer, Eylul1, Frommel, Sandra C.[2], Cheng, Phil3, Arenas-Ramirez, Natalia[4], McCabe, Michael T.5, Creasy, Caretha L.[5], Boyman, Onur[4], Santoro, Raffaella[2], Dummer, Reinhard[3], Sommer, Lukas[1]

[1]Institute of Anatomy, University of Zurich, Switzerland, [2]Institute of Veterinary Biochemistry and Molecular Biology, University of Zurich, Switzerland, [3]Department of Dermatology, University Hospital Zurich, Switzerland, [4]Department of Immunology, University Hospital Zurich, Switzerland, [5]GlaxoSmithKline, Collegeville, PA, USA

EZH2 catalyzes methylation of lysine 27 in histone 3 (H3K27me3), which induces chromatin compaction and consequently prevents gene expression. In neural crest stem cells (NCSC), the embryonic progenitors of a variety of cell types and tissues, EZH2 regulates mesenchymal fate acquisition, but is not required for trunk NCSC derivatives including melanocytes. In cutaneous melanoma, a cancer arising from melanocytes, EZH2 levels are elevated and connected to reduced patient survival. However, evidence for a functional role of EZH2 during melanomagenesis remains poor. Here we reveal central roles of EZH2 in promoting growth and especially metastasis of cutaneous melanoma. In a transgenic mouse model of melanoma, conditional Ezh2 ablation counteracted growth of skin tumors without affecting normal melanocyte biology. Importantly, whether Ezh2 was ablated before or after the onset of cutaneous melanomagenesis, emergence of distant metastases was completely prevented. Likewise, treatment of melanoma-bearing mice with the preclinical EZH2 inhibitor GSK503 virtually abolished metastasis formation. In vitro, depletion of Ezh2 induced a melanocyte differentiation program and a concomitant loss of NCSC / EMT transcription factors. The process of melanoma metastasis is thought to be triggered by acquisition of mesenchymal features. Thus, the role of EZH2 in melanoma appears to be analogous, at least in part, to its function in embryonic NCSCs. Furthermore, interference with EZH2 activity in human melanoma cells allowed the identification of novel EZH2 target genes (ETGs). Interestingly, a considerable number of these ETGs propagate diverse metabolic processes, such as AMD1, which is a key-enzyme in an amino acid biosynthesis network. Silencing of AMD1 promoted induction of NCSC / EMT genes and metastases in vivo, establishing this ETG as a tumor suppressor and epigenetic regulation of the AMD1 biosynthesis network as a prerequisite for melanoma metastasis. Thus, EZH2 acts as a central node in driving melanoma growth and metastatic progression through dynamic repression of, among others, metabolic processes, which makes EZH2 a highly promising target for novel melanoma therapies.

TARGETED REVERSAL OF INFLAMMATORY CYTOKINE DRIVEN ADAR1 LET-7 FAMILY EDITING IN CANCER STEM CELLS

Zipeto, Maria Anna, Court Recart, Angela, Jiang, Qingfei, Crews, Leslie A., Melese, Etienne, Jamieson, Catriona HM

Sanford Consortium for Regenerative Medicine, University of California San Diego, La Jolla, CA, USA

In advanced human malignancies, RNA sequencing (RNA-seq) has uncovered deregulation of adenosine deaminase acting on RNA (ADAR) editases that promote therapeutic resistance and cancer stem cell (CSC) generation. As an important paradigm for understanding CSC molecular evolution, chronic myeloid leukemia (CML) is initiated by BCR-ABL1 oncogene expression in hematopoietic stem cells (HSCs) but undergoes blast crisis (BC) transformation following aberrant self-renewal acquisition by myeloid progenitors harboring cytokine-responsive ADAR1 p150 overexpression. Emerging evidence suggests that adenosine to inosine editing at the level of primary (pri) or precursor (pre)-microRNA (miRNA), alters miRNA biogenesis and triggers their degradation. This may provide an additional source of epigenetic mutagenesis that might be responsible for broad changes in the transcriptome leading to CSC generation. However, relatively little is known about the role of inflammatory niche-driven ADAR1 miRNA editing in malignant reprogramming of progenitors into self-renewing CSCs. In this study, RNA-seq and qRT-PCR revealed that FACS purified BC CML expressed higher levels of JAK2 dependent inflammatory cytokine receptors than normal and chronic phase (CP) progenitors, as well as reduced levels of SC regulatory let-7 family of miRNA. Lentiviral human JAK2 transduction of CD34+ progenitors

enhanced ADAR1 activity, as revealed by RNA editing-specific qRT-PCR, and reduced levels of the let-7 family of miRNA. Notably, RNA-seq and qRT-PCR analysis of CD34+ progenitors transduced with wt-ADAR1, but not mutant ADAR1 lacking functional deaminase activity, reduced let-7 family miRNA levels. This suggested that inflammatory niche driven-ADAR1 regulates the let-7 family of miRNA in a RNA-editing dependent way. Lentiviral ADAR1 enhanced CP CML progenitor self-renewal. In contrast, targeted ADAR1 inhibition restored let-7 expression and prevented malignant progenitor self-renewal. This is the first demonstration that inflammation driven-ADAR1 drives CSC generation by impairing SC regulatory miRNA biogenesis. Targeted reversal of ADAR1-mediated miRNA editing may enhance eradication of inflammatory niche resident CSCs in a broad array of malignancies, including JAK2-driven myeloproliferative neoplasms.

INTERFERENCE WITH STEM CELL-SPECIFIC SURVEILLANCE MECHANISMS RESULTS IN SKIN TUMOUR INITIATION

Niemann, Catherin, Reuter, Karen

Department of Biochemistry, University of Cologne, Cologne, Germany

Recent studies have indicated that epidermal stem cells, which are crucial for maintaining skin homeostasis, respond differently to stress and DNA damage compared to their rapidly cycling progeny. Hair follicle (HF) bulge stem cells possess stem cell-specific surveillance mechanisms regulating the DNA damage response. In particular, multipotent HF stem cells are more resistant to DNA-damage-induced cell death, which has been linked to a higher expression of the pro-survival factor Bcl2 and attenuated p53 activation. Here, the relevance of these stem cell-specific gatekeeper functions for the process of skin tumour initiation has been investigated in vivo. To this end a mutant form of the transcription factor Lef1, mimicking mutations found in human epidermal tumours, was expressed specifically within the HF bulge stem cell compartment. Interestingly, targeted expression of mutant Lef1 results in stem cell-driven epidermal tumour formation, supporting recent lineage tracing experiments, which identified HF bulge stem cells as a cell-of-origin for skin tumours. Mechanistically, mutant Lef1 induces DNA damage and interferes with stem cell-specific functions normally protecting against accumulations of DNA lesions and cell loss. In particular, mutant Lef1 disturbs p53 response by antagonizing ATM-Chk2 dependent stabilization of p53. Furthermore, mutant Lef1 blocks the Bcl2 response in HF bulge stem cells and increased DNA damage induces apoptosis. To compensate the loss of bulge cells, proliferation was stimulated within the stem cell compartment, resulting in propagation of cells that escape normal cell cycle control, thereby supporting the accumulation of tumour-initiating mutations. Thus our data demonstrate that normal stem cell regulation is disrupted by mutant Lef1, representing a new mechanism of tumour initiating events in tissue stem cells and showing the importance of a tight control of these crucial stem cell-specific surveillance mechanisms to prevent tumourigenesis.

FRIDAY 26 JUNE, 13:15 - 15:10

CONCURRENT IIIC: TRANSDIFFERENTIATION AND REPROGRAMMING

VICTORIA HALL

SOX2-INDUCED CONVERSION OF NG2 GLIA INTO NEURONS IN THE ADULT CEREBRAL CORTEX FOLLOWING ACUTE INVASIVE INJURY

Heinrich, Christophe[1], Bergami, Matteo[2], Gascón, Sergio[3], Lepier, Alexandra[3], Viganò, Francesca[3], Dimou, Leda[3], Sutor, Bernd[3], Berninger, Benedikt[4], Götz, Magdalena[3]

[1]Grenoble Institute of Neurosciences-Inserm U 836, Grenoble, France, [2]Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Köln, Germany, [3]Ludwig-Maximilians University Munich, Physiological Genomics-Institute of Physiology, Munich, Germany, [4]University Medical Center-Johannes Gutenberg University Mainz, Institute of Physiological Chemistry, Mainz, Germany

Conversion of non-neuronal cells into clinically relevant neurons emerges as a novel strategy to regenerate lost neurons for brain repair. We and others have explored the possibility of converting brain resident glia and non-neural cells into induced neurons. This has led to the identification of astroglia and NG2 glia as well as brain pericytes as potential source cells for new neurons. Inducing the conversion of non-neuronal cells into neurons in the context of severe CNS injury remains a major challenge. Here we assessed whether glial cells proliferating during reactive gliosis can be reprogrammed in the adult mouse cerebral cortex following stab wound lesion. Conspicuously, forced expression of the potent reprogramming factors Neurog2 and Ascl1 failed in inducing neurogenesis. Based on our findings that co-expression of Sox2 and Ascl1 can reprogram adult human brain pericytes in vitro, we assessed the effect of combined expression of these factors within the lesioned brain. We observed that retrovirus-mediated expression of Sox2 and Ascl1, but surprisingly also of Sox2 alone, could reprogram cells proliferating in response to

stab wound injury. Intriguingly, the vast majority of the newly generated DCX-positive neurons originated from NG2 glia as revealed by genetic fate-mapping experiments. Sox2/Ascl1- and Sox2-induced neurons progressively acquire NeuN and a more complex neuronal morphology. Furthermore, patch-clamp recordings showed that Sox2- and/or Ascl1-reprogrammed cells acquire the ability to generate action potentials and receive synaptic inputs from neighboring neurons. Consistently, we found that endogenous interneurons formed synaptic boutons on processes of induced neurons. We next assessed whether stab wound-induced changes are required for glia-to-neuron conversion. We performed injections of Sox2-encoding lentivirus specifically targeting glial cells, in absence of prior stab wound injury. Strikingly, despite its massive expression Sox2 failed to convert both oligodendroglial and astroglial cells into neurons, indicating that prior lesion greatly facilitates or perhaps even preconditions Sox2-induced reprogramming. This raises the important question how prior injury alters the permissiveness of glial cells to undergo transcription-factor driven neurogenesis.

C/EBP ALPHA CREATES AN ELITE CELL STATE IN B CELLS

Graf, Thomas

Center for Genomic Regulation, Barcelona, Spain

Our earlier work has shown that the myeloid transcription factor C/EBPα induces B cells to transdifferentiate into macrophages at high efficiencies. More recently we reported that the transient expression of this factor in pre-B cells poises them for rapid and efficient reprogramming into induced pluripotent stem cells, following expression of Oct4, Sox2, Klf4 and c-Myc (OSKM). We have now found that reprogramming of the poised B cells by OSKM can be further enhanced under culture conditions of naïve pluripotent cells, resulting in the activation of endogenous Oct4 within 24 hours and the reprogramming of essentially all cells into iPS cells within approximately 1 week. The 'elite' cell state created in B cells by the transient activation of C/EBPα parallels that of granulocyte/macrophage progenitors, which are exquisitely sensitive to OSKM-induced reprogramming and whose formation strictly requires C/EBPα. We have now investigated how the transient expression of C/EBPα in B cells leads to the almost immediate establishment of the pluripotency program. These data will be presented.

HIGH-RESOLUTION MAPPING OF REPROGRAMMING EPIGENETICS FOLLOWING IDENTIFICATION OF MBD3/NURD COMPONENT GATAD2A AS A KEY TARGET FOR ACHIEVING DETERMINISTIC PLURIPOTENCY INDUCTION

Rais, Yoach, Mor, Nofar, Zviran, Asaf, Chomski, Elad, Novershtern, Noa, Hanna, Jacob H.

The Department of Molecular Genetics, Weizmann Institute of Science, Rehovot, Israel

A major revolution in stem cell research was achieved upon the discovery of cellular reprogramming. However, in most conventional reprogramming approaches, only a small fraction of the somatic cell population becomes pluripotent (iPSC), thus making this process hard to investigate at sufficient molecular depth. Our group has previously identified Mbd3/NuRD complex as a major roadblock for reprogramming, and that optimized depletion (50-80%) of Mbd3 at early stages of reprogramming can positively alter the process and leads to a near deterministic reprogramming in naïve pluripotency promoting conditions, where nearly all of the initial cell population became pluripotent in a synchronized manner after 8 days. Since complete ablation of Mbd3 rapidly yields a block in somatic cell proliferation, this has limited the flexibility for manipulating this pathway to achieve robust reprogramming. As such, by dissecting the role of Mbd3/NuRD complex during early stages of reprogramming, we aimed to identify ways to block Mbd3 dependent NuRD activity without the negative effect on somatic cell proliferation and viability. We identified Mbd3/Gatad2a/Chd4 as a functional and biochemical axis for blocking re-establishment of pluripotency. I will present our unpublished findings on the role of Gatad2a (also known as P66a), a NuRD specific subunit, whose complete ablation does not compromise somatic cell proliferation yet disrupts Mbd3/NuRD repressive activity on the pluripotent circuit and yields near deterministic reprogramming. Finally, we have used the Mbd3 and Gatad2a depleted deterministic reprogramming platforms, to conduct in depth molecular mapping of reprogramming every 24 hours throughout the 8 days until completion of reprogramming (RNA-seq, single cell RNA-seq, Chip-Seq, Ribo-Seq, ATAC-Seq, RRBS). I will present our key conclusions inferred from the first ever conducted high-resolution mapping of authentic and synchronized epigenetic dynamics during deterministic somatic cell reprogramming towards ground state naive pluripotency in mice.

PLURIPOTENCY FACTOR-INDUCED LINEAGE CONVERSION INVOLVES A TRANSIENT PASSAGE THROUGH AN IPS CELL STAGE

Bar-Nur, Ori[1], Verheul, Cassandra[1], Gianotti Sommer, Andreia[2], Brumbaugh, Justin[1], Schwarz, Benjamin A.[1], Lipchina, Inna[1], Huebner, Aaron J.[1], Mostoslavsky, Gustavo[2], Hochedlinger, Konrad[1]

[1]Stem Cell and Regenerative Biology, Harvard University, Boston, MA, USA, [2]Center for Regenerative Medicine, Boston University, Boston, MA, USA

Brief expression of pluripotency-associated factors such as OCT4, KLF4, SOX2 and c-MYC (OKSM), in combination with differentiation-inducing signals, was reported to trigger direct conversion of fibroblasts into alternative cell types, including hepatocytes, cardiomyocytes and induced neural stem cells (iNSCs). Here, we show that OKSM expression gives rise to both induced pluripotent stem cells (iPSCs) and iNSCs under conditions that were previously shown to induce only NSC transdifferentiation. Fibroblast-derived iNSC colonies silenced retroviral transgenes and reactivated silenced X chromosomes, both hallmarks of pluripotent stem cells. Moreover, lineage tracing via an Oct4-CreER labeling system demonstrated that virtually all iNSC colonies originate from cells transiently expressing Oct4, whereas ablation of Oct4-positive cells prevented iNSC formation. Lastly, use of an alternative transdifferentiation cocktail that lacks OCT4 and was reportedly unable to support induced pluripotency, yielded iPSCs and iNSCs carrying the Oct4-CreER-derived lineage label. Together, these data suggest that iNSC generation using OKSM and related reprogramming factors requires passage through a transient iPSC state. Our results have important implications for the mechanisms and potential therapeutic applications of direct reprogramming approaches.

UNRAVELLING THE DYNAMICS OF REPROGRAMMING OF FIBROBLASTS INTO NEURONS

Lee, Qian Yi[1], Treutlein, Barbara[2], Quake, Stephen[1], Wernig, Marius[1]

[1]Stanford University, Stanford, CA, USA, [2]Max Planck Institute for Evolutionary Anthropology, Leipzig, Germany

Direct lineage reprogramming involves dramatic changes in epigenetic and transcriptional states. We had previously established that during the reprogramming of fibroblasts into neurons (iNs or induced neurons), Ascl1 acts as a pioneering factor to open its cognate binding sites and initiate the process of iN conversion. However, iN reprogramming is still an inefficient process, and previous work had focused on bulk cell populations, which we presume are largely heterogeneous. In addition, the transcriptomal dynamics during iN reprogramming remains largely undefined. Here, we used single-cell RNA-seq at multiple time points to deconstruct the reprogramming path from fibroblasts to mature neurons. We found that in contrast to induced pluripotent stem cells, which go through an initial stochastic phase in response to transcription factor induction, there is a rapid and homogenous response to Ascl1 induction to initiate the neuronal program. Divergence in cell fates occurs later on in the reprogramming process. We observed that a subpopulation of cells eventually commits to a neuronal fate and goes through a maturation phase to upregulate neuronal and synaptic genes. We also found that the fraction of cells that fail to reprogram do not remain as MEFs, but rather veer off into distinct alternate cell fates. Together, these data provide a high resolution, temporal view of transcriptomal dynamics during direct lineage reprogramming, and allows us to better characterize various stages of reprogramming.

IDENTIFICATION OF A POTENT SIGNALLING PATHWAY THAT ORCHESTRATES BOTH REPROGRAMMING AND TRANSDIFFERENTIATION

Ruetz, Tyson Joel[1], Pfisterer, Ulrich[2], DiStefano, Bruno[3], Johnsson, Anna[4], Cohen, Erez I, Linnarsson, Sten[4], Graf, Thomas[3], Parmar, Malin[2], Kaji, Keisuke[1]

[1]Centre for Regenerative Medicine, University of Edinburgh, Edinburgh, United Kingdom, [2]Lund University, Lund, Sweden, [3]Center for Genomic Regulation, Barcelona, Spain, [4]Karolinska Institutet, Stockholm, Sweden

The exogenous expression of master transcription factors to drive somatic cell identity changes is an exciting approach to cell and tissue engineering. Here, we hypothesized that there may be shared underlying mechanisms during different forced cell identity changes. We first discovered that over-expression of either of 2 proteins of a ubiquitous signalling pathway, together with the 4 Yamanaka factors, could dramatically improve the efficiency and kinetics of reprogramming. Co-immunoprecipitation analysis during reprogramming revealed that one of the proteins interacts with the exogenously expressed Oct3/4 and Sox2, as well as a multitude of nucleosome remodelling complexes, including Brg1 (SWI/SNF family), p300, and Dpy30 (MLL complex). Furthermore, it increased interaction between Oct3/4 and Dpy30, suggesting a mechanism of enhanced chromatin remodelling at Oct3/4 target loci during reprogramming. Indeed, chromatin immunoprecipitation (ChIP) analysis confirmed the direct binding of our factors to pluripotency loci in ES cells and during reprogramming. Because these signaling molecules are widely expressed in

different cell types, we addressed if they could boost other master transcription factor mediated transdifferentiation processes. Excitingly, conversion of B cells to macrophages with C/EBPα, as well as myoblasts to adipocytes with C/EBPβ and PRDM16 were enhanced when expressed in combination with either of our identified proteins. Moreover, when they were used in the generation of induced neurons from human fibroblasts together with Ascl1, Brn2, Myt1L, and NeuroD1, mature neurons with the ability to fire spontaneous and repetitive action potentials were produced by day 23 of transdifferentiation, in contrast to 50 days in the control samples. These results reveal, for the first time, shared underlying mechanistic insight into forced cell identity changes, and have developed a tool to produce diverse cell types with profound efficiency and maturity.

FRIDAY 26 JUNE, 13:15 - 15:10

CONCURRENT IIID: PANCREAS, LUNG, LIVER, INTESTINE

ROOM A6

Supported by Novo Nordisk Foundation

HOW TO MAKE BETA CELLS FOR CELL THERAPY IN DIABETES

Semb, Henrik

Danish Stem Cell Center, Copenhagen, Denmark

Key challenges in stem cell-based therapy in diabetes include safe manufacturing of sufficient number of mature, functional beta cells in vitro. Furthermore, a better understanding the mode of action of growth factors/small molecules added to expand and differentiate heterogeneous human pluripotent stem cell (hPSC) cultures facilitates the conversion of experimental differentiation protocols into GMP conditions. Through systematic studies in mice and hPSCs we have addressed how key intermediate steps from the epiblast to the mature beta cell are regulated. Interestingly, many of the regulatory principles are conserved, which facilitated in depth mechanistic studies in the human system. By defining the mode of action of added growth factor/small molecule we have generated a robust protocol for coaxing hESCs into mature beta cells. To address the need for an expandable system we have identified unique cell surface markers in human multipotent pancreatic progenitors making it possible to purify and expand the progenitor population that normally is responsible for the growth of the pancreas. This system not only facilitates expansion of beta cell progenitors but it also removes undifferentiated hPSCs (and other cell types), which represents the major safety concerns in hPSC-based cell therapy. In addition, we have for the first time developed a system for re-seeding of purified beta cell progenitors and their efficient conversion into mature beta cells. Altogether, these results take us closer to the first clinical trials in diabetic patients using mature beta cells manufactured from purified expandable multipotent pancreatic progenitors.

IDENTIFICATION OF AN ENDODERM-DERIVED KDR+ PROGENITOR WITH A BI-POTENT LIVER AND ENDOTHELIAL FATE

Goldman, Orit[1], Han, Songyan[1], Hamou, Wissam[1], Lickert, Heiko[2], Gouon-Evans, Valerie[1]

[1]DRB, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Helmholtz Zentrum, Institute of Diabetes and Regeneration Research, München, Germany

Using the human and mouse embryonic stem cell differentiation system and early fetal livers, we have identified a novel human hepatic progenitor based on the unexpected expression of KDR (VEGFR2/Flk-1). Indeed, KDR expression was thought to be restricted to mesodermal derivatives including endothelial, hematopoietic, cardiac and skeletal muscle precursors. However, our in vitro studies provide evidence for the novel concept that KDR also marks a conserved mouse and human endoderm-derivative. We provide a definitive in vivo proof for the contribution of the KDR+ progenitors to liver development by a lineage tracing study in mice that marked all cells expressing KDR as well as their progeny. Analyses of fetal and adult livers identified a large subset of fetal hepatoblasts and subsequently adult hepatocytes that were generated from the KDR+ progenitors. More recently, we demonstrated that KDR+ progenitors give rise not only to hepatic cells but also endothelial cells. The in vivo functionality of the endothelial cells was shown by the visualization of many human CD31+ endothelial cells integrated in the repaired host vessels following transplantation into injured muscles of mice that underwent a femoral artery ligation. These results introduce the concept that endothelial cells can originate from endoderm, which was supported in an endoderm specific-lineage tracing mouse model. Taken together, analyses of lineage tracing mouse models and human ESC in vitro systems reveal the existence of a conserved endoderm-derived KDR+ liver progenitor with bi-potential hepatic and endothelial fate.

GENOME EDITING IN HUMAN PLURIPOTENT STEM CELLS REVEALS DISTINCT AND OVERLAPPING ROLES OF GATA6 AND GATA4 IN HUMAN ENDODERM AND PANCREAS DEVELOPMENT

Shi, Zhong-Dong, Lee, Kihyun, Li, Qing, Verma, Nipun, Huangfu, Danwei

Sloan Kettering Institute, New York, NY, USA

Understanding the development of human endoderm and its derivatives such as the pancreas has important implications for developing therapeutic strategies to treat diseases such as diabetes. Recently, it has been shown that GATA6 haploinsufficiency is the major cause of pancreatic agenesis and neonatal diabetes in human. However, conditional deletion of Gata6 in the mouse endoderm does not recapitulate this phenotype. Instead, the agenesis phenotype occurs only when both Gata6 and Gata4 are deleted in the mouse. Therefore, it is necessary to use a human-cell-based system to study this unique requirement of GATA6 in human pancreas development and to understand its mechanistic basis. We investigated the functions of GATA6 and GATA4 in human endoderm and pancreas development through combining genome editing and step-wise directed differentiation of human pluripotent stem cells. Deleting GATA6 but not GATA4 significantly compromised definitive endoderm (DE) differentiation evidenced by marked decrease in the percentage of CXCR4+SOX17+ cells. Deleting both GATA6 and GATA4 completely blocked DE differentiation. However, one wild type allele of GATA6 was sufficient for DE specification. During pancreatic lineage differentiation, mutations including frameshift and patient-specific missense mutations in one allele of GATA6 were not sufficient to cause impaired differentiation. However, with additional inactivation of one allele of GATA4 was sufficient to cause impaired pancreatic differentiation. Our findings reveal not only both unique and overlapping roles of GATA6 and GATA4 in human endoderm and pancreas development, but also suggest the presence of genetic modifiers that contribute to the disease phenotype in patients with GATA6 heterozygous mutations.

MODELING HUMAN BRANCHING MORPHOGENESIS USING HUMAN EMBRYONIC STEM CELLS IN VIVO

Chen, Ya-Wen, Huang, Sarah, Xuelian, Mumau, Melanie, Xia, Jinxing, Snoeck, Hans-Willem

Columbia Center for Translational Immunology, Columbia University, New York, NY, USA

Non-malignant lung disease kills approximately 120,000 Americans every year. Transplantation is a valid therapeutic option, although it is hampered by the low availability of donor organs as well as the surgical and medical complications related to the transplant procedure. Innovative approaches are therefore urgently needed. Though challenging, the ability to reconstruct lung tissue from human pluripotent stem cells (hPSCs) would fundamentally change the outlook of the field. Furthermore, as the pathogenesis of several diseases leading to end-stage respiratory failure is currently unclear, patient-specific hPSC-derived lung and airway cells would allow groundbreaking studies in disease pathogenesis and drug discovery. Though the initial stages of lung specification in the mouse are fairly understood, the differences involving airway histology and alveolar development dynamics between humans and mice are unknown. A hPSC-derived model that faithfully recapitulates human development would provide a better understanding of human lung development and is a prerequisite for the implementation hPSC-derived lung and airway cells in disease modeling, drug discovery and regenerative medicine. We have recently published a strategy to achieve the generation of lung progenitors capable of further differentiation into airway and, predominantly, distal lung cells in 2D cultures. Based on this strategy, we adopt the culture system from a 2D to a 3D environment and found that the cells formed spherical colonies (anterior foregut endoderm spheres, AFSs). These cells 1) universally expressed FOXA2 and SOX2, two anterior foregut endoderm markers, and 2) are capable of recapitulating lung development in vivo. Furthermore, the AFSs contain a mesodermal progenitor that generates pulmonary mesoderm, capable of supporting branching morphogenesis. This therefore represents the first tractable model of human lung branching morphogenesis.

DEFINING THE ROLE OF MULE IN INTESTINAL CANCER

Dominguez-Brauer, Carmen[1], Hao, Zhenyue1, Elia, Andrew[1], Chio, Iok In Christine[2], Haight, Jillian[1], Pollett, Aaron[3], Brauer, Patrick M.[4], Fortin, Jerome M.[1], Inoue, Satoshi1, Reardon, Colin[5], Marques, Ana[1], Reilley, Patrick T.[6], Van Es, Johan[7], Clevers, Hans[8], Sato, Toshiro[9], Mak, Tak W.[1]

[1]Ontario Cancer Institute, Toronto, ON, Canada, [2]Cold Spring Harbor, Long Island, NY, USA, [3]Pathology, Mount Sinai Hospital, Toronto, ON, Canada, [4]Immunology, Sunnybrook Research Institute,, Toronto, ON, Canada, [5]University California Davis, Davis, CA, USA, [6]National Cancer Centre Singapore, Toronto, Singapore, [7]Hubrecht Institute/KNAW, Utrecht, Netherlands, [8]Hubrecht Institute/KNAW,, Utrecht, Netherlands, [9]Keio University, Tokyo, Japan

The E3 ligase Mule has many substrates, two of which, c-Myc and p53, are involved in the multi-stage progression of colon cancer. C-Myc, an oncogene which is upregulated upon the hyperactivation of the Wnt pathway, initiates this process. This process culminates with the loss of function of the tumor suppressor P53, which drives the cancer to a carcinoma. Because c-Myc and p53 have opposing roles, and the impact of Mule deficiency on tumorigenesis has been controversial, we set out to understand the true function of Mule in the gut in vivo. We generated conditional Mule knockout (Mule cKO) mice in which Mule was selectively deleted in intestinal epithelial cells. We first bred our Mule cKO mice to the APCmin mouse model of colon cancer to determine whether loss of Mule would enhance tumorigenesis in this context. We also performed a detailed examination of aged Mule cKO mice (normal APC). Absence of Mule synergized with loss of APC function, accelerating the onset of disease and aggravating the APCmin phenotype. Mule cKO mice developed spontaneous intestinal tumors which were heavily populated by intestinal stem cells and paneth cells. Paneth cells establish the "stem cell niche" in the gut, and these cells were strikingly mislocalized in the intestinal crypts of Mule cKO mice. We found that the spontaneous tumors in these mutants were highly proliferative due to a lack of Mule-mediated regulation of c-Myc. Accordingly, genetic ablation of c-Myc in Mule cKO mice restored normal proliferation and thus blocked intestinal stem cell expansion.

HUMAN PLURIPOTENT STEM CELL MODELING OF AIRWAY EPITHELIAL DIFFERENTIATION

Benson, Katherine A.[1], Serra, Maria[1], Hawkins, Finn[1], Jacob, Anjali[1], Morrisey, Edward E.[2], Ikonomou, Laertis[1], Kotton, Darrell N.[1]

[1]Center for Regenerative Medicine, Boston University School of Medicine, Boston, MA, USA, [2]Institute for Regenerative Medicine, University of Pennsylvania, Philadelphia, PA, USA

Many chronic lung diseases involve perturbations of airway epithelial cell fate, such as secretory cell hyperplasia in asthma or COPD and squamous cell metaplasia after inhalational injuries. New model systems able to discern the mechanisms regulating airway epithelial cell fate are therefore desperately needed. One pathway of particular interest is the Wnt signaling pathway due to prior evidence that cyclical, stage-dependent oscillations in the activity of canonical Wnt signaling are critical for normal lung development. New studies utilizing purifiable populations of cells studied at high resolution are required to understand the developmental stage-specific effects and downstream consequences of this signaling. We have therefore employed a novel in vitro model system to derive endodermal lung progenitors from human pluripotent stem cells (hPSCs) to study the effects of Wnt signaling on lung progenitors post-lineage specification. We differentiated a knock-in NKX2-1GFP hPSC line to NKX2-1+ primordial lung progenitors via definitive endoderm at an efficiency of 10-50% by Day 15. We found that NKX2-1+ cells at this stage express multiple ligands, receptors, and targets of the Wnt signaling pathway. Modulation of Wnt signaling at this stage led to rapid changes within the NKX2-1+ population consistent with altered airway patterning. Specifically, withdrawal of the GSK3β inhibitor CHIR99021 post-specification resulted in increased expression of markers of proximal lung lineages in the NKX2-1+ population within 4 days. In contrast, sustained Wnt agonism was linked to inhibition of secretory cell marker expression both at 4 days and 15 days post-specification. Our findings suggest that sustained canonical Wnt signaling inhibits the proximal airway program in developing human lung progenitors consistent with in vivo murine models. Ongoing studies seek to understand the mechanisms driving this inhibition, with the goal of elucidating the key signals that regulate airway cell fate in development and disease. This novel system will provide the basis for the development of in vitro models of monogenic airway disease in patient-derived hPSCs, which remains a crucial barrier to applications of cell-based therapy and in vitro drug testing for patients with chronic lung disease.

FRIDAY 26 JUNE, 13:15 - 15:10

CONCURRENT IIIE: EPITHELIAL AND MESENCHYMAL STEM CELLS

ROOM A4

Supported by GE Healthcare Life Sciences

PLURIPOTENT-INDEPENDENT REGENERATION OF STABLE ORGANS ENABLED BY VASCULAR NICHE INDUCTION

Rafii, Shahin, Butler, Jason M., Lis, Raphael, Ding, BiSen

Weill Cornell Medical College, New York, NY, USA

Organ specific endothelial cells (ECs) are not just passive conduits to deliver oxygen and nutrients, but also establish an instructive vascular niche, which by elaboration of specific paracrine trophogens, (known as angiocrine factors), directly balance the rate of stem cell self-renewal and differentiation. Activation of Akt-mTOR pathway in the sinusoidal ECs (SECs) stimulates expression of angiocrine factors, including Notch-ligands, Wnts, FGFs and TGF-modulators, that induce expansion of authentic hematopoietic stem cells. After partial hepatectomy, SECs within the liver stimulated regeneration by angiocrine expression of Wnt2 and HGF without provoking fibrosis. Pulmonary capillary ECs (PCECs) by deploying MMP14 and release of EGF-ligands sustain lung regeneration. Notably, transplantation of tissue-specific ECs into mice restores organ regeneration. These data establish the previously unappreciated tissue-specific vascular heterogeneity in orchestrating organ regeneration. Indeed, each organ is arborized with specialized capillary ECs endowed with unique repertoire of angiocrine factors. Notably, as ECs can be provoked to instigate pro-fibrotic changes, we need to manufacture and transplant tissue-specific ECs that drive organ regeneration without promoting maladaptive fibrosis. To translate these findings to the clinical setting, we have differentiated human and mouse embryonic stem and iPSC cells into induced vascular ECs (iVECs). However, iVECs (like any other derivatives of iPSC-derived cells) are unstable and upon further stressful stimuli differentiate into other non-vascular cells. To circumvent this hurdle, we have developed new strategies by transcriptional (short term ETV2+Fli1+Erg1+TGFβ inhibition) reprogramming of mid-gestation amniotic cells into vascular ECs (rAC-VECs) without employing pluripotent transcription factors (TFs). rAC-VECs phenocopy the specialized tissue-specific function of ECs, supporting long-term expansion of repopulating cells, such as hematopoietic stem cells in xenobiotic-free conditions. We show that once transplanted intravenously, rAC-VECs home to regenerating tissues reconstructing a vascular niche that by production of specific angiocrine factors promote organ regeneration and repair without fibrosis. Since rAC-VECs can be HLA-typed, cryopreserved, and publicly banked, these cells establish an inventory for generating abundant tissue-specific vascular niche cells for organ regeneration.

P53 CONTROLS AIRWAY EPITHELIAL PROGENITOR CELL SELF-RENEWAL AND DIFFERENTIATION

Farin, Alicia M., Stripp, Barry R.

Cedars-Sinai Medical Center, Los Angeles, CA, USA

The tumor suppressor p53 is a well-known regulator of cell fate and one of the most commonly mutated genes in lung cancer. In the mammary, nervous, and hematopoietic systems, p53 has been shown to regulate stem cell self-renewal and differentiation. However, the role of p53 in controlling stem cell behavior in the lung is largely unknown. In the conducting airway of the mouse, Scgb1a1-expressing Club cells are the primary progenitor cells responsible for epithelial maintenance and repair. We hypothesized that p53 controls Club cell self-renewal and differentiation during both steady state and following injury. To follow the behavior of these progenitors, we used a lineage tracing system in which Scgb1a1-CreER; Rosa26R-Confetti; p53flox/- mice were exposed to tamoxifen to randomly introduce one of four fluorescent tags into individual Club cells. We found that p53 null progenitors generate more clonal patches with fewer cells per patch than the wild type controls. Morphologically the p53 deficient lungs look similar to controls; however, upon quantitation, we found more lineage tagged cells per unit basement membrane in p53 null airways. We also observed that p53 loss lead to a decrease in the number of ciliated cells, which are the differentiated progeny of Club cells. Additionally, we assessed the ability of wild type and p53 deficient Club cells to form spheroid colonies in a 3D in vitro co-culture system. We found that the p53 deficient Club cells had a higher colony forming efficiency than wild type controls. These data indicate that loss of p53 increases self-renewal and decreases differentiation of airway epithelial progenitor cells. In order to determine the role of p53 in airway epithelial regeneration, we exposed Scgb1a1-CreER; Rosa26R-Confetti; p53flox/- mice to the Club cell specific toxicant, naphthalene. Following naphthalene exposure, more p53 deficient Club cells contributed to regeneration as compared to controls. Interestingly, although the p53 deficient Club cells regenerate the airway, they undergo significant mitotic defects. Together, these data suggest that p53 controls airway progenitor self-renewal both at steady state and during repair.

This work is supported by the California Institute for Regenerative Medicine and NHLBI-Lung Repair and Regeneration Consortium.

A MOLECULAR CLASSIFICATION OF MESENCHYMAL STEM CELLS

Wells, Christine Anne, Rohart, Florian, Lê Cao, Kim-Anh, Mason, Elizabeth, Matigian, Nicholas, Mosbergen, Rowland, Korn, Othmar, Chen, Tyrone, Patel, Jatin, Khosrotehrani, Kiarash, Atkinson, Kerry, Fisk, Nicholas

The University of Queensland, Brisbane, QLD, Australia

Mesenchymal stem / stromal cells have been isolated from most tissues, but with growing focus on their clinical application there is an urgent need for improved molecular phenotyping of these cells. Controversies on the origin or efficacy of MSC isolated from different sources arise, in part, from the poor specificity of current immunopanels and the difficulties reproducibly isolating different subsets from human tissues. Typical studies of differentiation or therapeutic potential rely on small sample sizes and intrinsic donor-donor variability confounds traditional efforts towards an improved and reproducible molecular toolkit. To address the question of an overarching molecular MSC phenotype, we harnessed publicly available gene expression data from more than 1300 different human samples, including 300 MSC profiled from various human sources and derived from more than 85 experiments. We developed a new statistical framework to implement a sparse, partial least squares discriminant analysis (sPLS-DA) that included in-house improvements to cross-platform normalization, and developed new methods to evaluate the stability and informativeness of the output. We derived a 16-gene signature that robustly discriminated between MSC and nonMSC with greater than 97% accuracy. Using this method we determined a shared molecular phenotype between bone-marrow MSC and those isolated from placenta, umbilical cord, heart, lung, skin, tooth, brain, adipose tissue as well as hESC-derived MSC. Limbal stem cells were classified as MSC by our method, as were mesangioblasts. However pericytes, satellite cells and neural precursors from the olfactory lamina propria were classified as distinct, nonMSC classes by our statistical method. The signature accurately identified freshly isolated MSC, MSC grown in 3D scaffolds and MSC grown under hypoxic conditions. The signature also identified the transition point between MSC and differentiated progeny in osteogenic, adipogenic and chondrogenic time courses as well as in an adipose MSC-iPSC reprogramming study. All of the studies used in the derivation or testing of the MSC signature are freely available from the Stemformatics.org stem cell resource, and can be queried using the Rohart MSC test

ROLES FOR MACROPHAGES IN WOUND-INDUCED HAIR FOLLICLE NEOGENESIS

Guerrero-Juarez, Christian Fernando[1], Lewandowski, Daniel[2], Boissonnas, Alexandre[3], Combadiere, Christophe[3], Plikus, Maksim[1], Romeo, Paul-Henri[4], Gay, Denise[4]

[1]University of California, Irvine, Irvine, CA, USA, [2]CEA/iRCM, Fontenay-aux-Roses, France, [3]INSERM U1135, Paris, France, [4]INSERM UMR_967, Fontenay-aux-Roses, France

Skin regeneration after wounding typically results in the formation of a fibrous contracted scar and no regeneration of hair follicles. Here, we use a novel regeneration model in which large skin wounds can result in healthy non-fibrotic repair and de novo hair regeneration, termed Wound Induced Hair Neogenesis or WIHN (Ito et al. Nature 2007). Dogma asserts that non-scarring tissue regeneration is hampered in adults by immune responses. However, we have shown that gamma delta T cells, are requisite for initiation of de novo hair regeneration in WIHN (Gay et al. Nature Med 2013). In work presented here, we show that myeloid members of the innate immune system, specifically macrophages, also have essential positive roles in WIHN. We have found that clodronate-mediated macrophage depletion either prior to or in mid- wounding leads to delayed but successful healing whereas WIHN is completely abrogated. These results suggest that both early inflammatory M1 and later regenerative M2 macrophages are important for successful WIHN. In comparing wild type hairless and hair-bearing wounds, we discovered that hair-bearing wounds have fewer M2 macrophages, fewer myofibroblasts and decreased collagen I suggesting that although M2 macrophages are necessary for dermal remodeling, larger numbers may promote fibrotic repair rather than regeneration. In support of this hypothesis, a mouse knockout model with reduced numbers of M2 macrophages in the healing wound (Cx3cr1-knockouts), exhibits greatly increased WIHN. These findings suggest that macrophage responses to wounding must be strictly modulated in strength and duration to prevent fibrotic scarring and ensure successful tissue regeneration. We will discuss these results and their implications for extra cellular matrix (ECM) modeling to create a regenerative vs fibrotic setting and how modulation of myofibroblast Wnt activity may impact this.

CELL-SHEET BASED STEM CELL THERAPY FOR OCULAR SURFACE

Sugiyama, Hiroaki, Yamato, Masayuki, Okano, Teruo

Institution of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo, Japan

Tissue engineering and regenerative medicine have gained a great expectation to treat patients who don't have any approved alternative therapy. We have developed cell sheet-based regenerative medicine using temperature-responsive cell culture surface. At 37°C, the surfaces show relatively weak hydrophobicity. Therefore, cells adhere, spread, and proliferate on the surfaces, but all the cells detach from the surfaces upon temperature reduction below 32°C without need for proteases such as trypsin and dispase, since the surfaces change to hydrophilic. All the cell membrane proteins and deposited extracellular matrix are retained intact, because proteolytic enzymes are eliminated. We successfully treated human patients of limbal stem cell deficiency with transplantable epithelial cell sheets fabricated from patients' own oral mucosal epithelial cells. In the present study, the ocular surface of rabbit limbal stem cell deficient model was reconstructed by transplantation of autologous oral mucosal epithelial cell sheets fabricated on temperature-responsive cell culture surfaces. Four weeks after transplantation, reconstructed ocular surfaces were clear and smooth without defects. The central part of the reconstructed ocular surface was scraped to make a wound, after which proliferating epithelial cells covered the wounded area within a few days. The ocular surfaces were clear and smooth even after 24 weeks follow up with ten-time repeated scrapings. Keratin 6 (K6) expression in oral mucosal epithelial cells was significantly higher than that in corneal and conjunctival epithelial cells. K6 expression was detected in reconstructed ocular surface, while it was not detected in normal cornea. Keratin 12, a corneal epithelium specific marker, expression was detected in one of three reconstructed ocular surfaces. These results suggested that the reconstructed ocular surfaces were covered by only oral mucosal epithelial cells or heterogeneously mixed with corneal epithelial cells. This study demonstrated that transplanted cell sheets containing oral mucosal epithelial stem cells could reconstruct the ocular surface to maintain cornea homeostasis; moreover, they provide an ideal microenvironment to support the proliferation of remaining native limbal stem cells.

FDA-APPROVED PHASE I CLINICAL TRIAL INVESTIGATING INTRATHECAL MESENCHYMAL STEM CELL-DERIVED NEURAL PROGENITORS (MSC-NP) IN MULTIPLE SCLEROSIS: AN INTERIM ANALYSIS

Blackshear, Leslie, **Harris, Violaine K.**, Vyshkina, Tamara, Stefanova, Valentina, Sadiq, Saud A.

Tisch MS Research Center of New York, New York, NY, USA

Multiple sclerosis (MS) is a chronic autoimmune condition affecting the brain and spinal cord. The pathological course of disease involves an early predominantly inflammatory demyelinating disease phase that over a variable period evolves into a progressively degenerative phase. The physical and cognitive disabilities that characterize progressive MS are associated with axonal degeneration and oligodendroglial cell depletion, in addition to the hallmark demyelination. Currently available treatments target the inflammatory disease response but are largely ineffective against the degenerative phase of the disease. Thus, there is a critical unmet need to develop therapies that enable repair and neuroprotection. Mesenchymal stem cell-neural progenitors (MSCNPs) are an autologous bone marrow-derived cell population with regenerative potential. Preclinical studies in mouse EAE showed that three doses of MSCNPs delivered intrathecally (IT) resulted in improved neurological function associated with suppression of local inflammatory response and trophic support for damaged cells at the lesion site. The initial clinical experience with IT MSCNPs in six MS patients also supported the dosing, safety, feasibility, and potential efficacy of this therapeutic approach. The current study is an FDA-approved phase I clinical trial of autologous MSCNPs administered IT in 3 doses of up to 10 million cells per injection, spaced 3 months apart. Enrollment included twenty MS patients with established disability and relatively stable disease. Pre-administration quality testing of autologous MSCNPs expanded from bone marrow aspirates included analysis of sterility, purity, identity, and chromosomal stability. Primary safety outcomes include adverse event assessments. Secondary outcomes to observe trends in efficacy include neurological exam, MRI, evoked potentials, and urodynamics testing. Thirteen study participants have received autologous IT-MSCNPs to date. Six study participants have completed all 3 doses, and seven have received 1 or 2 doses. The interim safety outcomes indicate that this treatment is safe and well-tolerated. Efficacy trends will be presented. The MSCNP trial is the first of its kind to test IT administration of neural progenitors as a regenerative therapy in MS.

FRIDAY 26 JUNE, 16:00 – 17:55

PLENARY V: THERAPY WITH STEM CELLS

PLENARY HALL A1

Supported by Boehringer Ingelheim

CLINICAL TRANSLATION OF NEURAL STEM CELL TRANSPLANTATION: EMERGING SAFETY AND PRELIMINARY EFFICACY WITH HUMAN CENTRAL NERVOUS SYSTEM STEM CELLS, HUCNS-SC

Huhn, Stephen

StemCells, Inc, Newark, CA, USA

There are few effective therapies for diseases that impair normal function of the brain, spinal cord and eye. Human neural stem cell transplantation represents a potential new and innovative medical therapy which offers the prospect to treat a wide spectrum of human conditions. Human Central Nervous System Stem Cells (HuCNS-SC®) are a purified and expanded composition of adult human neural stem cells and the results of transplantation in disease specific animal models have demonstrated consistent biological properties and impact on the underlying pathophysiology. Preclinical studies have demonstrated durable cell engraftment and in vivo protection of host cells and/or improvements in functional deficits. These preclinical studies have provided critical proof-of-concept for approaches targeting neuroprotection and neural replacement in the human setting. Clinical development with HuCNS-SC transplantation has evolved to cover a spectrum of conditions and anatomic regions of the central nervous system. Each clinical study was supported by published preclinical research with relevant animal models and authorized by the U.S. FDA and other regulatory agencies. To date, clinical trial experience with HuCNS-SC has been acquired in four distinct human disorders; a fatal lysosomal storage disease, Neuronal Ceroid Lipofuscinoses (NCL); a fatal dysmyelination disorder, Pelizaeus-Merzbacher disease (PMD); traumatic spinal cord injury (SCI); and, advanced dry, age-related macular degeneration (AMD). The current clinical experience has demonstrated safety, feasibility, and tolerability of HuCNS-SC transplantation. In addition, the emerging preliminary efficacy data have revealed signs of biological activity that have supported advancing into multicenter Phase II proof-of-concept studies for SCI and AMD. The latest outcomes from these initial trials and a clinical summary covering all four indications will be presented.

GENERATING FUNCTIONAL HUMAN BETA CELLS FROM STEM CELLS

Melton, Douglas A.

Department of Stem Cell and Regenerative Biology, Harvard Stem Cell Institute, Cambridge, MA, USA

Insulin-dependent diabetics require regular blood glucose monitoring and insulin injection. In theory, transplanted human beta cells could satisfy both of these requirements and provide more accurate blood glucose control. To that end we have developed a method for the directed differentiation of embryonic and induced pluripotent stem cells that can produce very large numbers of functional human endocrine cells, including beta cells. Molecular and physiological tests for gene expression and physiological function ex vivo, as well as transplantation into immunocompromised mice, compare these stem cell-derived endocrine cells to their human islet counterparts.

DEVELOPMENT OF AN ENCAPSULATED STEM CELL THERAPY FOR DIABETES

Robins, Allan

ViaCyte, Inc, San Diego, CA, USA

Several recent advances have positioned pancreatic lineages derived from human pluripotent cells as leading candidates for in vitro-derived transplantable populations. ViaCyte first reported the generation of pancreatic endoderm cells (PEC-01) capable of regulating blood glucose following engraftment in mice and subsequently, scalable suspension-based approaches to manufacture PEC-01 for pre-clinical studies. ViaCyte's strategy centers on the expansion and step-wise differentiation of human embryonic stem cells (hESC) to sequential populations of mesendoderm, anterior definitive endoderm, primitive gut tube, posterior foregut and PEC-01 comprised of multipotent pancreatic progenitors and immature endocrine cells. PEC-01 grafts mature over the course of several months to form islet-like tissue capable of regulating blood glucose in rodents including models of hyperglycemia. Like islets, established grafts can sense elevated blood glucose and release insulin with a metered response, rapidly restoring glycemia to a human-like set point without hypoglycemia in glucose tolerance tests. Mature beta cell-like phenotypes observed include co-expression of NKX6.1/Insulin and NKX6.1/MAFA, characteristic insulin granule ultrastructure, and insulin release dynamics akin to a first phase response. Sorting studies have established pancreatic progenitor cells as the component of PEC-01 that can give rise to all the pancreatic lineages post-engraftment, including insulin expressing endocrine cells, whereas immature multi-hormonal endocrine cells give rise principally to glucagon

expressing cells. The grafts mature and function similarly at various sites in vivo, including the kidney capsule, epididymal fat pad and in the subcutaneous space. Based on a successful Investigational New Drug (IND) application with the Food and Drug Administration, ViaCyte has initiated a phase 1/2 clinical trial utilizing the VC-01TM combination product of PEC-01 in a durable macroencapsulation device (Encaptra® drug delivery system), termed STEP ONE; or Safety, Tolerability, and Efficacy of VC-01 Combination Product in Type 1 [www.clinicaltrial.gov identifier: NCT02239354].

BRINGING MESENCHYMAL STEM CELLS INTO THE CLINIC

Le Blanc, Katarina

Karolinska Institutet, Stockholm, Sweden

Mesenchymal Stromal Cells (MSCs) are non-hematopoietic progenitor cells that have immune-modulatory properties and promote peripheral tolerance. MSCs suppress alloreactive donor anti-host T-cell responses. Based on the immunomodulatory properties of MSCs along with the cells' ability to promote repair of injured tissue, it was hypothesized that MSCs may be beneficial in reversing inflammation. To date, MSCs have been infused intravenously to several hundred patients. No acute infusional toxicity has been reported. Many questions remain to be answered to optimize MSC treatment. As MSCs are poor stimulators of alloresponses, the majority of patients have received MSCs derived from third-party mismatched donors. However, if and to what degree HLA-matching influences response in humans remains unclear. Analysis of tissues following MSC therapy indicated limited long-term engraftment. MSCs and other stromal cells trigger an innate immune-attack, termed instant blood mediated inflammatory reaction (IBMIR), which has been shown to compromise the survival, engraftment and function of cellular therapeutics. MSCs express hemostatic regulators similar to those produced by endothelial cells, but display higher amounts of pro-thrombotic tissue factor on their surface, which triggers the IBMIR after blood exposure. This process is dependent on the cell dose, the choice of MSC donor, the cell passage number and cell handling before infusion. Freshly harvested, short-term expanded bone marrow MSCs trigger only weak blood responses, while extended culture, freeze-thawing, washing and resuspension in human AB-plasma, and co-culture with activated lymphocytes increases their pro-thrombotic profile. After MSC infusion to patients, we found increased formation of blood activation markers, but no formation of hyperfibrinolysis marker D-dimer or acute phase reactants with the currently applied dose of 1-3 x 106 cells per kilogram, demonstrating product safety. We conclude, that currently applied doses of low-passage clinical grade MSCs are safe and elicit only minor systemic effects, but higher cell doses, and particularly higher passage cells, should be handled with care. This deleterious reaction can compromise the survival, engraftment, and function of these therapeutic cells.

SATURDAY, 27 JUNE, 9:00 – 11:20

PLENARY VI: IMMUNOLOGY AND STEM CELLS

PLENARY HALL A1

Supported by Mesoblast

ADOPTIVE T CELL THERAPY WITH ENGINEERED T CELLS

June, Carl H.

University of Pennsylvania School of Medicine, Philadelphia, PA, USA

The field of adoptive cell transfer (ACT) currently comprised of CAR and TCR engineered T cells has emerged from principles of basic immunology to paradigm-shifting immunotherapy. These clinical advances are poised to enter mainstream medicine. The adoptive transfer of T cells engineered to express artificial receptors that target cells of choice is an exciting new approach for cancer, and holds equal promise for chronic infection and autoimmunity. Using the principles of synthetic biology, advances in immunology and genetic engineering have made it possible to generate human T-cells that display desired specificities and enhanced functionalities. In particular, clinical trials in patients with advanced B cell leukemias and lymphomas treated with CD19-specific CAR T cells have induced durable remissions in adults and children, leading to optimism that this approach will be useful for treating common solid tumors. The prospects for the widespread availability of engineered T cells have changed dramatically given the recent entry of the pharmaceutical industry to this arena. Here, I will discuss some of the challenges and opportunities that face the field of ACT.

HEMATOPOIETIC STEM CELL GENE THERAPY WITH LENTIVIRAL VECTOR IN 4 PATIENTS WITH CEREBRAL X-LINKED ADRENOLEUKODYSTROPHY: LONG-TERM OUTCOME

Aubourg, Patrick[1,2], Hacein-Bey-Abina, S[3], Bartholomä, C[4], Schmidt, M.[3], Bellesme, C.[1], Dufayet, G.[4], Bougnères, P.[5], Fischer, A.[6], Von Kalle, C.[3], Cavazzana-Calvo, M.[3], Cartier, N.[1,2]

[1]Department of Pediatric Neurology, Hôpital Bicêtre, Le Kremlin Bicêtre, France, [2]Inserm UMR1169, University Paris Sud, Le Kremlin Bicêtre, France, [3]Department of Biotherapy, Hôpital Necker-Enfants Malades, PARIS, France, [4]National Center for Tumor Diseases and German Cancer Research Center (DKFZ), Heidelberg, Germany, [5]Department of Pediatric Endocrinology, Hôpital Bicêtre, Le Kremlin Bicêtre, France, [6]Department of Pediatric Immuno-Hematology, Hôpital Necker-Enfants Malades, PARIS, France

The most severe form of X-linked adrenoleukodystrophy (ALD), an inherited peroxisomal disease involving the CNS, is characterized by rapidly progressive and lethal cerebral demyelination in childhood. The progression of cerebral demyelination of ALD can be arrested by allogeneic hematopoietic stem cell (HSC) transplantation (HCT), provided the procedure is performed at an early stage of the disease. The long term beneficial effects of HCT in ALD are likely due to the progressive replacement of brain microglia by myeloid progenitors after transplant. Allogeneic HCT remains associated with significant risk of mortality (17% with unrelated donor or cord blood), severe GVH (20%) and lack of engraftment (17%). Four boys with inflammatory cerebral ALD have been treated by the transplantation of autologous HSC genetically corrected ex vivo with a lentiviral vector (LV) following full myelo-ablation between 2006 and 2010. The procedure was very well tolerated without complications. In particular and with a follow-up between 4 and 8.5 years, high throughput sequencing of LV integrants in peripheral blood and bone marrow cells showed that the hematopoiesis remained polyclonal in the 4 patients without evidence of abnormal growth of some clones due to the integration of LV vector in the promoter regions of genes. The clinical benefit was similar to allogeneic HCT with an arrest of disease progression 16 months after transplant. In long-term, these 3 patients remain with good to very good quality of life. In a fourth patient, a relapse occurred 16 months after transplant and his cerebram disease arrested only 36 months after transplant with significant progression of cerebral demyelinating lesions. This patient has no motor deficit but severe cognitive deficits with bad quality of life. Overall this initial trial establish the safety and efficacy of the procedure. A new trial in a larger number of patients is now on-going.

FROM STEM CELLS TO T CELLS, IN VITRO APPLICATIONS AND IN VIVO IMPLICATIONS

Zuniga-Pflucker, Juan Carlos[1,2]

[1]Department of Immunology, University of Toronto, Toronto, ON, Canada,
[2]Sunnybrook Research Institute, Toronto, Ontario, Canada

The thymus provides the necessary environmental cues for the differentiation and generation of T-cells. The thymus is continuously colonized by a rare subset of bone-marrow derived progenitors, which in humans are characterized as CD34+CD45RA+CD7+ cells. Further characterization and directed expansion of this important progenitor subset would represent an important step in developing T-cell and thymus regenerative approaches. Here we show the induced generation of human progenitor T-cells (pro-T) with a thymus-colonizing phenotype from multiple sources of stem cells cocultured on OP9-DL1 stromal cells. To determine whether pro-T cells generated in vitro possess an intrinsic ability to home, engraft and reconstitute a thymus in vivo, sorted CD34+ CD7++ pro-T cells were injected into immunodeficient mouse strains, which can support human multi-lineage differentiation from CD34+ hematopoietic stem cells (HSCs). Our findings showed that T-lineage progenitors generated in vitro exhibit key properties of being able to home to, settle, and effectively reconstitute the thymus of immunodeficient mice. Additionally, in vitro-generated pro-T cells, when transferred together with purified HSCs, were able to dramatically enhance the thymus reconstituting ability of HSC-derived progenitors in vivo. Additionally, we used human induced pluripotent stem cells generated from dermal fibroblasts of patients with Rag1 mutations, which result in severe combined immunodeficiency (SCID) or Omenn syndrome, and differentiated these into T-lineage cells in vitro in order to assess the alterations in T cell development and V(D)J recombination. Taken together, the generation of humanized mice reconstituted with in vitro derived progenitor T-subsets offers a new means of therapeutic evaluation and the potential to rapidly restore the T-cell compartment for the treatment of immunodeficiencies.

REPRODUCIBLE RESEARCH: CRISIS OR OPPORTUNITY?

Ioannidis, John

Stanford University School of Medicine, Stanford, CA, USA

Empirical studies in diverse fields have shown that many high-profile published scientific results cannot be reproduced. This has created a lot of debate about how best to proceed to improve reproducibility. Even though cases of fraud catch the attention of mass media, lack of reproducibility is extremely rarely due to fraud. Science may be the field par excellence of human behavior that is least affected by fraud. Most commonly, lack of reproducibility reflects suboptimal methods and inefficient or poor research practices in the design, execution, publication, and dissemination of scientific results. Accordingly, a large number of solutions have been proposed that may enhance the efficiency and accuracy and reliability of scientific investigation both at the basic/preclinical and at the clinical stage. The lecture will review some of the aspects of this ongoing challenge and will show how identification and application of the best solutions may offer a great opportunity to strengthen the scientific record and the translational potential of biomedical research.

ISSCR- BD Biosciences Outstanding Young Investigator Lecture

PLURIPOTENT STEM CELL TECHNOLOGIES FOR UNDERSTANDING OLIGODENDROCYTE DEVELOPMENT AND DISEASE

Tesar, Paul J.

Case Western Reserve University, Cleveland, OH, USA

Oligodendrocyte progenitor cells (OPCs) are endogenous stem cells in the central nervous system that serve as the predominant source of myelinating oligodendrocytes. Oligodendrocyte loss or dysfunction can lead to significant motor and cognitive disability in patients due to myelination deficits. We have developed technologies that enable the rapid and robust generation of OPCs from pluripotent stem cells and via direct cell reprogramming technologies. These in vitro generated OPCs serve as a powerful platform to understand oligodendrocyte development and to discover therapeutic compounds for enhancing myelination. I will discuss our recent efforts to use high-throughput phenotypic screening of pluripotent stem cell-derived OPCs to uncover new aspects of oligodendrocyte biology.

SATURDAY, 27 JUNE, 13:15 - 15:10

CONCURRENT IVA: ROAD TO THE CLINIC

ROOM A4

RETINAL REPAIR THROUGH TRANSPLANTATION OF PHOTORECEPTORS

Ali, Robin

Institute of Ophthalmology, University College London, London, United Kingdom

Retinal degeneration is a leading cause of untreatable blindness in the developed world. Despite different aetiologies, age-related macular degeneration and most inherited retinal disorders culminate in the same final common pathway, the loss of photoreceptors. There are few effective treatments and none reverse the loss of vision. We are therefore developing a novel therapeutic approach that aims to restore sight by transplanting new photoreceptors. We have established previously that photoreceptor precursors at the correct ontogenetic stage are able to migrate and functionally integrate into the degenerate adult retina. We have also demonstrated restoration of vision following rod-photoreceptor transplantation into a mouse model of stationary night-blindness. To translate this therapeutic approach we need to establish a renewable source of correctly staged photoreceptor precursors. We have therefore investigated ES cell-derived retinal differentiation and the integration competence of ES cell-derived photoreceptor precursors and have optimized this culture system for the purposes of photoreceptor transplantation. We have now efficiently generated photoreceptor precursors at a stage equivalent to the early postnatal retina and following the transplantation of these cells we have observed, for the first time, successful ES cell-derived photoreceptor integration into the adult retina. Our focus is now on optimising human ES-derived photoreceptor differentiation and transplantation.

FIRST US PHASE I CLINICAL TRIAL OF GLOBIN GENE TRANSFER FOR THE TREATMENT OF BETA-THALASSEMIA MAJOR

Boulad, Farid[1], Maggio, Aurelio[2], Wang, Xiuyan[1], Moi, Paolo[3], Barone, Rita[2], Acuto, Santina[2], Riviere, Isabelle[1], Sadelain, Michel[1]

[1]Center for Cell Engineering, Memorial Sloan Kettering Cancer Center, New York, NY, USA, [2]Ospedale Cervello, Palermo, Italy, [3]Microcitemie, Palermo, Italy

Hematopoietic stem cell engineering is a promising therapy for the beta-thalassemias and sickle cell disease. The only curative therapeutic approach for beta-thalassemia major is allogeneic stem cell transplantation. However, most patients lack an HLA-matched sibling. The stable transfer of a functional globin gene into autologous CD34+ hematopoietic stem/progenitor cells (HSPCs) is an alternative curative approach that does not require immunosuppression and, furthermore, may not require myeloablative conditioning. We previously demonstrated successful globin gene therapy in murine thalassemia models, wherein the TNS9.3.55 vector increased hemoglobin levels by 4-6 g/dL per vector copy. In 2012, we obtained the first US Food and Drug Administration (FDA) approval to proceed to a clinical study in adult subjects with beta-thalassemia major (NCT01639690). We have infused 3 subjects, administering the transduced HSPCs after non-myeloablative conditioning. Subject 1 is a 23-year old female with ß039-IVS1,110 mutations. Subject 2 is an 18-year old female with ß039-IVS1,6 mutations. Subject 3 is a 39-year old male with ß039-ß039 mutations. All three patients were transfusion dependent and on iron chelation. G-CSF-mobilized CD34+ PBSCs were transduced with the lentiviral vector TNS9.3.55 encoding the normal human beta-globin gene. The average vector copy number (VCN) in bulk CD34+ cells for these three patients was respectively 0.37, 0.2 and 0.28 copies per cell. All 3 patients underwent non-myeloablative cytoreduction with busulfan administered at 8 mg/Kg. All three patients tolerated cytoreduction well and promptly recovered their blood counts. While they continue to be transfusion dependent, the first two patients showed a gradual rise in vector copy number in peripheral blood white blood cells and neutrophils, steadily increasing by 1-2% every month, stabilizing in the 5-8% vector copy range after 6 months. Patient 2 showed a decrease of transfusion requirement by approximately 50% over 1 year. Although the vector titer did not allow for high level peripheral blood gene marking, these studies strongly support the feasibility of this approach and the prospect of achieving therapeutic engraftment without myeloablative conditioning.

MITOCHONDRIAL COMPETITION AFTER NUCLEAR TRANSFER IN HUMAN OOCYTES

Yamada, Mitsutoshi[1], Emmanuele, Valentina[2], Sauer, Mark[3], Hirano, Michio[2], Egli, Dieter[1]

[1]The New York Stem Cell Foundation Research Institute, New York, NY, USA, [2]Department of Neurology, Columbia University, New York, NY, USA, [3]Center for Women's Reproductive Care, Columbia University, New York, NY, USA

Transfer of the nuclear genome between oocytes of the affected and an unaffected egg donor is being considered as a treatment to prevent the transmission of mitochondrial disease. In proof of principle experiments, it was found that even though a small amount of mitochondria are carried over with the nuclear genome, the exchange of the mitochondrial genotype was complete. Stem cells and cells derived from them carried exclusively the genotype of the unaffected egg donor. To determine the reproducibility of this procedure, we generated additional stem cell lines using cryopreserved cytoplasm or cryopreserved nuclei, reducing the need for synchronous oocyte retrieval. To confirm the exchange of the mitochondrial genotype, heteroplasmy was determined for 25 stem cell lines, and more than 50 preimplantation stage samples generated by nuclear transfer. In two specific mitochondrial haplotype combinations, we found that the mitochondrial genotype of the transferred nucleus was initially low, and then gradually increased, or even became dominant. Interestingly, mitochondria with either genotype showed normal activity in the presence of the same nuclear genome, arguing against a mechanism involving functional incompatibility between nuclear and mitochondrial DNA. However, the shift in mitochondrial genotype suggests a replication bias in some mtDNA combinations. We will present an update on the mechanisms of this replication bias, and provide an update on our efforts to translate mitochondrial replacement to the clinic.

THE MORAL RESPONSIBILITIES OF ACADEMIC RESEARCH INSTITUTIONS TO SAFEGUARD THE INTEGRITY OF RESEARCH

Master, Zubin[1], Martinson, Brian C.[2]

[1]Alden March Bioethics Institute, Albany Medical College, Albany, NY, USA, [2]HealthPartners Institute for Education and Research, Minneapolis, MN, USA

Safeguarding research integrity is not only the responsibility of scientists, but also of academic research institutions. In high-profile cases of research misconduct, scientists are typically labeled "bad apples" while their employing institutions escape opprobrium. Seldom are questions raised about the role of the institution to prevent misconduct or the organizational climate and culture, which may have led to misconduct. Yet institutions have moral obligations to their faculty, students, and to the public; traditionally their primary benefactor. This implied network of social contracts has, however, been shifting over several decades, blurring the lines of who is responsible to whom, and for what; introducing new challenges to research integrity. What happens when faculty become less valued for their pure intellectual contributions, and increasingly valued as "cash cows"? What are the implications of graduate and postdoctoral trainees being relied upon as relatively inexpensive skilled laborers? What role have such changes played in generating the hypercompetition science leaders have recently pointed to as a threat to research integrity? Stem cell researchers report feeling they are under greater scrutiny and have higher pressure to publish incomplete or unverified results, warranting concern that the current environment of high-stakes competition for increasingly scarce resources may be adversely affecting stem cell research and other fields. The STAP cell misconduct case at the Center for Developmental Biology (CDB) at RIKEN led an investigation committee to recommend dismantling the CDB and to the implementation of a plan to address misconduct, which may have contributed to the suicide of a CDB lead-scientist. This eye-opening example of the competitive, high-stakes nature of stem cell and biomedical research environments can be used to examine the dynamics of these settings, and where academic institutions need to take active roles in promoting research integrity, preventing misconduct, and reshaping the scientific research environment. Here, we explore the moral responsibilities of research institutions to prevent misconduct and other undesirable research-related behavior, and how they may begin redirecting the academic environment towards a more positive and sustainable future.

COMBINED TREATMENT OF SELF-ASSEMBLING PEPTIDES AND NEURAL PRECURSOR CELLS AFTER EXPERIMENTAL CERVICAL SPINAL CORD INJURY

Zweckberger, Klaus[1], Wang, Jian[2], Liu, Yang[2], Fehlings, Michael G. [3]

[1]Department of Neurosurgery, University of Heidelberg, Heidelberg, Germany, [2]Department of Genetics and Development, University of Toronto, ON, Canada, [3]Institutes of Medical Science, Department of Neurosurgery, University of Toronto, ON, Canada

The pathophysiology of spinal cord injury (SCI) involves inflammation and tissue scarring interfering with regeneration and recovery. A combined treatment approach with self-assembling peptides (SAP) and neural precursor cells (NPC) might improve this inhibitory environment and neuronal regeneration. Following cervical laminectomy, rats were subjected to SCI. After randomization (NPC, SAP, NPC+SAP, vehicle, sham) SAPsand NPCs were injected into the spinal cord 1 day and 14 days after trauma. All animals received growth factors subdurally and immunosuppressive therapy. Neurological function was assessed on a weekly basis. 4 weeks after SCI rats were sacrificed and cryosections were prepared for immunohistochemical staining. Animals treated with SAPs showed a larger amount of surviving NPCs (18.088 ± 4.044 vs. 11.493 ± 4.111; n=6; p=0.019) and greater levels of differentiation: neurons (8.7% vs.5.8%; p=0.015) and oligodendrocytes (11.6% vs. 9.1%; p=0.005). Furthermore, animals treated with SAPs alone or as a combined approach with NPCs had smaller intramedullary cysts (p=0.07) and a larger percentage of preserved tissue. In the combined treatment group, astrogliosis (GFAP density) and tissue scarring (CSPG density) were significantly reduced. Though the total number of motor neurons was diminished, there was no significant difference between the groups. Synaptic connectivity (Synaptophysin-density) was increased both in the NPC and in the combined treatment group. Behavioral assessments showed improvements favoring the animals treated combinatorially 4 weeks after SCI. Shaping the inhibitory environment using SAPs reduces astrogliosis and tissue-scarring, supports NPC survival and differentiation, and reduces intramedullar cyst formation leading to an improved neurological outcome.

* This work was funded by a grant of the German research society (DFG Forschungsstipendium), and the Krembil and CIHR foundations.

SIMULTANEOUS REPROGRAMMING AND GENE CORRECTION OF PATIENT FIBROBLASTS

Howden, Sara Emily[1], Thomson, James A.[2]

[1]Murdoch Childrens Research Institute, Parkville, VIC, Australia, [2]Regenerative Biology, Morgridge Institute for Research, Madison, WI, USA

Autologous cell therapies based on gene-corrected patient-derived induced pluripotent stem cells hold great promise for the treatment of many inherited and acquired diseases. The generation of genetically modified iPS cell lines typically involves multiple steps, requiring lengthy cell culture periods, drug selection, and several clonal events. We report the simultaneous generation of gene-targeted/corrected iPS lines following a single electroporation of patient-specific fibroblasts using episomal-based reprogramming vectors and the Cas9/CRISPR gene targeting system. Simultaneous reprogramming and gene targeting of somatic cells has been tested and achieved in two independent fibroblast lines with efficiencies ranging from 0.8-5% of the total iPS cell population. We have successfully targeted the DNMT3B and OCT4 genes with a fluorescent reporter gene and have corrected the disease-causing mutation in both patient fibroblast lines: one derived from an adult with autosomal dominant retinitis pigmentosa, the other from an infant with severe-combined immunodeficiency. Importantly, this procedure allows the generation of gene-targeted iPS lines with only a single clonal event in as little as 3 weeks and without the need for drug selection, thereby facilitating "seamless" single base pair changes. Gene-corrected iPS clones are also free of reprogramming vectors and exhibit normal karyotypes. Thus, the simultaneous reprogramming and gene-correction of patient-derived cells should facilitate transplantation medicine by enabling cells to be available to patients in a more timely manner whilst minimizing risks associated with extended cell culture.

SATURDAY, 27 JUNE, 13:15 - 15:10

CONCURRENT IVB: EPIGENETICS

ROOM A6

PAUSING OF RNA POLYMERASE II REGULATES MAMMALIAN DEVELOPMENTAL POTENTIAL THROUGH CONTROL OF SIGNALING NETWORKS

Adelman, Karen

National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA

The remarkable capacity for pluripotency and self-renewal in embryonic stem cells (ESCs) requires a finely-tuned transcriptional circuitry. In particular, the expression of cell lineage-specific regulators must be repressed in ESCs, but potentiated for efficient activation by developmental signals. Several mechanisms have been proposed to facilitate this plasticity, including pausing of Pol II during early transcription elongation and the presence of bivalent chromatin domains that contain both active and repressive histone modifications. However, the role of Pol II pausing or bivalency in shaping the gene expression program in ESCs has remained enigmatic, as has the relationship between these regulatory strategies To elucidate transcriptional control in mouse ESCs in the naïve, ground state, we defined the distribution of engaged RNA polymerase II (Pol II) at high-resolution using Global Run-on Sequencing (GRO-seq) and Start-RNA seq, and integrated this with gene expression data. Notably, we find that promoter-proximal pausing of Pol II is widespread, and highly enriched at genes regulating cell cycle and signal transduction. However, pausing was not, as expected, enriched at developmental genes or those with bivalent chromatin marks. Pol II pausing is essential in ESCs and during early mouse development: ablation of the primary pause-inducing factor NELF caused embryonic lethality and defects in ESC proliferation. But, loss of NELF did not increase expression of lineage markers, nor did it cause spontaneous differentiation as previously proposed. Instead, the disruption of pausing led to dysregulation of ESC metabolism and signaling pathways, particularly the FGF/ERK signaling cascade. In fact, ESCs lacking NELF have dramatically attenuated FGF/ERK activity, rendering them refractory to FGF signaling and lineage commitment. This work thus uncovers a key role for NELF-mediated pausing in establishing the responsiveness of stem cells to developmental cues.

COMPARATIVE EPIGENOMIC ANALYSIS OF REGULATORY ELEMENTS IN HUMAN AND CHIMPANZEE STEM CELLS

Narvaiza, Iñigo[1], Wang, Meiyan[1], Benner, Christopher[1], Marchetto, Maria Carolina[1], Ku, Manching[1], Swigut, Tomek[2], Wysocka, Joanna[2], Gage, Fred H.[1]

[1]Salk Institute for Biological Studies, La Jolla, CA, USA, [2]Stanford University School of Medicine, Stanford, CA, USA

We have previously shown that the comparison of gene expression in induced pluripotent stems (iPS) cells derived for human and non-human primates revealed differences in the control of mobile elements, which contribute to explain the higher levels of genome diversity in great apes. Here, we have further investigated the differences between humans and our closest living relatives by carrying out the first comparative epigenomic study in human and chimpanzee iPS cells. For epigenomic profiling we analyzed genome-wide chromatin accessibility, and histone modifications associated to active and repressed regulatory elements by chromatin immunoprecipitation and sequencing (ChIP-seq). We found that gene-specific modulation of bivalency directly correlates with differences in human and chimpanzee gene expression. We also identified a number of divergent enhancers that overlap with species-specific mutations in transcription factor binding motifs and target gene expression. Many regulatory elements overlap with transposable elements, however we observed that divergence in promoters is partially driven by species-specific mutations in ancient transposons that were mobile before the human-chimpanzee split. These findings reveal a novel mechanism for epigenomic evolution in humans and chimpanzees, and demonstrate the value of primate iPS cells for comparative and evolution studies.

STABLE X CHROMOSOME REACTIVATION IN FEMALE HUMAN INDUCED PLURIPOTENT STEM CELLS

Barakat, Tahsin Stefan[1], Ghazvini, Mehrnaz[2], Gribnau, Joost[3]

[1]University of Edinburgh, MRC Centre for Regenerative Medicine, Edinburgh, United Kingdom, [2]Reproduction and Development, Erasmus MC, University Medical Center, Rotterdam, Netherlands, [3]Erasmus MC, University Medical Center, Rotterdam, Netherlands

Mechanisms for balanced expression of X-linked genes in male and female placental mammals include X chromosome inactivation (XCI) in female somatic cells. XCI starts with accumulation of the X-transcribed non-coding XIST RNA in cis, on the future inactive X chromosome (Xi), in differentiating embryonic cells. It is expected that reprogramming of human adult female somatic cells to induced pluripotent stem cells (hiPSCs) will include transient or stable X chromosome reactivation (XCR). However, using hiPSCs conflicting results have been obtained, some investigators reporting XCR during reprogramming, whereas other studies concluded that the Xi remains silent. To obtain a better model system to study XCR and XCI during the reprogramming process, we generated hiPSC lines from female fibroblasts heterozygous for large X-chromosomal deletions. These fibroblasts show completely skewed XCI of the mutated X chromosome, enabling precise monitoring of XCR and XCI using allele-specific single cell expression analysis. XCI analysis of the hiPSC lines by XIST RNA FISH and immunohistochemistry showed that approximately 70% of the cells have lost markers of the Xi. Single cell RT-PCR on hiPSCs sorted for the expression of pluripotency-associated surface markers revealed bi-allelic expression of several X-linked genes, in most cells within each cell line. We also found a large population of hiPSCs expressing XIST from the wild type X chromosome, which is not found in the fibroblasts used to generate the hiPSCs, indicating de novo initiation of XCI after reprogramming. Indeed, analysis of allele-specific methylation at the X-linked androgen receptor locus in hiPSCs showed initiation of XCI on the X that is active in the founder fibroblast cell line. This approach revealed that XCR is robust under standard culture conditions, although these conditions do not prevent reinitiation of XCI, resulting in a mixed population of cells with either two active X chromosomes (Xa) or one Xa and one Xi. Importantly however, this mixed population of XaXa and XaXi cells is stabilized in naïve human stem cell medium (NHSM) allowing expansion of clones with two Xa's. Generation of hiPSC lines with stable XCR will advance the use of hiPSCs for modelling of X-linked diseases, and also provides a powerful model system to study human XCI.

SIGNALING COUPLES HAIR FOLLICLE STEM CELL QUIESCENCE WITH CHROMATIN STATES ASSOCIATED WITH PLASTICITY

Tumbar, Tudorita, Lee, Jayhun

Cornell University, Ithaca, NY, USA

Adult stem cell (SC) plasticity is essential for tissue homeostasis yet is poorly understood. In pluripotent SCs, plasticity has been previously linked with specialized chromatin states. Here we employ mouse hair follicles as adult organelles to examine specialized chromatin states previously associated with plasticity in embryonic stem cells. We find that at the stage of their fate determination in homeostasis hair follicle stem cells (HFSCs) present elevated plasticity-associated states. Specifically, quiescent

HFSCs: (1) can be more readily de-differentiated; (2) display higher chromatin-bound histone H2B exchange rates; and (3) have generally lower global levels of both activating and repressing histone epigenetic marks (H3K4me3, H3K27me3, and H3K9me3) than proliferative HFSCs and than differentiated cells. Strikingly, the erasure of histone marks in quiescent HFSCs did not govern gene expression, as defined by mRNA levels. Furthermore, chemical inhibition of this erasure during quiescence led to impaired HFSC activation and in hair cycle progression in the subsequent stage of homeostasis. Importantly, the same signals that control HFSC quiescence and hair cycle also modulate transcription of histone modifying enzymes, thus coupling some SC chromatin states previously associated with plasticity with tissue homeostasis.

A NOVEL DNA METHYLATION REPORTER FOR REAL TIME TRACING OF EPIGENETIC CHANGES DURING DEVELOPMENT AND REPROGRAMMING, AT SINGLE CELL RESOLUTION

Stelzer, Yonatan, Shivalila, Chikdu Shakti, Soldner, Frank, Marloulaki, Styliani, Jaenisch, Rudolf

Whitehead Institute for Biomedical Research, Cambridge, MA, USA

Mammalian DNA methylation is a heritable epigenetic mark, which plays an essential role during normal development and disease. Because DNA methylation is a dynamic process and current methods provide only a limited "snapshot" view of the methylation state of different cell types, a key challenge in the field is to generate tools that allow tracing real-time changes in DNA methylation. Nevertheless, the difficulty in translating second dimension real-time epigenetic changes into a traceable readout, is, to-date, a limiting factor in our ability to follow the dynamics of DNA methylation. Here, we establish a Reporter of Genomic Methylation (RGM) that relies on a synthetic imprinted gene promoter driving a fluorescent protein. We show that insertion of RGM in proximity of CpG islands, associated with gene promoters, allows faithful reporting on gain and loss of DNA methylation. We further asked whether RGM could be utilized to monitor DNA methylation dynamics associated with non-coding regulatory elements. For this we established cell lines reporting on the endogenous DNA methylation levels of the pluripotent specific miR290 and Sox2 super enhancer regions, both of which are known to regulate methylation states during differentiation. Loci-specific DNA methylation changes were visualized in mouse embryonic stem cells following cell state transition during induction of differentiation, and during reprogramming of somatic cells to pluripotency. Analyzing DNA methylation dynamics, and its synergy with transcription, at single-cell resolution allowed us to gain novel insights into these processes. RGM will allow the investigation of dynamic methylation changes during development and disease at single cell resolution. Furthermore, RGM enables isolation of cells according to their methylation state, which paves the way for mechanistic and therapeutic-based screens to identify regulators of DNA methylation.

REGULATION OF MAMMALIAN DNA METHYLATION BY TRANSCRIPTION FACTOR BINDING

Schmidt, Juliane[1], Krebs, Arnaud[1], Akalin, Altuna[2], Burger, Lukas[1], Schübeler, Dirk[1]

[1]Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland, [2]Max-Delbrück-Centrum für Molekulare Medizin, Berlin, Germany

In the eukaryotic nucleus, gene expression is regulated in the context of modified chromatin. DNA methylation constitutes such a chromatin modification that is generally linked to transcriptional silencing. Genome-wide methylation profiling in mammalian cells uncovered widespread cytosine methylation with reduced methylation at regulatory regions. Previous studies suggested that some DNA-binding factors could directly cause reduced DNA methylation. However, how transcription factors mediate changes in DNA methylation remains an open question. We used mouse embryonic stem cells to investigate the transcriptional repressor REST/NRSF, which is necessary and sufficient to induce hypomethylation at its binding sites. We ectopically expressed mutated versions of REST and profiled DNA methylation at binding sites. This revealed that hypomethylation at binding sites requires distinct functional interaction domains of REST, while DNA binding alone was not sufficient to cause reduced methylation. Interestingly, REST mutants that were competent to decrease DNA methylation also increased chromatin accessibility and nucleosome positioning. This links the ability of transcription factors to remodel chromatin to reduced hypomethylation at their binding sites.

SATURDAY, 27 JUNE, 13:15 - 15:10

CONCURRENT IVC: MODELING DISEASE WITH IPSCS

ROOM A2

ELUCIDATING METABOLIC DISEASE MECHANISMS USING HUMAN PLURIPOTENT STEM CELLS

Cowan, Chad

Harvard Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA

Our goal is to understand the molecular underpinnings of metabolic diseases such as type 2 diabetes mellitus and coronary artery disease, the leading cause of death in the world, and use these insights to develop new therapies. We use human cell-based models to understand how DNA variants affect gene and protein function or how lifestyle choices such as exercise and diet influence disease progression and then use these mechanistic insights to begin the process of developing new therapies that will benefit patients and populations. We have optimized the use of genome editing tools to generate specific DNA variants in human pluripotent stem cells which when differentiated into human-derived tissues provide genetic disease models. Our group has developed state-of-the-art protocols that enable the efficient production of human pluripotent stem cell-derived adipocytes, hepatocytes, endothelial and vascular smooth muscle cells to pursue disease in a dish studies. We also aim to use stem cells to enable regenerative medicine, in which a patient's own cells can be genetically cured or made resistant to disease and then transplanted back into the body as a durable treatment.

PATIENT-SPECIFIC IPSC DERIVED ENDOTHELIAL CELLS UNCOVER MECHANISMS RELATED TO PENETRANCE OF A BMPR2 MUTATION IN CAUSING PULMONARY ARTERIAL HYPERTENSION

Gu, Mingxia, Sa, Silin, Ma, Yu, Wu, Joseph C., Rabinovitch, Marlene

Stanford School of Medicine, Stanford, CA, USA

Familial (F) pulmonary arterial hypertension (PAH) is a heritable autosomal dominant disorder with low (20%) penetrance. Over 70% of the mutations associated with FPAH cause loss of function of the bone morphogenetic protein receptor (BMPR)2. Patient-specific iPSC derived endothelial cells (iPSC-ECs) provide a novel cell-based platform to model the propensity for PAH among family members with the same mutation. A cohort of six individuals from three FPAH families carrying three different BMPR2 mutations (Family 1: c.354T>G p.C118W; Family 2: c.2504delC p.T835fs; Family 3: c.G350A p.C117Y) and three gender matched controls were recruited for the study. Each family included one FPAH patient with a BMPR2 mutation (PAH-B), and one unaffected mutation carrier with identical BMPR2 mutation (U-B). From controls and families 1 and 2, iPSCs have been generated from skin fibroblasts and differentiated into iPSC-ECs using a directed monolayer approach, whereas generation of iPSC-ECs from family 3 is ongoing. Functional analysis revealed that iPSC-ECs from the PAH-B of both families showed markedly reduced adhesion to plastic and a number of extracellular matrix substrates including matrigel when compared to the iPSC-ECs from U-B or controls. BMP4 activation resulted in stimulation of p-SMAD1/5 at 15 and 60 minutes, and ID1 at 60 minutes in both control and U-B from both families whereas no activation of p-Smad or ID1 was evident in the iPSC-ECs from either PAH-B. We screened for molecules that could explain the compensatory signaling in the U-B family members and found an increase in the BMPR2 co-receptor LRP1 (family 1) and the BMPR2 interacting protein caveolin1 (family 2). This is the first study to use iPSC-ECs to show functional and signaling differences related to BMPR2 that distinguish PAH patients from unaffected BMPR2 mutation carriers. Since reduced function and expression of BMPR2 is also seen in patients with idiopathic and associated forms of PAH, these studies reveal compensatory mechanisms that might be targeted in developing novel therapies. Moreover, preservation of the disease phenotype through the differentiation process (fibroblast to iPSCs to iPSC-ECs) portends well for using patient-specific iPSC-ECs to screen for novel or personalized treatments of a variety of vascular pathologies in addition to PAH.

ENHANCED CHONDROGENESIS OF INDUCED PLURIPOTENT STEM CELLS FROM PATIENTS WITH NEONATAL-ONSET MULTISYSTEM INFLAMMATORY DISEASE OCCURS VIA THE CASPASE 1-INDEPENDENT CAMP/PKA/CREB PATHWAY

Toguchida, Junya[1], Yokoyama, Koji[2], Umeda, Katsutsugu[3], Saito, Megumu K.[2], Ikeya, Makoto[2], Tamaki, Sakura[1], Nakahata, Tatsutoshi[2], Heike, Toshio[3], Nishikomori, Ryuta[3]

[1]Institute for Frontier Medical Sciences, Kyoto University, Kyoto, Japan, [2]Center for iPS Cell Research and Application, Kyoto University, Kyoto, Japan, [3]Department of Pediatrics, Graduate School of Medicine, Kyoto University, Kyoto, Japan

Neonatal-onset multisystem inflammatory disease (NOMID) is a dominantly inherited

autoinflammatorydisease caused by NLRP3 mutations. NOMID pathophysiology is explained by the NLRP3 inflammasome, which produces interleukin-1 (IL-1). However, epiphyseal overgrowth in NOMID is resistant to anti-IL-1 therapy and may therefore occur independently of the NLRP3 inflammasome. This study was undertaken to investigate the effect of mutated NLRP3 on chondrocytes using induced pluripotent stem cells (iPSCs) from patients with NOMID. We established isogenic iPSCs with wild-type or mutant NLRP3 from 2 NOMID patients with NLRP3 somatic mosaicism. The iPSCs were differentiated into chondrocytes in vitro and in vivo. The phenotypes of chondrocytes with wild-type and mutant NLRP3 were compared, particularly the size of the chondrocyte tissue produced. Mutant iPSCs produced larger chondrocyte masses than wild-type iPSCs owing to glycosaminoglycan overproduction, which correlated with increased expression of the chondrocyte master regulator SOX9. In addition, in vivo transplantation of mutant cartilaginous pellets into immunodeficient mice caused disorganized endochondral ossification. Enhanced chondrogenesis was independent of caspase 1 and IL-1, and thus the NLRP3 inflammasome. Investigation of the human SOX9 promoter in chondroprogenitor cells revealed that the CREB/ATF-binding site was critical for SOX9 overexpression caused by mutated NLRP3. This was supported by increased levels of cAMP and phosphorylated CREB in mutant chondroprogenitor cells. Chondrocytes derived from iPSCS of NOMID patients successfully recapitulated patients' phenotype and demonstrated that the intrinsic hyperplastic capacity is independent of the NLRP3 inflammasome and depends on the cAMP/PKA/CREB pathway.

OPTICAL ACTION POTENTIAL RECORDING: A TOOL FOR CARDIAC DISEASE MODELING AND HIGH-THROUGHPUT DRUG SCREENING IN HIPSC-DERIVED CARDIOMYOCYTES

Chen, Zhifen, Sinnecker, Daniel, Moretti, Alessandra, Laugwitz, Karl Ludwig

Medical Department-Cardiology, Technical University of Munich, München, Germany

Cardiomyocytes (CMs) generated from patient-specific induced pluripotent stem cells (iPSCs) have been shown to recapitulate key features of heritable diseases and provide a promising platform for disease modeling and drug development. Screening assays for drug-induced QT interval prolongation are a promising application of these cells. The usefulness of conventional patch clamp electrophysiology in this context is restricted by its limited throughput. We aimed at establishing optical action potential (AP) recordings as a non-invasive and scalable assay to assess action potential characteristics and single-cell arrhythmias in healthy and diseased iPSC-derived cardiomyocytes (hiPSC-CM). Here we generated lentiviruses encoding an optical membrane potential indicator based on the Ciona intestinalis voltage sensor-containing phosphatase (Ci-VSP) fused with the FRET pair Clover and mRuby2 (VSFP-CR) in order to measure AP properties in patient-specific hiPSC-CMs. Promoter based VSFPs (e.g., hMLC2v-VSFP) allowed us to record AP in specific cardiomyocytes subtypes (e.g., ventricular cardiomyocytes). iPSC lines were generated from healthy controls and from individuals affected by long-QT syndrome type 1 (LQT1) and catecholaminergic polymorphic ventricular tachycardia type 1 (CPVT1), by retroviral transfer of the Yamanaka transcription factors into skin fibroblasts. We also generated KCNQ1 (R190Q) point mutation-rectified LQT1-iPSC line (LQT1 Corr) by homologous recombination. Optical imaging of APs in hiPSC-CMs with a genetically-encoded membrane potential sensor was suitable to assess AP characteristics as well as arrhythmias in single cells. Elongations of AP duration as compared to control cells were successfully recorded in both LQT1 CMs and LQT1 Corr CMs under the condition of external pacing by imaging hMLC2v-VSFP fluorescence. Moreover, hMLC2v VSFP-guided optical AP recording revealed the presence of arrhythmias but normal AP duration in CPVT CMs. Furthermore, after applying the QT prolonging drug Cisapride on hiPSC-CMs, our method could demonstrate AP prolongation and an increased vulnerability to arrhythmias in LQT1, LQT Corr and CPVT CMs. These results demonstrate that a genetically-encoded AP sensor could be employed as a tool for cardiac disease modeling and provide a potential alternative assay for high-throughput preclinical cardiac toxicity tests and candidate cardiac drug screening in hiPSC-derived CMs.

THERAPEUTIC STRATEGIES THAT TARGET GENETIC RISK FOR PSYCHIATRIC DISORDERS

Chenoweth, Josh[1], Hoeppner, Daniel[1], Colantuoni, Carlo[1], Shin, Joo-Heon[1], Kim, Suel-Kee1, Seo, Seungmae[1], Stein-Obrien, Genevieve1, Wesolowski, Steve[2], Burli, Roland[2], Wang, Yanhong[1], Olivares, Nick[1], Brandon, Nick[2], Cross, Alan[2], Hyde, Thomas[1], Weinberger, Daniel[1], McKay, Ronald[1]

[1]Lieber Institute for Brain Development, Baltimore, MD, USA, [2]AstraZeneca Neuroscience, Cambridge, MA, USA

Pharmacological manipulation of stem cells in vitro has yielded novel insight into how the AKT/PI3K signaling pathway can be activated to restore CNS function in vivo. These results are consistent with a powerful new idea that the molecular pathways regulating stem cell function in development also play key roles throughout

life in homeostasis and disease. Genes that confer risk for neurodevelopmental disorders such as Neuregulins and their ERBB receptors act through AKT/PI3K signaling to regulate human pluripotent stem cells and continue to play an important role in differentiated neurons. We have established a tiered screening strategy to identify compounds that target the NRG1/PI3K/mTOR pathway in neural development and also regenerate function in the brain. The first step in this strategy is a detailed analysis of the pharmacological responses of pluripotent cells. Informatic analysis of RNAseq data and high-content imaging reveals dynamic patterns that identify transient cellular sub-populations and correctly predicts differences in differentiation potential in iPSC lines from different donors. To assess the contribution of genetic risk in the AKT signaling pathway, six patient-specific induced pluripotent stem cells (Controls and Schizophrenics) were treated with NRG1 ligands. Phenotypic (Cell morphology) and biomarkers in this signaling pathway (phosphorylation of AKT/S6 residues) were assayed in individual cells using High-Content Imaging in the presence of well-annotated drugs. Remarkably, this approach defines distinct pharmacological responses in the multiple cell types that comprise the pluripotent state. NRG1 ligands have discrete effects on the PI3K\mTOR pathway and their downstream effectors. Deficits in animal models can be reversed by manipulating NRG1. Using this approach we propose to identify new compounds that modulate signaling mediated by the brain enriched NRG1 beta ligand in human cells. Annotating compounds for their effects on multiple human genomes through the entire program of brain development will define novel targets and link them to stratified patient cohorts.

INDUCED PLURIPOTENT STEM CELL (IPSC) MODELING REVEALS A ROLE FOR GROWTH DIFFERENTIATION FACTORS (GDFS) IN THE ETIOLOGY OF BETA-THALASSEMIA

Vanuytsel, Kim[1], Wang, Liz B.[1], Gianotti Sommer, Andreia[1], Leung, Amy[1], Park, Seonmi[1], Steinberg, Martin H.[2], Chui, David H. K.[2], Mostoslavsky, Gustavo[1], Murphy, George J.[1]

[1]Center for Regenerative Medicine (CReM), Boston University School of Medicine, Boston, MA, USA, [2]Section of Hematology and Medical Oncology, Department of Medicine, Boston University School of Medicine, Boston, MA, USA

β-thalassemia encompasses a heterogenous group of inherited mutations characterized by abnormal globin gene expression. Iron overload causes morbidity and mortality in β-Thalassemia, and the hepatic hormone hepcidin is the regulator of iron homeostasis. Deficiency of hepcidin may result from the suppressive effect of high erythropoietic activity on production of the hormone. Understanding the correlation between ineffective erythropoiesis and hepcidin dysregulation is hampered by the lack of a model for this complex disease. Using iPSC technology, we generated disease-specific lines from patients with β-thalassemia major. Through differentiation of patient-specific iPSCs into hepcidin producing hepatocytes and globin producing erythroblasts, we created a platform that allows for disease modeling in the genetic context of the patient. We demonstrate that β-thalassemia iPSC-derived erythroblasts secrete greater amounts of GDF15 and that exposure of the patient's iPSC-derived hepatocytes to supernatants of disease-specific erythroblasts decreases hepcidin expression, recapitulating important aspects of the disease. β-thalassemia iPSC-derived erythroblasts also demonstrate a maturation block resulting in perpetually immature cells, providing a potential novel mechanism contributing to the development of ineffective erythropoiesis. These results validate this iPSC-based, patient-specific in vitro system for testing new diagnostic approaches and therapeutic strategies targeting the correction of hepcidin dysregulation.

SATURDAY, 27 JUNE, 13:15 - 15:10

CONCURRENT IVD:TISSUE ENGINEERING; ORGAN DEVELOPMENT AND REGENERATION

VICTORIA HALL

FORCES, FORM, AND ENGINEERING CELL AND TISSUE FUNCTION

Chen, Christopher S.

Boston University and Harvard University, Boston, MA, USA

A long recognized tenet of biological systems is that structure gives rise to function. Local tissue structure defines the cellular environment, constraining how cells experience surrounding extracellular matrix substrates, neighboring cells, soluble growth factors, and physical forces. These microenvironmental signals in turn cooperate as central regulators of cellular functions such as proliferation, differentiation, migration, and suicide. Despite the realization that forces, form, and function permeate all living systems, we as a research community sorely lack methods to control the mechanics of the environment, the spatial organization of cells, or the architecture of cell-matrix and cell-cell interfaces, which collectively define the boundary conditions that stabilize multicellular structure and tissue function. Here, I will describe our efforts to design and build physical microenvironments that explicitly manipulate and monitor the structure and mechanics of cellular interactions with their surroundings, how we have used these approaches

to gain insights into their role in regulating cell and tissue structure, signaling, and function, and lastly how to use these approaches to build in vitro organotypic models that mimic native tissue functions. I will use our studies to illustrate how deeper insights into the structure-function links are critical to our ability to engineer stem cells to recapitulate differentiated function, and how engineered systems ultimately could have a major impact on biomedical research.

REGENERATION OF THE ADULT ZEBRAFISH BRAIN: THE ROLE OF LINEAGE CONVERSION

Brand, Michael

Developmental Genetics, TU Dresden, BIOTEC/CRTD, Dresden, Germany

Severe traumatic brain injury (TBI) of the adult mammalian central nervous system (CNS) leads to life-long loss-of-function, and neuronal regeneration does not occur. In contrast, adult zebrafish have a remarkable ability to regenerate adult brain, retina and spinal cord. Neurogenesis in adult rodents is limited to only two subregions of the telencephalon, but in adult zebrafish occurs along the entire length of the neuraxis, suggesting a mechanistic link to its regeneration ability. The cellular and molecular mechanisms that enable or prevent adult CNS regeneration are little known. To study these mechanisms in adult zebrafish, we developed TBI lesion assays, and analyzed cellular reactions to TBI. We find that adult zebrafish can efficiently regenerate brain lesions and lack permanent glial scarring. Several cell types proliferate as a consequence of the TBI. Using conditional Cre-loxP-based genetic lineage tracing, we asked which stem/progenitor cell types react to injury, proliferate and which contribute to neuronal replacement. We previously described that a subtype of ventricular radial glial stem cells proliferates and generates neuroblasts that migrate to the lesion site. The newly generated neurons survive for at least 3 months, are decorated with synaptic contacts and express mature neuronal markers. Here, we used hematopoietic stem cell transplantation and Cre/loxP lineage tracing to determine if proliferating non-neuronal stem cell lineages convert to generating neuronal-marker expressing cells after TBI, as was reported after HSC transplantation in mammals. So far, we find no new neurons of donor descent. Leukocytes, oligodendrocyte progenitors, mature myelin, endothelial cells and pericytes appear not to convert to a neuronal lineage following TBI. In vivo lineage conversion is currently discussed as a possible therapeutic strategy for neurodegenerative conditions in mammals, using misexpression of lineage converting transcription factors. Our results indicate that lineage conversion is rare in regeneration-capable adult zebrafish brain, in spite of the challenges of a traumatic brain lesion.

FUNCTIONAL SYSTEMS ANALYSIS OF THE ADULT MUSCLE STEM CELL IDENTIFIES CRUCIAL REGULATORS OF MUSCLE REGENERATION

Kim, Johnny, Braun, Thomas

Max Planck Institute for Heart and Lung Research, Bad Nauheim, Germany

Skeletal muscle stem cells (MuSC), also called satellite cells, are indispensable for maintenance and regeneration of adult skeletal muscles. Yet, a comprehensive picture of the regulatory events controlling the fate of MuSC is missing. We determined the proteome of purified adult MuSC from transgenic reporter mice against which we designed a high-throughput loss-of-function screen. This approach led to the systematic identification of 120 genes important for MuSC self-renewal and differentiation. In depth in vivo analysis of one candidate, the arginine methyltransferase Prmt5, revealed that MuSC-specific inactivation of Prmt5 in adult mice prevents expansion of MuSC, abolishes long-term MuSC maintenance and abrogates skeletal muscle regeneration by direct epigenetic silencing of the cell cycle inhibitor p21. We reason that Prmt5 generates a poised state, which keeps MuSC in a stand-by mode thus allowing rapid MuSC amplification under disease conditions. Strikingly, Prmt5 is dispensable for proliferation and differentiation of muscle progenitor cells during embryonic development demonstrating that epigenetic regulation via Prmt5 determines significant differences between embryonic myogenesis and adult muscle stem cell dependent regeneration.

MODELING HUMAN NEURAL TUBE ANATOMY THROUGH CULTURING OF STEM CELLS UNDER MICROFLUIDIC GRADIENTS

Kirkeby, Agnete[1], **Isaksson, Marc**[2], **Laurell, Thomas**[2], **Parmar, Malin**[1]

[1]*Developmental and Regenerative Neurobiology, Lund University, Lund, Sweden,*
[2]*Biomedical Engineering, Lund University, Lund, Sweden*

Knowledge about structural brain development is almost purely derived from studies performed in rodents or smaller model organisms, despite the fact that the human brain is much more complex and 2000 times larger than that of the mouse. This research bias is caused by the impossibility of performing dynamic studies on anatomical brain patterning in human embryos, resulting in a significant lack of knowledge on human-specific neural development. Here, we build a simplified 3D model of the developing human neural tube in vitro using human embryonic stem cells (hESCs). Taking advantage of established knowledge

on neural tube patterning, we have designed a closed microfluidic culturing chamber for differentiation of hESCs. In this chamber, the cells are exposed to a gradient of chemicals during the first days of differentiation to mimic the anatomical gradients of growth factors present in the embryo around the developing neural tube. We show that hESCs survive well and differentiate into neural precursor cells when cultured in the gradient chamber. Importantly, through culturing in the gradient chamber we were able to induce progressive caudalization of neural identity, obtaining pure forebrain cells in the left side of the culture chamber to midbrain cells in the middle and hindbrain cells in the right side of the chamber, indicating an anatomical resemblance to the rostro-caudal organization of the neural tube. Remarkably, we found the gene WNT1 to be very highly expressed in the area of the midbrain-hindbrain boundary in the culture chamber, indicating the formation of an in vitro equivalent to the anatomical structure of the Isthmic Organizer (IsO). Our model will be a unique and novel tool for studying important signaling between neighboring neural cell populations during development, and for investigating how human brain development differs from that of other species in order to achieve an extraordinary degree of complexity.

IMPAIRMENT IN FRACTURE HEALING IN A MOUSE MODEL OF TYPE 2 DIABETES IS DRIVEN BY SKELETAL STEM CELL NICHE DYSREGULATION

Tevlin, Ruth, Seo, Eun Yun (Elly), McArdle, Adrian, Marecic, Owen, Li, Shuli, Duldulao, Christopher, Wearda, Taylor, Rodrigues, Melanie, Mann, Zeshaan, Senarath-Yapa, Kshemendra, Atashroo, David, Hu, Michael S., Paik, Kevin, Walmsley, Graham G., Zielins, Elizabeth, Wan, Derrick C., Quarto, Natalina, Gurtner, Geoffrey C., Chan, Charles K.F., Weissman, Irving L., Longaker, Michael T.

Lokey Stem Cell Institute, Stanford University, Palo Alto, CA, USA

The incidence of diabetes is increasing worldwide. As a systemic disease, diabetes results in a decline in the regenerative capacity of bone and is associated with increased morbidity and mortality. Building upon our recent finding that the mouse skeletal system follows a program similar to that of hematopoiesis, with a multipotent stem cell generating various lineages in a niche that regulates differentiation, we evaluated the role of skeletal stem cells (SSCs) and the niche microenvironment in promoting the diabetic bone phenotype in response to fracture. Differences in skeletal regeneration were compared in C57Bl6 (Wild-type, WT) and Lep db -/- (Diabetic, Db) mice using a femoral fracture model. Heterogeneous parabiosis between Db and WT mice allowed for evaluation of the role of the skeletal niche in promoting a diabetic bone phenotype during normal homeostasis and in response to injury. The osteogenic potential, migration and replication of purified populations of SSCs from WT and Db fracture callus was assessed in vitro and in vivo. Transcriptional and metabolomic screens were used to identify differentially regulated pathways associated with impaired Db fracture healing. We observed a significantly reduced frequency of SSCs in the diabetic callus in comparison to WT following injury. Diabetes results in cell extrinsic changes in the SSC niche in the fracture microenvironment and, thus, a decline in regenerative potential. Heterogeneous parabiosis improves Db fracture mechanical strength and alters radiological callus accrual. Transcriptional and metabolomic assays revealed changes associated with the diabetes-related functional decline of SSCs. Local or systemic manipulation of signaling pathways (as identified by transcriptional and translational aberrancies) in the Db fracture microenvironment can rejuvenate the fracture niche by improving skeletal stem cell migration and fracture healing. Diabetic fracture healing is a complex process, with impairment largely attributed to cell extrinsic changes in the stem cell niche. We identified multiple differentially regulated transcriptional and metabolomic differences in Db SSCs in comparison to WT control; subsequent manipulation of these pathways in the SSC niche of the fracture microenvironment can augment diabetic fracture healing.

HUMAN EMBRYONIC STEM CELL DERIVED NEURAL CREST CELLS FOR PERIPHERAL NERVE REPAIR

Jones, Iwan[1], Novikova, Liudmila N.[2], Novikov, Lev N.[2], Ullrich, Andreas[3], Oberhoffner, Sven[3], Doser, Michael[3], Renardy, Monika[4], Müller, Erhard[4], Wiberg, Mikael[2], Carlsson, Leif[1], Kingham, Paul J.[2]

[1]Umeå Center for Molecular Medicine, Umeå University, Umeå, Sweden, [2]Department of Integrative Medical Biology, Umeå University, Umeå, Sweden, [3]ITV Institute of Textile Technology and Process Engineering, Denkendorf, Germany, [4]ITV Denkendorf Productservice GmbH, Denkendorf, Germany

Although the peripheral nervous system (PNS) has an innate regeneration capacity, the majority of peripheral nerve injuries require surgical intervention. Autologous nerve grafting is the gold standard for reconstructing nerve tissue gaps but this has limitations including loss of donor site sensation and neuroma formation. Therefore, alternative therapeutic treatments are needed. One such approach is to use nerve conduits whose components stimulate and accelerate the innate PNS regeneration process. An essential component of all conduits are cells that provide trophic support. Neural crest cells (NCC) are a transient cell population that delaminate from the developing neuroectoderm and are the parent population to many

PNS lineages including sensory neurons and myelinating Schwann cells. NCC are therefore ideal candidates to assess for their regenerative capacity within nerve conduits. In this study, NCC were differentiated from WA09 human embryonic stem cells using a dual SMAD inhibition protocol and isolated by magnetic-activated cell sorting. The differentiated NCC displayed classical stellate morphology and gene and protein expression patterns (p75+, HNK-1+, Sox10+, AP2+) that indicated their resemblance to native NCC. Moreover, the NCC secreted high levels of trophic factors including VEGF-A and IGF-1 and conditioned media derived from these cells significantly increased in vitro neurite outgrowth. These observations demonstrate the growth promoting potential of differentiated NCC. To address whether the differentiated NCC could recapitulate their in vivo function we diluted the cells in a fibrin matrix and seeded them into biodegradable tubular conduits made from ε-caprolactone, trimethylene carbonate and glycolide. The conduits were used to bridge a 10 mm gap in a rat sciatic nerve injury model. In the control group (matrix only), a few isolated pioneering axons were observed to establish the regeneration front. However, in conduits seeded with the differentiated NCC a robust regeneration front was observed across the entire lumen of the conduit. Our results demonstrate that the differentiated NCC are biologically active and provide trophic support to stimulate regeneration. Differentiated NCC are therefore a potential therapeutic agent to aid in peripheral nerve repair.

SATURDAY, 27 JUNE, 13:15 - 15:10

CONCURRENT IVE: STEM CELL NICHE

ROOM K1

PLASTIC INTERACTIONS BETWEEN NORMAL AND MALIGNANT HAEMATOPOIETIC CELLS AND THEIR BONE MARROW NICHES

Lo Celso, Cristina

Imperial College London, London, United Kingdom

Hematopoietic stem cells (HSCs) maintain the turnover of mature blood cells during steady-state and in response to systemic perturbations such as infections. Their function critically depends on complex signal exchanges with the bone marrow microenvironment in which they reside, but the cellular mechanisms involved in HSC-niche interactions and regulating HSC function in vivo remain elusive. Our current hypothesis is that external stress events, such as infections or leukaemia development, impact HSC fate by altering HSC-niche interactions. We used a natural mouse parasite, Trichinella spiralis, and multi-point intravital time-lapse confocal microscopy of mouse calvarium bone marrow to test whether HSC-niche interactions may change when haematopoiesis is perturbed. We find that steady-state HSCs stably engage confined niches in the bone marrow whereas HSCs harvested during acute infection are motile and therefore interact with larger niches. These changes are accompanied by increased long-term repopulation ability and expression of CD44 and CXCR4, and administration of a CXCR4 antagonist affects the duration of HSC-niche interactions. These findings suggest that HSC-niche interactions may be modulated during infection. Moreover, we have developed longitudinal tracking of leukaemia cells to enable us to obtain new insights on the cellular mechanisms of leukaemia growth and uncover whether leukaemia initiating cells as well as relapsing cells have specific niche requirements, and if so, whether they compete with normal haematopoietic stem cells for niche space or select or even carve their own niches.

WNT5A EXPRESSED BY THE NICHE IS REQUIRED TO MAINTAIN MIGRATORY PROPERTIES OF HEMATO-POIETIC STEM CELLS THROUGH THE PLANAR CELL POLARITY PATHWAY

Schreck, Christina[1], Istvanffy, Rouzanna[1], Ruf, Franziska[1], Ziegenhain, Christoph[2], Gärtner, Florian[3], Massberg, Steffen[4], Enard, Wolfgang[2], Peschel, Christian1, Oostendorp, Robert A.J.[1]

[1]3rd Department of Internal Medicine, Klinikum rechts der Isar der Technical University Munich, Munchen, Germany, [2]Anthropology and Human Genetics, Ludwig-Maximilians University Munich, Munchen, Germany, [3]1st Department of Internal Medicine, Klinikum der Ludwig-Maximilians-Universität München, Munchen, Germany, [4]1st Department of Internal Medicine, Klinik der Ludwig-Maximilians-Universität München, Munchen, Germany

We previously identified Wnt5a as a secreted factor that maintains HSCs in vitro (Buckley, et al., Exp Hematol. 2011) and as a factor responsible for decline of HSC function during aging (Florian et al., Nature. 2013). We here studied in detail how Wnt5a-deficiency affects the niche and its ability to maintain long-term repopulating HSC. The BM niche in Wnt5a-deficient mice show increased number of CD31+ endothelial cells. The number of mature and immature mesenchymal cells was not different, but multipotent stromal cells (MSCs) showed increased proliferation and calcification upon differentiation. Chimeric transplantation experiments showed that Wnt5a+/- HSCs engraft similarly to wild-type Wnt5a+/+ (WT) HSCs up to tertiary transplantations. To assess whether niche Wnt5a affects engraftment, and/or self-renewal capacity of HSCs,

wild-type (WT) HSCs were transplanted in Wnt5a-deficient recipients. We found that in primary recipients, engraftment was similar to that in WT recipients. Unexpectedly, however, WT donor LSK cells from the Wnt5a-deficient recipients completely failed to engraft in secondary recipients. Although the phenotype of the WT donor cells engrafted in either WT or Wnt5a+/- environments was similar, the sorted LSK cells from Wnt5a+/- recipients showed defective, apolar distribution of Cdc42 and F-actin, suggesting possible defects in migratory properties. Indeed, RNAseq of sorted donor LSK cells from Wnt5a+/- recipients showed highly divergent expression of molecules involved in heterotrimeric G-protein assembly and small GTPase-mediated planar cell polarity (PCP) signal transduction. Further experiments showed that WT donor LSK cells from Wnt5a+/- recipients showed defective lamellipodia formation, and only poorly homed to the bone marrow of recipient WT mice. In addition, mature T and B lymphocytes failed to migrate towards CXCL12. In conclusion, our experiments show that a Wnt5a-deficient niche allows for initial engraftment, but fails to maintain the ability of engrafted HSCs to properly home and engraft secondary recipients, due to defective PCP-regulated migratory properties of HSCs and mature lymphoid cells.

COLONIZATION OF A HEMATOPOIETIC STEM CELL NICHE REVEALED BY LIGHTSHEET LIVE IMAGING OF THE ZEBRAFISH KIDNEY MARROW

Tamplin, Owen J.[1], Kapp, Friedrich G.[2], Elliott, Hunter L.[3], Richardson, Douglas S.[4], Zon, Leonard I.[1]

[1]Hematology/Oncology and Stem Cell Program, Boston Children's Hospital, Boston, MA, USA, [2]Stem Cell and Regenerative Biology, Harvard University, Boston, MA, USA, [3]Image and Data Analysis Core, Harvard Medical School, Boston, MA, USA, [4]Harvard Center for Biological Imaging, Harvard University, Boston, MA, USA

Hematopoietic stem cells (HSCs) support the entire blood system and reside in a specialized microenvironment called the niche. In mammals the adult niche is in the bone marrow and in zebrafish it is in the kidney marrow. However, HSCs do not originate in the marrow and must travel there after emergence from the dorsal aorta and expansion in the mammalian fetal liver or zebrafish caudal hematopoietic tissue. Understanding of this process is significant because it is thought to be analogous to the homing and engraftment of HSCs after clinical transplantation. In mammals, colonization of the bone marrow cannot be directly visualized because it occurs prenatally in the long bones of the fetus. The zebrafish is an advantageous model because the embryos develop externally and are transparent. The kidney marrow niche is colonized by HSCs between 4 and 5 days post fertilization (dpf). We previously described a Runx:mCherry transgenic line that marks HSCs in all sites of definitive hematopoiesis throughout development and into adulthood. We have used this line to observe the earliest immigration events of HSCs as they arrive in the kidney marrow. First, we paralyzed embryos by injecting alpha-bungarotoxin protein directly into the circulation. Next we performed live imaging of the early kidney marrow niche. At 4-5 dpf the kidney marrow is at a depth of ~100 microns from the surface of the embryo and cannot be clearly imaged live using standard confocal microscopy. To overcome this challenge, we used lightsheet microscopy because its perpendicular objective lenses allow illumination from one angle and observation from another angle. We performed long term imaging (~16 hours) of the entire kidney marrow and quantified the total number of stem cells. The first wave of HSC colonization between 4-5 dpf reached a steady state of ~50-60 cells. Shortly before 5 dpf the stem cell pool began to expand at a rate of ~5 cells per hour. This increase could be from proliferation of HSCs present in the niche and/or migration of more HSCs into the niche, however the temporal resolution of the experiment does not distinguish between these two possibilities. We have visualized colonization of what will become the adult HSC niche and estimated the size of the stem cell pool that will persist throughout life.

DEEP IMAGING OF BONE MARROW SHOWS NON-DIVIDING HEMATOPOIETIC STEM CELLS ARE PERISINUSOIDAL

Acar, Melih[1], Kocherlakota, Kiranmai S.[2], Murphy, Malea M.[1], Peyer, James G.[1], Oguro, Hideyuki[1], Jaiyeola, Christabel[1], Zhao, Zhiyu[1], Luby-Phelps, Katherine[3], Morrison, Sean J.[2]

[1]Children's Research Institute and the Department of Pediatrics, UT Southwestern Medical Center, Dallas, TX, USA, [2]Children's Research Institute and the Department of Pediatrics, Howard Hughes Medical Institute, UT Southwestern Medical Center, Dallas, TX, USA, [3]Department of Cell Biology, UT Southwestern Medical Center, Dallas, TX, USA

Hematopoietic stem cells (HSCs) reside in a perivascular niche but the niche location relative to other bone marrow components remains controversial. HSCs are rare, so few can be found in tissue sections or upon live imaging, making it difficult to comprehensively localize dividing and non-dividing HSCs. Here we describe the ability to image all HSCs in large segments of optically cleared bone marrow using deep confocal imaging and digital tissue reconstruction. We discovered that in the hematopoietic system alpha-catulin is nearly uniquely expressed by HSCs. In alpha-catulinGFP/+ knock-in mouse model GFP was expressed by only 0.02% of bone marrow hematopoietic cells, including virtually all HSCs. One in 3.5 alpha-catulin-GFP+c-kit+ cells gave long-term multilineage reconstitution

of irradiated mice. We systematically localized all alpha-catulin-GFP+c-kit+ cells in optically cleared bone marrow. HSCs were more common in the central marrow than near bone surfaces. Nearly all HSCs contacted Leptin Receptor+ and Cxcl12high niche cells. Approximately 90% of HSCs were within 10μm of a sinusoidal blood vessel. The vast majority of HSCs were distant from arterioles, transition zone vessels, and bone surfaces. This was true of Ki-67+ dividing HSCs and Ki-67- non-dividing HSCs. Dividing and non-dividing HSCs thus reside in perisinusoidal niches throughout bone marrow marked by contact with Leptin Receptor+Cxcl12high niche cells.

FUNCTIONAL SCREEN IDENTIFIES NOVEL REGULATORS OF MURINE HEMATOPOIETIC STEM CELL ENGRAFTMENT

McKinney-Freeman, Shannon L., Holmfeldt, Per, Ganuza, Miguel, Marathe, Himangi, Hall, Trent, Pardieck, Jennifer, Saulsberry, Angelica, Cico, Alba

St. Jude Children's Research Hospital, Memphis, TN, USA

The paucity of hematopoietic stem cells (HSC) limits their application to treat disease. One way to overcome this limitation is to enhance HSC engraftment efficiency. We executed a screen to identify novel regulators of HSC repopulation. >1300 mice were transplanted to interrogate nearly 50 computationally prioritized genes. HSC transduced with control or gene-specific shRNAs were transplanted into ablated hosts along with mock-transduced competitor HSC. To focus on detecting genes regulating repopulation, rather than self-renewal or ex vivo maintenance, cells were transplanted within 24-hours of isolation and transduction. Each shRNA was functionally validated and, to ensure high resolution of Hits from non-Hits, robust cell transduction was verified for each transplant (>70% was typical). Each Hit was validated in a second transplant screen. We identified 18 regulators of HSC repopulation for a robust Hit rate of 36.7% (18/49 genes screened): Arhgef5, Armcx1, Cadps2, Crispld1, Emcn, Foxa3, Fstl1, Glis2, Gprasp2, Gpr56, Myct1, Nbea, Nfix, P2ry14, Smarca2, Sox4, Stat4, and Zfp251. Loss of each of these genes yielded a loss of function except Armcx1 and Gprasp2, whose loss enhanced repopulation. Gprasp2 and Armcx1 belong to the same family of G-protein Coupled Receptor Associated Sorting Proteins. 13 of these genes have never been implicated in HSC function. We confirmed in gene-deficient mice that Nfix and Foxa3 are required for HSC repopulation. P2ry14 has also been recently shown to regulate stress hematopoiesis, further validating the fidelity of our screen. Our Hits regulate many distinct processes that illuminate the complex orchestration required for stable repopulation: vesicular trafficking (Nbea, Cadsps2), receptor turnover (Armcx1, Gprasp2), adhesion and migration (Arhgef5, Gpr56, Emcn), the extracellular matrix (Fstl1 and Crispld1), epigenetics (Smarca2 and Foxa3), and stress (Nfix, P2ry14). The discovery of multiple genes that regulate vesicular trafficking, cell surface receptor turnover, and secretion of extracellular matrix components suggests that HSC must actively participate in conditioning the niche to facilitate stable repopulation and engraftment. Each Hit offers a window into the novel processes that regulate stable HSC engraftment into an ablated host.

MICROENVIRONMENTAL REMODELING AS A PARAMETER AND PROGNOSTIC FACTOR OF HETEROGENEOUS LEUKEMOGENESIS IN ACUTE MYELOID LEUKEMIA

Oh, Il-Hoan, Kim, Jin-A, Shim, Jae-Seung, Lee, Ga-Young, Yim, Hyeon Woo

Catholic High-Performance Cell Therapy Center, Catholic University of Korea, Medical School, Seoul, Korea

Acute myeloid leukemia (AML) is a heterogeneous disorder characterized by clonal proliferation of stem cell-like blasts in bone marrow (BM); however, their unique cellular interaction within the bone marrow microenvironment and functional significance remain unclear. Here, we assessed the BM microenvironment of AML patients and demonstrate that leukemia cells can induce transcriptional reprogramming of the normal mesenchymal stromal cells into the leukemic mesenchymal niche. The altered mesenchymal niche was characterized by loss of primitive subsets of MSCs and colony forming unit (CFU-F) in a manner dependent on clinical activity of leukemogenesis. The modified leukemic niche altered the expressions of cross-talk molecules (i.e., CXCL-12 and Jagged-1) in mesenchymal stromal cells to provide a distinct cross-talk between normal and leukemia cells, selectively suppressing normal primitive hematopoietic cells while supporting leukemogenesis and chemoresistance. Interestingly, self-renewal of mesenchymal cells were similarly lost in BMs of mice engrafted with MN-1 induced leukemia cells. Moreover, relative resistance of leukemic cells over normal HSCs under deteriorated niche was similarly observed when normal or MN-1 leukemic cells were transplanted into mice disrupted with Bis (BAG-3), where BM microenvironment is deteriorated with loss of CXCL-12 abundant reticular cells. These results demonstrate that leukemia-induced alteration of niche contribute to the clonal dominance of leukemic cells over normal hematopoietic cells in both animal and clinical leukemia conditions. Of note, when screened for mesenchymal alterations in AML patients, significant heterogeneity was observed in the alteration of mesenchymal stroma in bone marrow. Furthermore, each distinct pattern of stromal changes in leukemic bone marrow at initial diagnosis was associated with a

heterogeneous post-treatment clinical course with respect to the maintenance of complete remission for 5-8 years and early or late relapse. Thus, remodeling of mesenchymal niche by leukemia cells is an intrinsic self-reinforcing process of leukemogenesis that can be a parameter for the heterogeneity in the clinical course of leukemia and hence serve as a potential prognostic factor.

SATURDAY, 27 JUNE, 16:00 - 18:20

PLENARY VII: MAKING TISSUES AND ORGANS

PLENARY HALL A1

CELLULAR REPROGRAMMING APPROACHES FOR CARDIOVASCULAR DISEASE

Srivastava, Deepak

Gladstone Institutes, San Francisco, CA, USA

Heart disease is a leading cause of death in adults and children. We, and others, have described complex signaling, transcriptional and translational networks that guide early differentiation of cardiac progenitors and later morphogenetic events during cardiogenesis. We discovered networks of transcription factors and miRNAs function through intersecting positive and negative feedback loops to reinforce differentiation and proliferation decisions. By leveraging these networks, we have reprogrammed disease-specific human cells in order to model human heart disease in patients carrying mutations in cardiac developmental genes. Deep epigenetic and transcriptome analyses revealed perturbations in pivotal gene networks that contribute to disease that could be corrected by altering dosage of nodal points in the network. We also utilized a combination of major cardiac regulatory factors to induce direct reprogramming of cardiac fibroblasts into cardiomyocyte-like cells with global gene expression and electrical activity similar to cardiomyocytes. The in vivo efficiency of reprogramming into cells that are more fully reprogrammed was greater than in vitro and resulted in improved cardiac function after injury. We are exploring the molecular mechanisms underlying the progressive reprogramming process through the study of DNA-binding of reprogramming factors and the associated epigenetic and transcriptional changes. We have also identified a unique cocktail of transcription factors and small molecules that reprogram human fibroblasts into cardiomyocyte-like cells and are testing these in large animals. Knowledge regarding the early steps of cardiac differentiation in vivo has led to effective strategies to generate necessary cardiac cell types for disease-modeling and regenerative approaches, and may lead to new strategies for human heart disease.

LOCAL AND SYSTEMIC REGULATORS OF AGING PHENOTYPES IN MAMMALIAN TISSUES

Wagers, Amy

Joslin Diabetes Center, Harvard University, Cambridge, MA, USA

Effective functioning of the body's tissues and organs depends upon innate regenerative processes that maintain proper cell numbers during homeostasis and replace damaged cells after injury. In many tissues, regenerative potential is determined by the presence and functionality of dedicated populations of stem and progenitor cells, which respond to exogenous cues to produce replacement cells when needed. Understanding how these unspecialized precursors are maintained and regulated is essential for understanding the fundamental biology of tissues. In addition, this knowledge has practical implications, as stem cell regenerative potential can be exploited therapeutically by transplantation to replenish the stem cell pool or by pharmacological manipulation to boost the repair activity of cells already present in the tissue. Ongoing work in my laboratory focuses on defining how changes in stem cell activity impact tissue regeneration throughout life, and identifying physiological and pathological signals that modulate stem cell function in an age-dependent manner. Our recent data using parabiosis and transplantation models suggests that the circulatory system serves as a major source of such signals. In particular, exposure of aged tissues, including skeletal muscle, cardiac muscle and neural cells, to a "youthful" systemic environment appears to reverse many indicators of age-related pathology and restores robust regeneration following injury. Our studies further point to discrete metabolic, inflammatory and hormonal mediators as key effectors of this systemic rejuvenation response. Taken together, these studies highlight novel mechanisms by which stem cell activity may be coordinated with the physiological demands of the tissues these cells support, and suggest new strategies for therapeutic intervention to enhance endogenous repair activity or improve the efficacy of transplantation-based cell replacement.

RETINAL CELL THERAPY USING IPS CELLS

Takahashi, Masayo

RIKEN Center for Developmental Biology, Kobe, Japan

The first in man application of iPS-derived cells started in September 2014 targeted the incurable retinal disease called age-related macular degeneration (AMD). AMD is caused by the senescence of retinal pigment epithelium (RPE) that affects the center of the retina (macula). It is the major cause of visual impairment in advanced countries. We aim to develop a treatment that replaces damaged RPE with normal, young RPE made from a patients' own iPS cells to rescue photoreceptors in the neural retina. In the clinical study, we judged the outcome 1 year after the surgery. Grafted cell sheets went through various tests and tumorigenicity test using immunodeficient mice to check the safety. Primary endpoint is the safety and mainly the tumor formation and immune rejection will be checked. One of the issues of regenerative medicine is that expectation becomes hype. In this clinical study the efficacy such as retinal sensitivity increase is a secondary endpoint. Hype comes from the way of thinking that cure is the only way of solution. In retinal regenerative medicine, the visual function might stay low even after the successful treatment, so that the regenerative medicine will be accomplished following rehabilitation (low vision care). In Japan pharmaceutical law has been changed and a new chapter for regenerative medicine was generated. This is the first law specific for regenerative medicine in the world. It was determined with the co-operation of ministry and academia and its success will depend on the co-operation with ministry and academia. I will discuss about the future regenerative medicine in Japan.

Keynote Address

NEW MATERIALS AND TISSUE ENGINEERING

Langer, Robert

Massachusetts Institute of Technology, Cambridge, MA, USA

Approaches involving the synthesis and application of polymers to serve as implantable scaffolds for mammalian cells to create new tissues and organs are being studied. This talk will discuss the design of new materials in particular super biocompatible synthetic polymers, shape memory degradable polymers, novel rubbery polymers and other biomaterials. We will also examine the use of materials coupled with human embryonic stem cells or other cells, and the application of these approaches to the creation of new tissues. This approach has been used to create a variety of tissues such as skin, nerves, blood vessels, cartilage and other tissues in animals and humans.

THURSDAY, 25 JUNE

Irvine Scientific

Room A2
11:30 -12:30

OPTIMIZING EX VIVO EXPANSION, DIFFERENTIATION AND DMSO-FREE CRYOPRESERVATION OF MESENCHYMAL STEM/ STROMALCELLS

Cyndi Kwan, Ph.D.,
Senior Scientist II, R&D Department, Irvine Scientific
Jessie H.-T. Ni, Ph.D.,
Chief Scientific Officer, R&D Department, Irvine Scientific

Mesenchymal stem/ stromal cells (MSCs) have been studied in recent years as a potential therapeutic tool for clinical applications in tissue engineering and regenerative medicine. These cells have the capacity to differentiate into cells within the mesodermal tissue lineage, including adipose, cartilage, and bone. Beyond their differentiation potential, MSCs also display immunosuppressive properties, which have generated great interests in their ability to suppress local inflammation and tissue damage from a variety of inflammatory autoimmune diseases. A key component in supporting these applications and approaches involves the successful ex vivo expansion of MSCs to relevant therapeutic doses while retaining functional properties. In this workshop, we will review how MSC cultures have evolved in recent decades and focus on our newest products, that have been developed to improve MSC ex vivo expansion by reducing variability from animal-derived components. We will present data on our latest xeno-free expansion medium and our DMSO-free cryopreservation solution. In addition, we will also highlight key steps that can be implemented to ensure optimized scalability from bench to bedside applications.

Lonza

Room A4
11:30 -12:30

SMART TECHNOLOGIES FOR ADVANCING STEM CELL RESEARCH AND DISCOVERIES

Minh Hong Ph.D.,
Lonza Stem Cells Marketing Manager, Moderator
Pollyanna Goh, Ph.D.,
Post-Doctoral Research Associate, Centre for Genomics and Child Health, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London
Behnam Ahamadian, Ph.D.,
Lonza Senior Manager, Scientific PSC Programs
Richard L. Gieseck III, Ph.D. Candidate,
NIH-Cambridge Scholar, Wellcome Trust-Medical Research Council Stem Cell Institute, Anne McLaren Laboratory for Regenerative Medicine, Department of Surgery, University of Cambridge

To fully realize the potentials of human induced pluripotent stem cells (hiPSC) for research and clinical applications, Lonza has developed reliable cell culture systems and live imaging technologies to generate, expand, and monitor hiPSC discoveries. Presenting will be three examples from innovative researchers supported by Lonza technologies. Dr. Pollyanna Goh, Queen Mary University of London, will describe hiPSC generation from infant Down Syndrome patients. These hiPSCs can be reprogrammed from small amounts of blood utilizing Lonza L7™. Next, Dr. Behnam Ahamadian, Lonza Senior Manager, will present Lonza L7™ technology for manufacturing of hiPSCs from peripheral blood using non-integrating, defined, cGMP compatible, and xeno-free conditions employing CytoSMART™ technology for live monitoring of hiPSC cultures. We will conclude with Richard L. Gieseck, NIH-Cambridge Scholar and University of Cambridge, presenting a novel high-throughput culture method using pluripotent stem cell derived hepatocytes (PSC-Heps) cultured in 3D using the Lonza RAFT™ culture system. These PSC-Heps demonstrate a significant improvement in hepatocyte maturation markers, functional longevity, and drug metabolism.

Fluidigm Corporation

Room A6
11:30 -12:30

BRIDGING THE GAP BETWEEN CELL BIOLOGY, GENOMICS, AND SINGLE-CELL ANALYSIS

Adam Gracze, PhD.,
University of North Carolina, Chapel Hill
Candia Brown,
Fluidigm

We strive to partner with customers to pursue truth in the complex biological world. Leveraging our core technologies, microfluidics and mass cytometry, we provide simplified and elegant workflows for single-cell approaches to genomics and proteomics applications. Our C1™ and Biomark™ systems enabled the field of single-cell genomics. Partner with us on your quest to characterize and understand individual cell function. Engage with us at fluidigm.com.

Biological Industries
Victoria Hall
11:30 -12:30

AN INNOVATIVE SERUM-FREE, XENO-FREE, CULTURE SYSTEM FOR EXPANSION AND DIFFERENTIATION OF CLINICAL GRADE HUMAN MESENCHYMAL STEM CELLS

David Fiorentini,
Biological Industries

Human mesenchymal stem cells (hMSCs) are multipotent adult stem cells that can be isolated from variety of human tissues such as bone marrow, adipose, placenta, cord blood and Wharton jelly. hMSC have the ability to differentiate into bone, cartilage and fat cells and are the subject of many clinical trials for a range of regenerative and inflammatory diseases.

In most clinical applications hMSC are expanded in vitro before use. The quality of the culture media and auxiliary solutions is particularly crucial with regard to therapeutic applications, since hMSC properties can be significantly affected by medium components and culture conditions. The presentation addressed the development of an innovative xeno-free culture system, comprising of MSC NutriStem® XF culture medium and the required auxiliary solutions to support isolation, expansion and cryopreservation of clinical grade hMSC. In addition, novel serum-free, xeno-free differentiation media that efficiently generate mature adipocytes, osteoblasts and chondrocytes using hMSC from variety of sources.

Stemgent, part of the ReproCELL Group
Room K1
11:30 -12:30

DERIVATION OF CLINICALLY RELEVANT IPS CELL LINES FROM HUMAN BLOOD-DERIVED ENDOTHELIAL PROGENITOR CELLS USING SELF-REPLICATIVE RNA

Sarah Eminli-Meissner, Ph.D.,
Stemgent

Induced pluripotent stem (iPS) cells provides a unique, potentially limitless source of starting cells for regenerative medicine research and application. Ultimately the translation of iPS cell technology to the clinic for autologous cellular therapy with differentiated cell types will require comprehensive GMP-compatible workflows that are inclusive of integration-free derivation of iPS cells from easily obtainable patient-specific cell sources such as human blood.

We will present novel data demonstrating the unique application of microRNA and self-replicative RNA (srRNA) for the reproducible cellular reprogramming of human blood-outgrowth endothelial progenitor cells (EPCs) lines derived from human peripheral blood and cord blood. The simple two transfection no-split protocol is carried out on extracellular matrix and does not require any conditioned medium during the reprogramming process. Derived integration-free EPC-iPS cell lines exhibit unique genetic stability, making them an exceptional choice for applications requiring clinical grade iPS cells. Additional data will be presented demonstrating the applicability of this novel reprogramming methodology to other cell types, including adult human fibroblasts.

FRIDAY, 26 JUNE

Thermo Fisher Scientific
Room A2
11:30 -12:00

RAPID AND QUANTITATIVE ASSESSMENT OF HUMAN PLURIPOTENT CELL DIFFERENTIATION POTENTIAL

Alexander Meissner, Ph.D.,
Associate Professor, Harvard Stem Cell Institute

Human pluripotent stem cells (PSCs) can give rise to all cell types in the body and therefore hold enormous potential for tissue engineering and disease modeling. However, variation between PSC lines and culture conditions is a practical concern for both basic research as well as clinical applications and requires efficient and accurate ways of screening lines for their differentiation potential. Current characterization generally includes immunofluorescence staining for selected markers, in vitro differentiation and teratoma formation. We have previously shown that gene expression signatures can provide informative results that correlate well with established measures of differentiation efficiency. Here we describe a new qPCR-based assay and computational analysis that enables a faster, more quantitative assessment. We provide an in-depth characterization of the new signature panel through random and directed differentiation experiments as well as a comparison to the teratoma assay. We also demonstrate the utility of this platform for screening

small molecules, genetic perturbations and assessing culture conditions, which can be easily extended to other cell types and lineages.

Thermo Fisher Scientific
Room A2
12:00 -12:30

DEVELOPING A PATIENT-DERIVED CARDIAC DISEASE MODELING PLATFORM TO ACCELERATE EARLY STAGE DRUG DISCOVERY FOR HEART DISEASE

Andrew Lee, Ph.D,
Co-founder and Chief Scientific Officer, Stem Cell Theranostics, Inc.

Cardiovascular disease is the leading cause of morbidity and mortality worldwide. While there have been substantial improvements in healthcare options for hypertension and hypercholesterolemia, there are few effective therapies for acquired or genetic heart disease. The development of novel therapies for heart disease has been hampered by high failure rates due to the lack of pre-clinical models that predict clinical efficacy and toxicity. At Stem Cell Theranostics, we have developed a discovery platform that enables drug testing in patient-derived heart disease models. In this presentation we will describe a disease modeling case study using donor cells that harbor genetic forms of hypertrophic cardiomyopathy (HCM). After expansion of fibroblasts or CD71+ erythroid progenitor cells, induced pluripotent stem cells (iPSCs) were generated using the CytoTune®-iPS 2.0 Reprogramming Kit from Thermo Fisher Scientific and characterized for self renewal markers and karyotypic integrity. Cardiomyocytes were prepared using the Thermo Fisher Scientific's Gibco® PSC Cardiomyocyte Differentiation Kit. Finally, the cells were analyzed for presentation of disease phenotypes using a combination of traditional and phenotypic assays.

Ajinomoto
Room A4
11:30 -12:30

CULTURE SYSTEMS FOR THE SAFE AMPLIFICATION AND IN VITRO ORGANOGENESIS OF HUMAN PLURIPOTENT CELLS

(Chair) Professor Tariq Enver, PhD,
University College London Cancer Institute
Professor Peter Andrews, PhD,
The University of Sheffield, Center for Stem Cell Biology, Biomedical Science
Associate Professor Takanori Takebe MD,
Department of Regenerative Medicine, Yokohama City University Graduate School of Medicine

Realizing the full potential of human pluripotent cells in regenerative medicine requires in vitro systems that (i) afford expansion of genetically uncompromised cells and (ii) support the differentiation of pluripotent cells into functional effector cells in the context of organogenesis.

In this symposium, Peter Andrews from the University of Sheffield, UK, will explore how pluripotent cells become adapted to culture through in vitro selection of variant genotypes and how the mutations involved affect cell fate choices including self-renewal, differentiation, migration and survival. The development of culture conditions that maintain pluripotent cells in a pristine genetic state is a prerequisite for the safe generation of therapeutic cells. Lineage specified cells are key to therapy but increasing attention is focusing on their integration into in vitro generated organs.

In respect of this, Takanori Takebe, from the Yokohama City University Graduate School of Medicine Japan, will present recent findings on the development of 4-D culture systems to develop organ buds from induced pluripotent cells for therapeutic purposes.

STEMCELL Technologies
Room A6
11:30 -12:00

METHODS AND CULTURE REAGENTS TO MAINTAIN A SPECTRUM OF HUMAN PLURIPOTENT STEM CELL STATES FROM NAÏVE-LIKE TO PRIMED

Wing Chang, *Scientist*

Recent advances have shown that culture conditions can shift human pluripotent stem cells (hPSCs) between different pluripotent states: from ground or naïve-like to primed states. This presentation will describe the application of culture conditions (RSeT™ product line) to reset primed hPSCs to a naïve-like state and examine their distinct characteristics. The tutorial will highlight STEMCELL Technologies' integrated workflow for maintaining multiple pluripotent stem cell states and their subsequent downstream differentiation under defined culture conditions.

STEMCELL Technologies
Room A6
12:00 -12:30

INTEGRATED WORKFLOW FOR REPRODUCIBLY MODELING NEUROLOGICAL DISEASE USING NEURONAL SUBTYPES AND ASTROCYTES DERIVED

FROM HUMAN PLURIPOTENT STEM CELLS

Vivian Lee,
Senior Scientist
Xianmin Zeng,
XCell Science Inc. and Buck Institute

Mature neural cell types derived from human pluripotent stem cells (hPSCs) are valuable tools for modeling human nervous system development and neurodegenerative disorders. Reliable and reproducible generation of hPSC-derived neural cells, including neuronal and glial subtypes, requires robust protocols, rigorously optimized and standardized reagents. Here we describe a comprehensive, integrated workflow that will enable researchers to efficiently and reproducibly generate neuronal subtypes and astrocytes from normal and diseased hPSCs.

Corning
Victoria Hall
11:30 -12:30

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

Paula Flaherty,
Technology Manager
Deepa Saxena, PhD
Senior Development Scientist

Current stem cell applications make them critical for basic and clinical research. Required is the ability to expand undifferentiated cells and differentiate into specific cell types with homogeneity. We will discuss robust, easy to use, reproducible, scalable systems, including feeder-free and novel animal-free platforms for pluripotent and adult stem cell culture and differentiation, including Matrigel Matrix, pre-coated recombinant Laminin521, Fibronectin/ Collagen-I / Vitronectin peptide mimetic cultureware, hMSC expansion media, scalable vessel platforms and closed systems.

Bio-Techne
Room K1
11:30 -12:30

STANDARDIZED STEM CELL DIFFERENTIATION: FROM KITS TO INDIVIDUALIZED PROTOCOLS

Joy Aho,
Bio-Techne

Differentiated stem cell populations are increasingly used in regenerative medicine and toxicology screening. These studies require development of standardized differentiation protocols that minimize cross-experiment variability. Here we present tools and techniques to standardize stem cell differentiation for both novice and expert researchers, including various R&D Systems™ reagents and Tocris™ small molecules that simplify the development of consistent individualized protocols. We will also discuss ELISAs, Luminex® assays, and antibody-based arrays for stem cell analysis.

SATURDAY, 27 JUNE

BD Biosciences
Room A2
12:00 -12:30

FLOW CYTOMETRIC APPLICATIONS FOR DETERMINING THE QUALITY OF STEM CELL CULTURES

Nil Emre,
BD Biosciences

Heterogeneous stem cell populations need to be readily characterized and quantified to fully realize their utility. Utilizing pluripotent stem cells, MSCs, and neural, cardiac, and endodermal cells differentiated from hESCs as examples, this tutorial will discuss:

- The use of cell surface and intracellular flow cytometry to address cellular heterogeneity
- Effective stem cell sorting techniques to improve purity
- Novel fluorochromes to facilitate flow cytometry and immunofluorescence panel design

---

Merck Millipore
Room A4
12:00 -12:30

FROM RESEARCH TO GMP MANUFACTURING: A GUIDE TO TRANSLATING YOUR PROCESS

Julie Murrell,
Stem Cell Bioprocessing Group, EMD Millipore

When making the translation from research to the clinic, demonstrating efficacy is only the first step to a successful product. Long-term commercial viability requires early process scalability coupled with high quality ancillary materials that offer a safe and sustainable supply.

We will present a model for translating a human bone marrow MSC flask based process to a scalable manufacturing process including media, reagents, bioreactor expansion, and harvest. Maintaining key quality attributes at all scales is a focus along with assays to consider for demonstrating equivalence between processes.

A well thought out strategy for GMP processing requirements from phase I trials to commercialization is essential in successfully translating a potential therapy to a commercial product.

Miltenyi Biotech
Room A6
12:00 -12:30

TOWARDS CLINICAL WORKFLOWS FOR GENERATING IPSCS AND FUNCTIONAL DERIVATIVES

Dr. Sebastian Knöbel,
Miltenyi Biotec GmbH

We developed workflows for standardized preparations of primary fibroblasts, integration-free reprogramming, maintenance of pluripotency, and modulation of PSCs using modified mRNAs. For successful translation, regulatory requirements call for highest quality reagents, such as GMP media, cytokines, and antibodies. Likewise, cell product optimization through cell sorting and automation play pivotal roles in realizing PSC-derived cellular therapies. Therefore, we explore solutions for iPS-derived cellular therapy candidates, such as dopaminergic progenitors.

Union Biometrica
Victoria Hall
12:00 -12:30

LARGE PARTICLE FLOW CYTOMETRY FOR CELLS AND CELL CLUSTERS IN STEM CELL RESEARCH

Rock Pulak, Ph.D.,
Union Biometrica, Inc.

Cells growing in clusters communicate with each other and behave differently than cells grown as monolayers or in suspension. These interactions are likely to be important for proper function. Union Biometrica Large Particle Flow Cytometers automate the analysis, sorting and dispensing of objects too big (10-1500 microns) or too fragile for traditional cytometers including those studied by stem cell researchers such as embryoid bodies, neurospheres and other spheroids and organoids.

Merck Millipore
Room K1
12:00 -12:30

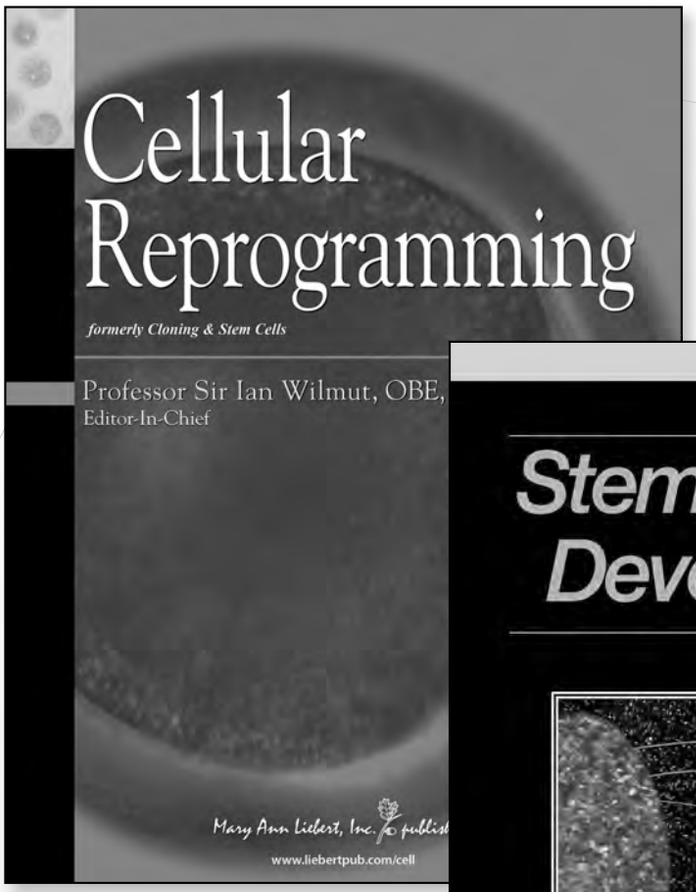
LIVE CELL ANALYSIS OF CANCER STEM CELL HETEROGENEITY BASED ON INTRACELLULAR BIOMARKERS AND FLUORESCENT LABELLING OF ALDHPOS CELLS

Vi Chu, Ph.D.,
Manager II, R&D, Assays & Platform Technologies, EMD Millipore
Victor Koong,
Product Manager, EMD Millipore

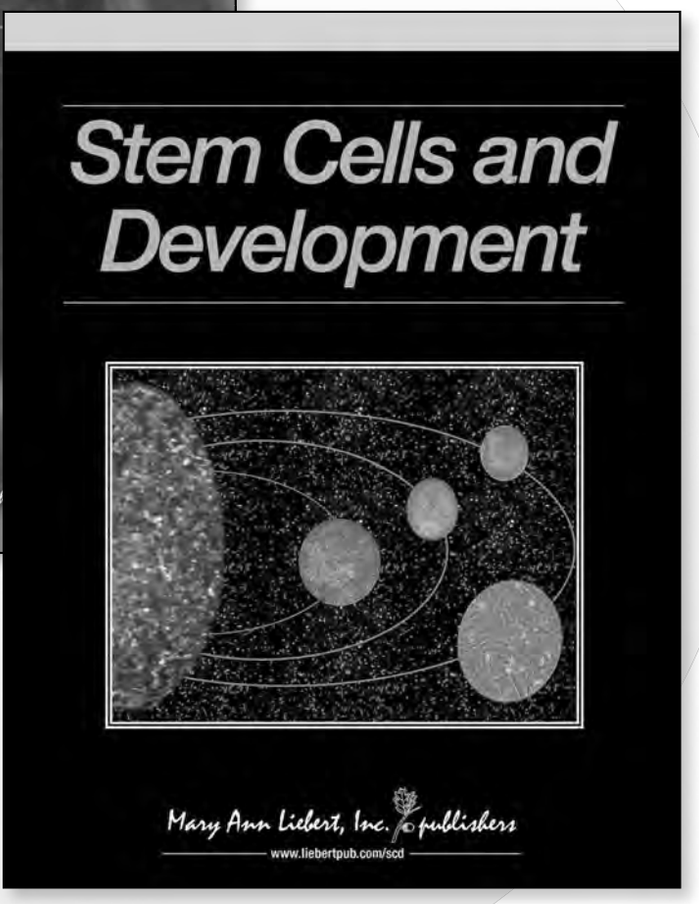
Phenotypic and functional heterogeneity are common among the cells within a tumor. Self-renewing cancer stem cells (CSC) are thought to drive tumor growth and recurrence, having important implications for cancer therapy. While there are many methods for detecting specific markers within the cells of interest such as antibodies or gene expression analysis, they are traditionally end point assays as they require cell destruction by permeabilization or lysis. We will show two live cell analysis tools that can be applied to the study of cancer stem cells. SmartFlare™ Probes enable live cell characterization utilizing a probe-based method to detect specific RNA at the single cell level. Additionally, our AldeRed 588A Reagent can be used to characterize cancer and cancer stem cell functionality based upon a red-shifted fluorescent substrate for the detection of aldehyde dehydrogenase (ALDH) activity. Since both technologies are based on fluorescence, the live cells can potentially be sorted by FACS and effectively enriched for further culture and downstream functional assays.

Premier Journals in Stem Cell and Cellular Reprogramming Research from

Mary Ann Liebert, Inc. publishers



Editor-in-Chief:
Professor Sir Ian Wilmut, OBE, FRS, FRSE



Editor-in-Chief:
Graham C. Parker, PhD

Stay connected to world-class research that is transforming the field
Visit **www.liebertpub.com** for more information

ISSCR
INTERNATIONAL SOCIETY
FOR STEM CELL RESEARCH

co-sponsored by:
CIRM
CALIFORNIA'S STEM CELL AGENCY

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

THE GLOBAL
STEM CELL EVENT

TRANSLATE
Promise TO **Progress**

Join us in San Francisco for
ISSCR 2016 to translate
Promise to **Progress**

WWW.ISSCR2016.ORG

CONNECT BEYOND THE ANNUAL MEETING

EXHIBITION HALL

LEARN, SHARE AND DISCOVER IN THE EXHIBITION HALL

Tools, services, equipment and publications focused on supporting your scientific efforts await you in the Exhibition Hall (Stockholmsmässan, Hall B). The ISSCR Exhibition Hall offers attendees the ideal setting and opportunity to discover how our exhibitors can enhance and support you and your research. Continue scientific session conversations during coffee breaks, participate in Meet-Up Hub sessions specific to focused topics, and browse over 1,750 posters.

The ISSCR 2015 Exhibition Hall features over 100 leading global suppliers and vendors focused on supporting stem cell science.

EXHIBITION HALL HOURS

Wednesday, 24 June, 2015 | 15:15 – 20:30
Thursday, 25 June, 2015 | 11:00 – 20:00
Friday, 26 June, 2015 | 11:00 – 20:00
Saturday, 27 June, 2015 | 11:00 – 16:00

NOTE: The Exhibition Hall is closed mornings. Poster presenters must hang their posters during scheduled poster set-up hours.

BREAKS AND POSTER RECEPTIONS

Enjoy refreshment breaks and poster presentation receptions in the Stockholmsmässan.

MORNING COFFEE AND TEA BREAKS IN THE PLENARY HALL FOYER

Thursday, 25 June - Saturday, 27 June, 2015 | 8:15 – 9:00

AFTERNOON REFRESHMENT BREAKS IN THE EXHIBITION HALL

Wednesday, 24 June, 2015 | 15:15 – 16:00
Thursday, 25 June, 2015 | 15:10 – 16:00
Friday, 26 June, 2015 | 15:10 – 16:00
Saturday, 27 June, 2015 | 15:10 – 16:00

POSTER RECEPTIONS IN THE EXHIBITION HALL

Wednesday, 24 June, 2015 | 18:05 – 20:30
Supported by WIRM
Thursday, 25 June, 2015 | 18:00 – 20:00
Supported by Lonza
Friday, 26 June, 2015 | 18:00 – 20:00
Presented by the 2015 and 2016 ISSCR International Symposia

ISSCR CENTRAL

Meet up with fellow ISSCR members at ISSCR Central. Make this your central meeting location while you collaborate with colleagues, view your email, and establish your meeting agenda. Learn all that membership in the ISSCR delivers at ISSCR Central:

- ISSCR Connect webinars
- ISSCR member benefits
- THE Stem Cell Podcast recordings, ISSCR's official podcast
- Stem Cell Report's commemorative issue
- ISSCR's Twitter wall following the latest posts on #ISSCR2015
- The ISSCR Job Board

MEET UP HUBS

Attend a Meet-Up session at one of the two Meet-up Hubs located in the Exhibition Hall (Stockholmsmässan, Hall B) to network with and learn from peers who share your particular passion. Helping researchers connect and share their work is the core of the ISSCR mission. See page 26 for descriptions of some of the scheduled Meet-Ups.

POSTER PRESENTATIONS

All poster presentations will take place in the Exhibition Hall (Stockholmsmässan, Hall B). Kindly note that posters left behind will be discarded the day after the scheduled presentation.

POSTER PRESENTATIONS

Wednesday, 24 June, 2015 | 18:30 – 20:30
Thursday, 25 June, 2015 | 18:00 – 20:00
Friday, 26 June, 2015 | 18:00 – 20:00

PLEASE NOTE:
ODD numbered poster boards are presented in the first hour.
EVEN numbered poster boards are presented in the second hour.

POSTER SET-UP

Wednesday, 24 June, 2015 | 15:15 – 18:30
Thursday, 25 June, 2015 | 11:15 – 13:00
Friday, 26 June, 2015 | 11:15 – 13:00

POSTER HELP DESK HOURS

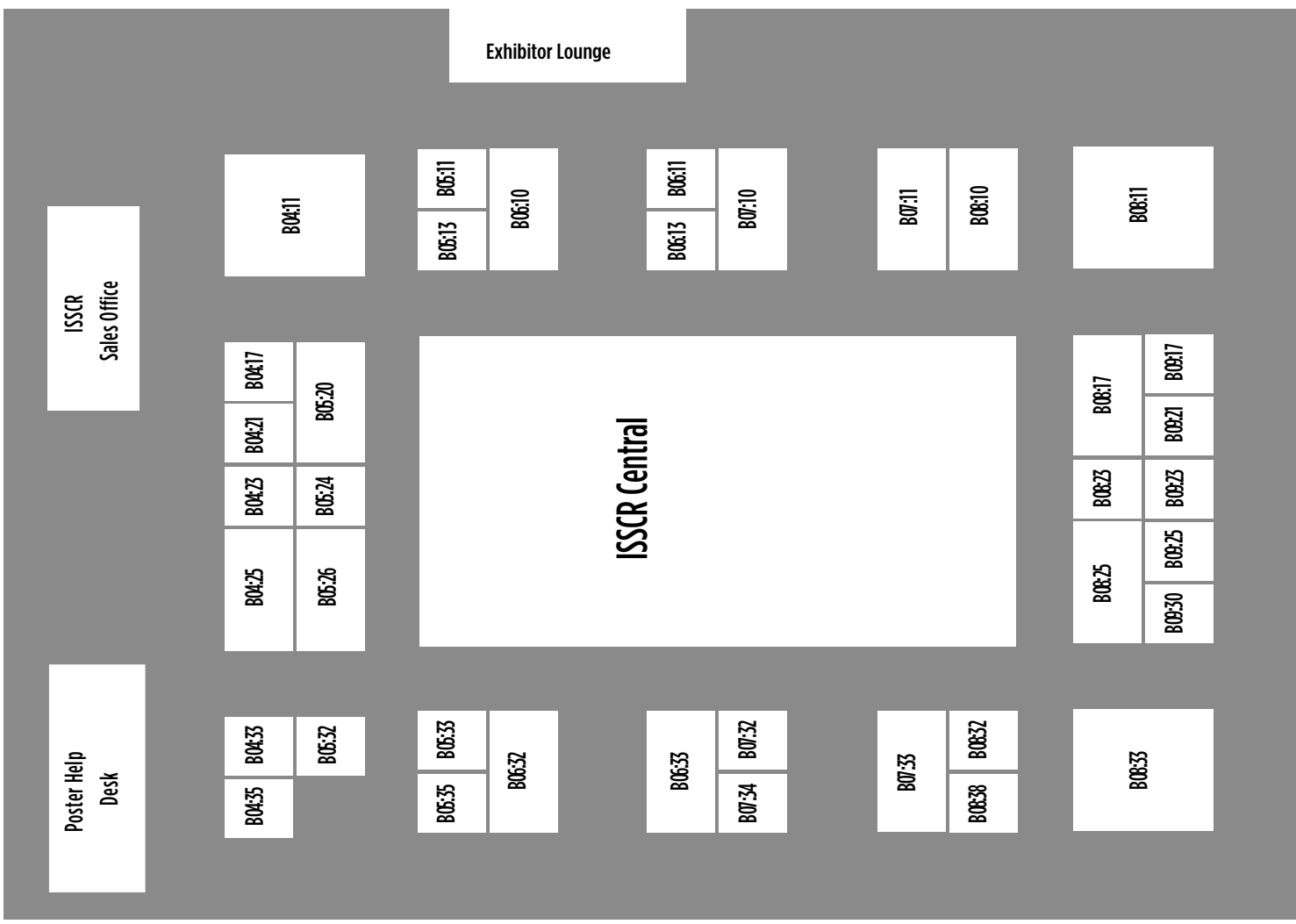
Wednesday, 24 June, 2015 | 15:15 – 20:30
Thursday, 25 June, 2015 | 11:15 – 13:00 and 15:15 – 20:30
Friday, 26 June, 2015 | 11:15 – 13:00 and 15:15 – 20:30

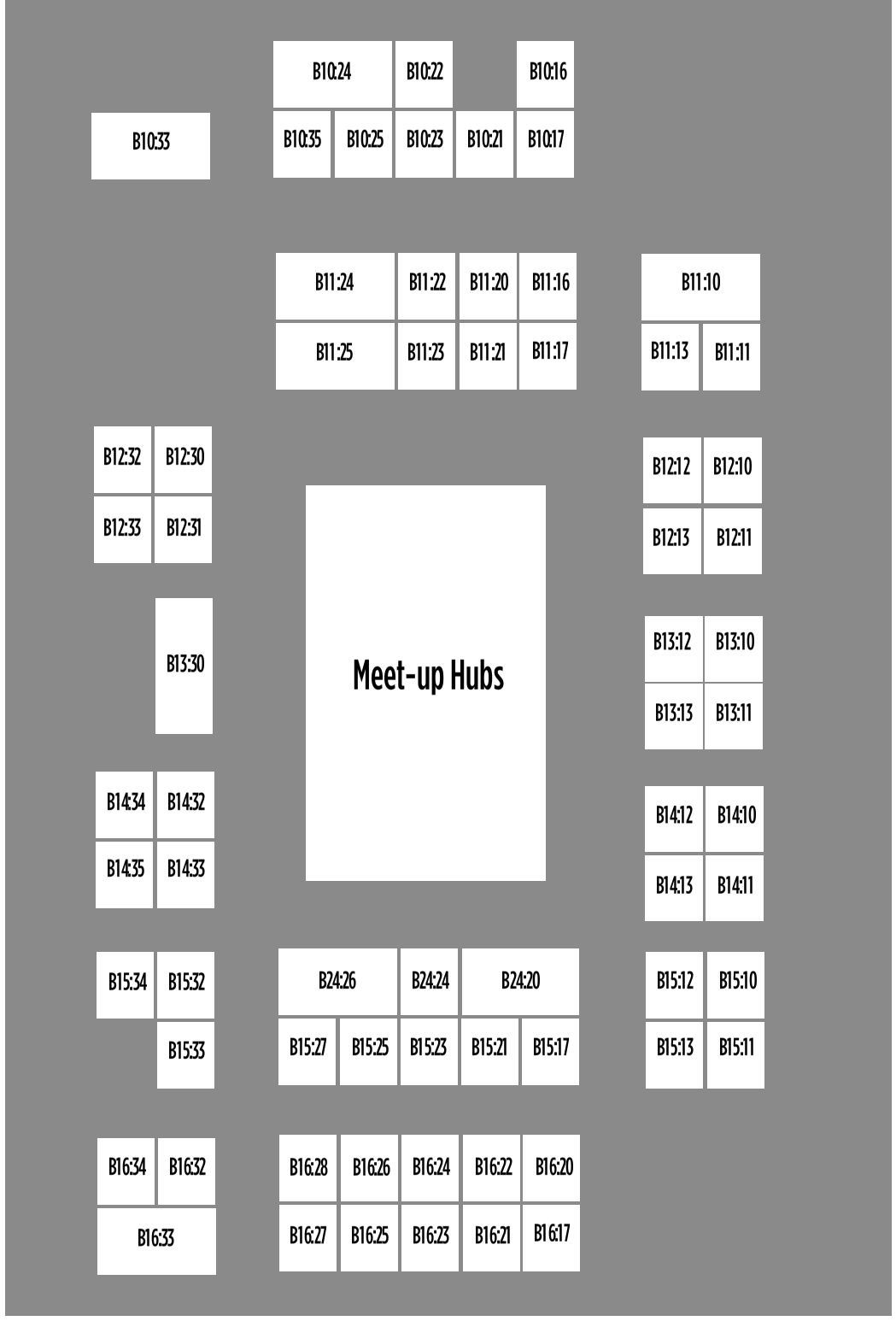
POSTER ABSTRACTS

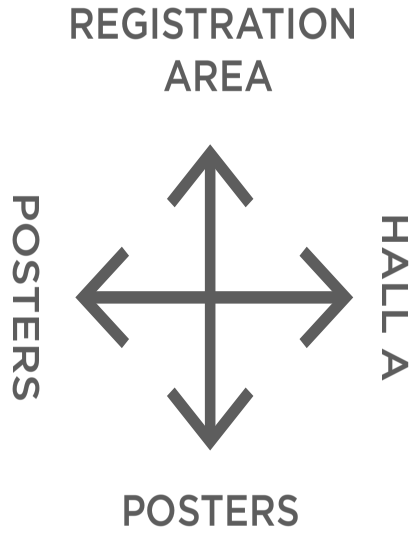
ISSCR provides poster abstracts electronically in three ways:
1. Downloadable Poster Abstract book
2. ISSCR online Program Planner
3. ISSCR 2015 Mobile App

To conserve paper, a printed poster abstract book has not been created. Stop into the Poster Help Desk or ISSCR Central in the Exhibition Hall to learn more.

EXHIBITION HALL MAP




B10:24
B10:22
B10:16
B10:33
B10:35
B10:25
B10:23
B10:21
B10:17
B11:24
B11:22
B11:20
B11:16
B11:10
B11:25
B11:23
B11:21
B11:17
B11:13
B11:11
B12:32
B12:30
B12:12
B12:10
B12:33
B12:31
B12:13
B12:11
Meet-up Hubs
B13:30
B13:12
B13:10
B13:13
B13:11
B14:34
B14:32
B14:12
B14:10
B14:35
B14:33
B14:13
B14:11
B15:34
B15:32
B24:26
B24:24
B24:20
B15:12
B15:10
B15:33
B15:27
B15:25
B15:23
B15:21
B15:17
B15:13
B15:11
B16:34
B16:32
B16:28
B16:26
B16:24
B16:22
B16:20
B16:33
B16:27
B16:25
B16:23
B16:21
B16:17


REGISTRATION AREA
POSTERS
HALL A
POSTERS

EXHIBITOR LISTING (by Company Name)

COMPANY NAME	STAND NUMBER
3H Biomedical AB	B15:23
Abcam Inc.	B24:20
ABCell Bio	B16:17
Advanced Cell Diagnostics	B15:13
Affymetrix	B16:27
Ajinomoto	B05:35
AllCells, LLC	B12:33
Alpha MED Scientific	B12:31
ALS Automated Lab Solutions GmbH	B15:34
AMSBIO	B12:32
Atlas Antibodies	B15:11
Axiogenesis AG	B16:20
Axol Bioscience Ltd.	B14:35
BD Biosciences	B05:20
Bio-Techne	B11:25
BioCision, LLC	B15:12
BIOINVISION	B14:33
BioLamina	B07:11
BioLegend	B14:34
Biological Industries	B07:32 and B07:33
BioMediTech - Institute of Biosciences and Medical Technology	B15:27
BioMedTech Laboratories	B05:11
BioNavis Ltd	B14:13
BioSpherix, Ltd.	B04:23
BTX Harvard Bioscience	B06:13
Cell Press	B06:10
Cell Signaling Technology	B12:12
Cell Therapy Catapult	B11:23

COMPANY NAME	STAND NUMBER
Cellara	B16:26
CellGenix GmbH	B04:17
Cellular Dynamics International	B06:11
Center for iPS Cell Research and Application (CiRA)	B05:32
ChemoMetec A/S	B10:35
Cline Scientific AB	B13:30
The Company of Biologists	B07:34
Corning	B07:10
DefiniGEN Ltd.	B04:33
Developmental Dynamics	B11:13
Don Whitley Scientific Ltd	B15:33
Elsevier	B12:10
Enzo Life Sciences	B12:13
Eppendorf	B11:22
ESI BIO - A Division of BioTime, Inc.	B11:24
FedEx Services	B11:20
Fluidigm Corporation	B08:11
GE Healthcare Life Sciences	B16:21
Genea Biocells	B11:10
Gradientech AB	B14:12
Hamilton Thorne, Inc.	B05:24
Humanzyme, Inc.	B15:17
Irvine Scientific	B08:10
LGC - ATCC	B16:33
Lonza	B04:11
Mabtech	B08:32
Macopharma	B16:32

EXHIBITOR LISTING (by Company Name)

COMPANY NAME	STAND NUMBER
Medeina Cell Technologies	B16:23
Merck Millipore	B12:30
Mill Creek Life Sciences	B13:10
Miltenyi Biotec GmbH	B08:33
Multi Channel Systems	B10:23
NanoEnTek Inc.	B09:30
NanoString Technologies	B10:22
The NYSCF Research Institute	B09:21
Nikon Instruments	B11:17
Nippi, Incorporated	B08:38
Nipro Corporation	B14:32
Nissan Chemical Industries Ltd.	B14:11
Olympus Europa SE & Co. KG	B09:23
Orla Protein Technologies LTD	B15:10
Oxford Optronix Ltd	B16:24
PBS - DYNC	B15:21
PeproTech Inc.	B05:26
PromoCell GmbH	B11:21
Proteintech Europe	B04:21
RI Life Sciences	B11:16
RoosterBio Inc.	B16:34
RUCDR Infinite Biologics	B04:35
SERVA Electrophoresis GmbH	B12:11
Sino Biological	B14:10
SONIDEL Limited	B10:17
Sony Biotechnology Inc	B10:24
Springer	B24:26
StemBioSys Inc.	B24:24

COMPANY NAME	STAND NUMBER
STEMCELL Technologies	B08:25
StemCulture	B09:25
Stemgent	B08:17
Stemiotics, Inc.	B10:16
stemTrak	B16:22
Stockholm – Center of Excellence Stem Cells	B13:12
Takara Clontech	B10:33
TAP Biosystems	B16:28
Terumo BCT	B13:13
Thermo Fisher Scientific	B06:32 and B06:33
Transposagen Biopharmaceuticals	B04:25
Trinova Biochem	B05:13
UK Stem Cell Bank	B13:11
Union Biometrica, Inc.	B05:33
UPM-Kymmene Corporation	B11:11
Wako Pure Chemicals Industries, Ltd.	B15:32
WiCell	B08:23
Wiley	B15:25
World Courier	B10:25
Wuhan Healthgen Biotechnology Co., Ltd.	B09:17
ZEISS	B10:21

EXHIBITOR LISTING (by Stand Number)

COMPANY NAME	STAND NUMBER
Lonza	B04:11
CellGenix GmbH	B04:17
Proteintech Europe	B04:21
BioSpherix, Ltd.	B04:23
Transposagen Biopharmaceuticals	B04:25
DefiniGEN Ltd.	B04:33
RUCDR Infinite Biologics	B04:35
BioMedTech Laboratories	B05:11
Trinova Biochem	B05:13
BD Biosciences	B05:20
Hamilton Thorne, Inc.	B05:24
PeproTech Inc.	B05:26
Center for iPS Cell Research and Application (CiRA)	B05:32
Union Biometrica, Inc.	B05:33
Ajinomoto	B05:35
Cell Press	B06:10
Cellular Dynamics International	B06:11
BTX Harvard Bioscience	B06:13
Thermo Fisher Scientific	B06:32 and B06:33
Corning	B07:10
BioLamina	B07:11
Biological Industries	B07:32 and B07:33
The Company of Biologists	B07:34
Irvine Scientific	B08:10
Fluidigm Corporation	B08:11
Stemgent	B08:17

COMPANY NAME	STAND NUMBER
WiCell	B08:23
STEMCELL Technologies	B08:25
Mabtech	B08:32
Miltenyi Biotec GmbH	B08:33
Nippi, Incorporated	B08:38
Wuhan Healthgen Biotechnology Co., Ltd.	B09:17
The NYSCF Research Institute	B09:21
Olympus Europa SE & Co. KG	B09:23
StemCulture	B09:25
NanoEnTek Inc.	B09:30
Stemiotics, Inc.	B10:16
SONIDEL Limited	B10:17
ZEISS	B10:21
NanoString Technologies	B10:22
Multi Channel Systems	B10:23
Sony Biotechnology Inc	B10:24
World Courier	B10:25
Takara Clontech	B10:33
ChemoMetec A/S	B10:35
Genea Biocells	B11:10
UPM-Kymmene Corporation	B11:11
Developmental Dynamics	B11:13
RI Life Sciences	B11:16
Nikon Instruments	B11:17
FedEx Services	B11:20
PromoCell GmbH	B11:21
Eppendorf	B11:22

EXHIBITOR LISTING (by Stand Number)

COMPANY NAME	STAND NUMBER
Cell Therapy Catapult	B11:23
ESI BIO - A Division of BioTime, Inc.	B11:24
Bio-Techne	B11:25
Elsevier	B12:10
SERVA Electrophoresis GmbH	B12:11
Cell Signaling Technology	B12:12
Enzo Life Sciences	B12:13
Merck Millipore	B12:30
Alpha MED Scientific	B12:31
AMSBIO	B12:32
AllCells, LLC	B12:33
Mill Creek Life Sciences	B13:10
UK Stem Cell Bank	B13:11
Stockholm – Center of Excellence Stem Cells	B13:12
Terumo BCT	B13:13
Cline Scientific AB	B13:30
Sino Biological	B14:10
Nissan Chemical Industries Ltd.	B14:11
Gradientech AB	B14:12
BioNavis Ltd	B14:13
Nipro Corporation	B14:32
BIOINVISION	B14:33
BioLegend	B14:34
Axol Bioscience Ltd.	B14:35
Orla Protein Technologies LTD	B15:10
Atlas Antibodies	B15:11

COMPANY NAME	STAND NUMBER
BioCision, LLC	B15:12
Advanced Cell Diagnostics	B15:13
Humanzyme, Inc.	B15:17
PBS - DYNC	B15:21
3H Biomedical AB	B15:23
Wiley	B15:25
BioMediTech - Institute of Biosciences and Medical Technology	B15:27
Wako Pure Chemicals Industries, Ltd.	B15:32
Don Whitley Scientific Ltd	B15:33
ALS Automated Lab Solutions GmbH	B15:34
ABCell Bio	B16:17
Axiogenesis AG	B16:20
GE Healthcare Life Sciences	B16:21
stemTrak	B16:22
Medeina Cell Technologies	B16:23
Oxford Optronix Ltd	B16:24
Cellara	B16:26
Affymetrix	B16:27
TAP Biosystems	B16:28
Macopharma	B16:32
LGC - ATCC	B16:33
RoosterBio Inc.	B16:34
Abcam Inc.	B24:20
StemBioSys Inc.	B24:24
Springer	B24:26

EXHIBITOR/SUPPORTER DIRECTORY

3H BIOMEDICAL AB - B15:23
Dag Hammarskjolds v. 34A
Uppsala
SE-751 83 Sweden
+46 18-50-44-00
www.3hbiomedical.com

3H Biomedical is an innovative Swedish biotech company that manufactures and sells more than 160 different types of primary human cells. As a global leader, we supply cell-based products, including stem cells, cytokines and media for drug development and regenerative medicine to the research community, biotech sector and pharmaceutical industry worldwide.

ABCAM INC. - B24:20
Cambridge
United Kingdom
+44 122-369-6000
www.abcam.com

Abcam plc is a leading provider of protein research tools and services, with an unrivalled range of products and expert technical support, enabling scientists to analyse living cells at the molecular level and improving the understanding of health and disease. To find out more, please visit www.abcam.com

ABCELL BIO - B16:17
Rue de la Caille
Paris
49 340 France
+33 2-41-46-42-42
www.biowest.net

ABCell-Bio designs and produces well-characterized primary human cells and the defined serum-free media for their expansion or specific differentiation, especially in vascular biology, hematopoietic, tissue regeneration and cell therapy fields. Based in France, ABCell-Bio is a key-actor in a powerful European network aiming at clinical applications of cell biology.

ADVANCED CELL DIAGNOSTICS - B15: 13
3960 Point Eden Way
Hayward, CA
94545 United States
+1 510-576-8800
www.acdbio.com

Advanced Cell Diagnostics, Inc. (ACD) is a leader in the field of molecular pathology, developing cell- and tissue-based diagnostic tests for personalized medicine. ACD's products and services are based on its proprietary RNAscope® Technology capable of detecting RNA biomarkers in situ at single molecule sensitivity.

AFFYMETRIX - B16:27
Mercury Park, Wycombe Lane
Wooburn Green
High Wycombe
HP10 0HH United Kingdom
+44 0-1628-552550
www.affymetrix.com

Affymetrix technologies enable multiplex and simultaneous analysis at the cell, protein, and gene level to facilitate rapid translation of bench-top research into clinical use for human health and wellness. In partnership with our pharmaceutical, diagnostic, and academic customers we enable biology for a better world. Visit booth B16:27 or www.affymetrix.com.

AJINOMOTO - B05:35
15-1, Kyobashi 1-Chome
Chuo-Ku Tokyo
104-8315 Japan
+81 3-5250-8134
www.ajinomoto.com/en

Ajinomoto Co., Inc. is the world's leading manufacturer of amino acids. Throughout our more than 100 years history, we have continually developed innovative manufacturing methods and applications of amino acids. "StemFit® media" is a high performance, high quality xeno-free media for ES and iPS cell culture based on proprietary technology in development at Ajinomoto Co., Inc.

ALLCELLS LLC - B12:33
1301 Harbor Bay Prkwy
Ste 200
Alameda CA
94502 United States
+1 510-521-2600
www.allcells.com

AllCells is a global biotechnology partner dedicated to improving research. We provide hematopoietic, immunological tissue and primary cell types for research around the world. Our large selection of healthy cells, diseased cells, animal cells, and bioservices help accelerate research and allow scientists to focus on results.

ALPHA MED SCIENTIFIC - B12:31

209, 7-7-1, Saito-asagi
Ibaraki
567-0085 Japan
+81 7-2648-7973
www.med64.com

Alpha MED Scientific manufactures and provides the MED64 Micro-Electrode Array system for in-vitro electrophysiology. With its industry's most-sensitive electrodes, the MED64 provides clean and accurate electrophysiological recordings, enabling advanced semi-automated drug screening and safety screening as well as evaluation for differentiated neurons/cardiomyocytes. The new medium throughput system will enable you to perform high-quality drug and safety screening for up to 8 samples simultaneously.

ALS AUTOMATED LAB SOLUTIONS GMBH - B15:34

Stockholmer Strasse 10
Jena
07747 Germany
+49 364-148-200
www.als-jena.com

We manufacture automated systems for cell culture analysis, single cell and colony picking. CellCelector™ platform is suited for automated clonal picking of newly derived iPS colonies, single cell or colony isolation for genome editing or isolating cell colonies differentiated into specific cell types. The system can be used for stem cell culture process monitoring and be integrated into a fully automated stem cell production facility.

AMSBIO - B12:32

184 Park Drive, Milton Park
Abingdon Oxfordshire
OX14 4SE United Kingdom
+44 0-123-582-8200
www.amsbio.com

AMSBIO's extensive portfolio supports every facet of stem cell research: from cell-based assays, through stem cells and feeders, to xeno-free, regulatory-friendly proteins and cryopreservation media. We supply one of the largest selections of 2D and 3D extracellular matrices, including BME 2: the matrix of choice for Organoid culture. AMSBIO provides expert technical support, and offers custom products and services.

ASTRAZENECA

ANNUAL MEETING GOLD SUPPORTER

83 Mölndal
SE-431 Sweden
+46 0-3-177-617-47
www.astrazeneca.com

AstraZeneca is a global, innovation-driven biopharmaceutical business that focuses on the discovery, development and commercialisation of prescription medicines, primarily for the treatment of cardiovascular, metabolic, respiratory, inflammation, autoimmune, oncology, infection and neuroscience diseases. AstraZeneca operates in over 100 countries and its innovative medicines are used by millions of patients worldwide.

ATLAS ANTIBODIES - B15:11

Roslagstullsbacken 15
Stockholm
SE-114 21 Sweden
+46 7-057-559-72
www.atlasantibodies.com

Atlas Antibodies is a Swedish manufacturer and distributor of highly characterized antibodies targeting all human proteins. Originally developed and validated within the Human Protein Atlas (HPA) project, our eighteen thousand antibodies come with a vast quantity of characterization data freely available on the HPA portal.

AXIOGENESIS AG - B16:20

Nattermannallee 1
Köln
50829 Germany
+49 221-998-180
www.axiogenesis.com

Since 2000, Axiogenesis has been in business to capture the promise of stem cells to revolutionize the fields of drug discovery & development and life sciences research in general. Axiogenesis develops and commercializes stem cell-derived, in vitro differentiated cardiomyocytes, neurons and other cell types, as well as drug development assays and disease models, to help researchers discover cures.

EXHIBITOR/SUPPORTER DIRECTORY

AXOL BIOSCIENCE LTD - B14:35
Moneta Bldg, Babraham Research Campus
Cambridge Cambridgeshire
CB22 3AT United Kingdom
+44 122-349-7119
www.axolbio.com

Axol specializes in human cell culture. In our labs we produce highly validated, human cells and critical reagents such as media and growth supplements. We have a passion for great science, delivering epic support and providing innovative future products to help our customers advance in their research.
Succeed with Axol - Your Human Cell Culture Specialists!

BD BIOSCIENCES - B05:20
2350 Qume Dr.
San Jose CA
95131 United States
+1 877-232-8995
www.bdbiosciences.com

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

BEIHAO STEM CELL AND REGENERATIVE MEDICINE TRANSLATIONAL RESEARCH INSTITUTE
No.12 Yuyan Road
Luogang District Guangzhou
China
+860-20-32052806-837

BeiHao Stem Cell and Regenerative Medicine Translational Research Institute, co-founded in 2014 by Peking University and Grandhope Biotech, is a unique collaborative dedicated to transferring basic stem cell research into new clinical practices and treatments. Beihao Institute brings together scientists, translational groups and hospitals to develop a new collaborative academic and industrial model for advancing stem cell biology into the clinic.

BIOCISION, LLC - B15:12
12 E. Sir Francis Drake
San Rafael CA
94939 United States
+1 415-785-8516
www.biocision.com

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

BIOINVISION - B14:33
781 Beta Dr
Ste E
Cleveland OH
44143 United States
+1 216-373-1500
www.bioinvision.com

BioInVision, based in USA, offers imaging instrumentation and methodologies critical to preclinical studies. The unique CryoViz instrument, utilizing the patented cryo-imaging technology, allows microscopical anatomical and molecular fluorescence imaging of laboratory small animals such as a mouse or organs excised from them with single-cell sensitivity. Applications include stem cell homing and biodistribution, cancer metastatis, imaging agents, drug discovery etc.

BIOLAMINA - B07:11
Lofstroms Alle 5A
Sundbyberg
17266 Sweden
+46 8-588-851-80
www.biolamina.com

BioLamina offers premium high technology, biorelevant cell culture matrices for stem and primary cells.
All our matrices are chemically defined and xeno-free and allow you to imitate the natural cell niche to maintain cellular phenotypes, efficiently expand cell populations and to make accurate in vitro models with relevant read-outs.

Our breakthrough technology is scientifically proven in high-impact journals.

BIOLEGEND - B14:34

9727 Pacific Heights
San Diego CA
92121 United States
+1 858-455-9588
www.biolegend.com

BioLegend develops and manufactures world-class, cutting-edge antibodies and reagents at an outstanding value. The broad product portfolio includes flow cytometry, cell biology, and functional reagents for research in immunology, neuroscience, cancer, and stem cells. Product development is accomplished through technology licensing, collaborations, and internal R&D. Custom services include assay development, sample testing, and conjugation.

BIOLOGICAL INDUSTRIES - B07:32 AND B07:33

Kibbutz Beit Haemek
25115 Israel
+972 0-4-9960594
www.bioind.com

30 years of design and manufacturing expertise in cell culture. BI line of products includes a complete xeno-free stem cell culture system for stem cells, innovative serum-free, xeno-free media for differentiation of hMSC and products for cell biology such as PCR Mycoplasma Test kit, mycoplasma elimination solutions and Cell proliferation kit

BIOMEDITECH - INSTITUTE OF BIOSCIENCES AND MEDICAL TECHNOLOGY - B15:27

Biokatu 10
Tampere
33520 Finland
+358 40-190-9834
www.biomeditech.fi

BioMediTech, a joint research institute of Tampere University of Technology and University of Tampere, brings together a powerful mix of multidisciplinary expertise in life sciences and medical technology. Within BioMediTech over 100 scientists conduct research in Human Spare Parts research programme combining top-level expertise in biomaterials, sensor technology, imaging and stem cells to develop solutions leading in the future to new therapies and drugs.

BIOMEDTECH LABORATORIES - B05:11

3802 Spectrum Blvd, Ste 154
Tampa FL
33612 United States
+1 813-985-7180
www.biomedtech.com

BioMedTech stem cell culture surfaces include surfaces supporting non-attachment and non-differentiation of stem cells. Spheroid-promoting surfaces enable 3D organotypic assays in High-Throughput and High-Content platforms. Surfaces supporting differentiated cells include dual-layer PDL/LAM and PLO/LAM. Stabilized cell-culture coatings include laminin, fibronectin, poly-ornithine, gelatin, BME, collagens, PDL and vitronectin. BioMedTech coats all microplates (1536-well to 6-well), flasks, dishes, inserts and bio-production vessels.

BIOSPHERIX, LTD. - B04:23

19 Demott St.
Lacona NY
26878 United States
+1 315-387-3414
www.biospherix.com

Cell Therapy: Xvivo System, first and only barrier isolator optimized for cells. Economical and practical alternative to cleanrooms for cGMP cell production.
Research: Wide range of hypoxia systems for In Vitro/In Vivo. Advanced features include multiple simultaneous levels, timed and intermittent exposures, uninterruptible hypoxia, dissolved oxygen cell culture, etc.

BIO-TECHNE - B11:25

614 McKinley Pine
Minneapolis MN
55413 United Kingdom
+44 0-12-35-52-9449
www.rndsystems.com

Bio-Techne provides researchers with world-class stem cell reagents that optimize workflow and promote scientific discovery. Combining the product offerings of R&D Systems, Novus Biologicals, and Tocris Bioscience, Bio-Techne is the source for high-quality proteins, antibodies, small molecules, and stem cell media. Visit booth B11:25 to learn about our stem cell product portfolio, including our unique differentiation kits and ProDots™ Proteins.

EXHIBITOR/SUPPORTER DIRECTORY

BOEHRINGER INGELHEIM INTERNATIONAL GMBH

Binger Straße 173
Ingelheim
55216 Germany
www.boehringer-ingelheim.com

ANNUAL MEETING SILVER SUPPORTER

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, Boehringer Ingelheim operates globally with 142 affiliates and a total of more than 47,400 employees. The focus of the family-owned company, founded in 1885, is researching, developing, manufacturing and marketing new medications of high therapeutic value for human and veterinary medicine

BTX HARVARD BIOSCIENCE - B06:13

84 October Hill Road
Holliston MA
01746 United States
+1 508-893-8999
www.btxonline.com

BTX is a leading supplier of electroporation systems for in vitro, in vivo, and high-throughput applications. We feature Gemini Twin-Wave Systems, capable of providing both square and exponential decay waveforms in a single unit. We support many cell/tissue types and provide a wide selection of electroporation chambers and tools.

BURROUGHS WELLCOME FUND

21 T.W. Alexander Drive
Research Triangle Park NC
27709 United States
+1 919-991-5100
www.bwfund.org/

ANNUAL MEETING SILVER SUPPORTER

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

CELL PRESS - B06:10

600 Technology Sq
Cambridge MA
02139 United States
+1-617-386-2121
www.cell.com

ANNUAL MEETING GOLD SUPPORTER

Cell Press is proud to publish Stem Cell Reports, the open access journal from ISSCR. Visit Cell Press booth # B06:10 for the latest high-quality stem cell research and to meet Cell Press editors! Pick up free journal copies, including Stem Cell Reports, Cell, Cell Stem Cell, Cell Reports, Developmental Cell, Neuron, Trends in Cell Biology, and Trends in Molecular Medicine.

CELL SIGNALING TECHNOLOGY - B12:12

3 Trask Lane
Danver MA
01923 United States
+1 978-867-2300
www.cellsignal.com/isscr

Founded by research scientists in 1999, Cell Signaling Technology (CST) is a family-owned company focused on applied systems biology research, and especially cancer. We believe you have the right to expect more reliable results from your antibodies and reagents so our scientists produce, validate and support all our antibodies in-house.

CELL THERAPY CATAPULT - B11:23

12th Floor Tower Wing, Guy's Hospital
London
SE1 9RT United Kingdom
+44 203-728-9500
www.ct.catapult.org.uk

ANNUAL CONTRIBUTOR MEETING

The Cell Therapy Catapult, supported by Innovate UK, is a centre of translational excellence for cell therapy and regenerative medicine. Based in the UK, our purpose is to grow a UK cell therapy industry delivering health and wealth by leading and supporting innovation, research and manufacturing within the industry to help companies and researchers bring commercially competitive products to the market and to patients.

CELLARA - B16:26
6601 Grand Teton Plaza
Madison WI
53719 United States
+1 608-213-4340
www.cellarabio.com

Cellara is developing innovative software solutions to simplify the daily management of stem cell cultures, critical materials and protocols. Unlike current LIM systems, the Cellara Cell Culture Management System (CCMS) is specifically designed to address the complexities of stem cell workflows, creating a comprehensive, documented history of every culture, from experimental design through daily tasks and into the cryovial.

CELLGENIX GMBH - B04:17
Am Flughafen 16
Freiburg
79108 Germany
+49 7-618-888-90
www.cellgenix.com

CellGenix manufactures and supplies high quality cytokines and serum-free media for the ex vivo cell culture of HSC, MSC, ESC & iPS, etc. CellGenix products are used in clinical trials in academia, commercial trials, production of vaccine and in translation, validation and testing or assay development by biotechnology partners.

CELLULAR DYNAMICS INTERNATIONAL - B06:11
525 Science Drive
Madison WI
53711 United States
+1 608-310-5100
www.cellulardynamics.com

Cellular Dynamics International is a leading developer of fully functional human cells derived from induced pluripotent stem (iPS) cells. Our iCell® and MyCell® products provide industrial quantities of high quality, highly pure human cells enabling disease modeling, drug discovery, toxicity testing, and cell therapy research.

CENTER FOR IPS CELL RESEARCH AND APPLICATION (CIRA) - B05:32
53 Kawahara-cho
Shogoin Yoshida
606-8507 Japan
+81 7-5366-7005
www.cira.kyoto-u.ac.jp

CiRA is the lead iPSC research center in Japan. It staffs a mix of basic researchers and clinicians, including its director, Nobel Laureate Shinya Yamanaka, all devoted to understanding the science of cell reprogramming and applying this knowledge to developing new therapies. CiRA expects to commence clinical research of two iPSC-based technologies in the next few years with more coming later.

CENTRE FOR COMMERCIALIZATION OF REGENERATIVE MEDICINE (CCRM)
ANNUAL MEETING SILVER SUPPORTER

110-100 College Street
Toronto ON
M5G 1L5 Canada
+ 416-978-3751
www.ccrm.ca

CCRM's mission is to create and sustain a global nexus for RM commercialization by unifying dynamic business leadership with high value innovative translational technology platforms based on demonstrated excellence in fundamental stem cell and biomaterial science.

CHEMOMETEC A/S - B10:35
Gydevang 43
Allerod
3450 Denmark
+45 48-13-10-20
www.chemometec.com

ChemoMetec develops, manufactures and sells equipment for counting and analyzing cells in fluids. Our instruments are used in fields such as life science research (e.g. cancer and stem cell research, development of new drugs) and production and quality control of a number of products such as pharmaceuticals, beer, animal semen and milk.

EXHIBITOR/SUPPORTER DIRECTORY

CLINE SCIENTIFIC AB - B13:30
Carl Skottsbergs Gata 22B
Goteborg
413 19 Sweden
+46 31-387-55-55
www.clinescientific.com

Cline Scientific provides in-vitro surface gradients. Use our Cline Nano Gradient with your biomolecule of choice for Stem Cell differentiation or cell-migration, with molecular precision!
Cline is a Swedish company that develops innovative products based on nanotechnology for Life Science applications.

CM TECHNOLOGIES OY - B14:13
Biokatu 12
33520 Finland
+358 10-759-5900
www.c-mtechnologies.com

CMT provides unique live cell imaging platforms, Cell-IQ® range, which combine incubator and imaging capability with easy automated analysis software. Cell-IQ is used routinely to study 2D & 3D cell cultures quantifying e.g. proliferation, differentiation, neurite, tubule or spheroid formation, single cell tracking, lineage & directionality plus much more.

THE COMPANY OF BIOLOGISTS - B07.34
Bidder Building, Station Road
Histon
Cambridge
CB24 9FL United Kingdom
+44 0-122-363-2877
www.biologists.com

The Company of Biologists is the not-for-profit publisher of the three distinguished journals Development, Journal of Cell Science and The Journal of Experimental Biology. The Company also publish two open access journals, Disease Models & Mechanisms and Biology Open. The Company also supports innovation in all aspects of biological research, providing grants in the areas in which it publishes.

CORNING - B07:10
900 Chelmsford St.
Tower 2, 4th Floor
Lowell MA
01851 United States
+1 978-442-2200
www.corning.com/lifesciences

Corning Life Sciences' line of advanced cell culture surfaces, scalable vessel platforms, and cell culture media provide innovative solutions for stem cell research. Products include the established Matrigel® Matrix, novel animal-free surfaces for defined stem cell expansion, and stemgro™ media for increased expansion of hMSCs.

DEFINIGEN LTD - B04:33
Maia, Building 270, Babraham Research Campus
Babraham Cambridge
CB22 3EB United Kingdom
+44 0-122-349-7113
www.definigen.com

DefiniGEN is a University of Cambridge spin-out company with world-leading expertise in the area of human induced pluripotent stem cell (iPSC) based metabolic disease modelling.
DefiniGEN offers human iPSC derived Hepatocytes (Def-HEP) and Pancreatic (Def-PANC) cells modelled on a range of Inherited Metabolic Disorders.
DefiniGEN also provides contract research services in the areas of iPSC based disease model development, drug safety and efficacy screening.

DEVELOPMENTAL DYNAMICS - B11:13
1656 E. Mabel Street
318
Tuscon AZ
85724 United States
+1 520-626-0453
www.developmentaldynamics.net

Developmental Dynamics provides a forum for communication among biologists studying the dynamic emergence of form and function during embryonic development and regeneration. We seek manuscripts presenting work at all levels of biological organization, in particular those that advance our understanding of stem cell biology and developmental basis of human disease.

DON WHITLEY SCIENTIFIC LTD - B15:33

14 Otley Road
Shipley West Yorkshire
BD17 7SE United Kingdom
+44 0-127-459-5725
www.dwscientific.co.uk

Don Whitley Scientific Ltd has been a leading international supplier of innovative equipment and service for nearly 40 years. We develop and manufacture a wide range of HEPA filtered workstations with precise control of oxygen and temperature variability, to replicate the physiological environment of the stem cell niche. These workstations improve experimental reliability by minimising unwanted variations that could potentially impact your results.

ELSEVIER - B12:10

San Diego CA
United States
+1 617 397 2885
www.elsevier.com

Elsevier is a world-leading provider of information solutions that enhance the performance of science, health, and technology professionals, empowering them to make better decisions, deliver better care, and sometimes make groundbreaking discoveries that advance the boundaries of knowledge and human progress. Elsevier provides web-based, digital solutions, publishes nearly 2,200 journals and over 33,000 book titles, including many iconic reference works.

ENZO LIFE SCIENCES - B12:13

10 Executive Blvd
Farmingdale NY
11735 United States
+1 800-942-0430
www.enzolifesciences.com

With over 30 years' experience, Enzo Life Sciences is a proven leader in labeling and detection technologies across research and diagnostic markets. Enzo offers a broad range of products to advance your stem cell research including modulators, antibodies, labeling kits, biochemical & reporter assays, and fluorescent-based assays.

EPPENDORF - B11:22

Slotsmarken 12
Hørsholm
2970 Denmark
+45 43-24-00-00
www.eppendorf.com

Eppendorf is synonymous with customer-oriented processes and innovative products, such as laboratory devices and consumables for liquid handling, cell handling and sample handling. The foundation of the company's expertise is its focus on its customers. Eppendorf will continue on this path in the future, true to the standard set by the company's founders: that of sustainably improving people's living conditions.

ESI BIO - A DIVISION OF BIOTIME, INC. - B11:24

1301 Harbor Bay Parkway
Alameda CA
94502 United States
+1 510-521-3390
www.esibio.com

ESI BIO's mission is to provide researchers with end-to-end research reagents from stem cell discovery through clinical manufacturing using products that are translatable to the clinic. Products include: PureStem® progenitors, HyStem® hydrogels, new UV-light hydrogels, small molecules, antibodies, ESI cell lines, and growth factors. ESI BIO is a division of BioTime, a pioneer in regenerative medicine and clinical-stage biotechnology company.

FEDEX SERVICES - B11:20

3540 Hacks Cross
Bdlg. D, 1st Floor
Memphis TN
38125 United States
+1 901-434-5198
www.fedex.com/healtcare

FedEx Corp. provides customers and businesses worldwide with a broad portfolio of transportation, e-commerce and business services. Consistently ranked among the world's most admired and trusted employers, FedEx inspires its more than 300,000 team members to remain "absolutely, positively" focused on safety, the highest ethical and professional standards and the needs of their customers and communities.

EXHIBITOR/SUPPORTER DIRECTORY

FLUIDIGM CORPORATION - B08:11

ANNUAL MEETING BRONZE SUPPORTER

7000 Shoreline Ct. Ste 100
San Francisco CA
94080 United States
+1 650-266-6000
www.fluidigm.com

We strive to partner with customers to pursue truth in the complex biological world. Leveraging our core technologies, microfluidics and mass cytometry, we provide simplified and elegant workflows for single-cell approaches to genomics and proteomics applications. Our C1™ and Biomark™ systems enabled the field of single-cell genomics. Partner with us on your quest to characterize and understand individual cell function.

GE HEALTHCARE LIFE SCIENCES

ANNUAL MEETING BRONZE SUPPORTER

The Maynard Centre – Forest Farm Estate
Cardiff, 14 7YT United Kingdom
+44 0-800-515-313
www.gelifesciences.com/webapp/wcs/stores/servlet/Home/en/GELifeSciences-uk

At GE Healthcare, we are dedicated to developing innovative, high quality products and services that protect the health of our workers, customers, and environment.

GE HEALTHCARE LIFE SCIENCES - B16:21

Tysksland, Filial Sveridge
Box 605
Uppsala
75125 Sweden
+46 070-5878590

www.gelifesciences.com/webapp/wcs/stores/servlet/Home/en/GELifeSciences-uk

At GE Healthcare, we are dedicated to developing innovative, high quality products and services that protect the health of our workers, customers, and environment.

GENEA BIOCELLS - B11:10

321 Kent St
Level 2
Sydney NSW
Australia
+61 284-847-662
www.geneabiocells.com

Genea Biocells develops unique disease-specific and unaffected human pluripotent stem cell lines, differentiated cells - including the first robust skeletal muscle differentiation kit, culture media and small molecule libraries for use in research, drug development and cell therapy. We partner with scientists in industry and academia to advance innovative projects using chemical biology and stem cell-driven approaches.

GRADIENTECH AB - B14:12

Uppsala Science Park
Uppsala
751 83 Sweden
+46 0-18-418-67-00
www.gradientech.se

Gradientech supplies microfluidic, cell-based assays for high-quality, dynamic analysis of cell behavior in response to stable gradients. Our CellDirector® product line for 2D and 3D cell culture, combines the advantages of controlled fluid flows with excellent cell conditions to mimic true physiological conditions.
The Tracking Tool™ PRO software offers automated live cell tracking of outstanding quality in an easy-to-use format.

HAMILTON THORNE INC. - B05:24

100 Cummings Ctr
465E
Beverly MA
01915 United States
+1 978-921-2050
www.hamiltonthorne.com

Hamilton Thorne presents our family of research lasers and enhanced imaging systems. Our XYClone® and XYRCOS® lasers for cell ablation along with optional Staccato® facilitate ICM excision for stem cell derivation and embryo biopsy. Hamilton Thorne also presents the Oosight™ enhanced imaging system to aid with enucleation and spindle transfer. Stop by our booth to learn what is new.

HARVARD STEM CELL INSTITUTE

ANNUAL MEETING BRONZE SUPPORTER

7 Divinity Avenue
Bauer Building, Administrative Suite
Cambridge MA
02138 United States
+1 617-496-4050
www.hsci.harvard.edu

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

HUMANZYME, INC. - B:15.17

2201 W Campbell Park Drive
#23
Chicago IL
60612 United States
+1 312-738-0127
www.humanzyme.com

HumanZyme, Inc. is an innovative provider of biologically relevant recombinant human cytokines and growth factors (HumanKine®) for stem cell research, including therapeutic and diagnostic applications. Our human cells expressed (HEK293) proteins offer superior quality, activity, and stability. HumanKine® proteins are also xeno- and animal product-free, and have correct folding and other authentic post-translational modifications.

IRVINE SCIENTIFIC - B08:10

1830 Warner Ave
Santa Ana CA
92705 United States
+1 949-261-7800
www.irvinesci.com

Irvine Scientific is a worldwide leader in the design and production of cell culture products for cell therapy, immunology, biopharmaceutical, cytogenetic, and ART applications. The company's extensive experience with culture media design, compliance with ISO and FDA regulations for medical devices, and GMP manufacturing, uniquely positions us to support cell therapy applications from the lab to the clinic, and ultimately to market.

JANSSEN RESEARCH & DEVELOPMENT, LLC

ANNUAL MEETING GOLD SUPPORTER

1000 Route 202 South
Raritan NJ
8869 United States
+1 908-704-4000
www.janssenrnd.com

At Janssen Research & Development, LLC, we are united and energized by one mission – to discover and develop innovative medicines that ease patients' suffering, and solve the most important unmet medical needs of our time.

KAROLINSKA INSTITUTET

ANNUAL MEETING GOLD SUPPORTER

Solnavägen 1
Solna
171 77 Sweden
+46 8-524-800-00
www.ki.se/en/startpage

Karolinska Institutet, located in Solna within the Stockholm urban area is one of Europe's largest and most prestigious medical universities.

LGC - ATCC - B16:33

Queens Road
London
TW11 OLY United Kingdom
+44 0-20-8943-7572
www.lgcstandards.com

ATCC has provided stem cell solutions to the research community for more than a decade, with a growing portfolio of cultures and reagents to choose from, including mouse embryonic stem cells, human mesenchymal stem cells (MSC), human iPS cells and media systems. LGC is the exclusive European distributor for ATCC's unique collections. All ATCC products purchased through LGC are the original materials supported by our in house expertise.

LONZA - B04:11

ANNUAL MEETING SILVER SUPPORTER

8830 Biggs Ford Road
Walkersville MD
21793 United States
+1 301-898-7025
www.lonza.com

Lonza supports stem cell research from the laboratory to clinical application. Discover how Lonza's L7™ hPSC Reprogramming and Culture System and CytoSMART™ Live Cell Imaging and Monitoring System can benefit your projects. Visit us at booth #B04:11 to learn more about our products and GMP process and manufacturing service offerings.

EXHIBITOR/SUPPORTER DIRECTORY

MABTECH - B08:32
Augustendalsv, 19
Stockholm
13152 Sweden
+46 70-768-97-06
www.mabtech.com

Mabtech is a world leader in advancing the ELISpot and Fluorospot methods and develops and manufactures high quality monoclonal antibodies and kits for ELISA, ELISpot and FluoroSpot. This is the result of a continuous effort to develop novel reagents and optimize protocols for these assays. Our strong research focus, with close academic and industrial collaborations, will pave the way for future developments which will aid in international research.

MACOPHARMA - B16:32
Rue Lorthiois
Nouvaux
59420 France
+33 3-20-11-84-00
www.macopharma.com

Macopharma is a leading worldwide manufacturer of medical devices for transfusion, infusion and biotherapy. The Biotherapy division provides solutions in the fields of cell and tissue therapy, regenerative medicine and transplantation. Their high quality, GMP-compliant, single use, sterile closed systems to collect, treat, expand and preserve cells, tissues and organs help to consistently improve and secure cellular therapy practices and clinical protocols.

MASSACHUSETTS GENERAL HOSPITAL CENTER FOR REGENERATIVE MEDICINE
185 Cambridge Street
Boston MA
02114 United States
+1 617-643-5380
www.massgeneral.org/regenmed

ANNUAL MEETING BRONZE SUPPORTER

OUR MISSION
The Center for Regenerative Medicine is dedicated to understanding how tissues are formed and may be repaired. Our primary goal is to develop novel therapies to regenerate damaged tissues and overcome debilitating chronic disease. The success of this effort requires a cohesive team of scientists and clinicians with diverse areas of expertise, but with a shared mission and dedication to the larger goal.

MERCK MILLIPORE - B12:30
Boulevard Industrial Park, Padge Road
Nottingham
NG9 2JR United Kingdom
+46 77-120-06-45
www.merckmillipore.com

Merck Millipore is the Life Science division of Merck KGaA, Germany, supporting research, development and production of biotech and pharmaceutical therapies. We offer technologies for cellular analysis, network elucidation and functional genomics, including virus-free, one-step reprogramming, cell culture media, supplements and bioreactor-based stem cell manufacturing.

MESOBLAST, LTD.
55 Collins Street
Level 38
Melbourne
03000 Australia
+61 800-896-376
www.mesoblast.com

ANNUAL MEETING SILVER SUPPORTER

Mesoblast Limited is a global leader in regenerative medicine. The Company has leveraged its proprietary technology platform, which is based on specialized cells known as mesenchymal lineage adult stem cells, to establish a broad portfolio of late stage product candidates. Mesoblast's allogeneic or 'off-the-shelf' cell product candidates target significantly advanced stages of diseases where there are highly unmet medical needs, including cardiovascular conditions, orthopedic disorders, immunologic and inflammatory disorders and oncology/hematology conditions. The lead therapeutic product candidates under investigation include MPC-150-IM for chronic congestive heart failure, in partnership with Teva Pharmaceutical Industries Ltd., MPC-06-ID for chronic discogenic low back pain, MSC-100-IV for acute graft versus host disease, and MPC-300-IV for biologic refractory rheumatoid arthritis and diabetic nephropathy.

MILL CREEK LIFE SCIENCES - B13:10

221 1st Ave SW
Suite 209
Rochester MN
55902 United States
+1 507-287-6257
www.millcreekls.com

Let the cows roam free! PLTMax® is a human-derived media supplement used to grow stem cells. Cells grown in PLTMax® (at half the concentration of fetal bovine serum) double in half the time.
PLTMax® is available in both clinical and research grades; covering your needs from bench to bedside. We have a proven track record in multiple clinical trials both internationally and domestically.

MILTENYI BIOTEC GMBH - B08:33

Friedrich-Ebert-Str 68
51429 Germany
+49 2204-8306-3190
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 more than 25 years of expertise includes immunology, stem cell biology, neuroscience, and cancer. Miltenyi Biotec has more than 1,400 employees in 25 countries.

MULTI CHANNEL SYSTEMS MCS GMBH - B10:23

Aspenhaustr. 21
Reutlingen
72770 Germany
+49 7121-9092-528
www.multichannelsystems.com

Multi Channel Systems focuses on the development of precise scientific measuring instrumentation in the field of electrophysiology for research groups at universities and for the pharmaceutical industry.
At ISSCR, we will present our MEA-Systems for in vitro electrophysiology, either on a single- or a multi-well platform.

NANOENTEK INC. - B09:30

12F, Ace High-end Tower
5, Digital-ro 26-gill, Guro-gu
Seoul
152-711 Republic of Korea
+82 2-6220-7728
www.nanoentek.com

We, NanoEnTek Inc., are the manufacturer of several research purposed instruments and the disposables, especially optimized in the field of cell biology.

NANOSTRING TECHNOLOGIES EUROPE LIMITED - B10:22

St. Mary's Court
The Broadway
Amersham
HP7 0UT United Kingdom
+44 -0-75-38-30-11-68
www.nanostring.com

NanoString Technologies provides life science tools for translational research and molecular diagnostic products. The company's nCounter® Analysis System, which has been employed in basic and translational research and cited in 500 peer review publications, has also now been applied to diagnostic use with the nCounter Dx Analysis System and uses the nCounter-based Prosigna™ Breast Cancer Prognostic Gene Signature Assay.

NATURE PUBLISHING GROUP

75 Varick Street
New York NY
10010 United States
+1 207-883-4000
www.nature.com

Nature Publishing Group (NPG) produces scientific information for researchers and the scientifically interested general public. Each month our high-impact journals, open access titles, news, apps, conferences and job listings help over 9 million users to advance their research, reputation, careers and knowledge.

THE NYSCF RESEARCH INSTITUTE – B09:21

1995 Broadway
Suite 600
New York NY
10023 United States
+1 212-365-7442
www.nyscf.org

The New York Stem Cell Foundation (NYSCF) is a non-profit organization whose mission is to accelerate cures for the major diseases of our time through stem cell research.

NIKON INSTRUMENTS - B11:17

Tripolis 100
Burgerweeshuispad 101
Amsterdam
1076 ER The Netherlands
+0031 0-64-6370-327
www.nikoninstruments.com/en_GB

Nikon Instruments Inc is a world leader in the development and manufacture of optical and digital imaging technology for biomedical and industrial applications. Nikon provides complete optical systems that offer optimal versatility, performance and productivity. Cutting-edge instruments include microscopes, precision measuring equipment, digital imaging products and software.

NIPPI, INCORPORATED - B08:38

1-1-1 senjumidori-cho
Adachi-ku
1208601 Japan
+81 3-3888-5184
www.nippi-inc.co.jp/english/tabid/168/Default.aspx

We sell extracellular matrix components, especially collagen and laminin. iMatrix-511, a short fragment of laminin-511, is good for xeno-free, feeder-free culture for iPS and ES cells

NIPRO CORPORATION - B14:32

3023, Nojicho
Osaka
5250055 Japan
+81 7-7564-0500
www.nipro.co.jp/en/index.html

Since its founding in 1954, Nipro Corporation has expanded the scope of its business from glass materials to medical devices and pharmaceutical products. The Company now offers products and technologies that meet the needs of patients and medical professionals in a wide range of fields, such as artificial organs, circulatory organs, test/diagnostic agents, injection/infusion solutions, ethical pharmaceuticals, and medical glass products.

NISSAN CHEMICAL INDUSTRIES LTD. - B14:11

7-1, Kanda-Nishiki-Cho, 3-Chome Chiyoda-ku
Kowa Hitotsubashi Building
Tokyo
101-0054 Japan
+81 3-3296-8391
www.nissanchem.co.jp/eng

Nissan Chemical Industries Ltd. (NCI) is Japanese chemical industrial company.
NCI have launched three dimensional ES/iPS cell culture material, FP001 since, Nov. 2014.

NORDIC LIFE SCIENCE DAYS - SWEDENBIO

Wallingatan 24
Stockholm
SE-11124 Sweden
+33 0-608-804-515
www.nlsdays.com

ANNUAL MEETING BRONZE SUPPORTER

NLSDays is the largest Nordic partnering conference for the global Life Science industry. Bringing together the best talents in Life Science, offering amazing partnering opportunities, providing content on the most recent trends. Based on advanced partnering and networking tools, NLSDays showcases the best the Nordic region has to offer.

NOVO NORDISK FOUNDATION

Tuborg Havnevej 19
Hellerup
2900 Denmark
+45 36-67-48-21
www.novonordiskfonden.dk/en

ANNUAL MEETING SILVER SUPPORTER

The Novo Nordisk Foundation is an independent Danish foundation that awards grants for research, innovation and education of the highest international standard and donates money for philanthropic purposes.
Grants are mainly awarded for research within the health sciences and biotechnology at public universities and hospitals in Denmark and the Nordic Countries.

OLYMPUS EUROPA SE & CO. KG - B09:23

Wendenstr. 14-18
Hamburg
20097 Germany
+49 40-23-77-35-781
www.olympus-lifescience.com

A world-leading manufacturer of professional opto-digital products, Olympus draws on cell biology expertise to provide life science imaging solutions. Discover at booth B9:23:

- IX3 inverted microscopes - unprecedented optical flexibility in live-cell imaging and clinical analysis via a customisable light path, opening new avenues for researchers in their work
- Cell Counter - accurate cell information displayed on a 5MP monitor

ONTARIO INSTITUTE FOR REGENERATIVE MEDICINE (OIRM)

ANNUAL MEETING SILVER SUPPORTER

Suite 1110-160 College Street
Toronto ON
M5S 3E1 Canada
+1 647-926-1228
www.oirm.ca

The Ontario Institute for Regenerative Medicine is a not-for-profit research and commercialization institute with a vision to revolutionize the treatment of degenerative diseases, making Ontario the global leader in the development of stem cell-based products and therapies.

ORLA PROTEIN TECHNOLOGIES LTD - B15:10

Biomedicine West Wing
International Centre for Life
Newcastly Upon Tyne
NE1 4EP England
+44 191-231-3127
www.orlaproteins.com

Orla Protein Technologies has developed a range of cell culture surfaces that mimic natural interactions providing reliable and consistent growth media. They utilise specially engineered animal and xeno-free proteins that mimic specific extracellular matrix components (laminins, vitronectin, collagen, and many more), growth factors (such as FGF, EGF and others) and numerous other proteins that control cell behaviour. These surfaces offer unmatched scalability and cost effectiveness.

OXFORD OPTRONIX LTD. - B16:24

19-20 East Central
127 Olympic Ave
Abingdon
OX14 4SA United Kingdom
+44 123-582-1803
www.oxford-optronix.com

Founded on innovation, Oxford Optronix is a global pioneer in the design, development and manufacture of sophisticated instrumentation for the life sciences. Our products are designed, developed and manufactured in-house by experienced scientists and engineers.

PBS - DYNC - B15:21

Hortensiastraat 8
Breda
4818GM The Netherlands
+31 76-5323-995
www.dync.eu

PBS Single Use Bioreactors are represented in Europe by DYNC. The PBS Bioreactors provide an ideal low shear scaleable platform for the production of your sensitive stem cells in a 3D setting. The PBS Bioreactors cause only 10% of the shear stress that the traditional stirred bioreactors cause. The reactors are fully scaleable and available from 0,1 ltr. all the way to 500 ltr.

PEPROTECH INC. - B05:26

5 Crescent Ave
Rocky Hill NJ
08553 United States
+1 800-436-9910 x9148
www.peprotech.com

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.

PROMOCELL GMBH - B11:21

Sickingenstr. 63/65
Heidelberg
69126 Germany
+49 6221-649-34-0
www.promocell.com

At PromoCell, we are committed to providing researchers worldwide with a broad range of human primary cells, stem cells, and blood cells as well as optimized cell culture media and a wide range of well proven products for your cell biology research (e.g. transfection reagents).

PROTEINTECH EUROPE - B04:21

Kilburn House
Manchester Lancashire
M15 6SE United Kingdom
+44 161-42-26-6144
www.ptglab.com

Proteintech is the original manufacturer of over 10,000 antibodies against over 10,000 "proteins".

RI LIFE SCIENCES - B11:16

Bickland Industrial Park
Falmouth
TR11 4TA United Kingdom
+44 0-132-637-2753
www.ri-lifesciences.com

RI Life Sciences (RI LS) specializes in micromanipulation, laser ablation and cell handling technologies for Life Sciences applications. RI LS is proud to be a division of Research Instruments Ltd., a world leader in the design and manufacture of specialist hardware and consumables for the human ART field.

ROOSTERBIO INC. - B16:34

4539 Metropolitan Court
Frederick MD
21704 United States
+1 301-360-3545
www.roosterbio.com

RoosterBio is a products and technology company focused on accelerating the development of a sustainable regenerative medicine industry, one customer at a time. RoosterBio's products are high volume, affordable, and well-characterized adult mesenchymal stem cells (MSCs) with highly engineered media systems. RoosterBio has simplified and standardized how stem cells are purchased, expanded, and used in development, leading to time and costs savings for customers. Our innovative products are ushering in a new era of productivity and standardization into the field (as seen by customer product reviews), and researchers spend new found time & money performing more high-value experiments, accelerating the road to discovery in Regenerative Medicine.

RUCDR INFINITE BIOLOGICS - B04.35

145 Bevier Road
Piscataway NJ
08854-8009 United States
+1 848-445-7096
www.rucdr.org

RUCDR Infinite Biologics provides comprehensive services in bioprocessing, genomics, sample analytics and biostorage to government agencies, academic institutions, foundations, and biotechnology and pharmaceutical companies within the global scientific community. Our scientists work to convert precious biosamples into renewable resources thereby extending research capabilities. The RUCDR Stem Cell Laboratory produces, expands, and distributes iPSC lines with extensive characterization and quality control.

SERVA ELECTROPHORESIS GMBH - B12:11

Pinnauallee 4
Heidelberg
25436 Germany
+49 412-271-2413
www.serva.de

We offer Collagenase NB products for high-yield isolation of viable cells. SERVA's superior Collagenase NB 6 GMP Grade is particularly suitable for isolation and passaging of stem cells destined for clinical applications. Pharmaceutical manufacturing standard guarantees stringent quality control, reliable lot-to-lot consistency and low endotoxin levels. Visit our booth for more information on SERVA's clinical and research grade enzymes.

SINO BIOLOGICAL - B14:10

B-310, 14 Zhong He Street, BDA
Beijing
100176 China
+86 10-5102-9809
www.sinobiological.com

Sino Biological Inc is quickly becoming the leading global biological solution specialist, offering a comprehensive set of value-added and cost-effective premium quality solutions (services and reagents) to accelerate life science research and biological product development worldwide. Its customers include top-10 global pharmaceutical and biotech companies, small biotech companies, and academic institutions worldwide.

SONIDEL LIMITED - B10:17

32 Tonlegee Drive, Raheny
Dublin
D5 Ireland
+353 0-1-4434358
www.sonidel.com

Transfect Everything! – SONIDEL is pleased to present the NEPA21 electroporation system that makes it possible to achieve high transfection efficiency and viability for difficult-to-transfect cells such as primary neurons, iPS cells, blood cells, etc WITHOUT using expensive special kits.
In addition to its in-vitro transfection capability, the NEPA21 is an ideal tool for in-vivo/in-utero/ex-vivo transfections.

SONY BIOTECHNOLOGY INC - B10:24

2100 S. Oak St.
Champaign IL
61820 United States
+1 800-275-5963
www.sonybiotechnology.com

Sony Biotechnology Inc. is dedicated to helping the immunology community of scientists achieve the best scientific results possible. By leveraging Sony's comprehensive expertise in electronics innovation and design and with our technological assets we are accelerating development of next-generation cell analysis systems. We bring a unique perspective to science's high-level instrumentation and are creating innovative products to address our customer's challenges.

SPRINGER - B24:26

Tiergartenstr. 17
Heidelberg
69121 Germany
+1 212-620-8476
www.springer.com

Looking to publish your research? Discover Springer's print and electronic publication services, including open access! Get high-quality review, maximum readership and rapid distribution. Visit our booth or springer.com/authors.

You can also browse key titles in your field and buy (e) books at discount prices. With Springer you are in good company.

STEM CELL PROGRAM AT BOSTON CHILDREN'S HOSPITAL

ANNUAL MEETING BRONZE SUPPORTER

300 Longwood Ave
Karp, 8215
Boston MA
02115 United States
+1 617-919-2083
www.stemcell.childrenshospital.org

The Stem Cell program at Boston Children's Hospital brings together premier physicians from many backgrounds and specialties to form one of the top stem cell research units in the world. Their research holds extraordinary potential for the development of therapies that may change the future for children throughout the world.

STEMBIOSYS INC. - B24:24

12500 Network Blvd
Ste 105
San Antonio TX
78249 United States
+1 210-877-9323
www.stembiosys.com

StemBioSys is located in San Antonio, Texas and proximate to the University of Texas Health Science Center San Antonio (UTHSC-SA) from which we have licensed proprietary and disruptive technology for the enhanced isolation, growth and delivery of stem cells for research, diagnostic and therapeutic applications.

STEMCELL TECHNOLOGIES INC. - B08:25

ANNUAL MEETING GOLD SUPPORTER

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

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

STEMCELLS, INC.

ANNUAL MEETING GOLD SUPPORTER

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

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

EXHIBITOR/SUPPORTER DIRECTORY

STEMCULTURE - B09:25
1 Discovery Dr
Rensselaer NY
12144 United States
+1 518-621-0846
www.stemculture.com

StemCulture scientists are committed to providing our colleagues with consistent, high quality reagents for better stem cell cultures.
StemBeads® is StemCulture's innovative solution utilizing reagents including FGF2, EGF, & Activin-A in multiple applications. Our microencapsulation technology & sustained release growth factors produce more homogenous cultures which yield better cells.
"Save Time | Better Cells"

STEMGENT - B08:17
One Kendall Square Ste
Cambridge MA
02139 United States
+1 617-245-0038
www.stemgent.com

ANNUAL MEETING BRONZE SUPPORTER

ReproCELL is an expanding global leader in providing researchers with integrated tools for translational research. ReproCELL, along with its Bioserve, Reinnervate and Stemgent brands offers a comprehensive suite of products and services from human biospecimen procurement to 3D cell culture, through cellular reprogramming and differentiation to readily-available differentiated cells.

STEMIOTICS, INC. - B10:16
3210 Merryfield Row
Janssen Labs
San Diego CA
92121 United States
+1 858-242-1540
www.stemiotics.com

Stemiotics offers a fast-turnaround, high-throughput human iPSC derivation service based on our footprint-free, feeder-free, xeno-free mRNA reprogramming pipeline, at a breakthrough price of just $1000 per line.

STEMTRAK - B16:22
186 Alewife Brook Parkway
Suite 300
Cambridge MA
02138 United States
+1 617-699-2150
www.stemtrak.com

stemTrak provides configurable, web-based, data management software solutions that enable Blood and Marrow Transplant (BMT) Programs and Stem Cell Researchers to optimize their processes and centralize their data while eliminating errors, variance, and duplicative data entry. Our solutions empower physicians, scientists, health care professionals, and data managers to easily access critical program data in an intuitive user-friendly interface.

STOCKHOLM – A GLOBAL CENTER OF EXCELLENCE FOR STEM CELL THERAPY - B13:12
Hälsovägen 7
Stockholm
141 57 Sweden
+46 0-708-380-459
www.flemingsbergscience.se

Stockholm is a city with an exceptional environment that holds great potential for fueling groundbreaking advances in the field of regenerative therapeutics. Come and learn how you can maximize your potential for discovery, development of therapeutic applications and commercial development. Become part of the stem cell cluster in Stockholm, today!

TAKARA CLONTECH - B10:33
2 AV DU President Kennedy
Saint Germain En Laye
78100 France
+33 1-39-04-68-80
www.clontech.com

Through its brand names TAKARA®, CLONTECH®, and CELLARTIS®, Takara Bio develops innovative technologies in the fields of Cell Biology, Molecular Biology, Proteomics, and Stem Cell Research.
With CELLARTIS®, Takara Bio has expanded its portfolio to the field of Stem Cell research and its application, by offering culture systems, undifferentiated and differentiated cells, and services of iPS cells generation, engineering, and differentiation.

TAKEDA PHARMACEUTICALS INTERNATIONAL

One Takeda Parkway
Deerfield IL
60015 United States
+1 224-554-6500
www.takeda.us

ANNUAL MEETING BRONZE SUPPORTER

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

TAP BIOSYSTEMS (PART OF THE SARTORIUS STEDIM BIOTECH GROUP) - B16:28

York Way
Royston Herts
SG8 5WY United Kingdom
+44 0-176-322-7200
www.tapbiosystems.com

TAP Biosystems (now part of Sartorius) is a leading global provider of automated cell culture and fermentation systems to the bio-pharma, regenerative medicine and industrial biotechnology sectors. Sartorius is a leading provider of equipment and services for the development, quality assurance and production processes of the biopharmaceutical industries. At this event we will showcase: CompacT SelecT system for multiple cell line maintenance and assay-ready plate production and Cellmate system for batch production of cells in rollers bottles.

TERUMO BCT - B13:13

Ikaroslaan 41
Zaventem
1930 Belgium
+32 2-710-58-80
www.terumobct.com

Terumo BCT is a global leader in blood component, therapeutic apheresis and cellular technologies.

THERMO FISHER SCIENTIFIC - B06:32 AND B06:33

5225 Verona Rd.
Building 3
Madison WI
53711 United States
+1 608-276-6100
www.thermofisher.com

Thermo Fisher Scientific is the world leader in serving science. We help our customers accelerate life sciences research, solve complex analytical challenges, improve patient diagnostics and increase laboratory productivity. Through our premier brands – Thermo Scientific, Applied Biosystems, Invitrogen, Fisher Scientific and Unity Lab Services – we offer an unmatched combination of innovative technologies, purchasing convenience and comprehensive support.

TRANSPOSAGEN BIOPHARMACEUTICALS - B04:25

535 W. Second St.
Lexington KY
40508 United States
+1 859-428-8561
www.transposagenbio.com

Partner with us for leading cell engineering capabilities utilizing the most advancedgene editing technologies. Cell Line services available include stem cells, transformed cell lines and primary cells. Through strategic alliances, we can provide beginning-to-end solutions for pluripotent cell engineering, starting with iPS patient specific samples to differentiated cells.

TRINOVA BIOCHEM GMBH - B05:13

Rathenau Strasse 2
Giessen
35394 Germany
+49 641-943-900
www.trinova.de

TRINOVA Biochem is the European distributor of HemoGenix® (USA) providing cell assays for stem cell quality evaluation, research and cytotoxicity testing. The portfolio includes methylcellulose CFU-assays and automated 96-well proliferation assays for bioluminescence, fluorescence and absorbance. TRINOVA Biochem also offers Irvine Scientific® stem cell and primary cell culture media (Prime-XV-Line).

EXHIBITOR/SUPPORTER DIRECTORY

UK STEM CELL BANK - B13:11

Blanche Lane
South Mimms
EN6 3QG United Kingdom
+44 0-170-764-1500
www.nibsc.org

The UK Stem Cell Bank is a global supplier of human stem cell lines for research and clinical trials. We provide expert advice and training in stem cell biobanking and lead international best practice initiatives in bioprocessing pluripotent stem cell lines for cell therapy. Based at NIBSC we are also a key component in the UK infrastructure for regenerative medicine.

UNION BIOMETRICA, INC. - B05:33

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

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

UPM-KYMMENE CORPORATION - B11:11

Tekniikantie 2C
Espoo
02150 Finland
+358 40-558-7829
www.growdex.com

As the frontrunner of the new forest industry UPM leads the integration of bio and forest industries into a new, sustainable and innovation-driven future. We create value from renewable and recyclable materials.
In 2014, UPM's sales was € 10 billion. The company employs 20,000 people worldwide. UPM shares are listed on the NASDAQ OMX Helsinki stock exchange

WAKO PURE CHEMICAL INDUSTRIES LTD - B15:32

Fuggerstrasse 12
Neuss
41468 Germany
+49 2131-3111-55
www.wako-chemicals.de

Wako Pure Chemical Industries offers one of the most comprehensive product lines for a variety of research and development applications in the fields of Life Science, Pharmaceutical and Chemical Industry, as well as academic institutions.

THE WALLENBERG INSTITUTE FOR REGENERATIVE MEDICINE (WIRM)

ANNUAL MEETING CO-SPONSOR

Karolinska Institutet
Novum, 141 52 Huddinge
Sweden
+46 852-487-323
www.wirmki.se

The Wallenberg Institute for Regenerative Medicine (WIRM) aims to advance research on the blood system at Karolinska Institutet, both during normal hematopoietic development and in disease. WIRM also builds new important research infrastructure for stem cell research and regenerative medicine, ranging from a state-of-the-art FACS facility to supporting core facilities for cellular reprogramming/iPS, GMP production of clinical grade cells, and live cell imaging.

WICELL - B08:23

505 S. Rosa Rd.
120
Madison WI
53711 United States
+1 608-577-6625
www.wicell.org

WiCell distributes high quality human pluripotent cell lines (ES, iPS, disease model, and modified). WiCell is continually expanding offerings, and cell line deposits are encouraged. Cytogenetic services include karyotype, FISH, fastFISH, SKY, SNP/CGH microarray, and identity by STR. Additionally, customizable services (e.g. quality control testing, cell banking services) are offered, allowing laboratories to optimize limited resources. Learn more at www.wicell.org.

WILEY - B15:25
The Atrium Chichester
138628 United Kingdom
www.wiley.com

Wiley is a global provider of content-enabled solutions to improve outcomes in research, education and professional practice with online tools, journals, books, databases, reference works and laboratory protocols. With strengths in every major academic, scientific and professional field, Wiley proudly partners with over 800 prestigious societies representing two million members.

WORLD COURIER - B10:25
Söderbyvägen 1A
Stockholm - Arlandastad
19525 Sweden
+46 854-649-904
www.worldcourier.com

Trust. It's why more leading pharmaceutical companies rely on World Courier than any other specialty logistics company in the world. No other specialty logistics company has the experienced personnel, global offices and in-market expertise required to ensure the optimal handling, transport and delivery of vital healthcare products.

WUHAN HEATHGEN BIOTECHNOLOGY CO. LTD. - B09:17
No. 666 GaoXin Avenue
East Development Lake Zone
WUHAN
430075 China
+86 27-5940-3931
www.oryzogen.net

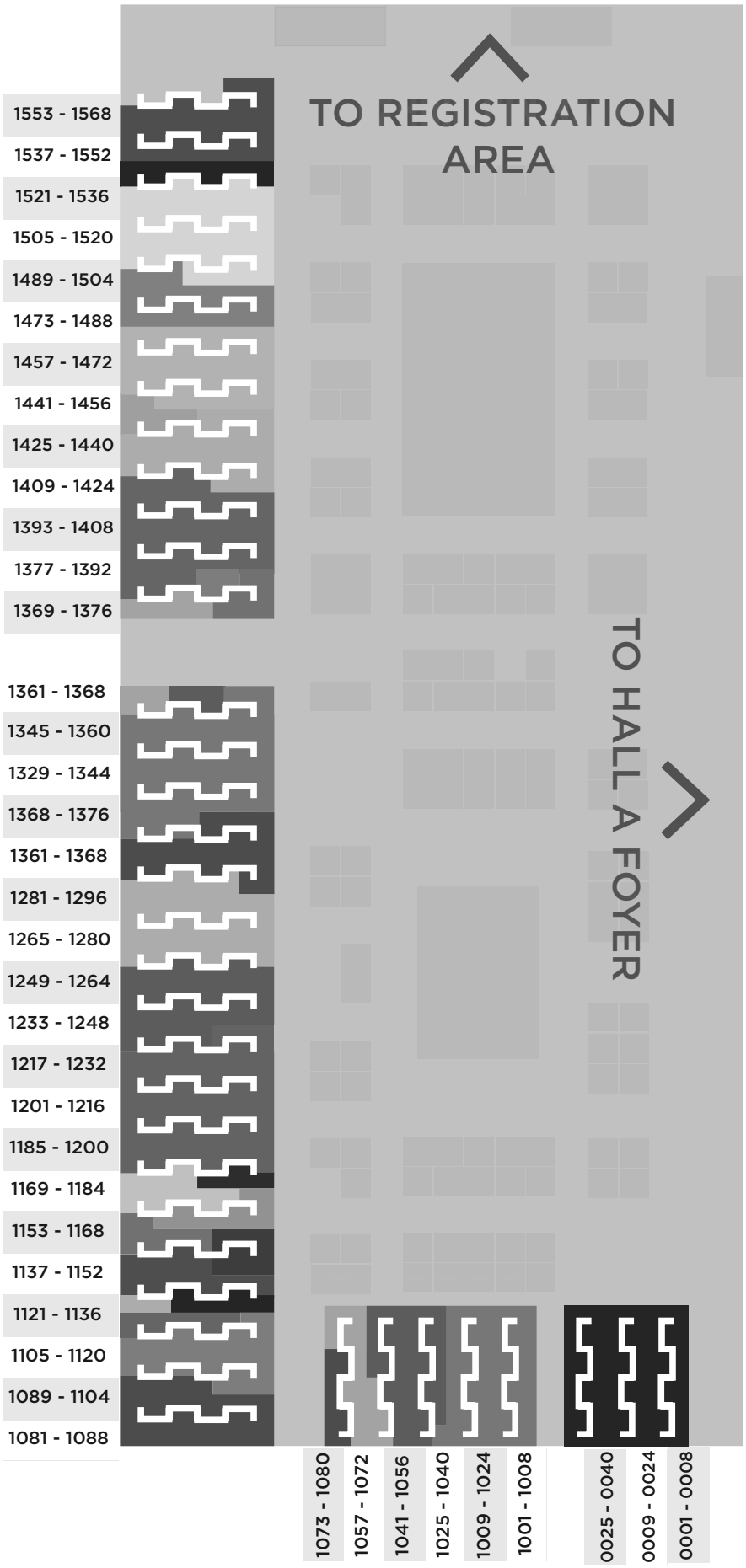
Healthgen Biotechnology has innovated one of the most expressive bioreactors OryzHiExp, which can highly express proteins and small peptides in cereal crop endosperm. We had successfully developed comprehensive products, including recombinant human serum albumin, recombinant bFGF, recombinant lactoferrin, recombinant IGF-1 and recombinant alpha-1 antitrypsin. All the recombinant components can optimize cell culture, improve protein productivity and shorten downstream process.

ZEISS - B10:21
Stockholm
Sweden
+46 845-925-00
www.zeiss.se

Throughout the world the name of Carl Zeiss stands for the highest quality and reliability. Carl Zeiss Microscopy is part of the Carl Zeiss group, a leading organization of companies operating worldwide in the optical industry.

Carl Zeiss Microscopy is a leading provider of microscope solutions in the life sciences.

MAP OF POSTER AREA (in Exhibition Hall)



POSTER TOPICS AND NUMBERS

Late Breaking Abstracts	0001-0040
Pre-clinical and Clinical Applications of Mesenchymal Cells	1001 - 1033
Mesenchymal Stem Cell Differentiation	1034 - 1060
Mesenchymal Cell Lineage Analysis	1061 - 1074
Hematopoietic Cells	1075 - 1101
Cardiac Cells	1102 - 1121
Muscle Cells	1122 - 1128
Kidney Cells	1129 - 1130
Pancreatic, Liver, Lung or Intestinal/Gut Cells	1131 - 1149
Endothelial Cells/Hemangioblasts	1150 - 1155
Epidermal Cells	1156 - 1161
Epithelial Cells (Not Skin)	1162 - 1169
Eye or Retinal Cells	1170 - 1180
Neural Cells	1181 - 1235
Reprogramming	1236 - 1264
iPS Cells	1265 - 1295
iPS Cells: Directed Differentiation	1296 - 1316
iPS Cells: Disease Modeling	1317 - 1362
iPS Cells: Epigenetics	1363 - 1366
Chromatin in Stem Cells	1367 - 1373
Germline Cells	1374 - 1377
Totipotent/Early Embryo Cells	1378 - 1380
Embryonic Stem Cell Differentiation	1381 - 1421
Embryonic Stem Cell Pluripotency	1422 - 1444
Embryonic Stem Cell Clinical Application	1445 - 1449
Tissue Engineering	1450 - 1480
Regeneration Mechanisms	1481 - 1499
Technologies for Stem Cell Research	1500 - 1536
Ethics and Public Policy; Society Issues; History of Stem Cell Research; Education and Outreach	1537 - 1544
Cancer Cells	1545 - 1570

AUTHOR INDEX

ISSCR 2015
ANNUAL MEETING
24-27 JUNE
Stockholmsmässan

AUTHOR INDEX

AUTHOR INDEX

AUTHOR INDEX

AUTHOR INDEX

M

AUTHOR INDEX

AUTHOR INDEX

AUTHOR INDEX

X

Y

Z