Welcome

Dear Colleagues:

On behalf of the International Society for Stem Cell Research, we are delighted to welcome you to our Annual Meeting, the world's pre-eminent gathering of scientists, researchers, clinicians and industry professionals devoted to stem cell research and regenerative medicine.

This year, on the occasion of our 12th Annual Meeting, we are proud to be in Vancouver, a city that features a vibrant biotech, life science and stem cell research community.

Our mission is to fuel scientific advancement by bringing together dedicated professionals from around the globe who share a passion for stem cell research. We have designed a diverse, engaging program that covers the latest findings in bioengineering, epigenetics, tissue repair, mesenchymal stromal cells, pluripotent stem cells and more.

Stem cell research is yielding fundamental scientific discoveries and unprecedented opportunities to cure disease. The ISSCR Annual Meeting provides an opportunity to share new data, learn from peers, and discover global advances within the stem cell field. With more than 3,600 professionals from more than 55 countries, the ISSCR Annual Meeting is the global source of the discoveries that are the basis for treatments of tomorrow.

The Annual Meeting features the largest exhibition hall dedicated to stem cell research. Our supporters and exhibitors help make our meeting possible. We encourage you to join us in thanking them for their support by exploring the newest tools and reagents to accelerate your research. Be sure to visit the ISSCR Central booth to pick up your June issue of Stem Cell Reports, get a glimpse of exclusive ISSCR Connect programming, and interact with other members at our membership station.

As always, we are grateful for your support - thank you for joining us. Whether you are learning about new discoveries during sessions, sharing ideas and making new connections at the poster receptions, or discovering new opportunities for your next collaboration at one of our special events, we believe you will agree that this year's meeting offers you an unprecedented opportunity to gain a comprehensive understanding of our important and dynamic field.

Best regards,

Fiona M. Watt
Program Chair

Janet Rossant
President

FROM THE CO-SPONSOR

STEMCELL™ TECHNOLOGIES

Scientists Helping Scientists™ | WWW.STEMCELL.COM

Dear Friends and Colleagues,

On behalf of my colleagues at STEMCELL Technologies, I would like to welcome you to the 12th Annual Meeting of the International Society for Stem Cell Research (ISSCR) here in beautiful Vancouver, British Columbia. Vancouver is blessed by nature, being situated on a sheltered inlet, surrounded by mountains that are snowcapped for most of the year, with a temperate climate - by Canadian standards! Protection of this magnificent environment is very important to us and that is why we are delighted to host this meeting in the Vancouver Convention Center, which is one of the greenest convention centers in the world. It features a living roof, seawater heating and cooling, and a fish habitat built into the foundation.

This conference comes at a time of exponential growth in our understanding of stem cell biology, with the horizons for potential new therapies becoming less distant each day. The ISSCR meeting is an opportunity for the best minds in this space to come together to share information, debate ideas and explore new frontiers.

As "Scientists Helping Scientists", we at STEMCELL Technologies are proud to support the exchanges and collaborations that will occur over the coming days. STEMCELL Technologies is a biotechnology company that develops specialty cell culture media, cell separation products and accessory reagents for life science research. Driven by science and a passion for quality, we deliver over 1500 products to more than 70 countries worldwide.

Vancouver is our home and we are very proud and privileged to be your host over the coming days. We hope that you enjoy the city and the beautiful surroundings, and have a successful and productive conference.

Warmest regards,

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

FROM THE PREMIER OF BRITISH COLUMBIA

BRITISH COLUMBIA

June 18-21, 2014

As Premier of the Province of British Columbia, it gives me great pleasure to welcome delegates to the International Society for Stem Cell Research 12th Annual Meeting, here at the Vancouver Convention Centre.

Each year this event brings together professionals in the area of stem cell research to share important information and discuss the latest research and practices. This collaborative atmosphere allows for great innovation and progress in the field, while also doing so much in promoting the importance of stem cell research and raising public awareness and understanding.

I would like to thank the co-sponsors, Stemcell Technologies, along with 2014 Program Committee, for their efforts in bringing the Annual Meeting to Vancouver and ensuring it is a great success. With such a variety of speakers addressing a range of issues, this will no doubt be an informative and productive event.

To those of you visiting from outside British Columbia, I hope you will enjoy your stay and have an opportunity to explore some of the beauty and charm this region of the province has to offer. Please accept my best wishes for an interesting and productive Annual Meeting.

Sincerely,

Christy Clark
Premier

FROM THE MAYOR OF VANCOUVER

CITY OF VANCOUVER

Mayor Gregor Robertson
Le maire Gregor Robertson
羅品信市長
ਗਰੈਗਰ ਰੌਬਰਟਸਨ, ਮੇਅਰ
Punong-bayan Gregor Robertson

niʔ ct xaɬəməɬəl̓, tə ɬniməɬ, tə təməxʷ ʔiʔ tə k̓ʷaχ̓kʷə l *
We watch over the land and sea and in turn they watch over us.

June, 2014

A Message from the Mayor

On behalf of the citizens of Vancouver, and my colleagues on City Council, I want to extend my warmest greetings to everyone attending the 2014 International Society for Stem Cell Research's 12th Annual Meeting in Vancouver.

The City of Vancouver is committed to building a sustainable and thriving health care system. By working to foster dialogue and the exchange of ideas we will ensure our communities are well cared for and receive the most up-to-date health care.

We are also very proud of the reputation Vancouver enjoys as one of the world's most beautiful and unique meeting destinations. I hope that in addition to attending the conference you are able to experience the many cultural and recreational activities the City has to offer. I know everyone involved in organizing the conference will ensure your time with us is special.

Once again, welcome to Vancouver, and I hope you enjoy the conference.

Yours truly,

Gregor Robertson
MAYOR

604.873.7621 604.873.7685 gregor.robertson@vancouver.ca vancouver.ca
Office of the Mayor, City of Vancouver, 453 West 12th Avenue, Vancouver, British Columbia, Canada V5Y 1V4


Tourism Vancouver / Vancouver Convention Centre

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STEMCELL™ TECHNOLOGIES

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STEMCELL Technologies is dedicated to providing standardized reagents and tools for all areas of stem cell research. Driven by science and a passion for quality, we provide over 1500 products to more than 70 countries worldwide. Maximize Your Pluripotential with the most complete, defined system for pluripotent stem cell reprogramming, maintenance and differentiation. We are committed to working with you as Scientists Helping Scientists. Access our knowledgeable technical support team and staff scientists through educational programs and training courses, or speak with them directly by phone. To learn more, please visit **www.stemcell.com**

GOLD

BD

CALIFORNIA'S STEM CELL AGENCY CIRM California Institute for Regenerative Medicine

Cell Stem Cell

CCRM Centre for Commercialization of Regenerative Medicine

janssen PHARMACEUTICAL COMPANIES OF Johnson & Johnson

STEMCELLS

SILVER

- Burroughs Wellcome Fund
- Cellular Dynamics International
- The Centre for Drug Research and Development (CDRD)
- Fate Therapeutics
- Fluidigm Corporation
- Life Technologies
- Mesoblast Ltd
- The New York Stem Cell Foundation Research Institute
- R&D Systems, Inc.
- Stem Cell Network

BRONZE

- BioLamina
- CIHR Institute of Cancer Research
- CIHR Institute of Genetics
- CIHR Institute of Neurosciences, Mental Health, and Addiction
- Harvard Stem Cell Institute
- The Hospital for Sick Children Research Institute
- Institute for Stem Cell & Regenerative Medicine at the University of Washington
- Lieber Institute for Brain Development
- Massachusetts General Hospital Center for Regenerative Medicine
- Nature Publishing Group
- Ontario Brain Institute
- Ontario Stem Cell Initiative (OSCI)
- Sanofi US
- Stem Cell Program at Boston Children's Hospital
- Stemgent, Inc.
- Takeda Pharmaceuticals

CONTRIBUTORS

- Genentech, Inc.
- JDRF
- Novartis AG
- Vertex Pharmaceuticals

SPECIAL EVENTS

JUNIOR INVESTIGATOR EVENTS

Attend networking and career-building sessions designed specifically for trainee members. Advance registration for these events is required. If you have not registered, check with the registration desk to see if there are slots still available.

MEET THE EXPERTS NETWORKING LUNCHES

Thursday, June 19
11:30 AM – 1:00 PM
West Level 2 Oceanside Foyer
Supported by the Institute for Stem Cell and Regenerative Medicine, University of Washington

Friday, June 20
11:30 AM – 1:00 PM
West Level 2 Oceanside Foyer
Supported by Takeda Pharmaceuticals

These popular networking events provide the opportunity for trainee members to meet stem cell leaders in a casual setting. Enjoy lunch and a small group discussion with fellow colleagues and a leading expert in the field. Experts will come from a variety of settings including industry, publishing, academia, and scientific laboratories and research centers.

JUNIOR INVESTIGATOR SOCIAL NIGHT

Thursday, June 19
9:30 PM – 1:00 AM
Commodore Ballroom,
868 Granville Street, Vancouver

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 dancing and entertainment will take place at Vancouver's historic nightclub, the Commodore Ballroom, located in the heart of the city's entertainment district and a short distance from the Vancouver Convention Centre.

ISSCR Badge and Photo ID required for entry. Must be 19 years or older for admittance.

CAREER PANEL: STRATEGIES FOR SUCCESS: TRANSITION TO AN INDEPENDENT CAREER

Saturday, June 21
11:30 AM – 1:00 PM
West Level 2 Oceanside Foyer

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

The transition to an independent career can be intimidating. Let our panel of experts guide you through key steps on the road to becoming an independent investigator. What qualities and experiences are hiring committees looking for? Once you get your job, how do you successfully compete for funding and write a winning grant application? How do you best learn to direct your group within the lab? Our panelists will share their own experiences, strategies and mistakes.

EARLY CAREER GROUP LEADER LUNCHEON
RESEARCH EXCELLENCE: TOWARDS A RELIABLE LITERATURE

Wednesday, June 18
11:30 AM – 1:00 PM

West Level 2 Oceanside Foyer
Advanced registration is required.
Supported by the Ontario Stem Cell Initiative

The ISSCR Board of Directors invites early-career group leaders to join them for table-level conversations followed by a group discussion exploring ways to promote rigor and integrity in publishing.

SPECIAL EVENTS

INDUSTRY WEDNESDAY SYMPOSIUM

Wednesday, June 18
8:30 AM – 12:30 PM
Open to all Annual Meeting attendees. Advance registration is not required.

CONQUERING ROADBLOCKS ASSOCIATED WITH STEM CELL DIFFERENTIATION AND DISEASE MODELING

Presented by Thermo Fisher Scientific
West Ballroom C/D

In this symposium, we will discuss challenges associated with stem cell differentiation, disease modeling, and regenerative medicine applications. We will offer solutions and tools to more effectively initiate and manipulate differentiation towards different lineages, demonstrate how genomic editing technologies can be used to specifically modify disease-relevant genes in stem cells. We also hope to start an intriguing discussion about bridging cutting-edge technologies and downstream applications upon finding a point of compromise in setting standards for industrializing pluripotent stem cells. Finally, we will explore principles for maintaining cryogenic temperatures to meet the challenges that exist in cold chain logistics for clinical trials.

8:30 AM – 8:45 AM	INTRODUCTION **Drs. Cindy Neeley and Mark Powers,** *Thermo Fisher Scientific*
8:45 AM – 9:30 AM	EFFICIENT CELL SPECIFIC DIFFERENTIATION SYSTEMS FOR IPSC **Mohan Vemuri, Ph.D.,** *R&D Leader (Cell Biology), Life Sciences Solutions Group, Thermo Fisher Scientific*
9:30 AM – 10:00 AM	THERMO SCIENTIFIC™ NUNCLON™ SPHERA – A NOVEL SURFACE TO SUPPORT THE THREE-DIMENSIONAL CULTURE OF STEM CELLS IN SUSPENSION **Laura Jensen, Ph.D.,** *Research Scientist, Laboratory Consumables Division, Thermo Fisher Scientific*
10:00 AM – 10:45 AM	EXPLORE STANDARDS FOR INDUSTRIALIZING PLURIPOTENT STEM CELLS **Hidemasa Kato, Ph.D.,** *Saitama Medical University, Research Center for Genomic Medicine*
11:00 AM – 11:45 AM	CREATION OF IPSC-BASED MODEL SYSTEMS TO STUDY PARKINSON'S DISEASE **Kurt Vogel, Ph.D.,** *Consultant, Life Sciences Solutions Group, Thermo Fisher Scientific*
11:45 AM – 12:30 PM	PHYSICS OF FAILURE: HOW MOTHER NATURE CONSPIRES TO RUIN YOUR CLINICAL TRIAL BEFORE YOU SHIP YOUR FIRST DOSE **Dan H. O'Donnell,** *Director of Cell Therapy Logistics, Fisher BioServices*

WEDNESDAY FOCUS SESSIONS

Wednesday, June 18
8:30 AM – 12:30 PM *
Open to all Annual Meeting attendees. Advance registration is not required. * Exact times may vary.

ENGAGING THE ENGINE: HOW PUBLIC/PRIVATE PARTNERSHIPS BETWEEN ACADEMIA AND INDUSTRY CAN FACILITATE MORE EFFICIENT TRANSLATION

Presented by the ISSCR Industry and Junior Investigators Committees
West Ballroom B

Collaborative partnerships between the private and public funding sectors have successfully delivered the translation of exciting science into clinical or commercial reality in other sectors by accelerating technology development. With their operational model, such partnerships afford a

SPECIAL EVENTS

versatile way in which investigators – both well established and newly appointed – can build relationships with research collaborators in industry. Join us as we hear from representatives of global initiatives and participate in a panel discussion to discover what has and hasn't worked well.

8:20 AM – 8:40 AM **PART I: CASE STUDIES**
Introduction: Timothy Allsopp, *Neusentis Regenerative Medicine*

8:40 AM – 10:00 AM **Moderator: Garrett Heffner,** *Bluebird Bio, Inc.*
Peter W. Andrews, *University of Sheffield*
Robert J. Deans, *Athersys Inc.*
Beth Hill, *Johnson & Johnson*
Michael May, *Centre for Commercialization of Regenerative Medicine*

10:30 AM – 11:45 AM **PART II: INTERACTIVE PANEL DISCUSSION AND AUDIENCE DISCUSSION**
Moderators: Timothy Allsopp, *Neusentis Regenerative Medicine* and **Lauren Drowley,** *AstraZeneca*
Beth Hill, *Johnson & Johnson*
Martin Pera, *The University of Melbourne*
Alan Trounson, *California Institute of Regenerative Medicine*
Brock Reeve, *Harvard Stem Cell Institute*
Charles Kessler, *European Commission DG Research & Innovation*
Margaret Sutherland, *NIH/NINDS*

TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY

Presented by COREdinates and WiCell Research Institute
West Ballroom A

Session 1: COREdinates: Core Faculty Consortium
Stem cell core facilities test, validate and standardize new technologies. We created a network of pluripotent stem cell core facilities (Stem Cell COREdinates) to save time, prevent duplication of resources and increase sampling across institutions. Most of our member labs focus on pluripotent stem cell culture, iPSC generation, engineering, differentiation and clinical work. Our goal is to share our experiences with each other and the field as a whole. This year, six of our member labs will present talks ranging from the role that stem cell cores plays to advance science and ending with the path to develop stem cell therapeutics.

Session 2: Advancing Stem Cell Treatments: Building Better Models
This focus session will bring together academic, pharmaceutical industry, and cure advocacy researchers who work on a variety of neural and muscular disorders to discuss current research tools, iPS cell-derived models, and the fields unmet needs. ISSCR members interested in the development of stem cell disease models, including genetic reprogramming tools and screening mechanisms involved, will benefit from the opportunity to engage panelists with diverse and unique viewpoints.

8:30 AM – 10:00 AM **PART I: COREdinates: CORE FACULTY CONSORTIUM**
Introduction and Moderator: Mark Tomishima, *COREdinates / Memorial Sloan-Kettering Cancer Center*
Richard Gronostajski, *University of Buffalo*
Jen Moore, *RUCDR*
Wenli Yang, *University of Pennsylvania*
Deborah French, *Children's Hospital of Philadelphia*
Sandra Engle, *Pfizer*
Stefan Irion, *Sloan Kettering Institute*

10:30 AM – 11:45 AM **PART 2: INTERACTIVE PANEL DISCUSSION-ADVANCING STEM CELL TREATMENTS: BUILDING BETTER MODELS**
Moderator: Timothy Kamp, *University of Wisconsin*
Lorenz Studer, *Sloan Kettering Institute*
Michelle Calos, *Stanford University*

SPECIAL EVENTS

Derek Hei, *Waisman Biomanufacturing*
Glyn Stacey, *National Institute for Biological Standards and Controls (NIBSC)*
Claudia Mitchell, *Limb Girdle Muscular Dystrophy 2I Research Fund*
Su-Chun Zhang, *University of Wisconsin-Madison*

ETHICS, STEM CELLS AND THE INFORMATION AGE

Presented by the ISSCR Ethics and Public Policy Committee
West Meeting Room 301-305

In recent years, science has been transformed by the emergence of various information technologies. Most ethical debates within the stem cell arena have centered on the materials we use to produce the information: the human subjects, embryos, and chimeras. This session will focus on ethical issues pertaining to information in the stem cell sciences, including recent initiatives surrounding the deposition, publication, circulation, and reuse of information.

THE ESTABLISHMENT OF GLOBAL RESOURCE NETWORKS FOR iPSC RESEARCH

Presented by RUCDR Infinite Biologics, Rutgers University
West Meeting Room 211-214

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.

8:30 AM – 10:00 AM

PART I: LARGE SCALE iPSC INITIATIVES AROUND THE WORLD

Moderator: Michael Sheldon, *RUCDR Infinite Biologics*
Michael P. Yaffe, *California Institute for Regenerative Medicine*
Ludovic Vallier, *Cambridge Biomedical Research Centre hIPSC core facility*
Chihiro Akazawa, *Tokyo Medical and Dental University (TMDU)*
Scott Noggle, *New York Stem Cell Foundation (NYSCF) Laboratory*

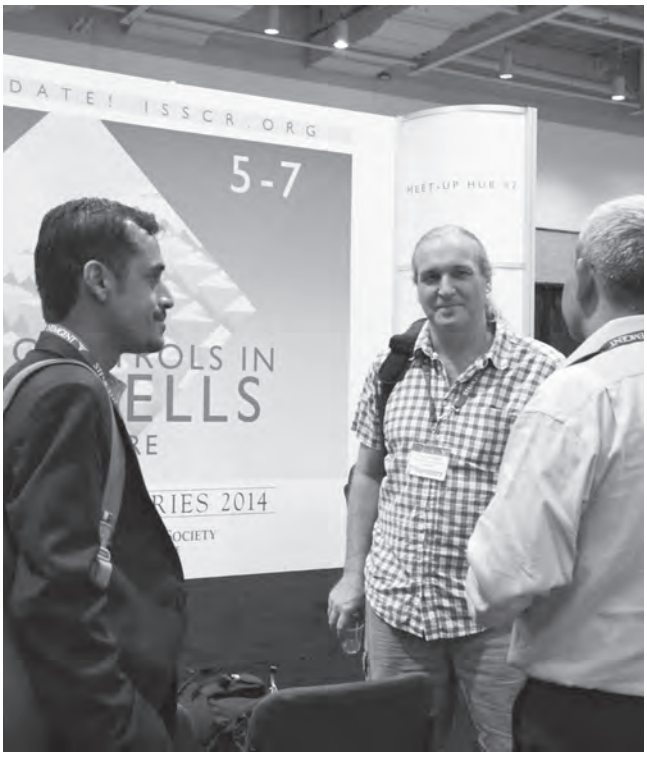
10:30 AM -12:15 PM

PART II: ESTABLISHING A GLOBAL NETWORK OF RESOURCES

David Panchision, *National Institute of Mental Health, NIH*
Christian Freund, *Leiden University Medical Centre*
Michael Sheldon, *RUCDR Infinite Biologics*
Tenneille Ludwig, *WiCell Stem Cell Bank*
Russ Hager, *BioStorage Technologies, Inc.*
Ludovic Vallier, *Cambridge Biomedical Research Centre*

SPECIAL EVENTS

MEET-UP SESSIONS



VISIT THE MEET-UP HUBS IN THE EXHIBITION HALL FOR A COMPLETE LIST OF PLANNED MEET-UPS EACH DAY.

MEET THE EDITORS OF STEM CELL REPORTS

Thursday, June 19
3:15 PM – 4:00 PM
Singapore Hub, West Exhibition Hall

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 second year.

CONTINUING THE CONVERSATION: HOW PUBLIC/ PRIVATE PARTNERSHIPS BETWEEN ACADEMIA AND INDUSTRY CAN FACILITATE MORE EFFICIENT TRANSLATION

Thursday, June 19
3:15 PM – 4:00 PM
Stockholm Hub, West Exhibition Hall

Following the Wednesday Focus Session Presented by the ISSCR Industry and Junior Investigators Committees, join us to continue our discussion on how collaborative partnerships between the private and public funding sectors have successfully delivered the translation of exciting science into clinical or commercial reality. Network with the panelists and your co-attendees from the sessions and be sure to bring any follow-up questions from the Focus Sesssion.

EXPLORING CAREERS OUTSIDE OF ACADEMIA

Friday, June 20
3:15 PM – 4:00 PM
Stockholm Hub, West Exhibition Hall

This Meet-up is a great way to connect with scientists who have moved from academia to work in areas including pharma, biotech, and publishing. This is your opportunity to learn about their career paths and what it is like to work at their companies. If you have ever thought about a career outside academia but weren't sure of the right path to get there, this is a must-attend event. This Meet-up will be held speed-dating style, so you will have the chance to speak with multiple representatives from the field.

GENERAL INFORMATION

REGISTRATION

REGISTRATION AND BADGE PICKUP

Pick up your attendee name badge at the Vancouver Convention Centre (VCC) West Level 1 Foyer during posted hours. Bring your confirmation email with bar code for faster badge retrieval. Name badges are required for admission to all sessions and the Exhibition Hall. Badges may be picked up during the following times:

Tuesday, June 17	2:00 PM - 6:00 PM
Wednesday, June 18	7:30 AM - 8:00 PM
Thursday, June 19	7:30 AM - 6:00 PM
Friday, June 20	7:30 AM - 5:00 PM
Saturday, June 21	8:00 AM - 5:00 PM

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

MEDIA ROOM

Credentialed members of the media may use work stations, wireless internet, and printer during posted hours in West Meeting Room 101-102 near the registration area. Please visit the media office for media panel details.

Wednesday, June 18	8:00 AM - 4:00 PM
Thursday, June 19	8:00 AM - 4:00 PM
Friday, June 20	7:30 AM - 4:00 PM
Saturday, June 21	8:00 AM - 12:00 PM

MEDIA PANELS

Thursday, June 19	11:30 AM - 12:30 PM
Friday, June 20	7:45 AM - 8:45 AM

LOST AND FOUND

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

TOURISM VANCOUVER DELEGATE SERVICES

Visit the Tourism Vancouver hospitality desk in the registration area (West Level 1 Foyer) to plan your dining, activities, and tours.

Tuesday, June 17	2:00 PM - 6:00 PM
Wednesday, June 18	8:30 AM - 6:00 PM
Thursday, June 19	8:30 AM - 6:00 PM
Friday, June 20	8:30 AM - 6:00 PM
Saturday, June 21	8:30 AM - 5:00 PM

MESSAGE CENTER

Post messages for friends and colleagues using the message board in the registration area (West Level 1 Foyer). 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 boards located in the West Level 1 Foyer.

GENERAL INFORMATION

EXHIBITION HALL

Decompress in the Vancouver Convention Centre's Exhibition Hall (West Exhibition Level). Find business solutions from exhibiting companies, relax in the ISSCR Lounge with coffee during breaks, participate in a Meet-Up Hub session, browse posters or visit ISSCR Central to mark your home location on the world map. You can also learn more about streaming Annual Meeting sessions after the meeting on ISSCR Connect.

The ISSCR 12th Annual Meeting Exhibition Hall features nearly 150 leading suppliers and vendors. Walk through the hall and support ISSCR Exhibitors who help make this meeting possible.

EXHIBITION HALL HOURS

Wednesday, June 18	3:30 PM - 8:30 PM
Thursday, June 19	11:00 AM - 8:00 PM
Friday, June 20	11:00 AM - 8:00 PM
Saturday, June 21	11:00 AM - 3:30 PM

NOTE: The Exhibition Hall is closed mornings. Poster presenters must hang their posters during scheduled poster set-up hours.

BREAKS AND POSTER PRESENTATION RECEPTIONS

Enjoy refreshment breaks and poster presentation receptions in the West Exhibition Level.

REFRESHMENT BREAKS IN THE PLENARY HALL FOYER

Thursday, June 19 - Saturday, June 21 8:00 AM - 9:00 AM

REFRESHMENT BREAKS IN THE EXHIBITION HALL

Wednesday, June 18	3:20 PM - 4:00 PM
Thursday, June 19	3:05 PM - 4:00 PM
Friday, June 20	3:05 PM - 4:00 PM
Saturday, June 21	3:00 PM - 3:40 PM

POSTER RECEPTIONS IN THE EXHIBITION HALL

Wednesday, June 18	6:30 PM - 8:30 PM
Thursday, June 19	6:00 PM - 8:00 PM
Friday, June 20	6:00 PM - 8:00 PM

CLOSING RECEPTION IN THE WEST BALLROOM FOYER

Saturday, June 21	6:00 PM - 7:00 PM

ISSCR CENTRAL

Find out what's new at ISSCR; collaborate with colleagues; check your email; plan your day and charge your portable devices in the center of the Exhibition Hall. Visit ISSCR Central to find out more about:

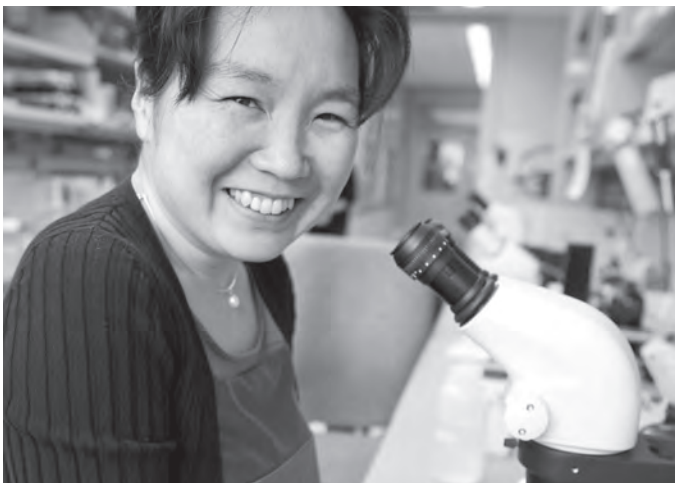
- ISSCR 13th Annual Meeting in Sweden and the Stockholm Visitor's Bureau
- ISSCR Connect webinars
- ISSCR member benefits
- ISSCR2014 mobile app assistance
- Stem Cell Report's one-year commemorative issue
- ISSCR's Twitter wall following the latest posts on #ISSCR2014

MEET-UP HUBS

Collaborate with your colleagues from around the world at Meet-Up Hubs in the Exhibition Hall. Helping researchers connect and share their work is the core of the ISSCR mission. Attend a Meet-Up Hub session to network with and learn from peers who share your particular passion. See Page 5 for descriptions of some of the scheduled Meet-ups.

ISSCR LOUNGE

The ISSCR Lounge in the Exhibition Hall offers charging stations for your mobile devices and seating to relax, visit with colleagues and recharge your batteries.



GENERAL INFORMATION

THINGS YOU SHOULD KNOW

RECORDINGS PROHIBITED

Still photography, video and/or audio taping of the sessions, presentations and posters at the ISSCR 12th Annual Meeting is strictly prohibited. Additionally, blogging, tweeting and other intent to communicate or disseminate results or discussion presented at the meeting is prohibited until the start of each individual presentation. Thank you for your cooperation.

SMOKING

Smoking is prohibited in the Vancouver Convention Centre.

INTERNET ACCESS

Enjoy complimentary Wi-Fi throughout the Vancouver Convention Centre thanks to our sponsor STEMCELL Technologies. A limited number of computer kiosks are also available at ISSCR Central in the Exhibition Hall. To connect to Wi-Fi:

- Enable your wireless and search for open networks
- Connect to the network called ISSCR_2014
- Open a web browser
- You will be redirected to the login page
- After accepting the terms and conditions, click connect

ISSCR2014 MOBILE APP

Have the Annual Meeting schedule in the palm of your hand. Download the free OASIS Mobile Meeting Planner Mobile App from the Apple Store or Google Play to your smart phone, tablet or laptop to have immediate access to many features in support of your Annual Meeting program experience:

- Build your personal itinerary on your mobile device or synchronize with the itinerary you built on the web-based program planner
- Browse or search for scientific content, presenters, exhibitors or events
- Transfer your itinerary to your device calendar or Outlook
- Take notes directly regarding sessions, speakers and exhibitors and export via email
- Receive up-to-the-minute updates and location information
- Browse through floor plans of the Exhibition Hall and the Vancouver Convention Centre

Need help accessing the Mobile App? Visit ISSCR Central or the registration area for access assistance.

COAT CHECK

For your convenience, complimentary coat check will be available in a designated zone near the registration area. Luggage will not be accepted.

Wednesday, June 18	8:00 AM – 9:00 PM
Thursday, June 19	7:00 AM – 8:30 PM
Friday, June 20	7:00 AM – 8:30 PM
Saturday, June 21	7:00 AM – 7:30 PM

MOTHERS' ROOM

West Meeting Room 103, near the registration area, is a semi-private room available Wednesday through Saturday, 8:00 AM - 5:00 PM. 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 West Meeting Rooms 114-115, 116, and 117. Sign-up sheets are posted outside each room listing available time slots for each day. Informal seating areas are also available throughout the Vancouver Convention Centre and Meet-Up Hubs in the Exhibition Hall.

PARKING

Parking is available at the Vancouver Convention Centre, West Building for $30 CND daily; $90 CND for four days.

SHOW YOUR BADGE FOR DISCOUNTS

Enjoy discounts at many Vancouver restaurants, bars, tours, museums, spas, and even whale watching just by showing your Annual Meeting badge at participating businesses. Find out more by visiting the Tourism Vancouver Delegate Services desk in the registration area.

GENERAL INFORMATION

NEARBY RESTAURANTS AND CAFÉS

There are many dining options in and around the Vancouver Convention Centre, across from the Vancouver Convention Centre or via an underground walkway from the Vancouver Convention Centre, East Building, the Waterfront Centre Food Court offers many dining options Monday – Saturday, 9:30 AM to 5:30 PM.

Locate affordable local food trucks in downtown Vancouver at **http://streetfoodapp.com/vancouver.**

Other restaurants within walking distance of the Vancouver Convention Centre include:

MAHONY & SONS PUBLIC HOUSE - COAL HARBOUR
#36-1055 Canada Place
Vancouver, BC V6C 0C3
604.647.7513
http://mahonyandsons.com

CAFE PACIFICA - PAN PACIFIC VANCOUVER
300 - 999 Canada Place
Vancouver, BC V6C 3B5
604.895.2480
www.panpacificvancouver.com/dining

DE DUTCH - VANCOUVER CONVENTION CENTRE
60 - 1055 Canada Place
Vancouver, BC V6C 3T4
604.647.7530
www.dedutch.com

HAPA IZAKAYA - COAL HARBOUR
909 West Cordova Street, Waterfront Centre Office Tower, Cordova Street Entrance
Vancouver, BC V6C 0A7
604.340.6202
http://www.hapaizakaya.com

BELLAGGIO LAZIZA
1055 Canada Place, Suite 26
Vancouver, BC V6C 0C3
604.568.9777
www.laziza.ca

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West Level 1
Monday – Friday 7:00 AM -5:00 PM
Saturday 8:00 AM – 5:00pm

FEATURED SPEAKERS

PRESIDENTIAL SYMPOSIUM
Wednesday, 1:00 PM

Olivier Pourquié
Strasbourg University Medical School, France

Olivier Pourquié is currently Professor at Strasbourg University Medical School in France. He was the director of the Institute for Genetics and Molecular and Cellular Biology in Strasbourg from 2009 to 2012 and prior to that he was a Howard Hughes Medical Institute Investigator at the Stowers Institute for Medical Research in Kansas City, USA. His lab provided the first evidence of the existence of a molecular oscillator -the segmentation clock- associated to the rhythmic production of vertebral precursors (the somites) in the embryo. This discovery was listed as one of 25 milestones in Developmental Biology in the 20th century by *Nature* magazine.

Brigid L. M. Hogan
Duke University Medical Center, USA

Brigid L. M. Hogan is a developmental biologist noted for her contributions to stem cell research and transgenic technology and techniques. She is the George Barth Geller Professor of Research in Molecular Biology and Chair of the Department of Cell Biology at Duke University, as well as the director of the Duke Stem Cell Program. Research in the Hogan lab is focused on the basic mechanisms underlying organogenesis and tissue regeneration, and how these processes involve stem and progenitor cells. They study the development, maintenance, and repair of the fore gut and lung, using the mouse as a model genetic organism. Believing that that basic knowledge about the regulation of lung progenitor cell behavior, proliferation and differentiation will yield important insights into clinical problems, the Hogan lab investigations delve into the development of the lungs of very low weight premature babies, the abnormal differentiation and remodeling of airways of patients with COPD, cystic fibrosis and chronic asthma, and the over-proliferation of matrix producing cells in lung fibrosis.

Gordon M. Keller
McEwen Centre for Regenerative Medicine, Canada

Gordon M. Keller is the Director of the McEwen Centre for Regenerative Medicine at the University Health Network in Toronto, Canada. Dr. Keller is also a founding member and past president of the Board of Directors of the International Society of Stem Cell Research and is a member of the Scientific Advisory Board for the Burnham Institute for Medical Research. Throughout his remarkable career, Dr. Keller has received numerous awards, including the "100 Alumni of Influence" Alumni award from the University of Saskatchewan and a Tier I Canada Research Chair in Embryonic Stem Biology. Dr. Keller is best known for his breakthrough success to differentiate human embryonic stem (ES) cells into cardiac lineages. His current research aims to elucidate a better understanding of the mechanisms that control mesoderm and endoderm induction and specification in mouse and human embryonic stem (ES) cell cultures. His studies focus specifically on the generation of the following derivative lineages: hematopoietic, vascular, cardiac, hepatic and pancreatic.

Lorenz Studer
Sloan Kettering Institute for Cancer Research, USA

Lorenz Studer is Director of the Sloan Kettering Center for Stem Cell Biology, a Member of the Memorial Sloan Kettering Cancer Center (MSKCC) Developmental Biology Program and a Professor in Neuroscience at Weill Cornell Medical College. A native of Switzerland, Dr. Studer graduated from medical school in 1991 and received his doctoral degree in Neuroscience at the University of Bern in 1994. As a postdoctoral fellow he joined the laboratory of Ron McKay at the NIH in Bethesda, Maryland where he demonstrated the first successful use of in vitro derived dopamine neurons in an animal model of Parkinson's disease. In 2000, he started his own research program at the MSKCC in New York, NY. His lab pioneered strategies for the directed differentiation of pluripotent stem cells. He also developed some of the first iPS cell-based disease models and is currently leading a large effort towards the clinical application of human pluripotent stem cells in Parkinson's disease.

FEATURED SPEAKERS

ERNEST MCCULLOCH MEMORIAL LECTURE

Plenary II, Wednesday, 5:40 PM

Connie J. Eaves

Terry Fox Lab, British Columbia Cancer Agency, Canada

Connie Eaves received her PhD in Immunology from the University of Manchester in the UK. She continued her post-doctoral training in experimental hematology at the Ontario Cancer Institute. Dr. Eaves and her husband co-founded the Terry Fox Laboratory in 1981, at the BC Cancer Agency and together built an internationally recognized research program in normal and cancer stem cell biology, leukemia and bone marrow transplantation. Throughout her training and subsequent productive scientific career she has received numerous awards and scholarships. She was elected a Fellow of the Royal Society of Canada in 1993 and, in 2003, she received the prestigious Robert L. Noble Prize for Excellence in Cancer Research from the National Cancer Institute of Canada. She is widely recognized as a world authority on the stem cells of the blood-forming system and their regulation in both normal and perturbed states, with a particular emphasis on chronic myeloid leukemia (CML). Since the early 1990s she has extended her contributions in understanding stem cell behavior to normal and malignant breast cells.

ANNE MCLAREN MEMORIAL LECTURE

Plenary IV, Friday, 10:45 AM

Robin Lovell-Badge

MRC National Institute for Medical Research, UK

Dr. Robin Lovell-Badge is Head of the Division of Stem Cell Biology and Developmental Genetics at the MRC National Institute for Medical Research in London, UK. Dr. Lovell-Badge has had long-standing interests in the biology of stem cells, in how genes work in the context of embryo development, and how decisions of cell fate are made. Major themes of his current work include sex determination, development of the nervous system, and the biology of stem cells within the early embryo, the CNS and the pituitary. He is also very active in both public engagement and policy work, notably around stem cells, genetics, human embryo and animal research, and in ways science is regulated and disseminated.

KEYNOTE ADDRESS

Plenary VII, Saturday, 5:10 PM

Susan Lindquist

Whitehead Institute for Biomedical Research, USA

Susan Lindquist is a member of Whitehead Institute, Professor of Biology at MIT, and a Howard Hughes Medical Institute investigator. Dr. Lindquist has shown that forces governing protein folding have a profound and unexpected impact on evolution and human disease. She discovered the disaggregating abilities of heat-shock proteins, identified prions as conduits of protein-based inheritance, and pioneered the use of yeast as a model system to study complex diseases and develop novel therapeutic strategies. Her work on the heat shock protein Hsp90 changed paradigms in evolutionary biology, showing that Hsp90 buffers naturally occurring variation allowing it to accumulate in a silent state and releasing it in times of stress. These findings provide the first plausible explanation for rapid bursts of evolution. Her lab has further established that the heat-shock response plays a key role in the evolution of fungal drug resistance and tumor progression.

2014 ISSCR AWARDS

JOIN US IN HONORING THE RECIPIENTS OF THE 2014 ISSCR AWARDS

McEWEN AWARD FOR INNOVATION
Presidential Symposium, Wednesday, 1:00 PM

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.

Azim Surani, PhD, Wellcome Trust/Cancer Research UK Gurdon Institute, UK, is the recipient of the 2014 McEwen Award for Innovation. He is recognized for his work on the cellular and molecular specification of the mammalian germ cell lineage. His research has helped uncover how the germ line is established and what molecular mechanisms are responsible for reprogramming the epigenome to achieve the totipotent state.

Join us for the 2014 award presentation which will take place during the Presidential Symposium on the afternoon of Wednesday, June 18.

ISSCR-BD BIOSCIENCES OUTSTANDING YOUNG INVESTIGATOR AWARD
Plenary V: INFLAMMATION AND TISSUE REPAIR, Saturday, 9:00 AM

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.

Valentina Greco, PhD, Yale University School of Medicine, USA, is the recipient of the sixth annual Outstanding Young Investigator Award. Dr. Greco is recognized for her research into the interactions between stem cells and their niches, including the first direct, real-time visualization of stem cell divisions in living animals.

Join us for the 2014 award presentation which will take place during Plenary Session V in the morning of Saturday, June 21.

2014 ISSCR AWARDS

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ISSCR PUBLIC SERVICE AWARD

Presidential Symposium, Wednesday, 1:00 PM

Supported by past and present members of the International Society for Stem Cell Research Board of Directors

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

The 2014 ISSCR Public Service Award is presented to **Paolo Bianco, MD**, Sapienza University of Rome, **Elena Cattaneo, PhD,** University of Milan, and **Michele De Luca, MD,** University of Modena and Reggio Emilia, Italy, in recognition of their recent involvement in public debate and policy-making in Italy and their championing of rigorous scientific and medical standards and stringent regulatory oversight in the introduction of new stem cell treatments into the clinic.

Paolo Bianco

Elena Cattaneo

Michele De Luca

Join us for the 2014 award presentation which will take place during the Presidential Symposium on the afternoon of Wednesday, June 18.

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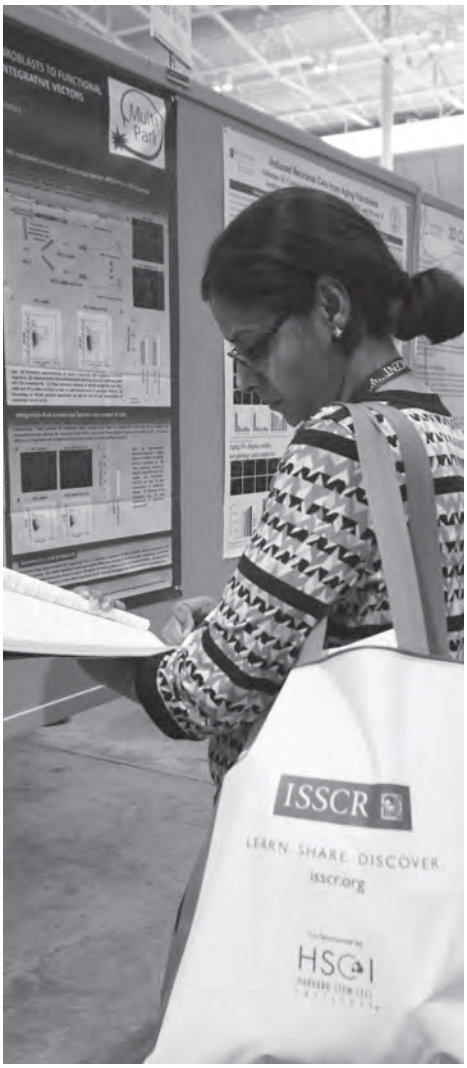

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2:00 PM - 6:00 PM	**REGISTRATION**	West Level 1 Foyer

WEDNESDAY, JUNE 18

7:30 AM - 8:00 PM	**REGISTRATION**	West Level 1 Foyer
8:30 AM - 12:30 PM	**PRE-MEETING EVENTS**	
8:30 AM - 12:30 PM	**INDUSTRY WEDNESDAY SYMPOSIUM** **Thermo Fisher Scientific** CONQUERING ROADBLOCKS ASSOCIATED WITH STEM CELL DIFFERENTIATION AND DISEASE MODELING	West Ballroom C/D
8:30 AM - 11:45 AM	**FOCUS SESSIONS** **Stem Cell COREdinates and WiCell Research Institute** TOOLS FOR BASIC AND APPLIED STEM CELL BIOLOGY	West Ballroom A
8:30 AM - 11:45 AM	**ISSCR Industry and Junior Investigator Committees** ENGAGING THE ENGINE: HOW PUBLIC/PRIVATE PARTNERSHIPS BETWEEN ACADEMIA AND INDUSTRY CAN FACILITATE MORE EFFICIENT TRANSLATION	West Ballroom B
8:30 AM - 12:15 PM	**RUCDR Infinite Biologics, Rutgers University** THE ESTABLISHMENT OF GLOBAL RESOURCE NETWORKS FOR IPSC RESEARCH	West Meeting Room 211-214
8:30 AM - 12:00 PM	**ISSCR Ethics and Public Policy Committee** ETHICS, STEM CELLS AND THE INFORMATION AGE	West Meeting Room 301-305
11:30 AM - 1:00 PM	**EARLY CAREER GROUP LEADER LUNCHEON:** RESEARCH EXCELLENCE: TOWARDS A RELIABLE LITERATURE *Supported by Ontario Stem Cell Initiative* Registration required	West Level 2 Oceanside Foyer
1:00 PM - 3:20 PM	**PRESIDENTIAL SYMPOSIUM** *Supported by Janssen Research & Development LLC* **Chair: Janet Rossant** *The Hospital for Sick Children Research Institute, Canada*	Plenary Hall
1:00 PM - 1:10 PM	**Welcome Remarks:** Allen Eaves, *STEMCELL Technologies, Canada*	
1:10 PM - 1:20 PM	**President's Address:** Janet Rossant, *The Hospital for Sick Children Research Institute, Canada*	
1:20 PM - 1:30 PM	**Presentation of the McEwen Award for Innovation to Azim Surani**	

PROGRAM SCHEDULE

VISIT THE EXHIBIT HALL. SAY THANK YOU TO THE EXHIBITORS WHO MAKE THIS MEETING POSSIBLE.

WEDNESDAY, JUNE 18 *(continued)*

1:30 PM - 1:40 PM	**Comments from the ISSCR Global Advisory Council**	
1:40 PM - 1:50 PM	**Presentation of the ISSCR Public Service Award to Paolo Bianco, Elena Cattaneo, Michele De Luca**	
1:50 PM - 2:10 PM	**Olivier Pourquie** *IGBMC, University of Strasbourg, France* MODELING DUCHENNE MUSCULAR DYSTROPHY WITH EMBRYONIC STEM CELLS	
2:10 PM - 2:30 PM	**Brigid L.M. Hogan** *Duke University Medical Center, USA* THE LIFE OF BREATH: STEM CELLS OF THE LUNG	
2:30 PM - 2:50 PM	**Gordon M. Keller** *McEwen Centre for Regenerative Medicine, University Health Network, Canada* MODELING HUMAN DEVELOPMENT WITH PLURIPOTENT STEM CELLS	
2:50 PM - 3:10 PM	**Lorenz Studer** *Sloan Kettering Institute for Cancer Research, USA* TOWARDS A HUMAN PLURIPOTENT STEM CELL SOURCE FOR TREATING PARKINSON'S DISEASE	
3:20 PM - 4:00 PM	REFRESHMENT BREAK	Exhibition Hall
3:30 PM - 8:30 PM	ISSCR EXHIBITION HALL OPEN	Exhibition Hall
4:00 PM - 6:20 PM	PLENARY II: CELL HETEROGENEITY *Supported By Fluidigm*	Plenary Hall
	Chair: Sean Morrison *UT Southwestern Medical Center, USA*	
4:00 PM - 4:25 PM	**John E. Dick** *Princess Margaret Cancer Centre, University Health Network, Canada* STEM CELLS IN CANCER: DO THEY MATTER?	
4:25 PM - 4:50 PM	**Kateri Moore** *Icahn School of Medicine at Mount Sinai, USA* INDUCING HEMOGENESIS IN FIBROBLASTS	
4:50 PM - 5:15 PM	**Alexander van Oudenaarden** *Hubrecht Institute, Netherlands* SINGLE-CELL TRANSCRIPT COUNTING IN STEM CELLS: FROM IMAGING TO SEQUENCING ONE MOLECULE AT A TIME	
5:15 PM - 5:25 PM	**Poster Teasers**	

PROGRAM SCHEDULE

ISSCR CONNECT COMPLIMENTARY ACCESS TO SELECT SESSIONS WILL BE AVAILABLE TO DELEGATES THROUGH THE ISSCR CONNECT PLATFORM IN JULY

WEDNESDAY, JUNE 18 *(continued)*

5:25 PM - 5:40 PM	**ISSCR Business Meeting**	
5:40 PM - 6:15 PM	**ERNEST McCULLOCH MEMORIAL LECTURE** **Connie J. Eaves** *Terry Fox Laboratory BC Cancer Agency, Canada* HEMATOPOIETIC STEM CELLS - AN EVOLVING PARADIGM	
6:30 PM - 8:30 PM	**POSTER PRESENTATION I** 6:30 - 7:30 PM Odd numbered posters presented 7:30 - 8:30 PM Even numbered posters presented	Exhibition Hall
6:30 PM - 8:30 PM	**POSTER RECEPTION I** *Supported by STEMCELL Technologies*	Exhibition Hall

THURSDAY, JUNE 19

7:30 AM - 6:00 PM	**REGISTRATION**	West Level I Foyer
8:00 AM - 8:30 AM	**INNOVATION SHOWCASES**	
	STEMCELL Technologies **Wing Chang and Steve Szilvassy** AN INTEGRATED WORKFLOW FOR THE ISOLATION, EXPANSION, AND CHARACTERIZATION OF HEMATOPOIETIC PROGENITORS AND THEIR CONVERSION TO INDUCED PLURIPOTENT STEM CELLS IN DEFINED CULTURE CONDITIONS	West Ballroom A
	R&D Systems **Joy Aho** DIFFERENTIATING STEM CELL POPULATIONS WITH SUCCESS	West Ballroom B
	Union Biometrica **Rock Pulak** LARGE PARTICLE FLOW CYTOMETRY PROVIDES HIGH THROUGHPUT ANALYSIS AND AUTOMATION FOR CELL CLUSTERS (EBS, SPHEROIDS) AND ENCAPSULATED 3D CELL CULTURES	West Meeting Room 211-214
	Nikon Corporation **Lee Rubin** USING STEM CELLS TO STUDY NEURODEGENERATIVE DISEASE	West Meeting Room 301-305

PROGRAM SCHEDULE

STOP BY ISSCR CENTRAL TO PICK UP YOUR JUNE ISSUE OF STEM CELL REPORTS AND INTERACT WITH OTHER MEMBERS

THURSDAY, JUNE 19 *(continued)*

9:00 AM - 11:20 AM — **PLENARY III: THERAPIES IN THE CLINIC** — Plenary Hall

Supported By California Institute for Regenerative Medicine

Chair: Irving L. Weissman
Stanford University, USA

9:00 AM - 9:25 AM
Leigh Turner
University of Minnesota, USA
U.S. CLINICS ADVERTISING AND ADMINISTERING UNPROVEN AUTOLOGOUS "STEM CELL" INTERVENTIONS: ETHICAL, SCIENTIFIC, AND LEGAL CONCERNS

9:25 AM - 9:50 AM
A.M. James Shapiro
University of Alberta, Canada
ISLET AND STEM CELL TRANSPLANTATION: DIABETES THERAPIES IN THE CLINIC

9:50 AM - 10:15 AM
Roger A. Barker
University of Cambridge, UK
TAKING STEM CELL-BASED THERAPIES TO THE CLINIC IN PARKINSON'S DISEASE

10:15 AM - 10:25 AM
Jennifer Molson
Patient Advocate, Canada
WHAT LED ME TO PARTICIPATE IN A CLINICAL STEM CELL TRIAL FOR MULTIPLE SCLEROSIS: A PERSONAL STORY

10:25 AM - 10:50 AM
Luigi Naldini
San Rafaele-Telethon Institute for Gene Therapy, Italy
GENETIC ENGINEERING OF HEMATOPOIESIS FOR TREATING GENETIC DISEASES AND CANCER

10:50 AM - 11:15 AM
Michel Sadelain
Memorial Sloan Kettering Cancer Center, USA
CAR T CELL THERAPY AND THE PROMISE OF T CELL ENGINEERING

11:00 AM - 8:00 PM — **ISSCR EXHIBITION HALL OPEN** — Exhibition Hall

11:20 AM - 1:15 PM — **LUNCH BREAK ON YOUR OWN**

11:30 AM - 1:00 PM — **MEET THE EXPERTS: NETWORKING LUNCH** — West Level 2 Oceanside Foyer

Junior Investigator event; registration required
Supported by the Institute for Stem Cell & Regenerative Medicine at the University of Washington

PROGRAM SCHEDULE

USE THE ISSCR MOBILE APP TO BUILD YOUR PERSONAL ITINERARY ON YOUR MOBILE DEVICE

THURSDAY, JUNE 19 *(continued)*

11:30 AM - 12:30 PM — **INNOVATION SHOWCASES**

STEMCELL Technologies — West Ballroom A
Huck-Hui Ng
INDUCTION OF A NATIVE STATE IN HUMAN PLURIPOTENT STEM CELLS

Lonza — West Ballroom B
Behnam Ahmadian Baghbaderani
BRIDGING RESEARCH TO THERAPY: NOVEL IPSC TOOLS AND TECHNOLOGIES

Fluidigm — West Ballroom C/D
Nianzhen Li
POWERING DISCOVERY THROUGH SINGLE-CELL BIOLOGY: UNRAVELING CELL FATE, DIFFERENTIATION AND LINEAGE

BD Biosciences — West Meeting Room 211-214
Robert Balderas and Christian Carson
CELL SURFACE MARKER SCREENING & ANALYSIS OF STEM CELL POPULATIONS

Life Technologies — West Meeting Room 301-305
Laurence Daheron
REPROGRAMMING SOMATIC CELLS USING THE SENDAI VIRUS TECHNOLOGY

1:15 PM - 3:05 PM — **CONCURRENT 1A: NEURAL STEM CELLS AND DEVELOPMENT** — West Ballroom A
Supported By StemCells, Inc.

Chair: Austin G. Smith
Welcome Trust-Medical Research Council Cambridge Stem Cell Institute, UK

1:20 PM - 1:45 PM
Freda D. Miller
The Hospital for Sick Children Research Institute, Canada
RECRUITING ENDOGENOUS NEURAL STEM CELLS FOR BRAIN REPAIR

1:45 PM - 2:00 PM
Wen-Hsuan Chang
University of Southern California, USA
SMEK1 AND 2 REGULATE MOUSE CORTICAL NEUROGENESIS THROUGH THE TRANSLOCATION OF THE CLEAVED WNT RECEPTOR RYK

PROGRAM SCHEDULE

VISIT THE EXHIBIT HALL. SAY THANK YOU TO THE EXHIBITORS WHO MAKE THIS MEETING POSSIBLE.

THURSDAY, JUNE 19 *(continued)*

2:00 PM - 2:15 PM	**Xiaoqun Wang** *Institute of Biophysics, Chinese Academy of Sciences, China* RCOR2 REGULATES SPECIFICATION OF NEURAL STEM CELL LINEAGES BY REPRESSING SHH SIGNALS IN THE DEVELOPING NEOCORTEX	
2:15 PM - 2:30 PM	**Yechiel Elkabetz** *Tel Aviv University, Israel* MODELING ONTOGENY OF HUMAN NEUROEPITHELIAL AND CORTICAL RADIAL GLIAL CELLS AT THE FUNCTIONAL, TRANSCRIPTIONAL AND EPIGENETIC LEVEL	
2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**Arnold R. Kriegstein** *University of California, San Francisco, USA* MOLECULAR MOTORS AND GENE NETWORKS IN HUMAN CORTICAL RADIAL GLIA	
1:15 PM - 3:05 PM	**CONCURRENT 1B: CONTROL OF PLURIPOTENCY** *Supported By Stemgent-Asterand*	West Ballroom C/D
	Chair: Hideyuki Okano *Keio University School of Medicine, Japan*	
1:20 PM - 1:45 PM	**Shinya Yamanaka** *Center for iPS Cell Research & Application, Japan* DISSECTING HUMAN REPROGRAMMING TOWARD PLURIPOTENCY	
1:45 PM - 2:00 PM	**Thorold Theunissen** *Whitehead Institute for Biomedical Research, USA* A CHEMICAL PLATFORM FOR INDUCTION AND MAINTENANCE OF NAIVE HUMAN PLURIPOTENCY	
2:00 PM - 2:15 PM	**Ido Sagi** *The Hebrew University of Jerusalem, Israel* EPIGENETIC STABILITY OF HUMAN PLURIPOTENT STEM CELLS DERIVED BY SOMATIC CELL NUCLEAR TRANSFER	
2:15 PM - 2:30 PM	**Tobias A. Beyer** *Swiss Federal Institute of Technology, Switzerland* SWITCH ENHANCERS: NOVEL REGULATORY ELEMENTS TO CONTROL CELL FATE CHOICE IN HUMAN BY INTEGRATION OF THE TGF-BETA AND HIPPO SIGNALING PATHWAY	

PROGRAM SCHEDULE

ISSCR CONNECT COMPLIMENTARY ACCESS TO SELECT SESSIONS WILL BE AVAILABLE TO DELEGATES THROUGH THE ISSCR CONNECT PLATFORM IN JULY

THURSDAY, JUNE 19 *(continued)*

2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**Manuel Serrano** *Spanish National Cancer Research Center, Spain* REPROGRAMMING IN VIVO AND ITS IMPACT ON TISSUE HOMEOSTASIS AND REGENERATION	
1:15 PM - 3:05 PM	**CONCURRENT 1C: ROAD TO THE CLINIC: CHALLENGES AHEAD**	West Ballroom B
	Chair: Timothy Allsopp *Neusentis Regenerative Medicine, UK*	
1:20 PM - 1:45 PM	**Alan Trounson** *California Institute for Regenerative Medicine, USA* SHIFTING THE ROADBLOCKS TO TRANSLATION OF STEM CELL THERAPIES	
1:45 PM - 2:00 PM	**Thomas Moritz** *Hannover Medical School, Germany* INTRA-TRACHEAL TRANSPLANTATION OF MACROPHAGE PROGENITORS DERIVED FROM MULTIPOTENT AND PLURIPOTENT STEM CELLS AS A NOVEL TREATMENT OPTION FOR HEREDITARY PULMONARY ALVEOLAR PROTEINOSIS	
2:00 PM - 2:15 PM	**Megan Munsie** *Stem Cells Australia, University of Melbourne, Australia* WHEN HOPES CLASH: PATIENT OPTIMISM CONFRONTS SCIENTIFIC EVIDENCE	
2:15 PM - 2:30 PM	**Jane S. Lebkowski** *Asterias Biotherapeutics, USA* PHASE 1 CLINICAL ASSESSMENT OF HUMAN EMBRYONIC STEM CELL (HESC) DERIVED OLIGODENDROCYTE PROGENITORS IN PATIENTS WITH NEUROLOGICALLY COMPLETE THORACIC SPINAL CORD INJURIES	
2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**Christopher Breuer** *Nationwide Children's Hospital, USA* RATIONAL DESIGN OF AN IMPROVED TISSUE ENGINEERED VASCULAR GRAFT	

PROGRAM SCHEDULE

STOP BY ISSCR CENTRAL TO PICK UP YOUR JUNE ISSUE OF STEM CELL REPORTS AND INTERACT WITH OTHER MEMBERS

THURSDAY, JUNE 19 *(continued)*

1:15 PM - 2:50 PM — CONCURRENT ID: REGENERATION — West Meeting Room 211-214

Supported By Ontario Brain Institute

Chair: Deepak Srivastava
Gladstone Institutes, USA

1:20 PM - 1:45 PM
Michael A. Rudnicki
Ottawa Hospital Research Institute, Canada
MOLECULAR REGULATION OF MUSCLE STEM CELL SELF-RENEWAL AND EXPANSION

1:45 PM - 2:00 PM
Fadi Najm
Case Western Reserve University, USA
A STEM CELL-BASED PLATFORM FOR DISCOVERY OF REMYELINATING THERAPEUTICS

2:00 PM - 2:15 PM
Jovica Ninkovic
Helmholtz Zentrum München, Germany
SUSTAINED NEUROGENESIS - AN INSTRUMENT FOR A SUCCESSFUL REGENERATION IN ADULT BRAIN

2:15 PM - 2:30 PM
Robert N. Judson
University of British Columbia, Canada
ROLE OF METHYLTRANSFERASE SET7 IN SKELETAL MUSCLE REGENERATION AND DEVELOPMENT

2:30 PM - 2:35 PM
Poster Teasers

2:35 PM - 2:50 PM
Makoto Takeo
Langone Medical Center and School of Medicine, New York University, USA
WNT ACTIVATION IN NAIL EPITHELIUM COUPLES NAIL GROWTH TO DIGIT REGENERATION

1:15 PM - 3:05 PM — CONCURRENT IE: AGING AND METABOLISM — West Meeting Room 301-305

Chair: Hongkui Deng
College of Life Sciences at Peking University, China

1:20 PM - 1:45 PM
Heinrich Jasper
Buck Institute for Research on Aging, USA
REGULATION OF INTESTINAL STEM CELL FUNCTION IN THE AGING INTESTINE

1:45 PM - 2:00 PM
Amy Wagers
Harvard University, USA
RESTORATION OF SYSTEMIC GDF11 LEVELS REVERSES AGE-ASSOCIATED DYSFUNCTION IN SKELETAL MUSCLE

PROGRAM SCHEDULE

USE THE ISSCR MOBILE APP TO BUILD YOUR PERSONAL ITINERARY ON YOUR MOBILE DEVICE

THURSDAY, JUNE 19 *(continued)*

2:00 PM - 2:15 PM	**Shyh-Chang Ng** *Genome Institute of Singapore, Singapore* ROLE OF REPROGRAMMING CELLULAR METABOLISM IN MAMMALIAN TISSUE REPAIR	
2:15 PM - 2:30 PM	**Gabrielle Kardon** *University of Utah, USA* MUSCLE STEM CELLS ARE CRITICAL FOR MUSCLE HOMEOSTASIS AND AGING	
2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**Kirsty Spalding** *Karolinska Institute, Sweden* ADIPOSE TISSUE TURNOVER IN MAN	
3:05 PM - 4:00 PM	REFRESHMENT BREAK	Exhibition Hall
3:15 PM - 4:00 PM	MEET THE EDITORS OF STEM CELL REPORTS	Singapore Meet-up Hub
3:15 PM - 4:00 PM	CONTINUING THE CONVERSATION: HOW PUBLIC / PRIVATE PARTNERSHIPS BETWEEN ACADEMIA AND INDUSTRY CAN FACILITATE MORE EFFICIENT TRANSLATION	Stockholm Meet-up Hub
4:00 PM - 5:50 PM	CONCURRENT IIA: NEURAL DIFFERENTIATION *Supported By Lieber Institute for Brain Development*	West Ballroom B
	Chair: Rudolf Jaenisch *Whitehead Institute for Biomedical Research, USA*	
4:05 PM - 4:30 PM	**Sally Temple** *Neural Stem Cell Institute, USA* CEREBRAL CORTICAL CELL DIFFERENTIATION: DRAWING AND READING THE BLUEPRINT	
4:30 PM - 4:45 PM	**Daniel Lim** *University of California, San Francisco, USA* THE LONG NON-CODING RNA PINKY REGULATES NEURAL STEM CELL DIFFERENTIATION AND PROGENITOR EXPANSION	
4:45 PM - 5:00 PM	**Giulia Gaudenzi** *Karolinska Institute, Sweden* FOXP2 AND NCOR REGULATE GENES ASSOCIATED WITH TOURETTE SYNDROME AND BRAIN EVOLUTION VIA A DISTAL REGULATORY ELEMENT IN NEURAL STEM CELLS	

PROGRAM SCHEDULE

VISIT THE EXHIBIT HALL. SAY THANK YOU TO THE EXHIBITORS WHO MAKE THIS MEETING POSSIBLE.

THURSDAY, JUNE 19 *(continued)*

5:00 PM - 5:15 PM	**Jinah Han** *Yale University School of Medicine, USA* VEGFR3 CONTROLS NEURAL STEM CELL ACTIVATION IN THE ADULT MOUSE HIPPOCAMPUS	
5:15 PM - 5:20 PM	**Poster Teasers**	
5:20 PM - 5:45 PM	**Ronald D. McKay** *Lieber Institute for Brain Development, USA* USING THE FUNCTIONAL IDENTITY OF HUMAN GENOMES	
4:00 PM - 5:50 PM	**CONCURRENT IIB: TRANSDIFFERENTIATION**	West Meeting Room 211-214
	Chair: Christine L. Mummery *Leiden University Medical Center, Netherlands*	
4:05 PM - 4:30 PM	**Melissa H. Little** *The University of Queensland, Australia* DIRECTED DIFFERENTIATION OF HUMAN PLURIPOTENT CELLS TO KIDNEY PROGENITOR POPULATIONS RESULTS IN FORMATION OF A SELF-ORGANISING EMBRYONIC KIDNEY	
4:30 PM - 4:45 PM	**Qiao Zhou** *Harvard University, USA* INDUCTION OF MULTIPLE GROUPS OF INSULIN+ BETA CELLS FROM THE ADULT GASTROINTESTINAL TRACT	
4:45 PM - 5:00 PM	**Atsuhiro Taguchi** *Institute of Molecular Embryology and Genetics, Kumamoto University, Japan* REDEFINING THE IN VIVO ORIGIN OF NEPHRON PROGENITORS ENABLES GENERATION OF THREE-DIMENSIONAL KIDNEY STRUCTURES FROM PLURIPOTENT STEM CELLS IN VITRO	
5:00 PM - 5:15 PM	**Lay Teng Ang** *Genome Institute of Singapore, Singapore* DYNAMIC DEVELOPMENTAL SIGNALING LOGIC UNDERLYING LINEAGE BIFURCATIONS DURING HUMAN ENDOERM INDUCTION AND PATTERNING FROM PLURIPOTENT STEM CELLS	
5:15 PM - 5:20 PM	**Poster Teasers**	
5:20 PM - 5:45 PM	**Lijian Hui** *Shanghai Institute of Biochemistry and Cell Biology, China* DIRECT REPROGRAMMING OF FIBROBLASTS TO FUNCTIONAL HEPATOCYTE-LIKE CELLS	

PROGRAM SCHEDULE

ISSCR CONNECT COMPLIMENTARY ACCESS TO SELECT SESSIONS WILL BE AVAILABLE TO DELEGATES THROUGH THE ISSCR CONNECT PLATFORM IN JULY

THURSDAY, JUNE 19 *(continued)*

4:00 PM - 5:40 PM CONCURRENT IIC: CANCER PLASTICITY — West Ballroom C/D

Chair: Fiona Watt
King's College, London, UK

4:05 PM - 4:30 PM
Luis F. Parada
UT Southwestern Medical School, USA
MOUSE MODELS OF MALIGNANT GBM: CANCER STEM CELLS AND BEYOND

4:30 PM - 4:45 PM
Pritinder Kaur
Peter MacCallum Cancer Centre, Australia
EVIDENCE FOR PERIVASCULAR MSC-LIKE CELLS AS POTENT MEDIATORS OF MALIGNANT METASTASES IN XENOGRAFT MODELS OF OVARIAN CANCER, CORRELATED WITH EARLIER RELAPSE AND MORTALITY IN HIGH-GRADE SEROUS OVARIAN CANCER PATIENTS

4:45 PM - 5:00 PM
Jeffrey Magee
Washington University, USA
THE FLT3 INTERNAL TANDEM DUPLICATION HAS AGE DEPENDENT EFFECTS ON HEMATOPOIETIC STEM CELL SELF RENEWAL AND LEUKEMOGENESIS

5:00 PM - 5:15 PM
Jody Jonathan Haigh
Monash University, Australia
ZEB2 DRIVES T-CELL LYMPHOBLASTIC LEUKEMIA DEVELOPMENT VIA ALTERED IL-7 RECEPTOR SIGNALING AND ENHANCED TUMOR-INITIATING POTENTIAL

5:15 PM - 5:20 PM
Poster Teasers

5:20 PM - 5:35 PM
Eva-Maria Hartinger
German Cancer Research Center and National Center for Tumor Diseases, Germany
RARE QUIESCENT TUMOR INITIATING CELL (TIC) CLONES IN COLORECTAL CANCER ARE CHEMOTHERAPY RESISTANT AND ACTIVATED TO DRIVE POST TREATMENT PROGRESSION

PROGRAM SCHEDULE

STOP BY ISSCR CENTRAL TO PICK UP YOUR JUNE ISSUE OF STEM CELL REPORTS AND INTERACT WITH OTHER MEMBERS

THURSDAY, JUNE 19 *(continued)*

4:00 PM - 5:50 PM — CONCURRENT IID: EPITHELIAL AND MESENCHYMAL STEM CELLS — West Ballroom A

Chair: Fabio Rossi
University of British Columbia, Canada

4:05 PM - 4:30 PM — **Nick Barker**
Institute of Medical Biology, Singapore
LGR5+ STEM/PROGENITOR CELLS CONTRIBUTE TO THE DEVELOPMENT AND MAINTENANCE OF THE OVARY AND TUBAL EPITHELIA

4:30 PM - 4:45 PM — **Filip J. Wymeersch**
University of Edinburgh, UK
INTRINSIC AND EXTRINSIC CONSTRAINTS ON NEUROMESODERMAL AND LATERAL MESODERM PROGENITORS

4:45 PM - 5:00 PM — **Fukuda Masayoshi**
Tokyo Medical and Dental University, Japan
SUCCESSFUL ENGRAFTMENT OF CULTURED SMALL INTESTINAL EPITHELIAL STEM CELLS ONTO DAMAGED COLONIC MUCOSA BY HETEROTOPIC TRANSPLANTATION

5:00 PM - 5:15 PM — **Aaron D. DeWard**
University of Pittsburgh, USA
IDENTIFICATION OF AN EPITHELIAL STEM CELL HIERARCHY IN THE MOUSE ESOPHAGUS

5:15 PM - 5:20 PM — **Poster Teasers**

5:20 PM - 5:45 PM — **Bruce Edgar**
German Cancer Research Center - Center for Molecular Biology Heidelberg Alliance, Germany
NICHE APPROPRIATION BY DROSOPHILA INTESTINAL STEM CELL TUMORS

4:00 PM - 5:50 PM — CONCURRENT IIE: STEM CELLS IN MODEL ORGANISMS — West Meeting Room 301-305

Chair: Haifan Lin
Yale University School of Medicine, USA

4:05 PM - 4:30 PM — **Hannele Ruohola-Baker**
University of Washington, USA
STEM CELL SURVIVAL PROGRAM

PROGRAM SCHEDULE

USE THE ISSCR MOBILE APP TO BUILD YOUR PERSONAL ITINERARY ON YOUR MOBILE DEVICE

THURSDAY, JUNE 19 *(continued)*

4:30 PM - 4:45 PM	**Ayelet Voskoboynik** *Stanford University School of Medicine, USA* A HISTOCOMPATIBILITY GENE THAT REGULATES PREDATORY STEM CELLS	
4:45 PM - 5:00 PM	**Catarina C.F. Homem** *IMBA - Institute of Molecular Biotechnology, Austria* ECDYSONE AND MEDIATOR TRIGGER A METABOLIC SWITCH UNCOUPLING CELL CYCLE FROM CELL GROWTH TO END PROLIFERATION IN DROSOPHILA NEURAL STEM CELLS	
5:00 PM - 5:15 PM	**Phong Dang Nguyen** *Monash University, Australia* IMAGING LIVE CELL DYNAMICS OF THE MUSCLE PROGENITOR CELL NICHE DURING ZEBRAFISH DEVELOPMENT	
5:15 PM - 5:20 PM	**Poster Teasers**	
5:20 PM - 5:45 PM	**Nadia Mercader Huber** *Centro Nacional de Investigaciones Cardiovasculares, Spain* CARDIAC REGENERATION VS FIBROTIC REPAIR: LESSONS FROM THE ZEBRAFISH	
6:00 PM - 8:00 PM	**POSTER PRESENTATION II** 6:00 - 7:00 PM Odd numbered posters presented 7:00 - 8:00 PM Even numbered posters presented	Exhibition Hall
6:00 PM - 8:00 PM	**POSTER RECEPTION II:** *Supported By Stem Cell Network*	Exhibition Hall
9:30 PM - 1:00 AM	**JUNIOR INVESTIGATOR SOCIAL NIGHT**	Commodore Ballroom 868 Granville St

PROGRAM SCHEDULE

VISIT THE EXHIBIT HALL. SAY THANK YOU TO THE EXHIBITORS WHO MAKE THIS MEETING POSSIBLE.

FRIDAY, JUNE 20

7:30 AM - 5:00 PM	**REGISTRATION**	West Level I Foyer
8:00 AM - 8:30 AM	**INNOVATION SHOWCASES**	
	STEMCELL Technologies	West Ballroom A
	Ravenska Wagey	
	INTRODUCING A NOVEL, ANIMAL COMPONENT-FREE (ACF) CULTURE SYSTEM FOR EFFICIENT ISOLATION, EXPANSION AND CRYOPRESERVATION OF HUMAN MSCS DERIVED FROM BONE MARROW AND ADIPOSE TISSUE	
	Miltenyi Biotec	West Ballroom B
	Sebastian Knoebel	
	NEXT-GENERATION TECHNOLOGIES FOR STEM CELL RESEARCH	
	BioLamina	West Ballroom C/D
	Kristian Tryggvason	
	THE LAMININ PROTEIN FAMILY – THE KEY TO PRIMARY CELL CULTURE DIFFICULTIES	
	PeproTech	West Meeting Room 211-214
	Rick I. Cohen	
	OPTIMIZING THE CULTURE OF PPSC USING NOVEL XENO AND INSULIN FREE LOW PROTEIN MEDIA	
	HumanZyme	West Meeting Room 301-305
	Dr. Mark Azam	
	THERMO-STABLE FGF-BASIC (APPLICATIONS & FUTURE)	
9:00 AM - 11:20 AM	**PLENARY IV: BIOENGINEERING**	Plenary Hall
	Supported By Burroughs Wellcome Fund	
	Chair: George Q. Daley	
	Boston Children's Hospital, USA	
9:00 AM - 9:25 AM	**Anthony Atala**	
	Wake Forest University, USA	
	TISSUE ENGINEERING AND REGENERATIVE MEDICINE: CURRENT CONCEPTS AND CHANGING TRENDS	
9:25 AM - 9:50 AM	**Jason A. Burdick**	
	University of Pennsylvania	
	ENGINEERING SYNTHETIC MICROENVIRONMENTS TO GUIDE STEM CELL BEHAVIOR	

PROGRAM SCHEDULE

ISSCR CONNECT COMPLIMENTARY ACCESS TO SELECT SESSIONS WILL BE AVAILABLE TO DELEGATES THROUGH THE ISSCR CONNECT PLATFORM IN JULY

FRIDAY, JUNE 20 *(continued)*

9:50 AM - 10:15 AM	**Molly Stevens** *Imperial College London, UK* EXPLORING AND ENGINEERING THE CELL-MATERIAL INTERFACE	
10:15 AM - 10:40 AM	**Peter W. Zandstra** *University of Toronto, Canada* DISTRIBUTED REGULATORY CONTROL OF STEM CELL IDENTITY AND FATE	
10:40 AM - 11:15 AM	ANNE McLAREN MEMORIAL LECTURE **Robin Lovell-Badge** *MRC National Institute for Medical Research, UK* SEX, STEM CELLS, PHYSIOLOGY AND POLICY	
11:00 AM - 8:00 PM	ISSCR EXHIBITION HALL OPEN	Exhibition Hall
11:20 AM - 1:15 PM	LUNCH BREAK ON YOUR OWN	
11:30 AM - 1:00 PM	MEET THE EXPERTS: NETWORKING LUNCH Junior Investigator event; Registration required *Supported by: Takeda Pharmaceuticals*	West Level 2 Oceanside Foyer
11:30 AM - 12:30 PM	INNOVATION SHOWCASES	
	Biological Industries **David Fiorentini** A NOVEL XENO-FREE CULTURE SYSTEM FOR ISOLATION AND EXPANSION OF HMSC FROM VARIOUS SOURCES TOWARD CELL THERAPY APPLICATIONS	West Ballroom A
	Corning **Zara Melkoumian and Deepa Saxena** ADVANCED TECHNOLOGIES FOR IN VITRO CULTURE OF CELL TYPES RELEVANT FOR CLINICAL RESEARCH	West Ballroom B
	EMD Millipore **Vi Chu** VIRUS-FREE, EFFICIENT REPROGRAMMING USING A SINGLE TRANSFECTION OF A SYNTHETIC, POLYCISTRONIC SELF-REPLICATING RNA	West Ballroom C/D
	Irvine Scientific **Ning Liu** EX VIVO EXPANSION, DIFFERENTIATION AND CRYOPRESERVATION OF MESENCHYMAL STROMAL/ STEM CELLS	West Meeting Room 211-214

PROGRAM SCHEDULE

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FRIDAY, JUNE 20 *(continued)*

	Stemgent-Asterand **Brad Hamilton** RNA-MEDIATED GENERATION OF INTEGRATION-FREE IPS CELL LINES FROM CELLS ISOLATED FROM HUMAN BLOOD	West Meeting Room 301-305
1:15 PM - 3:05 PM	**CONCURRENT IIIA: SENSORY SYSTEMS REPAIR** **Chair: Urban Lendahl** *Karolinska Institute, Sweden*	West Meeting Room 211-214
1:20 PM - 1:45 PM	**Steven Schwartz** *Jules Stein Eye Institute, USA* TITLE NOT AVAILABLE AT TIME OF PRINTING	
1:45 PM - 2:00 PM	**Hongjun Liu** *University of Pittsburgh School of Medicine, USA* RETINAL REGENERATION BY LGR5+ AMACRINE CELLS IN ADULT MAMMALS	
2:00 PM - 2:15 PM	**Sheldon S. Miller** *National Eye Institute, USA* DEVELOPING AUTOLOGOUS CELL THERAPY FOR MACULAR DEGENERATION USING IPS CELL DERIVED RPE TISSUE: A MODEL FOR PUBLIC-PRIVATE PARTNERSHIP	
2:15 PM - 2:30 PM	**Kathryn Cheah** *University of Hong Kong, Hong Kong* TRANSCRIPTIONAL CONTROL OF SENSORY VERSUS NON SENSORY PROGENITOR SPECIFICATION IN THE INNER EAR	
2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**Albert Edge** *Massachusetts Eye and Ear Infirmary, USA* COCHLEAR HAIR CELL GENERATION FROM LGR5-POSITIVE SUPPORTING CELLS	
1:15 PM - 3:05 PM	**CONCURRENT IIIB: MODELING DISEASE WITH iPSCs** *Supported By Cellular Dynamics International* **Chair: Sally Temple** *Neural Stem Cell Institute, USA*	West Ballroom C/D

PROGRAM SCHEDULE

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FRIDAY, JUNE 20 *(continued)*

1:20 PM - 1:45 PM	**Christine L. Mummery** *Leiden University Medical Center, Netherlands* CARDIAC AND VASCULAR DISEASE MODELED BY (ISOGENIC PAIRS OF) HUMAN PLURIPOTENT STEM CELLS	
1:45 PM - 2:00 PM	**Christoph Patsch** *Roche Pharma, Switzerland* HUMAN IPSC-BASED MODELLING OF ENDOTHELIAL DYSFUNCTION	
2:00 PM - 2:15 PM	**Shinichiro Ogawa** *McEwen Centre for Regenerative Medicine, Canada* DIRECTED DIFFERENTIATION OF FUNCTIONAL CHOLANGIOCYTES FROM HUMAN PLURIPOTENT STEM CELLS	
2:15 PM - 2:30 PM	**Christina V. Theodoris** *Gladstone Institute of Cardiovascular Disease and University of California, San Francisco, USA* IPSC-BASED MODELING OF HUMAN NOTCH1 MUTATIONS REVEALS NOVEL PATHWAYS REGULATING AORTIC VALVE DISEASE	
2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**Fred H. Gage** *Salk Institute for Biological Studies, USA* MODELING HUMAN NEUROLOGICAL AND PSYCHIATRIC DISEASE IN VITRO	
1:15 PM - 3:05 PM	**CONCURRENT IIIC: DIABETES** *Supported By Sanofi US*	West Ballroom A
	Chair: Timothy Kieffer *University of British Columbia, Canada*	
1:20 PM - 1:45 PM	**Maike Sander** *University of California San Diego, USA* EPIGENOMIC PRINCIPLES OF PANCREATIC LINEAGE COMMITMENT AND BETA-CELL DIFFERENTIATION	
1:45 PM - 2:00 PM	**Jeffrey Robert Millman** *Harvard University, USA* IN VITRO GENERATION OF PANCREATIC BETA CELLS FROM HUMAN PLURIPOTENT STEM CELLS	

PROGRAM SCHEDULE

VISIT THE EXHIBIT HALL. SAY THANK YOU TO THE EXHIBITORS WHO MAKE THIS MEETING POSSIBLE.

FRIDAY, JUNE 20 *(continued)*

2:00 PM - 2:15 PM	**Shoen Kume** *Institute of Molecular Embryology and Genetics, Kumamoto University, Japan* CHEMICAL GENETIC IDENTIFICATION OF SIGNALS THAT CONTROL LATE-STAGE PANCREATIC BETA CELL DIFFERENTIATION	
2:15 PM - 2:30 PM	**Ivan Carcamo-Orive** *Stanford School of Medicine, USA* IPSC-DERIVED ENDOTHELIAL CELLS REPRODUCE INSULIN RESISTANCE AND ENDOTHELIAL DYSFUNCTION IN VITRO	
2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**M. Cristina Nostro** *McEwen Centre for Regenerative Medicine, Canada* GENERATION OF PANCREATIC PROGENITOR CELLS FROM HUMAN PLURIPOTENT STEM CELLS	
1:15 PM - 3:05 PM	**CONCURRENT IIID: EPIGENETICS** *Supported by Nature Publishing Group*	West Ballroom B
	Chair: Kathrin Plath *University of California, Los Angeles School of Medicine, USA*	
1:20 PM - 1:45 PM	**Laurie Boyer** *Massachusetts Institute of Technology, USA* TRANSCRIPTIONAL REGULATION OF CARDIAC CELL FATE	
1:45 PM - 2:00 PM	**Jan Jakub Zylicz** *Gurdon Institute and Stem Cell Institute, University of Cambridge, UK* EPIGENETIC STATE REGULATING COMPETENCE OF THE IN VIVO POST-IMPLANTATION MOUSE EPIBLAST	
2:00 PM - 2:15 PM	**Christa Buecker** *Stanford University School of Medicine, USA* REORGANIZATION OF ENHANCER PATTERNS IN TRANSITION FROM NAÏVE TO PRIMED PLURIPOTENCY	
2:15 PM - 2:30 PM	**Peter J. Rugg-Gunn** *The Babraham Institute, UK* NANOG AND SALL1 REGULATE CHROMATIN ORGANISATION IN EMBRYONIC STEM CELLS	
2:30 PM - 2:35 PM	**Poster Teasers**	

PROGRAM SCHEDULE

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FRIDAY, JUNE 20 *(continued)*

2:35 PM - 3:00 PM	**Andras Nagy** *Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Canada* THE ROUTES OF REPROGRAMMING TO ALTERNATIVE STATES OF PLURIPOTENCY	
1:15 PM - 3:05 PM	**CONCURRENT IIIE: ASYMMETRIC CELL DIVISION**	West Meeting Room 301-305
	Chair: Arturo Alvarez-Buylla *University of California, San Francisco, USA*	
1:20 PM - 1:45 PM	**Roeland Nusse** *Stanford University School of Medicine, USA* WNT SIGNALING AND STEM CELL CONTROL	
1:45 PM - 2:00 PM	**Scott E. Williams** *University of North Carolina - Chapel Hill, USA* PAR3-INSC AND G-ALPHA-I3 COOPERATE TO PROMOTE ORIENTED EPIDERMAL DIVISIONS	
2:00 PM - 2:15 PM	**Ashley D. Sanders** *University of British Columbia, Canada* SISTER CHROMATID SEGREGATION IN ASYMMETRICALLY DIVIDING HUMAN HEMATOPOIETIC STEM CELLS	
2:15 PM - 2:30 PM	**Xiling Shen** *Cornell University, USA* SPATIOTEMPORAL CONTROL OF CANCER STEM CELL ASYMMETRIC DIVISION BY VERSATILE MICRORNA MECHANISMS	
2:30 PM - 2:35 PM	**Poster Teasers**	
2:35 PM - 3:00 PM	**Rong Li** *Stowers Institute for Medical Research, USA* MECHANISM OF ASYMMETRIC MEIOTIC CELL DIVISION IN MOUSE OOCYTES	
3:05 PM - 4:00 PM	**REFRESHMENT BREAK**	Exhibition Hall
3:15 PM - 4:00 PM	**GERMAN STEM CELL NETWORK**	Singapore Meet-up Hub
4:00 PM - 5:50 PM	**CONCURRENT IVA: MONITORING AND MODULATING THE NICHE**	West Meeting Room 211-214
	Chair: Elly Tanaka *DFG Research Center for Regenerative Therapies, Technische Universitaet Dresden, Germany*	

PROGRAM SCHEDULE

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FRIDAY, JUNE 20 *(continued)*

4:05 PM - 4:30 PM	**Melody Swartz** *Ecole polytechnique federale de Lausanne, Switzerland* LYMPHOID NEOGENESIS AND LYMPHANGIOGENESIS IN NICHE FORMATION: LESSONS FROM CANCER	
4:30 PM - 4:45 PM	**Owen Tamplin** *Boston Children's Hospital, USA* CORRELATIVE LIGHT AND ELECTRON MICROSCOPY REVEALS THE ULTRASTRUCTURE OF AN ENDOGENOUS HEMATOPOIETIC STEM CELL IN ITS NICHE AND A SURROUNDING POCKET OF ENDOTHELIAL CELLS	
4:45 PM - 5:00 PM	**Elia Piccinini** *University of Toronto Institute of Biomaterials and Biomedical Engineering, Canada* MODELING THE THYMIC MICROENVIRONMENT TO SUPPORT T CELL MATURATION AND THE CULTURE OF FUNCTIONAL THYMIC EPITHELIAL CELLS	
5:00 PM - 5:15 PM	**Joo-Hyeon Lee** *Boston Children's Hospital / Harvard Medical School / Harvard Stem Cell Institute, USA* MICROENVIRONMENTAL REGULATION OF LUNG STEM CELL DIFFERENTIATION	
5:15 PM - 5:20 PM	**Poster Teasers**	
5:20 PM - 5:45 PM	**Dennis Discher** *University of Pennsylvania, USA* STEM CELL NUCLEAR PROPERTIES IN RELATION TO THE NICHE	
4:00 PM - 5:40 PM	**CONCURRENT IVB: LARGE SCALE ANALYSIS OF CELL FATE DECISIONS** **Chair: Connie Eaves** *Terry Fox Laboratory, BC Cancer Agency, Canada*	West Ballroom A
4:05 PM - 4:30 PM	**Bruno Reversade** *Institute of Medical Biology, Singapore* EMBO YOUNG INVESTIGATOR LECTURE HORMONAL REGULATION OF SELF-RENEWAL IN HESCS	
4:30 PM - 4:45 PM	**Sundari Chetty** *Harvard University, USA* EPIGENETIC PRIMING TO PROMOTE PLURIPOTENT STEM CELL DIFFERENTIATION	

PROGRAM SCHEDULE

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FRIDAY, JUNE 20 *(continued)*

4:45 PM - 5:00 PM	**Luca Biasco** *San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET), Italy* COMPREHENSIVE CLONAL MAPPING OF HEMATOPOIESIS IN VIVO IN HUMANS BY RETROVIRAL VECTOR INSERTIONAL BARCODING	
5:00 PM - 5:15 PM	**Sean C. Bendall** *Stanford University, USA* ORDERED HALLMARKS AND REGULATORY COORDINATION POINTS OF HUMAN B CELL DEVELOPMENT VIA TRAJECTORY DETECTION	
5:15 PM - 5:20 PM	**Poster Teasers**	
5:20 PM - 5:35 PM	**Filipa A. C. Soares** *Cambridge Stem Cell Institute, UK* IMPACT OF CELL TYPE OF ORIGIN AND REPROGRAMMING METHOD ON HUMAN INDUCED PLUTIPOTENT STEM CELLS	
4:00 PM - 5:50 PM	**CONCURRENT IVC: STEM CELLS AND CANCER**	West Ballroom B
	Chair: David T. Scadden *Massachusetts General Hospital and Harvard University, USA*	
4:05 PM - 4:30 PM	**Catriona Jamieson** *University of California, San Diego, USA* THE ROLE OF RNA EDITING IN MALIGNANT REPROGRAMMING	
4:30 PM - 4:45 PM	**Chris Lengner** *University of Pennsylvania, USA* MSI1 INTEGRATES APC LOSS AND MTORC1 ACTIVATION TO PROMOTE INTESTINAL STEM CELL TRANSFORMATION	
4:45 PM - 5:00 PM	**Christopher Y. Park** *Memorial Sloan Kettering Cancer Center, USA* HEMATOPOIETIC STEM CELL ORIGIN OF A MATURE B CELL NEOPLASM	
5:00 PM - 5:15 PM	**Abby Sarkar** *Harvard Medical School, USA* ROLE OF SOX2 IN MOUSE GLANDULAR STOMACH HOMEOSTASIS AND TUMORIGENESIS	
5:15 PM - 5:20 PM	**Poster Teasers**	

PROGRAM SCHEDULE

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FRIDAY, JUNE 20 *(continued)*

5:20 PM - 5:45 PM

Qing Li
University of Michigan, USA
NRAS SIGNALING IN PRE-LEUKEMIC STEM CELL TRANSFORMATION

4:00 PM - 5:50 PM — CONCURRENT IVD: HEMATOPOIESIS — West Ballroom C/D
Supported By The Hospital for Sick Children Research Institute

Chair: Amy Wagers
Joslin Diabetes Center, USA

4:05 PM - 4:30 PM

Michael H. Sieweke
CIML - Centre d'Immunologie de Marseille-Luminy, France
INTEGRATION OF CELL INTRINSIC AND EXTRINSIC SIGNALS IN LINEAGE CHOICE OF HEMATOPOIETIC STEM CELLS

4:30 PM - 4:45 PM

Sacha Prashad
University of California, Los Angeles, USA
GPI80 DEFINES SELF RENEWAL ABILITY IN HEMATOPOIETIC STEM CELLS DURING HUMAN DEVELOPMENT

4:45 PM - 5:00 PM

Warren S. Alexander
The Walter & Eliza Hall Institute of Medical Research, Australia
REGULATION OF HEMATOPOIETIC STEM CELLS BY THEIR MATURE PROGENY: MPL EXPRESSION ON MEGAKARYOCYTES AND PLATELETS IS DISPENSABLE FOR THROMBOPOIESIS BUT ESSENTIAL FOR PREVENTION OF MYELOPROLIFERATION

5:00 PM - 5:15 PM

Nicola Vannini
Ecole polytechnique federale de Lausanne, Switzerland
MITOCHONDRIAL ACTIVITY DETERMINES HEMATOPOIETIC STEM CELL POTENTIAL

5:15 PM - 5:20 PM

Poster Teasers

5:20 PM - 5:45 PM

Stuart H. Orkin
Boston Children's Hospital, Dana-Farber Cancer Institute and Harvard Medical School, USA
GENETIC AND EPIGENETIC CONTROL OF HEMATOPOIETIC GENE EXPRESSION

4:00 PM - 5:50 PM — CONCURRENT IVE: GERMLINE BIOLOGY — West Meeting Room 301-305

Chair: Nissim Benvenisty
Hebrew University, Israel

PROGRAM SCHEDULE

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FRIDAY, JUNE 20 *(continued)*

4:05 PM - 4:30 PM	**Hiroyuki Sasaki** *Kyushu University, Medical Institute of Bioregulation, Japan* DNA METHYLATION AND GENE EXPRESSION PROFILES IN MOUSE GERM CELL DEVELOPMENT	
4:30 PM - 4:45 PM	**Matthew F. Pech** *Stanford University, USA* HIGH TELOMERASE LEVELS DEFINE THE SPERMATOGONIAL STEM CELL COMPARTMENT	
4:45 PM - 5:00 PM	**Shau-Ping Lin** *National Taiwan University, Taiwan* DNMT3L PROMOTES QUIESCENCE IN POSTNATAL SPERMATOGONIAL PROGENITOR CELLS	
5:00 PM - 5:15 PM	**Danny Leung** *Ludwig Institute for Cancer Research, USA* PERSISTENCE OF DNA METHYLATION IN EMBRYONIC STEM CELLS DEPENDS ON THE HISTONE METHYLTRANSFERASE SETDB1	
5:15 PM - 5:20 PM	**Poster Teasers**	
5:20 PM - 5:45 PM	**Amander T. Clark** *University of California, Los Angeles, USA* ARGININE METHYLATION IS REQUIRED FOR GROUND STATE NAÏVE PLURIPOTENCY AND GERM LINE POTENTIAL	
6:00 PM - 8:00 PM	**POSTER PRESENTATION III** 6:00 - 7:00 PM Odd numbered posters presented 7:00 - 8:00 PM Even numbered posters presented	Exhibition Hall
6:00 PM - 8:00 PM	**POSTER RECEPTION III** *Supported by Centre for Commercialization of Regenerative Medicine (CCRM)*	Exhibition Hall

PROGRAM SCHEDULE

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SATURDAY, JUNE 21

8:00 AM - 5:00 PM	**REGISTRATION**	West Level I Foyer
8:00 AM - 8:30 AM	**INNOVATION SHOWCASES**	
	LifeMap Sciences Inc. **Idit Livnat** LIFEMAP DISCOVERY® - THE ROADMAP FOR STEM CELL RESEARCH	West Ballroom A
	EMD Millipore **Julie R. Murrell** EXPANSION AND HARVEST OF ADULT STEM CELLS SUPPORTS LARGE SCALE MANUFACTURING	West Ballroom B
9:00 AM - 11:20 AM	**PLENARY V: INFLAMMATION AND TISSUE REPAIR**	Plenary Hall
	Chair: Shinya Yamanaka *Center for iPS Cell Research and Application, Japan*	
9:00 AM - 9:25 AM	**Ajay Chawla** *University of California, San Francisco, USA* TYPE 2 INNATE SIGNALS REGULATE MUSCLE REGENERATION	
9:25 AM - 9:50 AM	**Florian Greten** *Georg-Speyer-Haus, Germany* INFLAMMATION CONTROLLED CELL PLASTICITY AND STEMNESS IN COLON CANCER	
9:50 AM - 10:15 AM	**Frederic Geissmann** *King's College London, UK* TITLE NOT AVAILABLE AT TIME OF PRINTING	
10:15 AM - 10:40 AM	**Nicolas Buchon** *Cornell University, USA* EPITHELIAL DYNAMICS IN THE GUT OF DROSOPHILA IN RESPONSE TO INDIGENOUS AND PATHOGENIC MICROBES	
10:40 AM - 11:20 AM	**ISSCR-BD BIOSCIENCES OUTSTANDING YOUNG INVESTIGATOR AWARD PRESENTATION AND LECTURE** **Valentina Greco** *Yale University School of Medicine, USA* UNCOVERING CELLULAR AND SIGNALING MECHANISMS OF SKIN REGENERATION USING TWO-PHOTON MICROSCOPY	
11:00 AM - 3:30 PM	**ISSCR EXHIBITION HALL OPEN**	Exhibition Hall
11:25 AM - 1:00 PM	**LUNCH BREAK ON YOUR OWN**	

PROGRAM SCHEDULE

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SATURDAY, JUNE 21 *(continued)*

11:30 AM - 1:00 PM	**JUNIOR INVESTIGATOR EVENTS: CAREER PANEL LUNCHEON** *Supported by Massachusetts General Hospital Center for Regenerative Medicine, Stem Cell Program at Boston Children's Hospital, and Harvard Stem Cell Institute* STRATEGIES FOR SUCCESS: TRANSITION TO AN INDEPENDENT CAREER **Registration required**	West Level 2 Oceanside Foyer
1:15 PM - 3:00 PM	**PLENARY VI: MESENCHYMAL STROMAL CELLS** *Supported by Mesoblast Ltd.* **Chair: Leonard I. Zon** *Boston Children's Hospital, USA*	Plenary Hall
1:15 PM - 1:40 PM	**Paolo Bianco** *Sapienza University of Rome, Italy* "MESENCHYMAL" STEM CELLS BETWEEN COMMERCE AND PATHOPHYSIOLOGY	
1:40 PM - 2:05 PM	**Yufang Shi** *Institute of Health Sciences, China* IMMUNE REGULATION BY MESENCHYMAL STEM CELLS	
2:05 PM - 2:30 PM	**Simon Mendez-Ferrer** *Centro Nacional de Investigaciones Cardiovasculares, Spain* PATHOGENESIS RECAPITULATES ONTOGENESIS: LESSONS FROM THE HEMATOPOIETIC STEM CELL NICHE IN THE BONE MARROW	
2:30 PM - 2:55 PM	**T. Michael Underhill** *University of British Columbia, Canada* MESENCHYMAL STROMAL CELLS IN TISSUE HOMEOSTASIS AND REGENERATION	
3:00 PM - 3:40 PM	**REFRESHMENT BREAK**	Exhibition Hall
3:40 PM - 6:00 PM	**PLENARY VII: EPIGENETICS AND PLURIPOTENCY** *Supported By Fate Therapeutics* **Chair: Fred H. Gage** *Salk Institute for Biological Studies, USA*	Plenary Hall
3:45 PM - 3:55 PM	**PRESIDENT ELECT ADDRESS:** **Rudolf Jaenisch,** *Whitehead Institute for Biomedical Research, USA*	
3:55 PM - 4:20 PM	**Kathrin Plath** *University of California, Los Angeles School of Medicine, USA* REPROGRAMMING TO PLURIPOTENCY	

PROGRAM SCHEDULE

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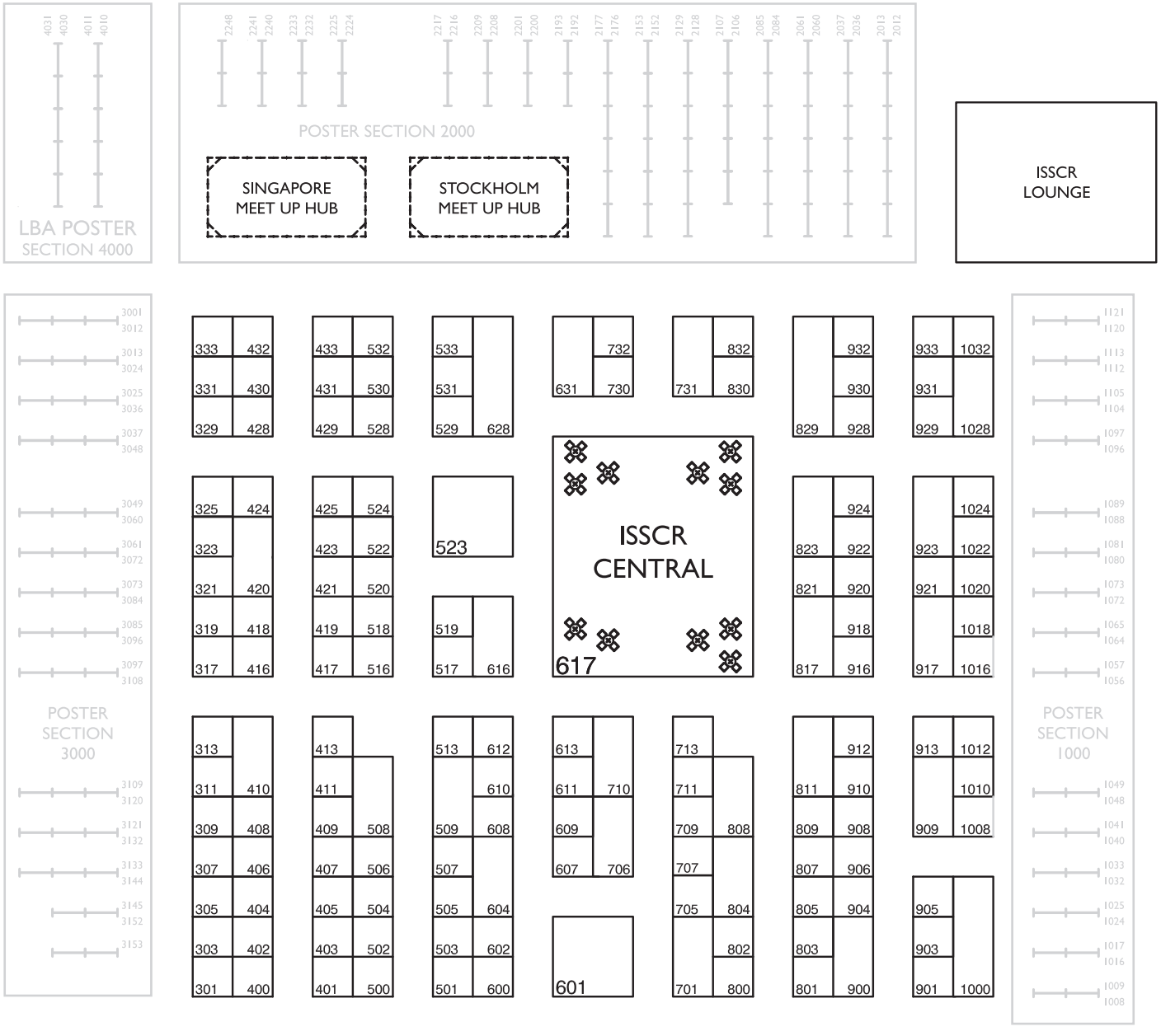
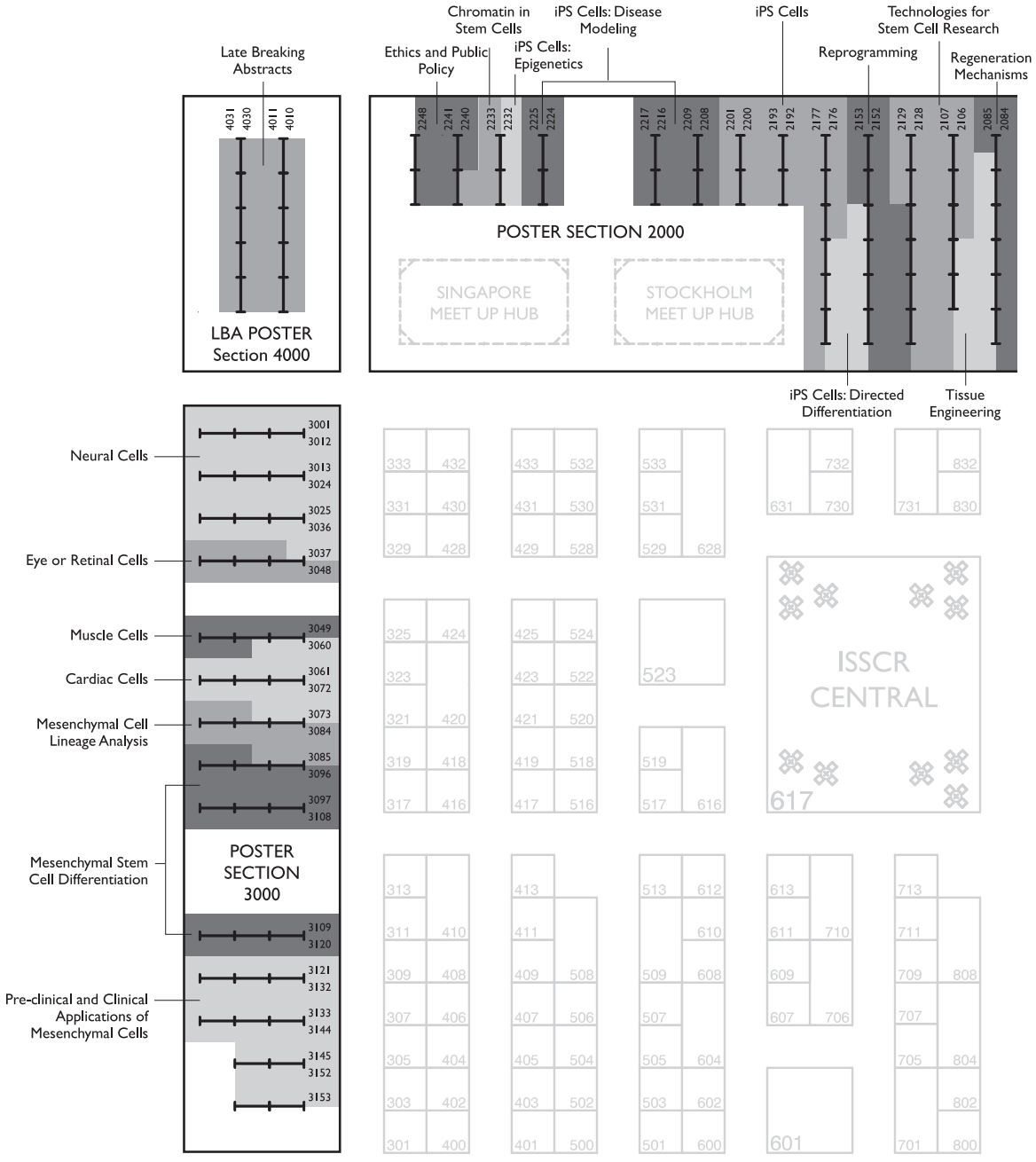
SATURDAY, JUNE 21 *(continued)*

4:20 PM - 4:45 PM	**Guo-liang Xu** *Institute of Biochemistry and Cell Biology, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, China* DNA OXIDATION TOWARDS TOTIPOTENCY IN MAMMALIAN DEVELOPMENT	
4:45 PM - 5:10 PM	**Hongkui Deng** *College of Life Sciences at Peking University, China* TITLE NOT AVAILABLE AT TIME OF PRINTING	
5:10 PM - 5:45 PM	CLOSING KEYNOTE ADDRESS **Susan Lindquist** *Whitehead Institute for Biomedical Research, USA* FROM YEAST CELLS TO HUMAN NEURONS - MODELING COMPLEX PROTEIN FOLDING DISEASES	
5:45 PM - 6:00 PM	CLOSING REMARKS	
6:00 PM - 7:00 PM	CLOSING RECEPTION	West Ballroom Foyer

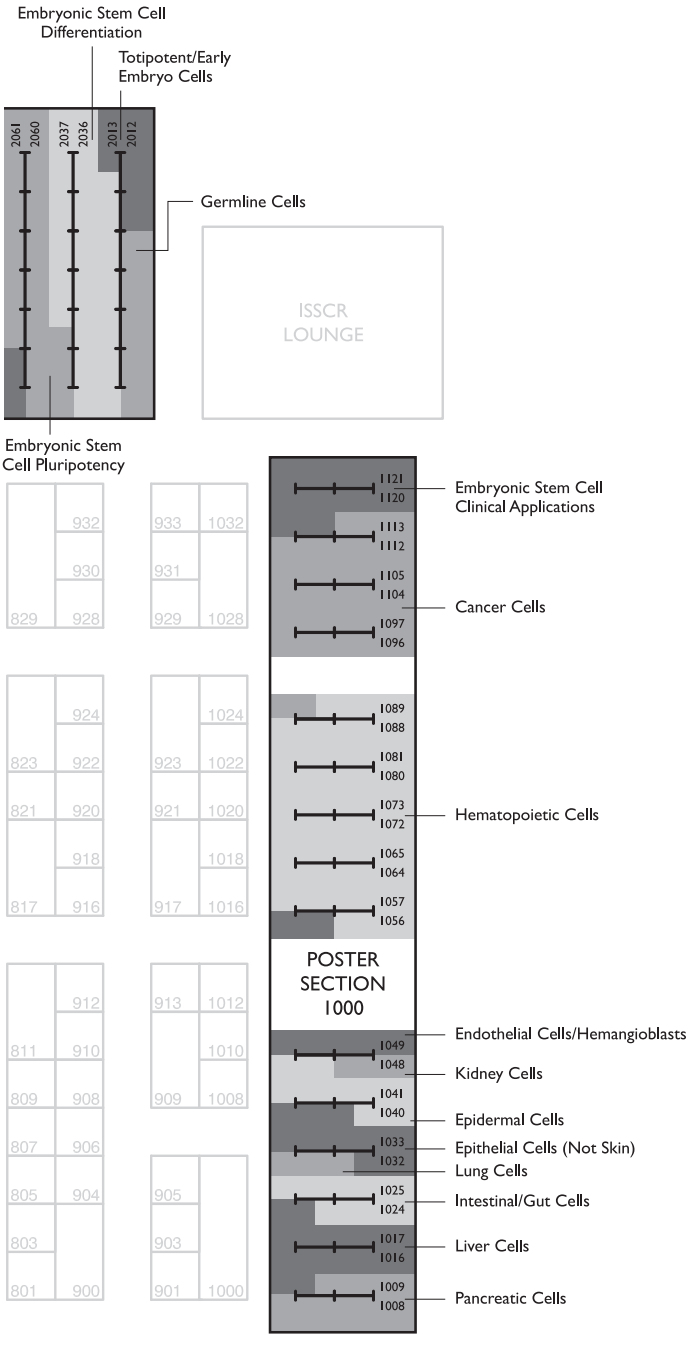
EXHIBITION HALL FLOOR PLAN



POSTER FLOOR PLAN



POSTER FLOOR PLAN



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POSTERS 1001-1122

POSTERS 2001-2246

POSTERS 3001-3037

POSTERS 4001-4034

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AMSBIO	600
Angiocrine Bioscience, Inc.	325
Applied Biological Materials	910
Applikon Biotechnology, Inc.	433
ATCC	802
Baker/Ruskinn	313
BD Biosciences	616
Bio-Rad Laboratories	317
BioCision, LLC	519
BioLamina	800
BioLegend	801
Biological Industries (BI)	731
BioMed Central	528
BioMedTech Laboratories	933
Biosafe America	400
Biosearch Technologies, Inc.	524
BioSpherix	908/909
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BTX/Harvard Apparatus	906
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Cell Press	509
Cell Signaling Technology	832
Cellectis AB	607
CellGenix GmbH	821
Cellular Dynamics International	701

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ChemoMetec USA, Inc.	931
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Compass Biomedical, Inc.	409
Connexon Creative	507
Coriell Institute for Medical Research	505
Corning Inc.	706
Custom Biogenic Systems	413
Dainippon Screen Mfg. Co., Ltd.	424
DefiniGEN Ltd	420
Diagenode Inc.	602
DRVision Technologies LLC	809
eBioscience	932
EMD Millipore	811
Enzo Life Sciences	732
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EPPENDORF CANADA LTD.	518
ESI BIO	508
Essen BioScience	423
Essential Pharmaceuticals	803
Exiqon, Inc	924
Extract Technology	920
FedEx Healthcare Services	428
Fluidigm	601
GE Healthcare	923
Genea Biocells	900
GlobalStem	922
Greiner Bio-One	608
Hamilton Thorne Inc	613
Hemasoft America Corp.	432
HumanZyme, Inc	805

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COMPANY	BOOTH NUMBER
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KITAGAWA IRON WORKS Co., Ltd.	531
Kuhner Shaker Inc.	901
Leica Microsystems	903
Life & Brain GmbH	429
Life Technologies, Inc.	829
Logos Biosystems, Inc.	516
Lonza	1000
Macopharma USA	407
Mary Ann Liebert, Inc.	1010
Medeina Cell Technologies Ltd	532
Medical Surface Inc.	406
Mill Creek Life Sciences	530
Miltenyi Biotec GmbH	523
Molecular Matrix Inc.	1024
Multi Channel Systems	333
NanoString Technologies	604
Nikon	610
Nippi, incorporated	1018
Nissan Chemical Industries Ltd.	421
Norgen Biotek Corporation	417
Novoprotein Scientific	1012
NYSCF Research Institute	918
Olympus America Inc.	401
Orla Protein Technologies Ltd	517
Pall Life Sciences	707
Panasonic	410
PeproTech Inc.	808
PERKINELMER	1028
PhalanxBio Inc	921
Plas-Labs, Inc	513
Progenitor Life Sciences	1032
PromoCell GmbH	1016
Proteintech Group Inc.	411
R&D Systems, Inc.	631
RayBiotech, Inc.	425
Repligen Corporation	402
ReproCELL, Inc.	711
Roche Custom Biotech	1022
RUCDR Infinite Biologics	506
Sony Biotechnology Inc.	917
Springer	804
Stem Cell Network	609
STEMCELL Technologies Inc.	817
StemCulture	830
Stemgent-Asterand	823
StemRD Inc.	520
StemTrak	533
STREX, Inc.	301
SUMITOMO Bakelite Co., Ltd.	522
SynGen, Inc	416
Synthecon Inc	1020
Thermo Scientific	628
Transposagen Biopharmaceuticals, Inc.	930
Trevigen, Inc.	904
Union Biometrica, Inc.	730
VisualSonics	905
Waisman Biomanufacturing	928
WiCell	929
Wiley	503
World Stem Cell Summit 2014	408
Worthington Biochemical Corp.	612
WuXi AppTec	705
XCell Science Inc.	502

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BOOTH NUMBER	COMPANY
301	STREX, Inc.
313	Baker/Ruskinn
317	Bio-Rad Laboratories
325	Angiocrine Bioscience, Inc.
333	Multi Channel Systems
400	Biosafe America
401	Olympus America Inc.
402	Repligen Corporation
403	Cellular Engineering Technologies Inc.
406	Medical Surface Inc.
407	Macopharma USA
408	World Stem Cell Summit 2014
409	Compass Biomedical, Inc.
410	Panasonic
411	Proteintech Group Inc.
413	Custom Biogenic Systems
416	SynGen, Inc
417	Norgen Biotek Corporation
418	Advanced Bioscience Resources, Inc.
419	Akron Biotechnology, LLC
420	DefiniGEN Ltd
421	Nissan Chemical Industries Ltd.
423	Essen BioScience
424	Dainippon Screen Mfg. Co., Ltd.
425	RayBiotech, Inc.
428	FedEx Healthcare Services
429	Life & Brain GmbH
432	Hemasoft America Corp.
433	Applikon Biotechnology, Inc.
500	CM Technologies / BioMediTech
501	Cell Line Genetics, Inc.
502	XCell Science Inc.
503	Wiley

BOOTH NUMBER	COMPANY
504	Biott Corp. / ABLE Corporation
505	Coriell Institute for Medical Research
506	RUCDR Infinite Biologics
507	Connexon Creative
508	ESI BIO
509	Cell Press
513	Plas-Labs, Inc
516	Logos Biosystems, Inc.
517	Orla Protein Technologies Ltd
518	EPPENDORF CANADA LTD.
519	BioCision, LLC
520	StemRD Inc.
522	SUMITOMO Bakelite Co., Ltd.
523	Miltenyi Biotec GmbH
524	Biosearch Technologies, Inc.
528	BioMed Central
529	ALS Automated Lab Solutions
530	Mill Creek Life Sciences
531	KITAGAWA IRON WORKS Co., Ltd.
532	Medeina Cell Technologies Ltd
533	StemTrak
600	AMSBIO
601	Fluidigm
602	Diagenode Inc.
604	NanoString Technologies
607	Cellectis AB
608	Greiner Bio-One
609	Stem Cell Network
610	Nikon
611	Centre for Commercialization of Regenerative Medicine
612	Worthington Biochemical Corp.
613	Hamilton Thorne Inc
616	BD Biosciences

EXHIBITOR LISTING (by Stand Number)

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628	Thermo Scientific
631	R&D Systems, Inc.
701	Cellular Dynamics International
705	WuXi AppTec
706	Corning Inc.
707	Pall Life Sciences
709	EpigenDx
710	Irvine Scientific
711	ReproCELL, Inc.
713	Alpha MED Scientific Inc.
730	Union Biometrica, Inc.
731	Biological Industries (BI)
732	Enzo Life Sciences
800	BioLamina
801	BioLegend
802	ATCC
803	Essential Pharmaceuticals
804	Springer
805	HumanZyme, Inc
807	AllCells, LLC
808	PeproTech Inc.
809	DRVision Technologies LLC
811	EMD Millipore
817	STEMCELL Technologies Inc.
821	CellGenix GmbH
823	Stemgent-Asterand
829	Life Technologies, Inc.
830	StemCulture
832	Cell Signaling Technology
900	Genea Biocells
901	Kuhner Shaker Inc.
903	Leica Microsystems
904	Trevigen, Inc.

BOOTH NUMBER	COMPANY
905	VisualSonics
906	BTX/Harvard Apparatus
908/909	BioSpherix
910	Applied Biological Materials
912	Abcam
913	Cedarlane
916	The Company of Biologists
917	Sony Biotechnology Inc.
918	NYSCF Research Institute
920	Extract Technology
921	PhalanxBio Inc
922	GlobalStem
923	GE Healthcare
924	Exiqon, Inc
928	Waisman Biomanufacturing
929	WiCell
930	Transposagen Biopharmaceuticals, Inc.
931	ChemoMetec USA, Inc.
932	eBioscience
933	BioMedTech Laboratories
1000	Lonza
1008	Carl Zeiss Microscopy, LLC
1010	Mary Ann Liebert, Inc.
1012	Novoprotein Scientific
1016	PromoCell GmbH
1018	Nippi, incorporated
1020	Synthecon Inc
1022	Roche Custom Biotech
1024	Molecular Matrix Inc.
1028	PERKINELMER
1032	Progenitor Life Sciences

EXHIBITOR / SUPPORTER DIRECTORY

ABCAM – Booth 912
1 Kendall Square, Suite B2304
Cambridge, MA 02139 United States
Phone: 888-772-2226
Fax: 877-774-8286
Website: www.abcam.com

Abcam plc is a provider of protein research tools and services, with an unrivalled range of products and expert technical support, enabling scientists to analyze living cells at the molecular level and improving the understanding of health and disease. To find out more, please visit www.abcam.com.

ADVANCED BIOSCIENCE RESOURCES, INC. – Booth 418
1516 Oak Street, #303
Alameda, CA 94501 United States
Phone: 510-865-5872
Fax: 510-865-4090

ABR, is a non-profit foundation, acquires and distributes human fetal tissues, placental tissues, maternal & adult blood, & umbilical cord blood for biomedical research. Certain tissues can be acquired per FDA 21 CFR 1271 GTB regulations. Bioinformatics services are offered through ABR's partnership with Novogenix Labs.

AKRON BIOTECH – Booth 419
1095 Broken Sound Pkwy Suite 100
Boca Raton, FL 33487 United States
Phone: 561-750-6120
Fax: 561-750-6140
Website: www.akronbiotech.com

Akron Biotech is ISO 9001-compliant company headquartered in South Florida, U.S., with a strategic focus on supplying GMP-qualified raw materials and services to the regenerative medicine industry. As global supplier, Akron manufactures a range of products for cell therapy discovery, development, and commercialization. These products include growth factors, sera and native purified proteins, custom-made cell culture media, tailored scaffolds with biomaterials, as well as, proprietary cryopreservation formulations.

ALLCELLS, LLC – Booth 807
1301 Harbor Bay Pkwy Suite 200
Alameda, CA 94502 United States
Phone: 510-521-2600
Fax: 510-521-7600
Website: 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, diseased cells, animal cells, and bioservices help accelerate research and allow scientists to focus on results.

ALPHA MED SCIENTIFIC – Booth 713
209, 7-7-15, Saito-asagi
Ibaraki Osaka 567-0085 Japan
Phone: +81-72-648-7973
Fax: +81-72-648-7974
Website: www.med64.com

The MED64 is a user-friendly micro-electrode array system for in-vitro electrophysiology. High-quality extracellular signals are acquired with its low-impedance electrodes. It is a powerful tool for drug screening with stem cell-derived cardiomyocytes/neurons, and long-term recordings during the differentiation process thanks to its non-invasive nature.

ALS AUTOMATED LAB SOLUTIONS – Booth 529
Stockholmer Straße 10
Thuringen D-07747 Germany
Phone: 49 (0) 3641 4820-0
Website: www.als-jena.com

The company offers a myriad of biological's and biochemical's to Life Science researchers and clinicians providing products from virtually all of the World's most renowned international manufacturers. Delivery is timely and all products are stored, received, and shipped at appropriate required temperatures. Employees work closely with both customers and suppliers offering a personalized and comprehensive experience to reflect the core value that customers are of the utmost importance. By providing a gateway to over two million global reagents customers have the advantage of freight consolidation and the convenience and cost savings inherent within.

AMSBIO – Booth 600
1035 Cambridge Street,
Cambridge, MA 02141 United States
Phone: 617-945-5033
Fax: 617-945-8218
Website: www.amsbio.com

AMSBIO is a leading provider of products to accelerate research into stem cells and regenerative medicine. Our range includes innovative 2D and 3D cell culture technologies and products that support all stages of research including stem cell growth and culture, characterization, modification, differentiation and storage.

ANGIOCRINE BIOSCIENCE, INC. – Booth 325
1300 York Ave., A-335
New York, NY 10065
Phone: 877-784-8496
Fax: 646-349-5223
Website: www.angiocrinebioscience.com

Angiocrine Bioscience has developed the VeraVecTM cellular platform for amplifying stem and progenitor cells, in both human and mouse models, by recapitulating the proliferative stimulation of the in vivo vascular niche in vitro. The expansion capacity is on an unprecedented scale when compared to any other competing technology, and it is achieved without the requirement for costly mediate additives.

EXHIBITOR / SUPPORTER DIRECTORY

APPLIED BIOLOGICAL MATERIALS INC. – Booth 910
8-13520 Crestwood Place
Richmond, BC V6V 2G2 Canada
Phone: 604-247-2416
Fax: 604-247-2414
Website: www.abmgood.com

We are a biotech company that develops innovative reagents for life science research. Activities in our facility include the research, development and commercialization of PCR products, mammalian cell lines, enzymatic proteins, growth factors and recombinant gene, siRNA, and miRNA expression vector libraries.

APPLIKON BIOTECHNOLOGY INC. – Booth 433
1180 Chess Drive
Foster City, CA 94404 United States
Phone: 650-578-1396
Fax: 650-578-8836
Website: www.applikonbio.com

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

ATCC – Booth 802
10801 University Blvd
Manassas, VA 20110 United States
Phone: 703-365-2700
Fax: 703-365-2701
Website: www.atcc.org

As the premier global biological materials resource and standards organization, ATCC serves and supports the worldwide scientific community with industry-standard products and innovative solutions. Visit booth 802 to learn about our growing portfolio of human induced pluripotent stem cells (hiPSCs), human mesenchymal stem cells (MSC), mouse embryonic stem cells, and stem cell culture reagents. Learn more at www.atcc.org.

BAKER RUSKINN – Booth 313
161 Gatehouse Road
Sanford, ME 04073 United States
Phone: 1(800) 992-2537
Fax: 207-324-3869
Website: www.bakerco.com

Baker Ruskinn is a global leader and supplier of anaerobic and modified atmosphere solutions for microbiology and tissue/cell culture applications. Its advanced line of anaerobic chambers, hypoxia workstations and media conditioning solutions help improve research results by providing precisely controlled conditions for anoxic and low-oxygen studies.

BD BIOSCIENCES – Booth 616
2350 Qume Dr.
San Jose, CA 95131 United States
Phone: 877-232-8995
Fax: 408-954-2009
Website: 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.

BIO-RAD LABORATORIES – Booth 317
1000 Alfred Nobel Dr.
Hercules, CA 94547 United States
Phone: 800-424-6723
Website: www.bio-rad.com

Depend on Bio-Rad for tools, technologies and expertise to enable genomic and proteomic analysis. Bio-Rad provides instrumentation and reagents for droplet digital PCR, conventional and real-time PCR, amplification reagents and primers, flow cytometry, xMAP technology, cancer biomarkers, electrophoresis, blotting-systems, chromatography, imaging, transfection, cell counting.

BIOCISION, LLC – Booth 519
12 E. Sir Francis Drake Blvd, Suite B
Larkspur, CA 94939 United States
Phone: 1-888-478-2221
Fax: 415-634-2350
Website: www.biocision.com

BioCision products improve standardization and eliminate variability in temperature-sensitive sample handling, storage and transport. BioCision products feature advanced thermal management technology and smart ergonomic design to address and support the workflow needs of pre-analytical bench top processes, bioprocessing and post-manufacturing cold chain logistics.

BIOLAMINA – Booth 800
Lofstroms Allé 5A
Sundbyberg (Stockholm) 17266 Sweden
Phone: +46-8-5888 5180
Fax: +46-8-5198 9288
Website: www.biolamina.com

BioLamina offers premium high technology, biorelevant cell culture matrices for stem and primary cells. By using cell type-specific recombinant Laminin-521 for hPSCs, cell expansion is robust, easy and reliable in a chemically defined and xeno-free environment. Our breakthrough technology is scientifically proven in high-impact journals.

EXHIBITOR / SUPPORTER DIRECTORY

BIOLEGEND – Booth 801
9727 Pacific Heights Blvd.
San Diego, CA 92121 United States
Phone: 858-455-9588
Fax: 877-455-9587
Website: www.biolegend.com

World-Class Antibodies, Proteins, Assays and Research Solutions. Complete Brilliant Violet™ Antibody Conjugates for the Violet Laser: BV510™, BV711™, BV785™. Personalized Multicolor Flow Cytometry Panel Design. New LEGENDScreen™ Human Cell Screening (PE) Kits. Request Bulk Cytokines & Chemokines for Bioassay. Ultra-LEAF™ (Low Endotoxin, Azide-Free) Antibodies. New ELISA Kits: IL-35, Active TGF- β1.

BIOLOGICAL INDUSTRIES (BI) – Booth 731
Kibbutz Beit Haemek
25115 Israel
Phone: 972-4-9960594
Fax: 972-4-9968896
Website: www.bioind.com

BI has 30 years of manufacturing expertise in cell culture products for research, further manufacturing and diagnostics. BI line of products includes a complete xeno-free stem cell culture system for hMSC, iPSc and embryonic stem cells, as well as products for cell biology such as PCR Mycoplasma Test kit and elimination solutions.

BIOMED CENTRAL – Booth 528
BioMed Central, Floor 6, 236 Grays Inn Road
London, UK WC1X 8HB United Kingdom
Phone: +442031 922102
Website: www.biomedcentral.com

BioMed Central is a global open access scientific and medical publishing organisation, publishing over 270 journals across biology, medicine and chemistry. Stem Cell Research & Therapy publishes peer-reviewed open access research articles with an emphasis on basic, translational, and clinical research into stem cell therapeutics. Visit us at booth 528 for more information.

BIOMEDTECH LABORATORIES – Booth 933
3802 Spectrum Blvd., Suite 154
Tampa, FL 34612 United States
Phone: 813-985-7180
Fax: 813-558-2000
Website: www.biomedtech.com

Stem cell culture surfaces are featured, including surfaces supporting non-attachment and non-differentiation of stem cells. Coatings supporting differentiated cells include laminin, BME, fibronectin, collagens, gelatin, and new double-coat laminin with poly-ornithine and laminin with PDL. BioMedTech coats all microplate formats, flasks, dishes, and bio-production vessels.

BIOSAFE AMERICA – Booth 400
1225 North Loop West Suite 120
Houston, TX 77008 United States
Phone: 832-431-5822
Fax: 713-456-2766
Website: www.biosafeamerica.com

Biosafe develops and manufactures innovative solutions for cell processing in both adult stem cell banking and regenerative medicine. The Sepax cell processing technology and related accessories provide the necessary flexibility and customization through a combination of application-specific software protocols and single-use kits.

BIOSEARCH TECHNOLOGIES, INC. – Booth 524
2199 So. McDowell Blvd.
Petaluma, CA 94954-6904 United States
Phone: 415-883-8400
Fax: 415-883-8488
Website: www.biosearchtech.com

Biosearch Technologies is a manufacturer of custom oligonucleotides, including Dual-Labeled BHQ® probes and primers for real-time PCR, multiplex qPCR, and SNP genotyping applications. We also offer Stellaris® RNA FISH probes which provide a means to localize, detect, and quantify RNA molecules at the subcellular level.

BIOSPHERIX LTD. – Booth 909
19 Demott Street
Lacona, NY 13083 United States
Phone: 315-387-3414
Fax: 315-387-3415
Website: 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.
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BIOTT CORPORATION/ABLE CORPORATION – Booth 504
6-10, Nishigokencho
Shinjuku-ku Tokyo 162-0812 Japan
Phone: +81-3-3260-0415
Fax: +81-3-3260-0407
Website: http://www.able-biott.co.jp/en/

BIOTT/ABLE is a manufacturer of bioreactors. Exhibiting items are bellows.
1. 100ml Single Use 30ml Vessel
2. 30ml Single Use Vessel
3. Magnetic Stirrer for the single use vessels

EXHIBITOR / SUPPORTER DIRECTORY

STEM CELL PROGRAM AT BOSTON CHILDREN'S HOSPITAL

300 Longwood Avenue
Boston, MA 02115 United States
Phone: 617-919-2069
Fax: 617-730-0222
Website: http://stemcell.childrenshopital.org

The mission of the Stem Cell Program at Children's Hospital Boston is to explore and understand the promise of stem cell biology as a key to treatments for disease, and to translate that promise into effective clinical therapies.

BTX/HARVARD APPARATUS – Booth 906

84 October Hill Road
Holliston, MA 01746 United States
Phone: 508-893-8999
Fax: 508-429-5732
Website: www.btxonline.com

BTX is a leading supplier of in vitro, in vivo, and high-throughput electroporation systems. We feature Gemini Twin-Wave Systems that provide both square and exponential decay waveforms in a single unit. We support most cell/tissue types, and provide a wide selection of chambers and tools.

BURROUGHS WELLCOME FUND

21 T.W. Alexander Drive
Research Triangle Park, NC 27709 United States
Phone: 919-991-5100
Website: http://www.bwfund.org/

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

CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE (CIRM)

210 King St
San Francisco, CA 94107 United States
Phone: 415-396-9100
Website: cirm.ca.gov

CIRM was established in November 2004 with the passage of Proposition 71, the California Stem Cell Research and Cures Act. The statewide ballot measure, which provided $3 billion in funding for stem cell research at California universities and research institutions, was overwhelmingly approved by voters, and called for the establishment of an entity to make grants and provide loans for stem cell research, research facilities, and other vital research.

CARL ZEISS MICROSCOPY, LLC – Booth 1008

One Zeiss Drive
Thornwood, NY 10594 United States
Phone: 800-233-2343
Website: www.zeiss.com/microscopy

As the world's only manufacturer of light, X-ray, electron/ion microscopes, ZEISS offers tailor-made microscope systems for 3D imaging in biomedical research, life sciences and healthcare. A well-trained salesforce, an extensive support infrastructure and responsive service team enable customers to use their ZEISS microscopes to full potential.

CEDARLANE – Booth 913

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Burlington, ON L7L 5R2 Canada
Phone: 800-268-5058
Fax: 1.289-288-0020
Website: www.cedarlanelabs.com

Providing researchers with quality products, Cedarlane is a vital resource to the Life Science industry. Cedarlane's customers take advantage of access to over 2 million products from over 1000 top global suppliers. Open six days a week, you save money through consolidation and affordable delivery.

CELL LINE GENETICS – Booth 501

510 Charmany Drive Suite 254
Madison, WI 53719 United States
Phone: 1-608-441-8160
Fax: 1-608-441-8162
Website: www.clgenetics.com

Cell Line Genetics is a leading provider of services and products for stem cell and cell therapy research. Services include multi-species karyotyping, DNA fingerprinting, FISH, aCGH and custom assay development. All results delivered through StemCloud™ HIPAA compliant facility.

CELL PRESS – Booth 509

600 Technology Square
Cambridge, MA 02139 United States
Phone: 617-661-7057
Website: www.cell.com

Visit Cell Press booth #509 for the latest high-quality stem cell research and meet Cell Press editors! Pick up free journal copies including *Cell, Cell Stem Cell* (special issue on epigenetics), *Cell Reports, Trends in Molecular Medicine,* and the new OA journal from ISSCR, *Stem Cell Reports.*

EXHIBITOR / SUPPORTER DIRECTORY

CELL SIGNALING TECHNOLOGY – Booth 832

3 Trask Lane
Danvers, MA 01923 United States
Phone: 978-867-2300
Fax: 978-867-2400
Website: www.cellsignal.com

Founded by research scientists, Cell Signaling Technology (CST) is active in applied systems biology research, particularly as it relates to cancer. Understanding the importance of using antibodies with high levels of specificity and consistency, CST scientists produce, validate, and support all our antibodies in-house.

CELLECTIS AB – Booth 607

Arvid Wallgrens Backe 20
Gothenburg SE-413 46 Sweden
Phone: +46 31 758 0951
Fax: +46 31 758 0910
Website: www.cellectis-bioresearch.com

Cellectis AB is a world leader in stem cell technology with hESC and iPSC derived hepatocytes and cardiomyocytes ideal for ADMET and Safety Pharmacology studies. In addition, a clinical grade xeno-free media DEF-XF, for culturing of human undifferentiated stem cells, will be presented.

CELLGENIX GMBH – Booth 821

AM Flughafen 16
Freiburg D-79108 Germany
Phone: 603-373-0408 (U.S. office)
Fax: 603-373-8104 (U.S. office)
Website: www.cellgenix.com

CellGenix manufactures GMP reagents for ex-vivo cell culture of DC's, T-Cells, NK-Cells, HSC's, and MSC's. We follow strict guidelines to ensure reliability, safety and reproducible results for pre-clinical and clinical applications. CellGenix products are used in clinical centers world-wide in cancer and regenerative medicine.

CELLULAR DYNAMICS INTERNATIONAL – Booth 701

525 Science Drive
Madison, WI 53711 United States
Phone: 1-608-310-5100
Fax: 1-608-310-5101
Website: 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® product lines provide industrial quantities of pure human cells enabling disease modeling, drug discovery, and toxicity testing.

CELLULAR ENGINEERING TECHNOLOGIES – Booth 403

2500 Crosspark Rd.
Suite E232
Coralville, IA 52241 United States
Phone: 1-319-665-3000
Fax: 1-319-665-3003
Website: www.celleng-tech.com

CET specializes in stem cell research, tissue engineering and cancer biology. We develop media, provide and conduct research on stem cells obtained from human non-embryonic sources, such as adipose tissue, bone marrow, Wharton's jelly, umbilical cord blood, and placentas. In addition, CET's mission is to be a leading provider of induced pluripotent (IPS) stem cells derived from normal human volunteers and patients with various clinical conditions. Our engineering focus is on preclinical drug discovery and high throughput drug screening and discovery applications for various human diseases. CET's cancer biology focus is on the isolation and culture of solid tumors from cancers of the breast, colon, kidney, lung and prostate.

CENTRE FOR COMMERCIALIZATION OF REGENERATIVE MEDICINE – Booth 611

100 College Street
Suite 110
Toronto, Ontario M5G1L5 Canada
Phone: 647-309-1830
Fax: 416-978-1368
Website: www.ccrm.ca

CCRM is a Canadian non-profit, public-private consortium funded by the federal government, six Ontario based institutional partners and over 30 companies representing key sectors of the RM industry. CCRM supports the development of technologies that accelerate the commercialization of stem cell- and biomaterials-based technologies and therapies.

CDRD - THE CENTRE FOR DRUG RESEARCH AND DEVELOPMENT

2405 Wesbrook Mall, Fourth Floor
Vancouver, BC V6T 1Z3 Canada
Phone: 604-827-1147
Website: www.cdrd.ca

The Centre for Drug Research and Development (CDRD) is Canada's fully-integrated national drug development and commercialization centre, providing expertise and infrastructure to enable researchers from leading health research institutions to advance promising early-stage drug candidates. Our mandate is to de-risk discoveries stemming from publicly-funded health research and transform them into viable investment opportunities for the private sector — thus successfully bridging the commercialization gap between academia and industry, and translating research discoveries into new therapies for patients.

EXHIBITOR / SUPPORTER DIRECTORY

CIHR INSTITUTE OF CANCER RESEARCH

University of Calgary
Faculty of Medicine
Health Research Innovation Centre
Room 2AA-07
3280 Hospital Drive NW
Calgary AB, T2N 4Z6
Canada
Phone: 403-210-8135
Website: http://www.cihr-irsc.gc.ca/e/12407.html

The Institute of Cancer Research (ICR) funds cancer research in Canada based on internationally accepted standards of excellence, which bear on preventing and treating cancer, and improving the health and quality of life of cancer patients. CIHR is one of the leading cancer research funders in Canada.

CIHR INSTITUTE OF GENETICS

McGill University
3649 Promenade Sir William Osler
Room 279
Montreal, QC H3G 0B1 Canada
Phone: 514-398-3414
Website: http://www.cihr-irsc.gc.ca/e/13102.html

The Institute of Genetics (IG) supports research on the human and model genomes and on all aspects of genetics, basic biochemistry and cell biology related to health and disease, including the translation of knowledge into health policy and practice, and the societal implications of genetic discoveries.

CIHR INSTITUTE OF NEUROSCIENCES, MENTAL HEALTH AND ADDICTION

Strangway Building
University of British Columbia
430 - 5950 University Blvd.
Vancouver, BC V6T 1Z3 Canada
Phone: 604-822-0379
Website: http://www.cihr-irsc.gc.ca/e/8602.html

The Institute of Neurosciences, Mental Health and Addiction (INMHA) supports research to enhance mental health, neurological health, vision, hearing, and cognitive functioning and to reduce the burden of related disorders through prevention strategies, screening, diagnosis, treatment, support systems, and palliation.

CHEMOMETEC USA, INC. – Booth 931

One Capital Mall Suite 670
Sacramento, CA 95814 United States
Phone: 415-990-9273
Website: www.chemometec.com

ChemoMetecs core technology consists in photographing a prepared fluid sample through a microscope and then implements an automatic cell counting and analysis using digital imaging. This technology allows for count and analyses a large number of cells with very high precision and at competitive prices.

CM TECHNOLOGIES OY – Booth 500

Biokatu 12
Tampere 33520 Finland
Phone: +358 10 759 5900
Fax: +358 10 759 5930
Website: www.c-mtechnologies.com

CM Technologies Oy provides a unique live cell imaging and analysis platform Cell-IQ®. The integrated system combines incubator, imaging capability (phase contrast & fluorescence) with automated data analysis software. Cell-IQ can be used to study 2D & 3D samples automatically quantifying cell number, differentiation and movement. Cell-IQ has been utilised in regenerative medicine, stem cell research, oncology, toxicology, neurology, spheroid formation, cell tracking and much more.

THE COMPANY OF BIOLOGISTS – Booth 916

Bidder Building, 140 Cowley Road
Cambridge, Cambridgeshire CB4 0DL United Kingdom
Phone: 44 (0) 1223 424430
Fax: 44 (0) 1223 423353
Website: 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.

COMPASS BIOMEDICAL – Booth 409

7710 Euclid Avenue
Cleveland, OH 44103 United States
Phone: 216-456-9654
Website: www.compassbiomed.com

Compass Biomedical is a leading biotechnology company dedicated to the commercialization of novel technologies and products for translational research. Established in 2012 as part of the Arteriocyte Family, Compass Biomedical currently includes a portfolio of products for stem cell expansion and stem cell therapy and is devoted to providing innovative solutions to scientists and clinicians to bridge the gap between research and clinical applications.

EXHIBITOR / SUPPORTER DIRECTORY

CONNEXON CREATIVE – Booth 507
375 West 5th Ave, Suite 201
Vancouver, BC V5Y 1J6 Canada
Phone: 604-675-7811
Fax: 604-675-7833
Website: www.connexoncreative.com

Connexon Creative produces 15 free, weekly science e-newsletters to help scientists keep current with their fields while saving time. These include Cell Therapy News, ESC & iPSC News and several other stem cell focused newsletters, as well as three immunology newsletters and seven cancer-focused publications.

CORIELL INSTITUTE FOR MEDICAL RESEARCH – Booth 505
403 Haddon Avenue
Camden, NJ 08103 United States
Phone: 856-668-2071
Fax: 856-964-0254
Website: www.coriell.org

The Coriell Institute is exploring the promise of induced pluripotent stem cells and their role in disease research and drug discovery and collaborating as the world's leading biobank resource, distributing biospecimens and offering custom research services to scientists around the globe.

CORNING INC. – Booth 706
836 North St, Building 300 Suite 3401
Tewksbury, MA 01876-1253 United States
Phone: 1-978-442-2200
Fax: 1-978-442-2476
Website: 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.

CUSTOM BIOGENIC SYSTEMS – Booth 413
74100 Van Dyke
Bruce Township, MI 48065 United States
Phone: 586-331-2600
Fax: 586-331-2588
Website: www.custombiogenics.com

Displayed will be a complete range of equipment for bone marrow, cord blood, and stem cell cryopreservation. The -190 C ISOTHERMAL sample storage freezers, controlled rate freezing systems, and Ln2 dry shipping containers. Also displayed will be canister and frame inventory systems for storing bags along with rack and box systems for storing tubes.

DAINIPPON SCREEN MFG. CO, LTD. – Booth 424
Tenjinkaita-machi 1-1
Teranouch-agaru 4-chrome
Horikawa-dori, Kamigyo-ku Kyoto, Japan 602-8585
Phone: 81-75-414-7073
Website: http://www.screen.co.jp

Dainippon Screen Manufacturing has focused on research and development from its very beginnings, and our management philosophy, Shi Kou Ten Kai (thinking, considering, developing and opening new businesses, products and technologies), reflects this fact. Based on this philosophy, we have leveraged the photolithography and image processing technologies cultivated over many years to develop new businesses and products by constantly monitoring the needs of our customers and society at large.

DEFINIGEN LTD. – Booth 420
Maia, Building 270, Babraham Research Campus
Babraham, Cambridge CB22 3AT United Kingdom
Phone: 01223 497113
Website: www.definigen.com

The company has world-leading expertise in the area of hIPSC-derived human cell production and metabolic disease modelling. The application of these technologies in drug discovery provides pharmaceutical companies with more predictive in vitro cell products enabling the development of safer and more effective treatments. In addition the technology platform utilises fully defined and humanized conditions required for the development of regenerative medicine cellular therapies. Definigen builds on intellectual property and knowledge resident at the University of Cambridge Regenerative Medicine Department at Addenbrokes Hospital and in addition has in-licensed the Yamanka induced pluripotent stem cell IP portfolio from iPS Academia Japan Inc.

DIAGENODE INC. – Booth 602
400 Morris #101
Denville, NJ 07834 United States
Phone: 650-814-8195
Website: www.diagenode.com

Diagenode, the leading provider of complete solutions for epigenetics research, offers innovative shearing and automation instruments, reagent kits, and high quality antibodies to streamline DNA methylation, ChIP, and ChIP-seq workflows. Our latest innovations include a full automation system, ChIP-seq kits for only 10,000 cells, and the industry's most validated antibodies.

EXHIBITOR / SUPPORTER DIRECTORY

DRVISION TECHNOLOGIES LLC – Booth 809
15921 NE 8th St., Suite 2000
Bellevue, WA 98008 United States
Phone: 425-653-5589
Fax: 425-746-0859
Website: www.drvtechnologies.com

DRVision software, SVCell, changes the way image recognition is done - enabling users to develop and execute analyses of unsurpassed quality, without image processing expertise. Simple to learn and operate, SVCell provides everything needed to detect, track, measure and classify objects in microscopy images.

EBIOSCIENCE, AN AFFYMETRIX COMPANY – Booth 932
10255 Science Center Drive
San Diego, CA 92121 United States
Phone: 888-999-1371
Fax: 858-642-2046
Website: www.ebioscience.com

eBioscience, an Affymetrix company, provides innovative technology to see cells differently. Phenotype cells and simultaneously detect three RNA transcripts using branch DNA technology on a standard flow cytometer. Alternatively use microscopy to visualize proteins and RNA to gain a deeper insight into your cell's signature. Partner with the industry leader of translational science.

EMD MILLIPORE – Booth 811
290 Concord Road
Billerica, MA 01821 United States
Phone: 800-645-5476
Website: www.emdmillipore.com

EMD 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.

ENZO LIFE SCIENCES, INC. – Booth 732
10 Executive Blvd
Farmingdale, NY 11735 United States
Phone: 800-941-0430
Fax: 610-941-9252
Website: www.enzolifesciences.com

The Enzo Life Sciences portfolio of fluorescent labels & dyes, ELISAs, enzyme activity assays, biochemicals, antibodies, and proteins enables stem cell research & discovery. The comprehensive offering includes innovative assays for epigenetics, Wnt pathway analysis, and markers of stem cell characterization, differentiation, and death pathways.

EPIGENDX, INC. – Booth 709
96 South Street
Hopkington, MA 01748 Unites States
Phone: 508-497-9400
Fax: 508-497-9450
Website: www.epigendx.com

EpigenDx was incorporated in 2006 as a genomic and epigenomic research company specializing in disease biomarker discovery, validation and molecular diagnosis, with unmatched expertise in the field of DNA methylation analysis. EpigenDx provides products and laboratory services for researchers from academic, government and industrial communities.

EPPENDORF CANADA LTD. – Booth 518
2810 Argentia Road, Unit 2
Mississauga, ON L5N 8L2 Canada
Phone: 905-826-5525
Fax: 905-826-5424
Website: www.eppendorf.ca

Eppendorf is proud to debut our new micromanipulators for research use only, the TransferMan 4r. Along with robust and reliable micromanipulators and microinjectors, Eppendorf offers many products required for reproductive research including micromanipulation and microinjection consumable, centrifuges, pipettes, ultra-low temperature, freezers and CO2 incubators.

ESI BIO – A DIVISION OF BIOTIME, INC. – Booth 508
1301 Harbor Bay Parkway, Suite 100
Alameda, CA 94502 United States
Phone: 510-521-3390
Fax: 510-521-3389
Website: www.esibio.com

A unique research reagent organization that markets and distributes products designed to translate to the clinic. Products include human embryonic stem cell lines, human embryonic progenitors, hyaluronan-based hydrogels, cell culture media, small molecules, and kits for stem cell differentiation and reprogramming.

ESSEN BIOSCIENCE – Booth 423
300 West Morgan Road
Ann Arbor, MI 48108 United States
Phone: 734-769-1600
Fax: 734-769-7295
Website: www.essenbioscience.com

Essen BioScience offers in vitro assays, reagents, contract discovery services and instrumentation that target functional measurement of living cells over time. Designed as the first microscope in incubator, the IncuCyte live-cell imagers provide an automated tool for conducting time-lapse microscopy and quantitative image analysis.

EXHIBITOR / SUPPORTER DIRECTORY

ESSENTIAL PHARMACEUTICALS LLC – Booth 803
770 Newtown Yardley Rd. Suite 212
Newton, PA 18940 United States
Phone: 267-757-0112
Fax: 267-757-0119
Website: www.essentialpharma.com

Essential Pharmaceuticals offers quality cell culture media products for the next generation of research. Conduct cell culture with all the benefits and none of the negative consequences of serum use. Cell-Ess® serum replacement is chemically defined and fully synthetic. Save time. Regain control. Be certain.

EXIQON, INC. – Booth 924
12 Gill St., Suite 1650
Woburn, MA 01801 United States
Phone: 888-647-2879
Fax: 781-376-4152
Website: www.exiqon.com

Exiqon is a leading supplier microRNA research tools based on proprietary LNA™ technology. Researchers around the world are using our products to make groundbreaking discoveries about the correlation between gene activity and the development of disease. Exiqon Services offers expertise in microRNA profiling and biomarker discovery from clinical samples.

EXTRACT TECHNOLOGY LTD / WALKER BARRIER SYSTEMS – Booth 920
Bradley Junction Industrial Estate, leeds rd
Huddersfield, West Yorkshire HD2 1UR United Kingdom
Phone: 01484 317009
Fax: 01484 432 659
Website: www.extract-technology.com

Extract Technology Ltd and Walker Barrier systems are leading worldwide supplier of containment and aseptic systems for the pharmaceutical, healthcare, biotech and chemical markets.

With a Head Office and manufacturing facility in Huddersfield, UK and Wisconsin, USA Extract Technology and Walker Barrier Systems has over 30 years experience in the design and manufacture of innovative, bespoke, high quality solutions to meet all requirements.

FATE THERAPEUTICS, INC.
3535 General Atomics Court
Suite 200
San Diego, CA 92121 United States
Phone: 858-875-1800
Website: http://fatetherapeutics.com/

Fate Therapeutics is a clinical-stage biopharmaceutical company engaged in the discovery and development of pharmacologic modulators of adult stem cells to treat orphan diseases. The Company uses small molecules and biologics to enhance the therapeutic potential of adult stem cells via well characterized biological mechanisms. The Company has built a hematopoietic stem cell (HSC) modulation platform, which seeks to optimize the therapeutic potential of HSCs for treating hematologic malignancies and rare genetic disorders, and a muscle satellite stem cell modulation platform, which seeks to activate the regenerative capacity of muscle. Fate has also developed an industrial platform for the generation of human induced pluripotent stem cells, which utilizes small molecules to enhance iPSC generation and culture expansion. The Company is currently applying this platform to the exploration of hiPSC-based cellular therapeutics.

FEDEX HEALTHCARE SERVICES
3640 Hacks Cross Road
Bldg. D 1st FLOOR
Memphis, TN 38125 United States
Phone: 901-434-5198

In the healthcare industry, one size doesn't fit all. Whether you're shipping pharmaceuticals, lab samples or other critical items, count on us for specialized and cost-effective packaging, monitoring, secure shipping and supply chain management to meet all of your medical shipping needs.

FLUIDIGM – Booth 601
7000 Shoreline Ct. Suite #100
South San Francisco, CA 94080 USA
Phone: 1-650-266-6000
Fax: 1-650-871-7152
Website: www.fluidigm.com

Fluidigm develops, manufactures, and markets life science systems based on integrated fluidic circuits (IFCs). This technology furthers research by minimizing costs and enhancing sensitivity for applications such as single-cell gene expression, high-throughput SNP genotyping, and next-generation sequencing. Single-cell gene expression profiling has recently emerged as a powerful method to uncover heterogeneity in cell populations. In response to this, Fluidigm has developed a streamlined and automated workflow for capturing and analyzing single cells. The C1™ Single-Cell Auto Prep System isolates single cells starting with low cell number input.

EXHIBITOR / SUPPORTER DIRECTORY

GE HEALTHCARE LIFE SCIENCES – Booth 923
800 Centennial Ave
Piscataway, NJ 08854 United States
Phone: 1-800-526-3593
Fax: 1-877-295-8102
Website: www.gelifesciences.com

GE Healthcare Life Sciences provides tools for drug discovery, biopharmaceutical manufacturing and cellular technologies so research scientists worldwide can be more productive, effective and creative. Our vision is to be the partner of choice in cell and protein research and the leader in Life Sciences.

GENEA BIOCELLS – Booth 900
321 Kent Street, level 3
Sydney, NSW 2000 Australia
Phone: +61 2 9229 6453
Website: http://www.geneabiocells.com.au/

Genea Biocells develops disease specific and unaffected human pluripotent stem cell lines, custom differentiation protocols, high-content screens, gene editing strategies and culture media for use in research, drug development and cell therapy applications.
We partner with industry and academia to advance stem cell-driven innovative approaches.

GENENTECH, INC.
1 DNA Way
South San Francisco, CA 94080 United States
Phone: 650-225-1000
Website: www.gene.com

We are passionate about helping people combat the world's hardest-to-treat diseases. So we constantly challenge ourselves to expand our scientific expertise, increase our technological understanding, and pursue our passion. To us, science is personal.

GLOBALSTEM – Booth 922
9430 Key West Avenue, Suite 130
Rockville, MD 20850 United States
Phone: 301-545-0238
Fax: 301-424-1989
Website: www.globalstem.com

GlobalStem develops high-quality, standardized stem cell reagents and innovative technologies for life science and neurobiology research. Our products include primary and iPSC-derived neural cells, neuronal culture media & supplements, pluripotent stem cells and stem cell culture media, feeder cells, and transfection reagents for hard-to-transfect cells. With a rapidly expanding stem cell research market and continuing need for optimized and standardized tools, GlobalStem is filling the gap to support today's stem cell and neuroscience research challenges.

GREINER BIO-ONE – Booth 608
Mackenzie Farone
4238 Capital Dr
Monroe, NC 28110 United States
Phone: 1-704-261-7860
Website: us.gbo.com

Greiner Bio-One offers a broad product range of plastic products for high throughput screening, tissue culture, liquid handling and other product applications in the academic and clinical research field.

HAMILTON THORNE, INC. – Booth 613
100 Cummings Center, Suite 465E
Beverly, MA 01915 United States
Phone: 978-921-2050
Fax: 978-921-0250
Website: www.hamiltonthrone.com

Hamilton Thorne presents our family of research lasers: XYClone® and XYRCOS® lasers with Staccato® facilitate ICM excision for stem cell derivation and embryo biopsy. Stiletto® with automated stage offers precision and consistency for adherent cell culture maintenance, including ablation of unwanted cells and colony scoring.

HARVARD STEM CELL INSTITUTE
Richard A. and Susan F. Smith Campus Center,
Suite 727W
1350 Massachusetts Ave.
Cambridge, MA 02138 United States
Phone: 617-496-4050
Fax: 617-496-6625
Website: www.hsci.harvard.edu

HSCI is a scientific collaborative aimed at fulfilling the promise of stem cells. HSCI has pushed the field of stem cell biology forward and made substantial progress toward the ultimate goal of truly understanding disease processes and the development of treatments.

HEMASOFT – Booth 432
124 3rd Street Unit 3
Cambridge, MA 02141 United States
Phone: 414-326-6154
Website: www.hemasoft.com

Hemasoft is an International IT Company specialized in providing Web-enabled software applications to Healthcare organizations. Our software suite e-Delphyn© module dedicated to Cell Therapy Management provides these institutions with a process automation tool, streamlining, securing and tracking all steps of their process flow. Our solution provides an automated tool helping organizations going through their accreditation audits while satisfying all regulatory requirements in terms of documentation and audit trail.

EXHIBITOR / SUPPORTER DIRECTORY

THE HOSPITAL FOR SICK CHILDREN RESEARCH INSTITUTE

555 University Ave
Toronto, ON M5G 1X8 Canada
Tel: 416-813-1500
Website: http://www.sickkids.ca/index.html

The Hospital for Sick Children (SickKids), affiliated with the University of Toronto, is Canada's most research-intensive hospital and the largest centre dedicated to improving children's health in the country. As innovators in child health, SickKids improves the health of children by integrating care, research and teaching.

HUMANZYME, INC. – Booth 805

2201 West Campbell Park Dr.
Chicago, IL 60612 United States
Phone: 312-738-0127
Fax: 312-276-8128
Website: www.humanzyme.com

Humanzyme, Inc. is the global leader in supplying cytokines, growth factors, and other proteins derived from their proprietary human cell expression system. Humanzyme's proteins are xeno & animal free, and can be made under cGMP conditions for cell and stem cell therapy applications.

INSTITUTE FOR STEM CELL & REGENERATIVE MEDICINE UNIVERSITY OF WASHINGTON

850 Republican Street
Campus Box 358056
Seattle, WA 98109 United States
Phone: 206-685-1954
Website: http://depts.washington.edu/iscrm/

The Institute for Stem Cell and Regenerative Medicine (ISCRM) is committed to the ethical pursuit of basic research to unleash the enormous potential of stem cells and thereby develop therapies that improve patient health worldwide. The Institute, founded in March 2006, consists of a world-class team of over 130 faculty conducting basic research on stem and progenitor cells. The Institute is linked by the shared commitment of the faculty to leverage this research to develop improved therapies, and cures, for patients.

IRVINE SCIENTIFIC – Booth 710

1830 E. Warner
Santa Ana, CA 92705-5505 United States
Phone: 949-261-7800 x236
Fax: 949-261-6522
Website: www.irvinesci.com

Irvine Scientific is a worldwide leader in the design, manufacture and distribution of medical devices, including Cell Therapy, Industrial Cell Culture, Cytogenetic, and Assisted Reproductive Technology products. Our extensive experience in cell culture, regulatory compliance, and industrial scale manufacturing provides customers with unique capabilities and support.

JANSSEN RESEARCH & DEVELOPMENT, LLC

1000 Route 202 South
Raritan, NJ 08869 United States
Phone: 908-218-6000
Website: www.janssenrnd.com

As one of the Janssen Pharmaceutical Companies, our strategy is to identify the biggest unmet medical needs and match them with the best science, internal or external, to find solutions for patients worldwide. We leverage our world-class discovery and development expertise, and operational excellence, to bring innovative, effective treatments in five therapeutic areas:

- cardiovascular and metabolism
- immunology
- infectious diseases and vaccines
- neuroscience
- oncology

JDRF

26 Broadway
New York, NY 10004 United States
Phone: (800) 533-CURE (2873)
Website: http://jdrf.org/

JDRF is the leading global organization funding type 1 diabetes (T1D) research. JDRF's goal is to progressively remove the impact of T1D from people's lives until we achieve a world without T1D. JDRF collaborates with a wide spectrum of partners and is the only organization with the scientific resources, regulatory influence, and a working plan to better treat, prevent, and eventually cure T1D.

KITAGAWA IRON WORKS CO., LTD – Booth 531

Kasumi Research Build. #210 1-2-3 Kasumi Minami-ku
Hiroshima 734-0037 Japan
Phone: +81 82 257 1501
Fax: +81 82 257 1501
Website: http://www.spacebio-lab.com/ENG-index.html

"Gravite" is a novel developing gravity controller collaborated with Space Bio-Laboratories. Experiments in Space suggested cells responded sensitively to gravity. In fact, micro-gravity inhibits cell differentiation, and hyper-gravity accelerates cell differentiation. "Gravite" is only one device to provide you both hypo- and hyper- gravity environment.

KUHNER SHAKER INC. – Booth 901

120 Glenn Way, Unit #1
San Carlos, CA 94070 United States
Phone: 650-595-1997
Fax: 650-595-1448
Website: www.kuhner.com

Kühner Shaker manufactures precision CO2 shaker incubators for the life science market. Based in Basel, Switzerland, Kühner offers bench top, floor standing and industrial shaker machines of the highest quality. Additionally accessories, applied technology and technical scientific seminars regarding shaken cultivation systems are also available.

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LEICA MICROSYSTEMS – Booth 903
1700 Leider Lane
Buffalo Grove, IL 60089 United States
Phone: 800-248-0123
Fax: 847-405-0164
Website: www.leica-microsystems.com

Leica Microsystems will show the latest microscopy and imaging equipment for stem cell research.

LIEBER INSTITUTE FOR BRAIN DEVELOPMENT
855 N. Wolfe Street, 3rd Floor
Baltimore, MD 21205
United States
Phone: 410-955-1000
Website: www.libd.org

The mission of the Lieber Institute for Brain Development is to translate basic genetic and molecular mechanisms of schizophrenia and related developmental brain disorders into clinical advances that change the lives of affected individuals.

LIFE & BRAIN GMBH – Booth 429
Sigmund-Freud-Straβe 25
Bonn, North Rhine-Westphalia 53127 Germany
Phone: +49 228 6885 100
Fax: +49 228 6885 101
Website: www.lifeandbrain.com

Life & Brain is a biomedical enterprise focusing on the discovery and development of novel strategies for the diagnosis and therapy of nervous system disorders. The company is delivering the next generation of products for disease modeling and prediction, compound development and tissue regeneration.

LIFE TECHNOLOGIES, INC. – Booth 829
5791 Van Allen Way
Carlsbad, CA 92008
Phone: 760-603-7200
Fax: 760-602-6500
Website: www.lifetechnologies.com

The Life Technologies™ family of instruments, everyday tools, and services offers high-quality, innovative life science solutions for every lab and every application. As a premier brand of Thermo Fisher Scientific, we believe in the power of science to transform lives.

LOGOS BIOSYSTEMS, INC. – Booth 516
#930 Doosan Venturedigm, Pyungchon-dong, Dongan-gu
Anyang-si, Gyunggi-do 431-755 Republic of Korea
Phone: +82-31-478-4184
Fax: +82-31-478-4184
Website: www.logosbio.com

Logos Biosystems has been developing lab automation and imaging instruments for cell/molecular biology. Our product line is an automated cell counter including the LUNA (Bright Field) for cultured cell lines, LUNA-FL (Dual Fluorescence) for most nucleated cells, and LUNA-STEM (Dual Fluorescence) for SVF.

LONZA – Booth 1000
8830 Biggs Ford Rd.
Walkersville, MD 21793 United States
Website: www.lonza.com

Lonza supports stem cell research from the laboratory to clinical application. Visit our booth to learn more about our new L7 hPSC Reprogramming and Culture System and to discover how Lonza's products and services are enabling translation of stem cell research.

MACOPHARMA USA – Booth 407
3675 Crestwood Parkway Suite 260
Duluth, GA 30019 United States
Phone: 770-450-8754
Website: www.macopharmausa.com

Macopharma USA, (formerly UnitedPharma®), a pharmaceutical / medical device company headquartered in Atlanta, Georgia, offers quality blood collection, processing systems and services. Our turnkey approach provides blood centers with the key system components - from the filter-to-the-bag. Macopharma USA is the exclusive United States importer & distributor of Macopharma® branded products & services.

MARY ANN LIEBERT, INC. – Booth 1010
140 Huguenot Street
New Rochelle , NY 10801 United States
Phone: 914-740-2100
Fax: 914-740-2105
Website: www.liebertpub.com

Stem Cells and Development is globally recognized as the trusted source for critical, even controversial coverage of emerging hypotheses and novel findings. An Official Journal of the British Society for Gene and Cell Therapy. For more information visit us at www.liebertpub.com/scd.

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MASSACHUSETTS GENERAL HOSPITAL CENTER FOR REGENERATIVE MEDICINE

185 Cambridge St. 4th Floor
Boston, MA 02114 United States
Phone: 617-643-5380
Fax: 617-724-2662
Website: www.massgeneral.org/regenmed

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.

MEDEINA CELL TECHNOLOGIES LTD – Booth 532

Viikinkaari 6
Helsinki 00790 Finland
Phone: +358 50 52 55 871
Fax: +358 93 19 36 341
Website: www.medeina.fi

Custom mass generation of iPSC's from client's cell material at highly competitive prices. Fully automated sorting of forming iPSC's reduces the turnaround time to as low as 35 days and increases both cost-efficiency and cell quality. We can accommodate single orders of 1-500 cell lines.

MEDICAL SURFACE INC. – Booth 406

303 Wyman St Suite 300
Waltham, MA 02451 United States
Phone: 781-392-7910
Website: www.medical-surface.com

We are a leading provider of high quality, long lasting surfaces for medical devices, laboratory equipment and hand held electronic devices.

MESOBLAST LTD

Level 39
55 Collins Street
Melbourne 3000 Australia
Phone: +61 3 9639 6036 / +1 212 880 2060
Website: www.mesoblast.com

Mesoblast is developing biotherapeutics based on its proprietary adult cell-based and protein technologies. The Company's technology platforms have the potential to deliver a diverse portfolio of clinical-stage products to treat major conditions with unmet medical needs. Mesoblast's cell-based core technologies include its highly purified, immunoselected Mesenchymal Precursor Cells (MPCs), culture-expanded Mesenchymal Stem Cells (MSCs), Dental Pulp Stem Cells (DPSCs), and expanded Hematopoietic Stem Cells (HSCs). Mesoblast's protein technologies are based on factors derived from its proprietary cellular platforms, including Stromal Derived Factor-1 (SDF-1).

MILL CREEK LIFE SCIENCES – Booth 530

221-1st Ave SW Suite 209
Rochester, MN 55902 United States
Phone: 507.287.6257
Fax: 507.289.2066
Website: www.millcreekls.com

PLTMax® is a natural media supplement derived from human platelets, offering un-paralleled stem cell growth. Cells grow at half the concentration of FBS and double in half the time. PLTMax® is available in both clinical and research grades; covering your needs from bench to bedside.

MILTENYI BIOTEC GMBH – Booth 523

Friedrich-Ebert-Strasse 68
Bergisch Gladbach 51429 Germany
Phone: +49 2204 83060
Fax: +49 2204 85197
Website: www.miltenyibiotec.com

With over 1400 employees worldwide, Miltenyi Biotec helps move basic research to the clinic. Innovative tools for stem cell research and clinical applications support biomedical scientists in their studies of adult stem cells, as well as ES and iPS cells.

MOLECULAR MATRIX INC. – Booth 1024

2062 John Jones Road, Suite 110
Davis, CA 95616 United States
Phone: 530-400-2169
Website: www.molecularmatrix.com

Molecular Matrix Inc. is a 3D tissue regeneration company. Molecular Matrix has developed a scaffold for 3D tissue modeling and bioengineering. This unique scaffold has potential to revolutionize traditional 2D cell culture systems with a 3D substrate for cell attachment and growth that allows a close representation of native tissue structure.

MULTI CHANNEL SYSTEMS – Booth 333

60 Marine Street
Farmingdale, NY United States
Phone: 631-393-6401
Fax: 631-393-6407
Website: www.alascience.com

ALA Scientific and MultiChannel Systems develop recording and perfusion instruments for electrophysiology. Leading stem cell researchers' use our Multielectrode Array (MEA) system to electrophysiologically characterize stem cell derived cardiomyocytes and neurons. The MEA System is easy to use and reveals reliable electrophysiological information on stem cell derived cardiomyocytes and neurons.

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NANOSTRING TECHNOLOGIES – Booth 604
530 Fairview Ave N Suite 2000
Seattle, WA 98109 United States
Phone: 888-358-6266
Fax: 206-378-6288
Website: http://www.nanostring.com

NanoString Technologies is a privately-held provider of life science tools for translational research and developer of molecular diagnostic products. The company's nCounter® Analysis System delivers highly-multiplexed, direct profiling of individual molecules in a single reaction without amplification. Applications include Gene Expression, Single-Cell, miRNA and CNV.

NATURE PUBLISHING GROUP (NPG)
75 Varick St
9th Floor
New York, NY 10013 United States
Phone: 212-726-9266
Website: www.nature.com

Nature Publishing Group (NPG) is a publisher of high impact scientific and medical information in print and online. NPG publishes journals, online databases, and services across the life, physical, chemical and applied sciences and clinical medicine.

THE NEW YORK STEM CELL FOUNDATION RESEARCH INSTITUTE – Booth 918
1995 Broadway Ste 600
New York, NY 10023 United States
Phone: 212-365-7444
Fax: 212-787-5844
Website: www.nyscf.org

The NYSCF Research Institute is a nonprofit organization dedicated to accelerating stem cell research through its independent research laboratories, collaborations, grants, scientific conferences & public education.

NIKON CORPORATION – Booth 610
Shin-Yurakucho Bldg., 12-1, Yurakucho 1-chome, Chiyoda-ku,
Tokyo 100-8331 Japan
Phone: +81-3-3216-2375
Fax: +81-3-3216-2385
Website: http://www.nikon.com/products/instruments/special/ct/

Nikon BioStation CT is an automated cell culture observation instrument specialized for stem cell research. Advanced image analysis technology enables live cell based screening, quantitative evaluation and a better understanding of the reprogramming/differentiation process and disease modeling.

NIPPI, INCORPORATED – Booth 1018
1-1-1 Senjumidori-cho
Adachi-ku 120-8601 Japan
Phone: +81-3-3888-5184
Fax: +81-3-3888-5136
Website: http://www.nippi-inc.co.jp

We have been carrying on the study of the functions of ExtraCellular Matrix (ECM) proteins, and Manufacture the ECM proteins (Collagen gelatin and laminin) for cell culture and DDS in the field of the life science and the regenerative medicine.

NISSAN CHECMICAL INDUSTRIES, LTD. – Booth 421
Kowa Hitotsubashi Building
7-1 Kanda-Nishiki-Cho 3 Chome
Chiyoda-Ku, Tokyo 101-0054 Japan
Phone: 81-3-3296-8391
Website: http://www.nissanchem.co.jp/english/

NORGEN BIOTEK CORP. – Booth 417
3430 Schmon Parkway
Thorold, Ontario L2V 4Y6 Canada
Phone: 905-227-8848
Fax: 905-227-1061
Website: www.norgenbiotek.com

Norgen Biotek provides researchers with innovative kits for Molecular Diagnostics (MDx), Sample Collection/Preservation [from Urine, Stool, Plasma/Serum/Blood, Saliva] and microRNA/RNA/DNA/Protein Purification/Clean-Up (spin-column/96-well). Our kits feature exceptional quality, ease-of-use and sensitivity. Norgen Biotek provides researchers with the tools to address any sample preservation and preparation challenge.

NOVARTIS PHARMA AG
WSJ-386.13.40
P.O.Box
CH-4002 Basel Switzerland
Phone: +41-61-3245278
Website: www.novartis.com

Our mission is to care and cure. We want to discover, develop and successfully market innovative products to prevent and cure diseases, to ease suffering and to enhance the quality of life.

EXHIBITOR / SUPPORTER DIRECTORY

NOVOPROTEIN SCIENTIFIC INC – Booth 1012
47 Maple St. Suite L8
Summit, NJ 07901 United States
Phone: 973-671-8010
Fax: 888-253-6691
Website: www.novoprotein.com

Novoprotein Scientific INC is a biotech company which offers a comprehensive portfolio of custom protein services and carries a catalog of 1000 plus cytokine /recombinant proteins. The service scope includes protein expression, process development, custom antibody production etc. The capacity of the four well-established protein expression systems: E.coli, yeast, baculovirus/insect cell and mammalian cell systems, has reached gram scale.

OLYMPUS AMERICA INC. – Booth 401
3500 Corporate Parkway
Center Valley, PA 18034 United States
Phone: 484-896-5000
Fax: 484-896-7131
Website: www.olympusamerica.com

Olympus is a precision technology leader, creating innovative opto-digital solutions in healthcare, life science and consumer electronics products. Olympus provides innovative microscope imaging solutions for doctors, clinicians, researchers, and educators. Olympus microscope systems offer unsurpassed optics, superior construction and system versatility to meet the ever-changing needs of microscopists.

ONTARIO BRAIN INSTITUTE
438 University Avenue
Suite 1618
Toronto, ON M5G 2K8 Canada
Tel: (647) 847-9000
Website: http://www.braininstitute.ca/homepage

The Ontario Brain Institute is a provincially-funded, not-for-profit research centre seeking to maximize the impact of neuroscience and establish Ontario as a world leader in brain discovery, commercialization and care. Convergent partnerships are created between researchers, clinicians, industry, patients, and their advocates to foster discovery and deliver innovative products and services that improve the lives of those living with brain disorders.

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#110-100 College Street
Toronto, Ontario M5G 1L5 Canada
Phone: 647-926-1228
Website: www.ontariostemcell.ca

The Ontario Stem Cell Initiative (OSCI) is a virtual network of more than 100 stem cell and regenerative medicine research programs in Ontario. OSCI's slogan, Innovate & Challenge Fate, encompasses the work of its scientists who are challenging cell and disease fate through their innovative work.

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The Stem Cell Network (SCN) is a Canadian not-for-profit funded by Canada's Networks of Centres of Excellence (NCE). In 2001, SCN was established to catalyze the translation of stem cell research into clinical applications, commercial products and public policy.

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PROGRAM AND ABSTRACTS

WEDNESDAY, JUNE 18, 1:00 PM - 3:20 PM

PRESIDENTIAL SYMPOSIUM

PLENARY HALL

Supported by Janssen Research & Development

MODELING DUCHENNE MUSCULAR DYSTROPHY WITH EMBRYONIC STEM CELLS

Pourquie, Olivier
IGBMC, University of Strasbourg, France

Key cell types including skeletal muscle have proven difficult to differentiate in vitro from pluripotent cells. Differentiation of mature contractile muscle fibers in vitro from mouse or human pluripotent cells has so far not been reported. During embryonic development, skeletal muscles arise from somites, which derive from the presomitic mesoderm (PSM). Based on our understanding of PSM development, we established conditions allowing efficient differentiation of monolayer cultures of mouse embryonic stem (ES) cells into PSM-like cells without introduction of exogenous genetic material or cell sorting. To optimize the differentiation of Embryonic Stem (ES) cells toward the muscle lineage, we used a series of reporter ES cell lines, expressing fluorescent proteins under the control of genes specific for key stages of myogenic development. These reporter lines were used to sequentially optimize the differentiation conditions in order to reach maximal differentiation for each population. Our optimized conditions were inferred based on the development of the PSM in vivo and from a microarray series of early developmental stages of this tissue. We next established simple conditions to recapitulate primary and secondary/foetal myogenesis in vitro from these PSM-like cells. Our strategy allowed for the production of contractile fibers from pluripotent cells in vitro with an efficiency comparing well with current cardiomyocytes differentiation protocols. The muscle fibers produced are striated and multinucleated and exhibit post-natal characteristics. They also provide a niche allowing the development of Pax7-positive satellite-like cells. We used these conditions to differentiate ES cells derived from dystrophin-deficient mdx mice. We show that these fibers exhibit a strikingly abnormal organization of the myofibrils accompanied by a dramatic increase in the number of branches. While such a branched phenotype has been reported in vivo in mdx animals or in Duchenne patients, it has been attributed to fusion defects consequent to the cycles of regeneration occurring in dystrophic muscles. Our results rather argue that the defect is intrinsic to the fibers thus challenging current views on the origin of the pathology of Duchenne Muscular Dystrophy. Thus our work opens the possibility to study pathological mutations in mouse models for muscular dystrophies in vitro.

THE LIFE OF BREATH: STEM CELLS OF THE LUNG

Hogan, Brigid L.M.
Duke University Medical Center, USA

Cell turnover in the lung is normally very slow, relative to other organ systems such as the intestine and skin. However, if lung epithelial cells are damaged by toxic agents or viral infection, or placed under stress by partial pneumonectomy, the lung reveals an impressive capacity for regrowth and repair. By combining a variety of injury/repair models with in vivo cell lineage tracing experiments, new imaging methods, and 3D organoid culture, evidence has accrued that different regions of lung contain different populations of epithelial stem and progenitor cells. For example, in the larger airways lined by pseudostratified mucociliary epithelium the major stem cell population is the basal cell. By contrast, in the distal gas exchange alveolar region there are no basal cells and type 2 alveolar epithelial cells are largely responsible for long term maintenance and repair. This conclusion is complicated, however, by recent studies in a number of labs that show considerable plasticity in the phenotype of epithelial progenitor cells in response to different injuries. A major goal is to identify the cellular and molecular components of the niches in which lung stem cells reside and to identify the signaling pathways by which the components interact with each other. Research is also directed towards understanding how these niches are formed during development and how they change in response to injury, infection, inflammation and aging.

MODELING HUMAN DEVELOPMENT WITH PLURIPOTENT STEM CELLS

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

The directed differentiation of functional cell types from human pluripotent stem cells is dependent on accurately recapitulating the key embryonic stages of development in vitro, including the formation of a primitive streak-like (PS) population, the induction of the appropriate germ layer and the specification of this germ layer to the desired lineage. Studies over the past decade have identified the key signaling pathways that control these early developmental steps in the differentiation cultures and have provided strategies for the generation of endoderm-, mesoderm- and ectoderm-derived populations. With these advances, it is now possible to investigate the regulatory pathways that control the development of organ specific cellular subpopulations with the long-term goal of engineering functional tissues. Recent studies in our lab have identified signaling pathways that specifically regulate primitive and definitive hematopoiesis, the generation of atrial and ventricular cardiomyocytes, the development of functional hepatocytes and

PROGRAM AND ABSTRACTS

cholangiocytes and the differentiation of articular chondrocytes and cartilage from human pluripotent stem cells. Findings from the functional analyses of these cells and their application to modeling diseases in vitro will be presented.

TOWARDS A HUMAN PLURIPOTENT STEM CELL SOURCE FOR TREATING PARKINSON'S DISEASE

Studer, Lorenz
Sloan Kettering Institute for Cancer Research, USA

Dopamine neuron replacement has been proposed as an experimental therapeutic strategy in patients with Parkinson's disease (PD) since the 1980s with more than 300 patients grafted world-wide using human fetal tissue. While those studies have demonstrated the feasibility of dopamine neuron replacement the clinical results have been mixed. One main challenge of fetal tissue grafting has been the limited supply and the variable nature of tissue for transplantation. Over the last 5 years there has been renewed interest in the dopamine neuron replacement paradigm, triggered by a re-analysis of grafted patients > 10 years after transplantation suggesting remarkable long-term benefit in a subset of individuals. Furthermore, novel sources of dopamine neurons have become available to resolve issues such as limited supply or variability of the tissue for transplantation.

Here I will present ongoing work aimed at establishing a clinical grade source of dopamine neurons from human pluripotent stem cells (PSCs). We have previously shown that differentiation protocols that go through a distinct floor plate intermediate yield large numbers of authentic dopamine neurons from hESCs or hiPSCs. Current work is geared towards the prospective isolation of selective subtypes of midbrain dopamine neurons at the developmental stage optimal for cell therapy. We also present data on how to improve graft integration in vivo by engineering the cell surface properties of the transplanted ESC-derived dopamine neurons. An important open question for any transplantation paradigm to the central nervous system is the mechanism of graft action. Using in vivo optogenetic studies in Parkinsonian mice, we have started to probe - in real time - the role of human neuronal activity and graft integration in triggering behavioral recovery. Insights from those studies provide additional rationale for the choice of an optimal cell source for treating PD. Finally, I will discuss some of the remaining challenges for translating our pre-clinical findings in mouse, rat and monkey hosts towards eventual clinical use including studies that address safety and scalability of the cells. Those efforts are geared towards an early phase clinical trial of human ESC-derived dopamine neurons in PD patients.

WEDNESDAY, JUNE 18, 4:00 PM - 6:20 PM

PLENARY II: CELL HETEROGENEITY

PLENARY HALL

Supported by Fluidigm

STEM CELLS IN CANCER: DO THEY MATTER?

Dick, John E.
Princess Margaret Cancer Centre,
University Health Network, Canada

The cellular and molecular basis for intra-tumoral heterogeneity is poorly understood. Tumor cells can be genetically diverse due to mutations and clonal evolution resulting in intra-tumoral functional heterogeneity. Often proposed as mutually exclusive, cancer stem cell (CSC) models postulate that tumors are cellular hierarchies created due to epigenetic programs that are sustained by CSC. I will focus on three lines of evidence showing these models are highly integrated. Gene signatures specific to either AML LSC or normal HSC are highly similar and define a common stemness program. Compared to non-stem cell transcriptional programs, only stem cell signatures were significant independent predictors of patient survival in 4 large clinical databases of >1000 samples. Thus, determinants of stemness influence clinical outcome of AML across a spectrum of mutations indicating that many genetic abnormalities coalesce around stem cell properties. Secondly, we have carried out a series of combined genetic and functional studies of the LSC from either B-ALL or AML that point to commonalities between clonal evolution and CSC models of cancer. LSC from diagnostic patient samples were genetically diverse and reconstruction of their genetic ancestry showed that multiple LSC subclones were related through a complex branching evolutionary process and specific genetic events influence L-IC frequency. Also study of paired diagnostic (Dx) and relapse (Rx) samples are revealing that individual subclones possess distinct functional growth properties and that rare Dx subclones are chemotherapy resistant and become enriched at Rx. Thus the clonal evolution models are highly relevant in cancer but need to be extended to adopt the concept that CSC are subject to clonal evolutionary forces. Finally, the combined genetic and functional analysis of AML is revealing fundamental insights into the cell of origin, nature and biological consequences of initiating lesions and order of subsequent mutations; concepts that demonstrate how highly integrated the CSC and genetic evolution models must be. Highly purified hematopoietic stem cells (HSC), progenitor and mature cell fractions from the blood of AML patients were found to contain recurrent DNMT3a mutations (DNMT3amut) at high allele frequency, but without coincident NPM1 mutations (NPM1c) present in AML blasts. DNMT3amut-bearing HSC exhibited multilineage repopulation advantage

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over non-mutated HSC in xenografts, establishing their identity as pre-leukemic-HSC (preL-HSC). PreL-HSC were found in remission samples indicating that they survive chemotherapy. Thus DNMT3amut arises early in AML evolution, likely in HSC, leading to a clonally expanded pool of preL-HSC from which AML evolves. For therapy to be more effective, our findings indicate that each genetic subclones must be targeted and that any cells that possess stemness properties, whether they are LSC or ancestral preL-HSC, must also be eradicated.

INDUCING HEMOGENESIS IN FIBROBLASTS

Moore, Kateri, Pereira, Carlos-Filipe, Lemischka, Ihor R.
Icahn School of Medicine at Mount Sinai, USA

Definitive hematopoiesis emerges via an endothelial-to-hematopoietic transition in the aorta-gonad-mesonephros (AGM) region and placenta. We have recently demonstrated the induction of hematopoietic stem/progenitors (HSPCs) from mouse fibroblasts with the combination of transcription factors (TFs) Gata2, cFos, Gfi1b and Etv6. The induction recapitulates an endothelial-to-hematopoietic transition progressing through an endothelial-like precursor cell. Guided by our in vitro programming experiments we analyzed mouse placentas for the presence of the precursor cell phenotype. We identified a small population of CD34+ Sca1+Prom1+ (34PS) cells in mid-gestation placentas that do not express the pan-hematopoietic marker CD45. After isolation and culture 34PS cells acquire CD45 and generate large hematopoietic as well as cobblestone colonies. Prom1+ cells localize to the placental vascular labyrinth where HSPCs emerge and express the programming transcription factors. Global gene expression profiles of placental 34PS cells correlate with AGM-derived hemogenic endothelium and fibroblast-derived precursors. Remarkably, when co-cultured with stroma placental 34PS cells give rise to B/T lymphoid cells as well as mixed colonies containing erythroid, myeloid and megakaryocytic cell lineages. We recently transferred the hemogenic reprogramming to the human system. We observed the emergence of colonies in TF transduced human dermal and neonatal fibroblasts. Between days 25 and 35 we observed hematopoietic-like cells that express CD34 and CD49f. Our results demonstrate the TF-mediated induction of a human HSC phenotype in fibroblasts. Genome-wide profiling reveals silencing of fibroblast-specific genes and dynamic activation of endothelial and hematopoietic markers in induced cells. When transplanted into immunodeficient NSG mice we detected human chimerism in peripheral blood. In summary, we show that direct in vitro conversion of mouse fibroblasts provided valuable information for the isolation of hemogenic precursors in vivo. In addition, the identified minimal transcription factor network can also be applied for the hemogenic induction of human fibroblasts. This research will shed light on the basic principles of blood specification and may provide powerful means to produce HSPCs in vitro for cell replacement therapy.

SINGLE-CELL TRANSCRIPT COUNTING IN STEM CELLS: FROM IMAGING TO SEQUENCING ONE MOLECULE AT A TIME

van Oudenaarden, Alexander
Hubrecht Institute, Netherlands

In this talk I will present our recent progress on quantifying and understanding cell-to-cell variability in gene expression. We recently developed several new microscopy-based methods to quantify transcript levels in single cells and sort cells based on transcript abundance. Additionally I will report on our recent advances in quantifying the genome and transcriptome of single cells using sequencing-based methods.

POSTER TEASERS:

F-2058 DEPROGRAMMING REPROGRAMMING: UNCOVERING MECHANISMS AND INDUCERS OF PLURIPOTENCY VIA COMBINATORIAL ANTIBODY SCREENING

Blanchard, Joel W., Xie, Jia, Lerner, Richard A., Baldwin, Kristin K.
The Scripps Research Institute, La Jolla, CA, USA

W-2239 STEM CELLS IN SOCIAL MEDIA: IMPLICATIONS FOR PUBLIC POLICY

Robillard, Julie[1], Kwon, Brian[2], Illes, Judy[3]
[1]National Core for Neuroethics, University of British Columbia, Vancouver, BC, Canada, [2]Department of Orthopaedics, University of British Columbia, Vancouver, BC, Canada, [3]University of British Columbia, Vancouver, BC, Canada

W-1067 CENTRAL CHOLINERGIC SIGNALS REGULATE HEMATOPOIETIC STEM CELL MOBILIZATION

Pierce, Halley[1], Magnon, Claire[1], Lucas, Daniel[1], Huggins, Matthew[1], Schwartz, Gary[2], Frenette, Paul S.[1]
[1]Cell Biology, Gottesman Stem Cell Institue, Albert Einstein College of Medicine, Bronx, NY, USA, [2]Dominick P. Purpura Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, USA

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POSTER TEASERS (cont'd):

W-3071 CREATING ENGINEERED, 3D CARDIAC TISSUES FROM HUMAN INDUCED PLURIPOTENT STEM CELLS USING A ONE-STEP, SCALABLE DIFFERENTIATION SYSTEM

Kerscher, Petra[1], Hodge, Alexander J.[1], Kim, Joonyul[1], Turnbull, Irene C.[2], Bussie, Blakely S.[1], Seliktar, Dror[3], Easley, Christopher J.[1], Costa, Kevin D.[2], Lipke, Elizabeth Ann[1]
[1]Auburn University, Auburn, AL, USA, [2]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Technion-Israel Institute of Technology, Haifa, Israel

F-1078 WNT5A/NOTCH SIGNALING AFFECTS HEMATOPOIETIC STEM CELL AGING AND SYMMETRIC/ASYMMETRIC DIVISION

Florian, Maria Carolina[1], Nattamai, Kalpana J.[2], Soller, Karin[1], Marka, Gina[1], Überle, Bettina[1], Schiemann, Matthias[3], Eckl, Christina[3], Oostendorp, Robert A.J.[3], Scharffetter-Kochanek, Karin[4], Kestler, Hans A.[5], Zheng, Yi[2], Geiger, Hartmut[2]
[1]Institute of Molecular Medicine and Stem Cell Aging, University of Ulm, Ulm, Germany, [2]Cincinnati Children's Hospital Medical Center Experimental Hematology, Cincinnati, OH, USA, [3]Technical University Munich, Munchen, Germany, [4]Experimental Dermatology, University of Ulm, Ulm, Germany, [5]Department of Bioinformatics and Systems Biology, University of Ulm, Ulm, Germany

Ernest McCulloch Memorial Lecture

HEMATOPOIETIC STEM CELLS - AN EVOLVING PARADIGM

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

Hematopoietic stem cell research was launched with the recognition in the 1950's that adult bone marrow contains cells able to repopulate a damaged hematopoietic system and regenerate multilineage blood cell production for sustained periods of time. This finding, coupled with an inability to use histological methods to recognize these cells, suggested that a retrospective, transplantation-based approach to detect their clonal progeny might be devised to enable their enumeration, isolation and characterization. The successful development and application of this principle has revolutionized the fields of hematopoiesis and leukemia and has led to discoveries of major relevance to other tissues. Interestingly, this same approach is now revealing new layers of biological and molecular heterogeneity in cells with extensive hematopoietic regenerative properties as they evolve during development and aging. The present era of cell state reversibility, together with increasing knowledge of the potentially profound effects external cues can have on primitive cells, is also adding exciting new challenges and opportunities to use these cells in the future for greater clinical benefit.

THURSDAY, JUNE 19, 9:00 AM - 11:20 AM

PLENARY III: THERAPIES IN THE CLINIC

PLENARY HALL

Supported by California Institute for Regenerative Medicine

U.S. CLINICS ADVERTISING AND ADMINISTERING UNPROVEN AUTOLOGOUS "STEM CELL" INTERVENTIONS: ETHICAL, SCIENTIFIC, AND LEGAL CONCERNS

Turner, Leigh
University of Minnesota, USA

Clinics advertising autologous, adipose-derived, mesenchymal "stem cell" interventions are proliferating across the United States. These businesses market putative "stem cell therapies" for Amyotrophic Lateral Sclerosis, Parkinson's disease, multiple sclerosis, muscular dystrophy, and many other diseases and medical conditions. Such clinics do not provide access to licensed medical products. Rather, doctors at such clinics typically claim that they are engaged in the "practice of medicine". They deny that they are promoting and administering biological drugs that are supposed to go through regulatory review and receive approval from the FDA before entering the marketplace. In many cases, available evidence suggests that this "practice of medicine" rationale is incorrect. Rather, by advertising unproven and unlicensed biological drugs, clinics appear to violate regulatory standards, ethical norms, and guidelines for the responsible conduct of research.

Acknowledging the scientific and ethical case for evaluating adipose-derived, mesenchymal stem cells-based interventions in carefully designed, independently reviewed, and scrupulously conducted clinical trials, the spread of clinics engaging in "direct-to-consumer" marketing of autologous stem cell interventions raises serious ethical, scientific, and legal concerns. For example, such businesses use medical devices that are supposed to separate mesenchymal stem cells from fat tissue, isolate them, and prepare them for infusion or injection. Many "stem cell clinics" use medical devices that are not cleared or approved for use in the U.S. Other clinics use medical devices cleared for a particular intended use but not cleared or approved for adipose-derived stem cell processing. Use of unapproved, untested, or inadequately tested medical devices prompts troubling questions about safety and efficacy

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of advertised "stem cell" interventions. Enthusiastic marketing of stem cell "therapies" generates concern that prospective patients are not provided with comprehensive account of risks and benefits associated with undergoing unproven autologous stem cell interventions. Conflation of treatment with research, as when clinics advertise "stem cell treatments" available in "patient-funded clinical trials", suggests that many clinics promote the therapeutic misconception. Administration of what appear to be nonhomologous, more-than-minimally-manipulated adipose-derived stem cell products for ALS, multiple sclerosis, and other diseases suggests that clinics are charging for biological drugs that are supposed to be reviewed by IRBs and the FDA and, in general, made available free of charge until their safety and efficacy is established and they have entered the marketplace as licensed products. In addition, administration of purported stem cell interventions by physicians who appear to be operating outside their scope of competence prompts concerns about whether some clinics are failing to provide patients with a professional standard of medical care.

Clinics promoting ostensible "stem cell treatments" tap into broad cultural currents of hope and enthusiasm for the promise of stem cell therapies. It is understandable that some patients are drawn to such businesses by powerful rhetorical claims, dramatic testimonials, and convincing company websites. However, premature commercialization of putative "stem cell treatments" generates many ethical, legal, and scientific concerns.

ISLET AND STEM CELL TRANSPLANTATION: DIABETES THERAPIES IN THE CLINIC

Shapiro, A.M. James
University of Alberta, Canada

While injected insulin remains the mainstay treatment for all patients with Type 1 Diabetes (T1DM), bolus subcutaneous therapy fails to prevent insidious micro and macrovascular complications in most patients, shortens lifespan, and in a subset, despite intensive insulin therapy and optimized monitoring, leads to recurrent disabling hypoglycemic reactions. Whole pancreas transplantation has previously been advocated as an option to stabilize glycemic control and provide insulin independence, but is fraught with risk of perioperative complications from major surgery, and potent immunosuppression is required. Clinical islet transplantation can achieve similar impact to whole pancreas transplantation but without recourse to major surgery, as islets of Langerhans are infused intraportally to the liver. The Edmonton Protocol series (NEJM 2000) led to high rates of one year insulin independence in a small number of patients. Most returned to insulin therapy at low dose by 3 to 5 years. Recent further advances in clinical islet transplantation have been substantial, and now at least 6 centres report insulin independence rates of over 50% at 5 years with T-depletional inductional immunosuppression combined with anti-inflammatory antibodies. A large Phase 3 trial in North America, conducted under FDA jurisdiction, will likely lead to Biological Licensure for islet transplantation in the US within the next 2 years. Islet transplantation is critically dependent upon deceased human organ donor supply. If cellular transplantation is to be expanded and made more broadly available, then alternative human insulin secreting cell sources will be needed, combined with strategies to minimize or eliminate the need for lifelong immunosuppression. Progress in embryonic and adult inducible pleuripotential stem cell therapies has occurred exponentially, and human trials will begin during 2014 in patients with T1DM. A summary of recent progress and outcomes in clinical islet transplantation will be provided, together with a discussion of approaches to stem cell transplantation (autologous and allogeneic) as a means to control autoimmunity, and provide alternative expanded beta cell sources for clinical application.

TAKING STEM CELL-BASED THERAPIES TO THE CLINIC IN PARKINSON'S DISEASE

Barker, Roger A.
University of Cambridge, UK

Parkinson's Disease (PD) is a common disorder that has, as part of its core pathology, the loss of the dopaminergic nigrostriatal neurons and the formation of alpha synuclein positive Lewy bodies. Whilst it is now recognised that PD has a much more complex pathology than this, most patients respond well to dopaminergic drug therapies in the early stages of disease but with time this efficacy wears off and side effects develop. Thus there is a need for a better, more biological, way to deliver dopamine to the parkinsonian brain which, whilst not curing the patient, should substantially improve their dopaminergic responsive symptoms and signs.

One approach has been to use dopamine producing cells grafted into the striatum, of which the most successful have been those derived from the developing human fetal ventral mesencephalon (hfVM). The use of this tissue was the subject of many successful open label trials in the late 1980s and 1990s, but at the turn of the century two "double blind placebo group" trials showed that this therapy was ineffective and produced side effects in the form of graft induced dyskinesias (GIDs). The outcome of these two trials essentially brought the field of cell based therapies in PD to a halt at a time when stem cell based approaches were still being actively pursued and developed.

In order to try and better reconcile this paradox, a re-evaluation of the data from all these hfVM trials was undertaken. This suggested that this therapy may work if targeted to a more specific population of patients with PD with greater standardization of the protocols for delivering and supporting the grafted tissue. This has led to a new EU funded trial of hfVM tissue in younger patients with earlier

stage PD (TRANSEURO). This trial is seen as creating a template for taking future dopaminergic cells derived from stem cell sources to clinic, as the ethical and logistical problems of using human fetal tissue precludes it from every becoming a main stream treatment for PD. As to which stem cells will act as the source of such neurons remains unresolved but it is likely to be human ES cell lines in the first instance.

In this talk I will confine my discussion to the history of neural grafting in PD and how stem cells could be trialled in patients with this disorder. In addition I will discuss some of the issues that will need to be resolved to ensure that these stem cell derivatives are true authentic nigral dopaminergic neurons.

My work in PD is supported by an NIHR award of a Biomedical Research Centre and Unit to Addenbrooke's Hospital/University of Cambridge; Parkinson's UK; Michael J Fox Foundation; Cure-PD; Rosetrees Trust; EU-FP7; and MRC.

WHAT LED ME TO PARTICIPATE IN A CLINICAL STEM CELL TRIAL FOR MULTIPLE SCLEROSIS: A PERSONAL STORY

Molson, Jennifer
Patient Advocate, Canada

I was diagnosed with Relapsing Remitting MS at the age of 21. After failed therapies and worsening condition of my disease, I chose to put my life on the line and participate in a clinical trial involving stem cells. This is my story of the past 18 years living with MS, the challenges and the success.

GENETIC ENGINEERING OF HEMATOPOIESIS FOR TREATING GENETIC DISEASES AND CANCER

Naldini, Luigi
San Rafaele-Telethon Institute for Gene Therapy, Italy

Not available at time of printing.

CAR T CELL THERAPY AND THE PROMISE OF T CELL ENGINEERING

Sadelain, Michel
Memorial Sloan Kettering Cancer Center, USA

T cell engineering is emerging as a powerful means to rapidly generate large supplies of tumor-targeted T cells for cancer immunotherapy. Over the past two decades, a new toolbox of synthetic receptors used to genetically enhance patient T lymphocytes has been created, the best known of which are chimeric antigen receptors (CARs). CARs are recombinant receptors for antigens that retarget and reprogram T cell function to enable sustained T cell persistence and function in the tumor microenvironment. Other receptors, such as chimeric costimulatory receptors (CCRs) and inhibitory CARs (iCARs) complement this new armamentarium. We previously reported that human T cells targeted to CD19 could eradicate established, systemic B cell malignancies in xenogeneic tumor models. Over the past two years, three groups, including our own, reported objective tumor responses when infusing autologous T cells genetically modified with CD19-targeted CARs into patients with chronic lymphocytic leukemia (CLL), indolent non-Hodgkin lymphomas (NHL) and, most dramatically, relapsed chemorefractory acute lymphoblastic leukemia (ALL). We recently reported the largest CAR study published to date, achieving a complete remission in 14 of 16 patients with refractory ALL. The CD19 model has emerged as the paradigm for CAR therapy and paves the way for extending this cell-based treatment to other cancers. CARs, CCRs and iCARs represent a new class of drugs that are the foundations for cell-based approaches to treat cancer and potentially other disorders. We recently initiated a program exploring the therapeutic potential of T cells derived from induced pluripotent stem cells, and demonstrated that human iPS cell-derived CAR-expressing T cells could eradicate tumors in mice. This approach holds promise for generating T cells with optimized features to broaden the usage of T cell therapies.

THURSDAY, JUNE 19, 1:15 PM - 3:05 PM

CONCURRENT IA: NEURAL STEM CELLS AND DEVELOPMENT

WEST BALLROOM A

Supported By StemCells, Inc.

RECRUITING ENDOGENOUS NEURAL STEM CELLS FOR BRAIN REPAIR

Miller, Freda D.
The Hospital for Sick Children Research Institute, Canada

One of the fundamental questions in human biology is how a pool of proliferating neural stem cells in the embryonic brain can ultimately generate the complex functional neural circuitry that comprises the adult brain. This lecture will address that question, focusing upon the cerebral cortex, one of the key centers for cognition, and will ask how neural stem cells are regulated both during normal development, and in genetic disorders that cause cognitive dysfunction. A second key question is whether or not the information that we derive from the study of developing stem cells can ultimately provide therapies for the injured nervous system. This lecture will also address that question, describing how pharmacological stem cell activators can potentially be used

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to recruit the endogenous neural stem cells that are present in the developing brain and in so doing promote neural repair and/or enhance cognition.

SMEK1 AND 2 REGULATE MOUSE CORTICAL NEUROGENESIS THROUGH THE TRANSLOCATION OF THE CLEAVED WNT RECEPTOR RYK

Chang, Wen-Hsuan, Choi, SiHo, Lu, Wange
Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research, University of Southern California, Los Angeles, CA, USA

Wnt signaling is known to play an important role in neurogenesis through regulating self-renewal and differentiation in neural progenitor cells. However, the molecular mechanism has remained elusive due to the intricacy of Wnt signaling. We previously reported the role of the Wnt transmembrane-receptor Ryk in specifying neural cell fate during cortical neurogenesis. A unique and key event in this neural progenitor signaling process is the cleavage of the intracellular domain (ICD) of the Ryk receptor. Upon Wnt signaling, the Ryk ICD translocates to the nucleus and plays a role in regulating GABAergic neuron specification. However, it the mechanism by which the Ryk-ICD moves into the cell nucleus and regulate neural differentiation remains unclear. We have recently identified Smek1/2 as Ryk-ICD interacting proteins. These proteins possess a nuclear localization signal (NLS). We propose that interactions between Smek1/2 and the Ryk ICD may aid in translocating Ryk to the nucleus and allowing further downstream signaling processes to occur. Smek1&2 have both been shown to be expressed in mouse neural progenitor cells and mature neurons in vivo but are distributed differently in distinct cell types. The unique protein distribution pattern shows the importance of Ryk cellular localization in determining cell fate. To further examine the roles of Smek1/2 in neurogenesis in vivo, we have generated Smek1/2 double knock out mice. We demonstrated that Smek1 and 2 are required for cortical neurogenesis and serve to directly regulate the expression of Dlx1/2 transcription factors. This data suggests that Smek1/2 may play a key role in the regulation of Wnt-Ryk signaling in mouse neural development.

RCOR2 REGULATES SPECIFICATION OF NEURAL STEM CELL LINEAGES BY REPRESSING SHH SIGNALS IN THE DEVELOPING NEOCORTEX

Wu, Qian[1], Wang, Yixuan[2], Gao, Shaorong[2], **Wang, Xiaoqun[1]**
[1]*Institute of Biophysics, Chinese Academy of Sciences, Beijing, China,* [2]*Tongji University, Shanghai, China*

Regionally restricted neural stem cells (NSCs) help specify the diversity of neuronal progeny during neocortical development. However, the mechanisms underlying spatial specification of NSCs lineages in embryonic proliferative zones are still largely unknown. Here, we report that the LSD1 associated corepressor, Rcor2, is a key regulator of NSC proliferation, migration, and differentiation during neocortical development. Conventional mutant and conditional knock-out mice demonstrate that loss-of-function of Rcor2 specifically in forebrain NSCs prevents NSC proliferation and neuronal migration. Moreover, Rcor2 specifies NPC progeny cell lineage and fate determination in the developing neocortex by suppressing sonic hedgehog (Shh) expression in the dorsal lateral ventricular zone, maintaining appropriate production of excitatory neurons. Remarkably, enrichment of the Rcor2-LSD1 complex at the promoter regions of Shh and Nkx2.1 genes suggests an epigenetic regulation mechanism of regional specification in neocortical development. Our findings provide the first evidence that Rcor2 is critical for NPC proliferation and specification.

MODELING ONTOGENY OF HUMAN NEUROEPITHELIAL AND CORTICAL RADIAL GLIAL CELLS AT THE FUNCTIONAL, TRANSCRIPTIONAL AND EPIGENETIC LEVEL

Edri, Reuven[1], Yaffe, Yakey[1], Ziller, Michael[2], Ziv, Omer[1], Zartisky, Assaf[3], David, Eyal[4], Gat-Viks, Irit[4], Meissner, Alexander[2], **Elkabetz, Yechiel[1]**
[1]*Cell and Developmental Biology, Tel Aviv University, Tel Aviv, Israel,* [2]*Stem Cell and Regenerative Biology, Broad Institutre, Cambridge, MA, USA,* [3]*Department of Cell Biology, UT Southwestern Medical Center, Dallas, TX, USA,* [4]*Cell Reseaech and Immunology, Tel-Aviv University, Tel-Aviv, Israel*

Human pluripotent stem cell derived models that accurately recapitulate the development in vitro of distinct neural progenitor cell stages, which in turn allow for the generation of specific neuronal subtypes, are a major focus in the stem cell and biomedical research communities. Two of the key challenges are addressing heterogeneity of progenitor cells as they dynamically progress in culture, and in-depth molecular characterization of stage specific markers as well as regulatory determinants that establish and maintain the desired cellular states. To begin to address these fundamental challenges, we used genetically labeled human PSCs to prospectively isolate and characterize distinct, lineage related neural stem / progenitor cell types during long-term culture based on their Notch activation state. We first demonstrate that Notch active cells correspond to highly proliferative neuroepithelial cells with broad Notch dependent anterior-posterior patterning potential. In the absence of a caudalizing activity, neuroepithelial cells develop an anterior bias and then progress to early and then mid neurogenic phase cerebral radial glial cells. These later transform into gliogenic radial glia, which following long-term culture, transform to progenitors with adult like molecular identity.

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We also reveal that these isolated neural stem / progenitor cell stages display distinct cytoarchitectonic and kinetic patterns, suggesting structure-function relations in maintaining neurogenic radial glial cells in vitro. Extensive epigenetic profiling for histone modifications, DNA methylation and transcription factors combined with novel computational approaches for integrative data analysis allowed us to dissect the molecular basis of these transitions in cell fate potential. We uncover a core gene regulatory network of stably expressed transcription factors that dynamically interacts with stage specific factors and signaling pathways to regulate commitment and proper differentiation towards neuronal and glial cell types. Notably, gene regulatory elements involved in this process appear to be frequently disrupted by SNPs associated with different neurological pathologies, providing insights into potential causes and mechanisms. Additionally, we observe widespread DNA methylation changes from the pluripotent state to the neural lineage that are targeted to transcription factor binding sites and gene regulatory elements involved in the early, but also subsequent stages of differentiation. This is in sharp contrast to stage-specific dynamics that occur in the consecutively appearing neural progenitor cell populations. Taken together, this study provides a first mechanistic insight into human NSC ontogeny and proposes a well-controlled platform for understanding the development of normal and pathogenic neuroepithelial and cerebral radial glial cells and their progeny.

POSTER TEASERS:

T-3037 A TRANSCRIPTION FACTOR CODE FOR BRAIN-WIDE DISCRIMINATION OF NEUROANATOMIC IDENTITY AND DEVELOPMENTAL STAGE IN MOUSE

Menon, Vilas[1], Martinez, Salvador[2], Ng, Lydia[1], Lee, Changkyu[1], Glattfelder, Katie[1], Sunkin, Susan M.[1], Henry, Alex[1], Dang, Chinh[1], Raquel, Garcia-Lopez[2], Almudena, Martinez-Ferre[2], Pombero, Ana[2], Rubenstein, John L.R.[3], Wakeman, Wayne B.[1], Hohmann, John[1], Nguyen, Thuc-Nghi[1], Hawrylycz, Michael[1], Puelles, Luis[4], Jones, Allan R.[1], Thompson, Carol[1]

[1]Allen Institute for Brain Science, Seattle, WA, USA, [2]Instituto de Neurociencias, Alicante, Spain, [3]University of California, San Francisco, San Francisco, CA, USA, [4]University of Murcia, Murcia, Spain

POSTER TEASERS: (cont'd)

T-3035 EPIGENETIC MECHANISMS UNDERLYING THE GENERATION AND DIFFERENTIATION OF NEURAL STEM CELLS

Hitoshi, Seiji[1], Hayashi, Yoshitaka[1], Fuchigami, Takahiro[1], Fuke, Satoshi[1], Ishino, Yugo[2], Ikenaka, Kazuhiro[2]

[1]Department of Integrative Physiology, Shiga University of Medical Science, Otsu, Japan, [2]Division of Neurobiology and Bioinformatics, National Institute for Physiological Sciences, Okazaki, Japan

T-3036 EZH2 CONTROLS NEURAL PROGENITOR POOL SIZE AND REGIONAL IDENTITY IN THE DEVELOPING MOUSE MIDBRAIN

Zemke, Martina[1], Draganova, Kalina[1], Schoeler, Anne[2], Koseki, Haruhiko[3], Schuebeler, Dirk[4], Sommer, Lukas[1]

[1]Institute of Anatomy, University of Zürich, Zürich, Switzerland, [2]German Research Center for Environmental Health, Helmholtz Zentrum München, Neuherberg, Germany, [3]RIKEN Research Center for Allergy and Immunology, RIKEN Yokohama Institute, Yokohama, Japan, [4]Friedrich Miescher Institute for Biomedical Research, Basel, Switzerland

MOLECULAR MOTORS AND GENE NETWORKS IN HUMAN CORTICAL RADIAL GLIA

Kriegstein, Arnold R., Lui, Jan, Pollen, Alex, LaMonica, Bridget, Nowakowski, Tomasz, Oldham, Michael

University of California, San Francisco, USA

Recent insights from studies of the developing cerebral cortex highlight potential evolutionary changes that may contribute to features of the human brain. The developing human cortex contains a massively expanded subventricular zone (SVZ), not present in rodents, that is thought to account for most cortical neurogenesis. Evolutionary expansion of the neocortex is partially attributed to an abundance of radial glia-like cells (oRGs) within this zone. We found that oRG cells uniquely display mitotic somal translocation (MST) where the soma rapidly translocates towards the cortical plate prior to cytokinesis. We examined the molecular motors driving MST and found that they include activation of the Rho effector ROCK and non-muscle myosin II, but not microtubule polymerization or centrosomal guidance. Many neurodevelopmental disease genes target the Rho-ROCK-myosin pathway and are expressed by oRGs, suggesting possible involvement in neurodevelopmental diseases.
We have begun to characterize gene expression patterns and gene regulatory networks of human RG cells using two complementary approaches to disentangle cell-type and cell-state specific gene expression patterns from heterogeneous tissue. First, we developed

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a strategy that exploits variation in cellular abundance across serial sections to reveal cell type-specific gene expression patterns. Second, we directly sequenced mRNA from single cells for unbiased classification of cell identity and for detection of candidate effector genes of activated pathways. Transcriptional profiles of human and mouse RG diverged for specific signaling pathways, and provided evidence that local production of growth factors by RG may support the expanded germinal region and progenitor heterogeneity of the developing human brain.

CONCURRENT IB: CONTROL OF PLURIPOTENCY

WEST BALLROOM C/D

Supported By Stemgent

DISSECTING HUMAN REPROGRAMMING TOWARD PLURIPOTENCY

Yamanaka, Shinya

Center for iPS Cell Research and Application, Japan

Pluripotency can be induced in somatic cells by transduction of defined reprogramming factors during the process of iPSC (induced pluripotent stem cell) generation. We have been exploring several approaches to elucidate its molecular reprogramming process.

We previously reported that human cells positive (+) for tumor related antigen (TRA)-1-60 induced by OCT3/4, SOX2, KLF4 and c-MYC are intermediate reprogrammed cells to being iPSCs. Gene expression analysis of these cells revealed that primitive streak-like mesendodermal genes are transiently activated during reprogramming and re-suppressed in iPSCs. Based on these findings, we discovered that forkhead box H1 (FOXH1), a transcription factor required for anterior primitive streak specification during early development, significantly enhances the reprogramming efficiency of human fibroblasts by promoting their maturation, including the mesenchymal to epithelial transition and the activation of late pluripotent markers. These results demonstrated that during the reprogramming process, human somatic cells go through a transient state that resembles mesendoderm.

We also focused on the role of human endogenous retroviruses (HERVs) during reprogramming or differentiation, as they are highly expressed in differentiation-defective iPSC clones in our previous report. Long terminal repeats (LTRs) of HERV type H (HERV-H), LTR7s, were transiently activated during reprogramming to levels much higher than in embryonic stem cells (ESCs) and then re-suppressed upon completion of iPSC generation. Failure in re-suppression of HERV-H LTR7s resulted in defective neural differentiation. Knockdown of LTR7s or a HERV-H -driven long non-coding RNA, lincRNA-RoR, markedly reduced the efficiency of iPSC generation. One of reprogramming factors, KLF4, but not NANOG contributes to LTR7 activation during reprogramming associated with the recruitment of OCT3/4 and SOX2. Forced expression of KLF4 in ESCs led to HERV-H activation and defective neural differentiation. Furthermore, the suppression of aberrant expressed KLF4 or LTR7s in differentiation defective-iPSCs canceled their abnormality in neural commitment. Therefore KLF4/HERV-H axis controls both reprogramming efficiency and differentiation capacity of iPSCs.

These results provide insights into the both reprogramming efficiency and differentiation capacity of iPSCs.

A CHEMICAL PLATFORM FOR INDUCTION AND MAINTENANCE OF NAIVE HUMAN PLURIPOTENCY

Theunissen, Thorold[1], Powell, Benjamin[1], Wang, Haoyi[1], Zhang, Jianming[2], Gray, Nathanael[2], Jaenisch, Rudolf[1]

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Embryonic stem cells (ESCs) of mice and humans have distinct molecular and biological characteristics. In the mouse, pluripotent cells have been isolated from two different developmental stages: (i) classical embryonic stem cells (ESCs) are derived from the ICM of the blastocyst and (ii) EpiSCs are derived from the epiblast of the implanted embryo, representing naive and primed states of pluripotency. While human ESCs are isolated from explanted pre-implantation blastocysts, they share multiple defining features with mouse EpiSCs rather than mouse ESCs, suggesting that the primed state may be the default pluripotent state in humans. This has raised a fundamental biological question: do naive pluripotent cells exist in humans or, alternatively, have culture conditions not been devised that would capture and maintain the naive state in vitro if it were present? We have investigated this question by constructing endogenous reporter systems for the naive state in human ESCs using TALE nuclease-assisted gene editing. Dual inhibition of MAP kinase and GSK3, also known as the 2i cocktail, induced differentiation into primitive neural stem cells. However, doxycycline-inducible expression of transcription factors specific to naive pluripotency together with 2i treatment resulted in the emergence of dome-shaped colonies with naive reporter activity. As these cells remained strictly dependent on the expression of exogenous transgenes, we undertook a comprehensive chemical screen to identify small molecules that support the long-term maintenance of naive human pluripotency. Iterative screening in the presence of 2i revealed a combination of three small molecules that maintained naive reporter activity over multiple passages in the absence of doxycycline. When applied directly to conventional human ESCs, the optimized conditions enabled the induction and maintenance of naive reporter activity in the complete absence of exogenous transgenes. These genetically unmodified naive

human cells were pluripotent and had unique transcriptional and epigenetic properties. We surmise that the use of specific reporter alleles together with a comprehensive chemical screen can unlock authentic naive human pluripotency.

EPIGENETIC STABILITY OF HUMAN PLURIPOTENT STEM CELLS DERIVED BY SOMATIC CELL NUCLEAR TRANSFER

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Cellular reprogramming to pluripotency can be induced by defined factors, producing induced pluripotent stem cells (iPSCs), or achieved by somatic cell nuclear transfer (SCNT), a process through which embryonic stem cells (NT-ESCs) can be derived. The recent discovery that SCNT is feasible in humans has revitalized an ongoing debate on whether SCNT might be advantageous over other reprogramming approaches, especially with regards to the therapeutic potential of human pluripotent stem cells (hPSCs). To assess the epigenetic stability of human NT-ESCs, we undertook an analysis of parental genomic imprinting, a major epigenetic phenomenon which is uniquely regulated during preimplantation development. Genomic imprints are characterized by DNA methylation that differentiates the maternal and paternal genomes, and underlies the parent-of-origin regulation of imprinted genes. As dysregulation of imprinted genes is known to cause certain disorders and promote oncogenesis, we aimed to investigate the effects of SCNT-based reprogramming on the stability of genomic imprints. Comparing the global gene expression of various hPSC lines indicated that both induced pluripotency and SCNT yield cells that highly resemble normal human ESCs. Furthermore, human NT-ESCs and iPSCs preserved an overall stable transcriptional signature of most imprinted genes, although a minority of them showed variable expression. To address the possibility of loss-of-imprinting at specific imprinted loci, we analyzed allele-specific gene expression in two isogenic sets of early-passage NT-ESC and iPSC clones. Following identification of heterozygous polymorphisms in eight imprinted genes, we found both gene- and clone-specific imprinting aberrations in NT-ESCs as well as in iPSCs, supporting a stochastic model of loss-of-imprinting during both reprogramming processes. Two of the most prominent aberrations were found at the H19 and MEG3 genes, both of which are known for their variable instability in hPSCs and their association with growth disorders and cancer. Nonetheless, the imprinting status of human NT-ESCs appears largely intact, reflecting the general notion of imprinting integrity in hPSCs. Our results suggest that human NT-ESCs share common epigenetic features of other hPSCs, indicating their general status of epigenetic stability and reprogramming efficiency. The occurrence of epigenetic aberrations in some imprinted loci in both NT-ESCs and iPSCs imply that they are inherent to reprogramming and are not dependent on the underlying technique. Future studies should evaluate the consequences of these aberrations for the use of reprogrammed hPSCs for basic research and therapeutic purposes.

SWITCH ENHANCERS: NOVEL REGULATORY ELEMENTS TO CONTROL CELL FATE CHOICE IN HUMAN BY INTEGRATION OF THE TGF-BETA AND HIPPO SIGNALING PATHWAY

Beyer, Tobias A.[1], Weiss, Alexander[2], Wrana, Jeffrey L.[3]
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A small toolkit of morphogens is used repeatedly to direct development, raising the question of how context dictates interpretation of the same cue. One example is the TGFβ pathway that in human embryonic stem cells fulfills two opposite functions: pluripotency maintenance and mesendoderm (ME) specification. Using proteomics coupled to analysis of genome occupancy, we uncover a regulatory complex comprised of transcriptional effectors of the Hippo pathway (TAZ/YAP/TEAD), the TGFβ pathway (SMAD2/3) and the pluripotency regulator OCT4 (TSO). TSO collaborates with NuRD repressor complexes to buffer pluripotency gene expression, while suppressing ME genes. Importantly, the SMAD DNA binding partner FOXH1, a major specifier of ME, is found near TSO elements, and upon fate specification we show that TSO is disrupted with subsequent SMAD-FOXH1 induction of ME. These studies define switch enhancer elements and provide a framework to understand how cellular context dictates interpretation of the same morphogen signal in development.

PROGRAM AND ABSTRACTS

POSTER TEASERS:

T-1031 IN VITRO GENERATION OF 3D MULTICELLULAR LUNG TISSUE FROM HUMAN PLURIPOTENT STEM CELLS

Nadkarni, Rohan[1], Pilquil, Carlos[2]
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T-2067 POLYCOMB GROUP PROTEIN PCGF6 REPRESSES MESODERMAL AND SPERMATOGENESIS SPECIFIC GENES IN ES CELLS AND REPLACES SOX2 IN IPS REPROGRAMMING

Muller, Albrecht[1], Zdzieblo, Daniela[1], Becker, Matthias[1], Lin, Qiong[2], Zenke, Martin[2]
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T-2139 SMALL COMPOUNDS FACILITATE RAPID AND SYNCHRONOUS REPROGRAMMING OF SOMATIC CELLS INTO IPS CELLS BY DEFINED FACTORS

Brumbaugh, Justin[1], Bar-Nur, Ori[1], Verheul, Cassandra[2], Apostolou, Eftychia[1], Walsh, Ryan[1], Hochedlinger, Konrad[3]
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REPROGRAMMING IN VIVO AND ITS IMPACT ON TISSUE HOMEOSTASIS AND REGENERATION

Serrano, Manuel
Spanish National Cancer Research Center, Spain

Reprogramming into induced pluripotent stem cells (iPSCs) has opened new therapeutic opportunities, however, little is known about the possibility of in vivo reprogramming within tissues. We have generated transgenic mice with inducible expression of the four Yamanaka factors. Interestingly, transitory induction of the reprogramming factors results in dedifferentiated of multiple tissues and expression of markers of late reprogramming, such as NANOG. After this transient induction of reprogramming, tissues revert to their normal state. Nonetheless, after a latency period of 1-2 months, teratomas appear at multiple locations, which is indicative of reprogramming events that reached full pluripotency. Remarkably, induced reprogrammable mice also present circulating iPSCs in the blood. These in vivo-generated iPSCs can be purified and grown (in the absence of further induction of the reprogramming factors). Strikingly, at the transcriptome level, the in vivo-generated iPSCs are closer to embryonic stem cells (ESCs) than to standard in vitro-generated iPSCs. Moreover, in vivo-iPSCs efficiently contribute to the trophectoderm lineage, suggesting that they achieve a more plastic or primitive state than ESCs. Finally, in vivo-iPSCs show an unprecedented capacity to form embryo-like structures upon intraperitoneal injection, including the three germ layers of the proper embryo and extraembryonic tissues, such as extraembryonic ectoderm and yolk sac-like with associated embryonic erythropoiesis. These capacities are absent in ESCs or in standard in vitro-iPSCs. In summary, in vivo-iPSCs represent a more primitive or plastic state than ESCs or in vitro-iPSCs. These discoveries could be relevant for future applications of reprogramming in regenerative medicine.

CONCURRENT IC: ROAD TO THE CLINIC: CHALLENGES AHEAD

WEST BALLROOM B

SHIFTING THE ROADBLOCKS TO TRANSLATION OF STEM CELL THERAPIES

Trounson, Alan
California Institute for Regenerative Medicine, USA

Translating stem cell discoveries takes a strong motivation for academic researchers and considerable financial resources from both non-profit and for-profit sectors. In many respects it is best achieved by merging academic-medical researchers with focused and experienced industry resources. This model enables soundly based scientific discoveries to transit from the lab to the clinic with deep enough research resources and infrastructure to address unexpected barriers. It does require substantial financial resources – such as those that were available to CIRM. Frequently, the mode of action of cell products remain obscured because the cells disappear rapidly even though some evidence for their therapeutic benefit can be registered in pre- and clinical trials. However, it is important to understand the mechanism of action of any cell product. This may be obscured by a lack of understanding the actual pathways causing disease perturbation and is also commonly one of limiting factors in cell-based therapies. Immune tolerance of allogeneic cell transplants remains a serious roadblock for regenerative medicine. Cell therapies aimed at long-term repopulation of damaged or diseased tissues, requires knowledge of the appropriate cell type and maturity needed for therapy (progenitor or mature end-differentiated cell). As are animal models that poorly or only approximately represent the scope of human disease. Age of the human population is not often accounted for in experimental

studies but regenerative properties of tissues vary dramatically with age.

CIRM has been managing the translation and developmental portfolio in a unique way for a granting body with in-house scientists experienced with the preclinical and clinical trial pathways, development of milestones and go, no-go decisions. The teams also present to and meet with (12 monthly) an external panel of experts in the disease, cell manufacturing, regulatory requirements, clinical delivery, business and venture capital. The report is used to modify the approach by the team, or to terminate or redirect the team to an earlier stage. The process appears to increase the success of progression of teams to the clinic.

INTRA-TRACHEAL TRANSPLANTATION OF MACROPHAGE PROGENITORS DERIVED FROM MULTIPOTENT AND PLURIPOTENT STEM CELLS AS A NOVEL TREATMENT OPTION FOR HEREDITARY PULMONARY ALVEOLAR PROTEINOSIS

Lachmann, Nico[1], Happle, Christine[2], Ackermann, Mania[1], Hetzel, Miriam[1], Skuljec, Jelena[2], Bankstahl, Jens[3], Hansen, Gesine[2], **Moritz, Thomas[1]**

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Hereditary pulmonary alveolar proteinosis (herPAP) constitutes a rare lung disease caused by mutations in the granulocyte/macrophage-colony-stimulating factor (GM-CSF) receptor genes (CSF2RA or CSF2RB), resulting in disturbed alveolar macrophage (AM) differentiation, massive alveolar proteinosis, and life-threatening respiratory insufficiency. So far, treatment is symptomatic only including repetitive whole lung lavage in general anesthesia. We here introduce the concept of intratracheal transplantation of macrophage progenitors (ITT-MP)) as a novel, cause directed, and well-tolerated therapy for herPAP.

In a Csf2rb-/- mouse-model, ITT-MP yielded selective pulmonary engraftment of donor cells on flow- and chipcytometry. Profound reduction of alveolar-protein levels and significant improvement of clinical parameters such as normalisation of lung function parameter and lung densities on computer tomography (CT) scans were observed for more than nine months. Subsequent in situ analysis of donor cells revealed in vivo differentiation towards an AM phenotype characterized by CD11chi, CD11blo, MHC-II+, CD14+, F4/80+ surface markers, poor antigen presentation capacity, high phagocytic activity and AM-typical morphology on electron microscopy. Moreover, in a humanized herPAP mouse model intra-tracheal administration of human CD34+-derived MPs profoundly improved symptoms, led to long-term human cell engraftment, reduced alveolar-fluid proteins by 50-70%, and significantly improved herPAP related signs on CT scans for at least six months.

To pave the way for a gene therapy of herPAP we further have generated SIN-lentiviral constructs expressing the codon-optimized human CSF2RA-cDNA in combination with EGFP (Lv. EFS.CSF2RA.EGFP). Conferring this vector to CD34+ cells of a CSF2RA-deficient patient rescued hGM-CSF dependent colony formation as well as granulocytes and monocyte differentiation, while G-CSF control treatment revealed no differences between gene corrected vs. uncorrected cells. As gene-corrected MPs derived from patient-specific iPSC appear as a particularly safe and readily available autologous cell source for ITT-MP, we have generated these cells from a CSF2RA deficient herPAP patient utilising CD34+ bone marrow cells and OCT4/SOX2/KLF4/c-Myc-based reprogramming. When these PAP-iPSC clones were genetically corrected with the Lv.EFS.CSF2RA.EGFP vector, moderate but stable CSF2RA-expression was observed with no detectable effects on iPSC growth, pluripotency, or differentiation capacity. Hematopoietic differentiation yielded macrophages of typical morphology and phenotype (CD14, CD11b, CD45) displaying stable CSF2RA-expression and complete reconstitution of GM-CSF dependent functions such as CD11b activation, GM-CSF uptake, and downstream signalling via STAT5.

Thus, we here describe a new, cause directed treatment approach to herPAP based on the intra tracheal application of differentiated hematopoietic cells which may serve as a proof-of-principle to extend current HSC-based gene therapy concepts to strategies targeting mature, long-lived cells. In addition, we describe the generation of suitable gene corrected MPs from multipotent (HSCs) as well as pluripotent (iPSC) sources, thus further supporting the feasibility of this strategy.

WHEN HOPES CLASH: PATIENT OPTIMISM CONFRONTS SCIENTIFIC EVIDENCE

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How does 'hope' guide actions in health and healthcare? What does it mean for patients, their families and clinicians, to be 'hopeful' in a context of risk, uncertainty, and apparent 'hopelessness'? What happens when patients' hopes for new treatments come into conflict with scientific views on medical evidence?

The language of hope infuses contemporary discussions about the treatment of the ill and disabled in healthcare. To remain hopeful has become an imperative of contemporary citizenship, especially

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as regards those who are ill or disabled. Over the last few decades, medicine and other health sciences have recognized the significance of hope for the recovery of patients, with efforts made to instill hope in those who are seen to 'lack' hope. For the stem cell science and the regenerative medicine sector, hope invested by those who seek benefit from this technology, represents a unique challenge. Hopes can't be allowed to become so high that patients will risk all to seek out treatments that are yet to be proven safe and effective. Nor is it desirable to extinguish hope for the future benefit, although the realities of progress in translating stem cell science mean that access to new therapies will most likely be limited for many years to come. This paper explores the intersection between patients' hopes and scientific hopes for promising new stem cell treatments. Drawing on interviews with Australian scientists, clinicians and representatives of patient groups who receive enquiries from patients about stem cell treatments, the paper examines how these groups construct hope and evidence in relation to stem cell treatments, and how they seek to manage patient's optimism in light of what they perceive as the current state of scientific knowledge. The interviews reveal the complexities involved in 'managing hope', in maintaining patients' optimism while acknowledging the reality of the science and the risks posed by unproven treatments. While focused on attitudes and experiences of Australians travelling abroad, the paper will also explore the growth of autologous cell-based therapies being offered across Australia and the additional considerations that this poses patients, doctors and regulators. The paper will conclude by discussing the sociological and policy implications of the findings, as well as their significance for further thinking and research on hope in relation to promising new biomedical technologies.

PHASE I CLINICAL ASSESSMENT OF HUMAN EMBRYONIC STEM CELL (HESC) DERIVED OLIGODENDROCYTE PROGENITORS IN PATIENTS WITH NEUROLOGICALLY COMPLETE THORACIC SPINAL CORD INJURIES

Lebkowski, Jane S.[1], Fessler, Richard[2], Jones, Linda[3], Steinberg, Gary[4], McKenna, Stephen[5], Apple, David[6], Wirth, Edward[1]
[1]Asterias Biotherapeutics, Menlo Park, CA, USA, [2]Neurosurgery, Rush University, Chicago, IL, USA, [3]Craig Nielson Foundation, Encino, CA, USA, [4]Stanford School of Medicine, Stanford, CA, USA, [5]Medicine, Santa Clara Valley Medical Center, Santa Clara, CA, USA, [6]Shepherd Center, Atlanta, GA, USA

Spinal cord injury (SCI) produces numerous clinical sequelae including impaired limb function, spasticity, autonomic dysfunction, thromboses, increased infections, decubitus ulcers, and chronic pain, which can significantly impact quality of life and be life threatening. SCI leads to complex pathology including severed axons, parenchymal cavitation, demyelination, inflammation, and scarring. In animal models, transplantation of oligodendrocyte progenitors (OPCs) into the lesion site elicits repair through multiple mechanisms. Methods have now been developed to differentiate hESCs into OPCs under cGMP at scales suitable for clinical development. These OPCs are referred to as AST-OPC1 (formerly GRNOPC1). Preclinical studies using AST-OPC1 have shown that these cells survive, migrate throughout the injury site, reduce parenchymal cavitation, induce the presence of myelinated fibers in the injury site, and improve locomotor activity. No toxicity, tumors, or allodynia were induced by AST-OPC1. A phase 1 clinical trial assessing the safety of AST-OPC1 was initiated in subjects with neurologically-complete T3-T11 thoracic spinal cord injury. Subjects enrolled in the trial consented to two protocols: 1) the primary protocol under which subjects were followed for 1 year, and 2) a long-term follow-up protocol under which subjects are being followed for an additional 14 years. Five patients were enrolled from October 2010 to November 2011. All subjects were administered a low dose of 2 x 106 AST-OPC1 5mm caudal of the lesion epicenter in a separate dedicated surgical procedure within 14 days of injury using a specially designed syringe positioning device to facilitate controlled dose delivery. Subjects received a low dose of tacrolimus for 46 days which was tapered and eventually discontinued at day 60. The primary endpoint of the study was safety with the secondary endpoint being neurological function. Safety was assessed with respect to AST-OPC1 itself, the procedure to deliver the cell product and the transient immunosuppression used subsequent to implantation. Multiple MRIs and neurological exams were performed during the first year of study to assess safety of AST-OPC1. To date, all five patients have been followed for over 2 years. There have been no serious adverse events related to AST-OPC1, tacrolimus, or the injection procedure. There were 5 adverse events judged to be possibly related to AST-OPC1. One of these AEs was a brief mild elevation of body temperature. The remaining four AEs all occurred in 1 subject and were primarily neuropathic pain reported as a burning sensation in the trunk and lower extremities. Pain of this type and distribution is also a common complication of SCI. Regarding the delivery procedure or use of tacrolimus, all possibly related adverse events were assessed as grade 1 or 2. Serial MRI scans indicate that lesion cavity formation at the AST-OPC1 injection sites was substantially reduced through 2 years of follow up in 4 of 5 subjects. In addition, there were no reports of abnormal cyst formation or enlarging masses at the injection sites on MRI scans. There were no unexpected changes in neurological function. The data to date suggest that AST-OPC1 can be safely administered to patients in the subacute period after spinal cord injury. Future plans include dose escalation and inclusion of subjects with cervical injuries where the anatomy and outcomes measures provide a superior opportunity to measure potential activity of the cells.

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POSTER TEASERS:

T-1060 GENERATION OF "SEMI-UNIVERSAL DONOR STEM CELLS" THAT EXPRESS A SINGLE FUNCTIONAL HUMAN LEUKOCYTE ANTIGEN (HLA) CLASS I ALLELE

Gornalusse, German[1], Festag, Marvin[1], Hirata, Roli[1], Riolobos, Laura[1], Turtle, Cameron[2], Riddell, Stan[2], Russell, David W.[1]

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T-3153 AN EXPLORATORY CLINICAL TRIAL FOR IDIOPATHIC OSTEONECROSIS OF FEMORAL HEAD BY CULTURED AUTOLOGOUS MULTIPOTENT MESENCHYMAL STROMAL CELLS AUGMENTED WITH VASCULARIZED BONE GRAFTS

Toguchida, Junya, Aoyama, Tomoki, Goto, Koji, Kakinoki, Ryosuke, Kasai, Yasunari, Maekawa, Taira, Tada, Harue, Teramukai, Satoshi, Nakamura, Takashi, Matsuda, Shuichi

Kyoto University, Japan

RATIONAL DESIGN OF AN IMPROVED TISSUE ENGINEERED VASCULAR GRAFT

Breuer, Christopher

Nationwide Children's Hospital, USA

We developed the first tissue engineered vascular graft to be used in humans. Results of our clinical investigation have demonstrated that the tissue engineered vascular graft is the first man made vascular graft with growth capacity making it uniquely suited for use in children. Results of our clinical study also demonstrate that stenosis is the primary graft related complication. In order to rationally design an improved second generation tissue engineered vascular graft, we developed a murine model and have used it to elucidate the cellular and molecular mechanisms underlying vascular tissue formation. In this presentation we will update the audience on our recent efforts to develop strategies for inhibiting the formation of tissue engineered vascular graft stenosis based on the fundamental mechanisms underlying vascular neotissue formation.

CONCURRENT ID: REGENERATION

WEST MEETING ROOM 211-214

Supported By Ontario Brain Institute

MOLECULAR REGULATION OF MUSCLE STEM CELL SELF-RENEWAL AND EXPANSION

Rudnicki, Michael A.

Ottawa Hospital Research Institute, Canada

Satellite cells in adult skeletal muscle are a heterogeneous population composed of stem cells and committed progenitors. Wnt7a signalling through the Fzd7 the receptor activates the planar cell polarity (PCP) signaling pathway, and dramatically stimulates the symmetric expansion of satellite stem cells. In differentiated myofibers, Wnt7a binding to Fzd7 directly activates the Akt/mTOR growth pathway thereby inducing myofibre hypertrophy. Thus Wnt7a/Fzd7 activates distinct pathways at different developmental stages during myogenic lineage progression. Wnt7a treatment also resulted in a significant increase in strength of the muscle as determined by generation of specific force. We found that Syndecan-4 (Sdc4) and Frizzled-7 (Fzd7) form a co-receptor complex in satellite cells and that binding of the glycoprotein Fibronectin (FN) to Sdc4 stimulates the ability of Wnt7a to induce the symmetric expansion of satellite stem cells. Newly activated satellite cells dynamically remodel their niche by transient high-level expression of FN. Knockdown of FN in prospectively isolated satellite cells severely impairs their ability to repopulate the satellite cell niche following transplantation into regenerating muscle. Conversely, in-vivo over-expression of FN with Wnt7a dramatically stimulates the expansion of satellite stem cells in regenerating muscle. Therefore, activating satellite cells remodel their niche through autologous expression of FN that provides feedback to stimulate Wnt7a signaling through the Fzd7/Sdc4 co-receptor complex. Thus, FN and Wnt7a together regulate the homeostatic levels of satellite stem cells and satellite myogenic cells during regenerative myogenesis. We generated a truncated Wnt7a variant, consisting of the C-terminal 137 amino acids lacking the conserved palmitoylation sites, which retains full biological activity in skeletal muscle. This includes binding to and signaling through its receptor Fzd7 to stimulate symmetric expansion of satellite stem cells by activating the planar cell polarity pathway, and inducing myofibre hypertrophy by signaling through the AKT/mTOR pathway. Furthermore, this truncated Wnt7a shows enhanced secretion and dispersion compared to the full-length protein. We recently determined that Wnt7a/Fzd7 acts at a third level to increase the polarity and directional migration of murine satellite cells and human myogenic progenitors through activation of Dvl2 and the small GTPase Rac1. Importantly, these effects can be exploited to potentiate the outcome of myogenic cell transplantation into dystrophic muscles. We observed that a short Wnt7a treatment

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markedly stimulated tissue dispersal and engraftment leading to significantly improved muscle function. Moreover, myofibers at distal sites that fused with Wnt7a-treated cells were hypertrophic suggesting that the transplanted cells deliver activated Wnt7a/Fzd7 signaling complexes to recipient myofibers. Taken together, we describe a viable and effective ex vivo cell modulation process that profoundly enhances the efficacy of stem cell therapy for skeletal muscle. Together, these findings open important new avenues for the development of a Wnt7a as a treatment for muscle wasting diseases and have broad implications for the therapeutic use of Wnts as biologics.

A STEM CELL-BASED PLATFORM FOR DISCOVERY OF REMYELINATING THERAPEUTICS

Najm, Fadi[1], Zaremba, Anita[2], Madhavan, Mayur[1], Shick, Elizabeth[1], Karl, Robert[1], Sargent, Alex[2], Factor, Daniel C.[1], Miller, Tyler[3], Quick, Kevin[4], Tang, Hong[5], Papoian, Ruben[5], Miller, Robert[2], Tesar, Paul J.[6]

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Millions of patients worldwide suffer from neurological disorders, diseases, or injuries involving central nervous system (CNS) demyelination. However no approved therapeutics currently exist which can promote repair of damaged myelin. We have developed a platform for the rapid production of pure, highly expandable populations of rodent oligodendrocyte progenitor cells (OPCs), the premyelinating cells in the CNS, from pluripotent stem cells. This provides a system for high throughput phenotypic screening for small molecules that enhance the generation of mature oligodendrocytes from OPCs. We performed a primary phenotypic screen using both drug repurposing libraries and diversity collections of novel chemical entities. Hits were identified with activity 5 standard deviations above vehicle and validated across an 8-point dose curve. Validated primary hits were then subjected to functional assays to assess their ability to promote precocious myelination in ex vivo rodent brain slice cultures and in vivo in early postnatal mouse pups. Functional assay hits were then tested in the MOG35-55 chronic EAE rodent model of multiple sclerosis where 3 compounds showed significant enhancement of remyelination and reduction of clinical severity. When tested on human OPCs in vitro, these compounds also enhanced the generation of mature human oligodendrocytes providing direct relevance to human OPC biology. Our screening pipeline provides a powerful platform to discover candidate small molecule therapeutics that enhance remyelination in the CNS.

SUSTAINED NEUROGENESIS - AN INSTRUMENT FOR A SUCCESSFUL REGENERATION IN ADULT BRAIN

Barbosa, Joana, Di Giaimo, Rossella, Irmler, Martin, Götz, Magdalena, **Ninkovic, Jovica**

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The regenerative capacity in the CNS differs greatly between different vertebrate species. Importantly, wide-spread, life-long neurogenesis is often associated with the remarkable regenerative potential. Indeed, the neural progenitors from the neurogenic zones of zebrafish telencephalon engage in the repair process without impairment of the constitutive neurogenesis. Therefore, we followed the response of a different type of progenitors to the brain injury at the single cell level in vivo. We first could show that only fast dividing progenitors, labelled with the retroviral vectors, immediately react to the injury, leave the neurogenic zone and migrate towards the injury site. In contrast to fast dividing progenitors, the injury induced proliferation of neural stem cells, the radial glia-like cells, is delayed and coincident with the full tissue restoration. To assess the role of radial glia-like cells in the regeneration process, we continuously followed them for more than 1 month using the two-photon live imaging. Our data suggest the activation of previously quiescent radial glia-like cells in response to the injury, but with the different mode of division. The radial glia in the intact telencephalon show either asymmetric or self-renewing symmetric divisions, while the symmetric non-gliogenic division becomes the predominant type of symmetric division in response to injury. This change in the division mode leads to the depletion of some activated radial glia-like cells and production of the transit amplifying progenitor population that is used up in the neuronal regeneration process, but necessary for the constitutive neurogenesis. We could, further, identify the injury-induced activation of several pathways in progenitor cells. The activation of these pathways, using the small molecules, elicited both proliferation of progenitor cells and gene expression comparable to the injury. Moreover, the activation of these pathways in the injured mouse cortex increased the de-differentiation of the reactive astrocytes and increased their neurosphere-forming capacity. Taken together, our data describe for the first time the reaction of the endogenous progenitors to the injury at the single cell level and identify evolutionary conserved molecular pathways, involved in the initiation of the repair process by the endogenous progenitors in the vertebrate brain.

PROGRAM AND ABSTRACTS

ROLE OF METHYLTRANSFERASE SET7 IN SKELETAL MUSCLE REGENERATION AND DEVELOPMENT

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In spite of its post-mitotic nature, skeletal muscle maintains a remarkable regenerative potential, thanks to a potent population of adult tissue-resident stem cells (satellite cells). In response to muscle injury, satellite cells expand and then differentiate to regenerate damaged myofibres. Manipulation of satellite cells remains a promising strategy for the treatment degenerative muscle diseases; however greater understanding of their basic molecular regulation is critical in order to unlock their therapeutic potential. Recent evidence has implicated several methyltransferases as powerful regulators of myogenic linage commitment, which act by controlling both the chromatin landscape required for myogenic progression (via methylation of histone proteins) as well as regulating key signaling molecules involved in myogenesis (via methylation of non-histone proteins). In particular, Set7, a H3K4 methyltransferase has been shown to influence myoblast differentiation in cell lines, hinting at a potentially novel role for this protein in controlling muscle stem cell function in vivo. The aim of this study was to investigate the function of Set7 in satellite cells and muscle regeneration in vivo. Using immunohistochemistry and qPCR we found Set7 is expressed in activated MyoD+ satellite cells and becomes up regulated during myogenic differentiation of plated primary myoblasts. Set7 was localized to the nucleus of myoblasts but translocates to the cytoplasm of large multi-nucleated myotubes in vitro. Interestingly, Set7-/- mice displayed normal muscle development and little defects in regenerative potential following notexin injury. However, when satellite cells were isolated from Set7-/- mice and cultured ex vivo they displayed enhanced proliferation and significantly impaired myogenic differentiation. Crossing of mice harboring a Set7 floxed allele with Pax7CreERT2 mice allowed conditional deletion of Set7 in adult satellite cells after tamoxifen administration. In these mice, ablation of Set7 expression in satellite cells induced impaired muscle regeneration as judged by a significant reduction in myofibre size at 14 and 21 days following notexin injury compared to litter mate controls. Although studies examining the role of methyltransferases in complex biological systems in vivo are currently lacking, these findings reveal Set7 as a novel regulator of muscle stem cell function and tissue regeneration. Current work is now focused on elucidating mechanisms of how Set7 is functioning in satellite cells using RNASeq and ChIPSeq approaches.

POSTER TEASERS:

T-2085 NEURAL PRECURSOR CELL ACTIVATION IN THE AGED MOUSE BRAIN CONTRIBUTES TO FUNCTIONAL RECOVERY AND TISSUE REPAIR FOLLOWING STROKE

Sachewsky, Nadia, Zarin, Taraneh, Son, Andrey, Rahman, Aashiq, Hunt, Jessica, Kovatcheva, Marta, Morshead, Cindi M.
University of Toronto, Toronto, ON, Canada

T-3051 ACUTE INFLAMMATION IS REQUIRED FOR MUSCLE STEM CELL PROLIFERATION AND MUSCLE REGENERATION

Hu, Ping, Fu, Xin, Xiao, Jun, Sheng, Li, Yin, Jie, Liu, Yan, Hongyan, Wang
Institute of Biochemistry and Cell Biology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai, China

T-3064 CARDIAC PROGENITOR CELLS AND HEART REGENERATION: DEVELOPMENT AND VALIDATION OF A PHENOTYPIC SCREEN FOR MULTI-LINEAGE DIFFERENTIATION

Drowley, Lauren[1], Jonebring, Anna[1], Andersson, Henrik[1], Kattman, Steven[2], Koonce, Chad[2], Anson, Blake[2], Swanson, Bradley[2], Plowright, Alleyn[1], Wang, Qing-Dong[1], Brolen, Gabriella[1]
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WNT ACTIVATION IN NAIL EPITHELIUM COUPLES NAIL GROWTH TO DIGIT REGENERATION

Ito, Mayumi, **Takeo, Makoto**
New York University, Langone Medical Center and School of Medicine, USA

The tips of mammalian digits can regenerate after amputation, like those of amphibians. It is unknown why this capacity is limited to the area associated with the nail. Here we show that nail stem cells (NSCs) reside in the proximal nail matrix and that the mechanisms governing NSC differentiation are coupled directly with their ability to orchestrate digit regeneration. Early nail progenitors undergo Wnt-dependent differentiation into the nail. After amputation, this Wnt activation is required for nail regeneration and also for attracting nerves that promote mesenchymal blastema growth, leading to the regeneration of the digit. Amputations proximal to the Wnt-active nail progenitors result in failure to regenerate the nail or digit. Nevertheless, β-catenin stabilization in the NSC region induced their regeneration. These results establish a link between

PROGRAM AND ABSTRACTS

NSC differentiation and digit regeneration, and suggest that NSCs may have the potential to contribute to the development of novel treatments for amputees.

CONCURRENT IE: AGING AND METABOLISM

WEST MEETING ROOM 301-305

REGULATION OF INTESTINAL STEM CELL FUNCTION IN THE AGING INTESTINE

Jasper, Heinrich
Buck Institute for Research on Aging, USA

Proliferation of stem and progenitor cells has to be precisely balanced to maintain long-term regenerative capacity of high-turnover tissues while preventing cancer. As a genetically accessible model in which to explore the control of proliferative plasticity of somatic stem cells, we study the Drosophila intestine. Our work focuses on the regulation of intestinal stem cell (ISC) proliferation by stress and growth factor signaling, and we have explored age-related changes in stem cell activity. ISCs over-proliferate in aging flies due to excessive stress signaling, and conditions that improve proliferative homeostasis in this cell lineage extend lifespan of the organism. These conditions include reduced Insulin/IGF or Jun-N-terminal Kinase (JNK) signaling activities, as well as over-expression of cytoprotective genes in the ISC lineage. Interestingly, proliferative activity in aging intestinal epithelia predicts longevity over a range of genotypes, with maximal lifespan when intestinal proliferation is reduced but not completely inhibited. These results highlight the importance of strategies to maintain the balance between processes that promote regenerative capacity and ones that prevent hyper-proliferative disorders, and demonstrate that promoting proliferative homeostasis in aging metazoans is a viable strategy to extend lifespan.

In recent work, we have explored some of the underlying causes of the hyperproliferative phenotype, and have established an interaction between Foxo and the Rel/NFkB innate immune signaling pathway as a driver of age-related immunosenescence in the intestinal epithelium. Immunosenescence causes dysbiosis of the commensal bacterial population in the gut, resulting in increased inflammatory signaling. We have identified genetic interventions that allay the development of dysbiosis, inflammation and dysplasia, and that extend lifespan of flies. These include modulation of Rel/NFkB signaling within differentiated intestinal epithelial cells, as well as control of interactions between blood cells (hemocytes) and the intestinal epithelium. Our findings deepen our understanding of the regulation of proliferative homeostasis in the aging intestinal epithelium and suggest potentially conserved mechanisms by which proliferative homeostasis can be preserved in the long term.

RESTORATION OF SYSTEMIC GDF11 LEVELS REVERSES AGE-ASSOCIATED DYSFUNCTION IN SKELETAL MUSCLE

Sinha, Manisha[1], Jang, Young[1], Oh, Juhyun[1], Khong, Danika[1], Wu, Elizabeth[1], Manohar, Rohan R.[2], Miller, Christine[2], Regalado, Samuel[1], Loffredo, Francesco[3], James, Pancoast[3], Michael, Hirshman[2], Lebowitz, Jessica[2], Shadrach, Jennifer[1], Cerletti, Massimiliano[1], Kim, Mi Jeong[2], Serwold, Thomas[2], Goodyear, Laurie[2], Rosner, Bernard[4], Lee, Richard T.[3], **Wagers, Amy[1]**
[1]Harvard University, Cambridge, MA, USA, [2]Joslin Diabetes Center, Boston, MA, USA, [3]Brigham and Women's Hospital, Cambridge, MA, USA, [4]Harvard School of Public Health, Boston, MA, USA

Recent studies involving heterochronic parabiosis indicate that impaired regeneration in aged animals is in part systemically controlled and reversible by exposure to a young circulation. While prior studies have identified a handful of systemic "aging" factors, discovery of the humoral "rejuvenating" factors that act on tissue stem cells to restore regenerative function has been relatively more elusive. Here, we demonstrate that the circulating hormone Growth Differentiation Factor 11 (GDF11) is a rejuvenating factor for skeletal muscle. Supplementation of systemic GDF11 levels, which normally decline with age, using either heterochronic parabiosis or systemic delivery of recombinant protein, is sufficient to reverse functional impairments and restore genomic integrity in skeletal muscle stem cells (satellite cells). Augmentation of GDF11 levels further improved structural and functional features of resting skeletal muscle, resulting in increased strength and enhanced endurance exercise capacity. Taken together, these data reveal critical mechanisms in the systemic regulation of aging and identify a promising candidate therapeutic for the reversal of age-related skeletal muscle and stem cell dysfunction.

ROLE OF REPROGRAMMING CELLULAR METABOLISM IN MAMMALIAN TISSUE REPAIR

Ng, Shyh-Chang
GIS Fellow, Genome Institute of Singapore, Singapore, Singapore

As discussed by Charles Darwin and others, regeneration capacity declines with aging, but why juvenile organisms show enhanced tissue repair had remained unexplained. Using a variety of injury models, we found that a stem cell factor, Lin28a, can improve tissue repair upon reactivation in adult mice. Lin28a reactivation improves hair regrowth by promoting anagen in epidermal hair follicles, accelerates regrowth of cartilage, bone and mesenchyme

after appendage injuries, and enhances skeletal muscle regeneration. Although Lin28 inhibits let-7 microRNA biogenesis, let-7 repression alone is insufficient to enhance repair. In fact, Lin28a enhances tissue repair by directly binding and enhancing the translation of mRNAs for several metabolic enzymes, thereby increasing glycolysis and oxidative phosphorylation (OxPhos) flux. Lin28a-mediated enhancement of tissue repair is negated by mild OxPhos inhibition, whereas a pharmacologically-induced increase in mitochondrial OxPhos promotes tissue repair. Our latest experiments reveal that Lin28a reactivation can synergize with increased mitochondrial activity due to PPARβ/δ and PPARγ activation, to further enhance tissue repair. Here we report new findings which underscore the importance of reprogramming cellular metabolism in tissue repair and regenerative medicine.

MUSCLE STEM CELLS ARE CRITICAL FOR MUSCLE HOMEOSTASIS AND AGING

Lawson, Jennifer A., Keefe, Alexandra, Fox, Zac, **Kardon, Gabrielle**
Human Genetics, University of Utah, Salt Lake City, UT, USA

A key to adult human health is the maintenance of muscle mass. However, during aging, even healthy individuals progressively lose muscle mass, in a process termed sarcopenia. This loss of muscle mass not only impairs locomotion and increases the risk for injury, but increases the incidence of insulin resistance and type 2 diabetes. Muscle is composed of multinucleate myofibers, and with age muscle mass is lost due to both loss of myofibers and decrease in myofiber size. Because muscle is post-mitotic, maintenance of myonuclei and myofibers needs to be mediated by a dedicated muscle stem cell, the satellite cell. Satellite cells are resident in muscle and express the transcription factor Pax7. Recently we generated tamoxifen-inducible Pax7CreERT2 mice, and we (Murphy et al. 2011) and others (Lepper et al. 2011, Sambasivan et al. 2011) definitively demonstrated that satellite cells are the stem cells necessary and sufficient for muscle regeneration. It has been hypothesized that satellite cells are also critical for muscle homeostasis and that a decline in satellite cell-mediated replenishment of muscle is a major determinant of sarcopenia, but this has never been explicitly tested in vivo. Using Pax7CreERT2 mice to genetically label and ablate satellite cells, we test for the first time whether satellite cells contribute to and are required for muscle homeostasis during adulthood and aging. We demonstrate that satellite cells do indeed contribute to maintenance of all muscles during homeostasis. In addition, ablation of satellite cells adversely affects the maintenance of myofibers, particularly fast fibers (which are most vulnerable in aging humans). Most surprisingly, ablation of satellite cells not only affects maintenance of muscle, but also negatively impacts whole body metabolism. Thus we show for the first time that satellite cells are critical for muscle homeostasis and aging and consequently for whole body metabolism.

POSTER TEASERS:

T-2233 SIRT1-DEFICIENT HEMATOPOIETIC STEM AND PROGENITOR CELLS RECAPITULATE AN AGING-LIKE PHENOTYPE

Ghaffari, Saghi[1], Bigarella, Carolina[1], Izac, Brigitte[1], Donovan, Michael[1], Dieguez-Gonzalez, Rebeca[1], Brugnara, Carlo[2], Sinclair, David[2], Rimmele, Pauline[1]
[1]Icahn School of Medicine at Mount Sinai, New York, NY, USA, [2]Harvard Medical School, Boston, MA, USA

T-1057 HEMATOPOIETIC STEM CELL QUIESCENCE ATTENUATES DNA DAMAGE REPAIR AND RESPONSE CONTRIBUTING TO AGE-DEPENDENT DNA DAMAGE ACCUMULATION

Beerman, Isabel[1], Seita, Jun[2], Inlay, Matthew A.[3], Weissman, Irving L.[4], Rossi, Derrick J.[5]
[1]Stem Cell and Regenerative Biology, Harvard Medical School, Boston, MA, USA, [2]Stem Cell Biology and Regenerative Medicine, Stanford Institute, Stanford, CA, USA, [3]Department of Molecular Biology and Biochemistry, University of California Irvine, Irvine, CA, USA, [4]Stanford University, Stanford, CA, USA, [5]Harvard Medical School, Boston, MA, USA

T-3118 MITOCHONDRIAL DYNAMICS REGULATES MOUSE SKIN MESENCHYMAL STEM CELL (msMSC) FATE

Forni, Maria Fernanda, Peloggia, Julia, Kowaltowski, Alicia Juliana
Universidade de São Paulo, São Paulo, Brazil

ADIPOSE TISSUE TURNOVER IN MAN

Spalding, Kirsty
Karolinska Institute, Sweden

Owing to the increase in obesity, life expectancy may start to decrease in developed countries for the first time in recent history. In humans the generation of fat cells (adipocytes) is a major factor behind the growth of adipose tissue during childhood. The factors determining the fat mass in adults, however, are not fully understood. Increased fat storage in fully differentiated adipocytes, resulting in enlarged fat cells, is well documented and thought to be the most important mechanism whereby fat depots increase in adults. Using a recently developed method, which is based on the incorporation of 14C from nuclear bomb tests into genomic DNA and molecules, we can now also analyse the turnover of adipocytes, their progenitor cells and lipid stores. Results from studies looking

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at adipocyte and lipid turnover in adult humans, in health and pathology, will be discussed. Understanding the dynamics of adipocyte and lipid turnover may shed new light on potential treatments for obesity.

THURSDAY, JUNE 19, 4:00 PM - 5:50 PM

CONCURRENT IIA: NEURAL DIFFERENTIATION

WEST BALLROOM B

Supported By Lieber Institute for Brain Development

CEREBRAL CORTICAL CELL DIFFERENTIATION: DRAWING AND READING THE BLUEPRINT

Temple, Sally
Neural Stem Cell Institute, USA

The cerebral cortex is a highly ordered and interconnected brain region that is responsible for integrating and responding to sensory and cognitive inputs. It is characterized by layers of excitatory pyramidal neurons with intertwined modulatory interneurons that function together as vertical columns of information processing. Each area of the cortex performs specialized functions.
Cerebral cortical development is precisely choreographed, with each layer appearing at a designated time in a particular species. Previously we demonstrated that isolated embryonic mouse cortical progenitor cells could recapitulate this program, undergoing repeated asymmetric cell divisions to produce diverse progeny at a particular time in vitro. Timelapse recording of single cells showed that early born cells in the lineage trees are Reelin+ Cajal-Retzius cells, that subsequent layer-specific neurons form in an inside-out manner, and glial progeny follow neuronal progeny, as they do in vivo. The switch from neurogenesis to gliogenesis is often a discrete point in the lineage trees at which remarkable changes occur. Now we have found that lineages are patterned differently in different areas of the cortex, helping to explain how neural progenitor cells interpret the co-ordinates embedded in the embryonic neuroepithelium to generate area-appropriate cell fates. Lessons learned from the mouse can help us generate precise areas of the human cerebral cortex in vitro, including the medial prefrontal cortex, a desirable model for studying psychiatric disorders.

THE LONG NON-CODING RNA PINKY REGULATES NEURAL STEM CELL DIFFERENTIATION AND PROGENITOR EXPANSION

Ramos, Alexander, Andersen, Rebecca, Liu, John, Nowakowski, Tomasz, Gertz, Caitlyn, Kriegstein, Arnold R., **Lim, Daniel**
University of California San Francisco, San Francisco, CA, USA

The role of long noncoding RNAs (lncRNAs) in the regulation of stem cell populations in vivo is poorly understood. During neurogenesis, neural stem cells (NSCs) in both the adult and embryonic brain give rise to an intermediate progenitor cell, which divides several times before producing neuroblasts. We utilized RNA-seq, ChIP-seq maps, and FACS-purified cells of a defined neurogenic lineage to identify Pinky, an lncRNA that regulates the transition between NSCs and their neurogenic progenitors. In situ hybridizations and cell fractionation studies showed Pinky to be a predominantly nuclear-localized transcript. The Pinky sequence contains two short regions with high conservation among mammals, and strand-specific RNA-seq of the developing human brain demonstrated transcription at the homologous genomic region. Pinky was specifically expressed in the ventricular zone of the developing cortex of both mouse and human, and Pinky knockdown in embryonic progenitors accelerated neurogenesis and depleted the embryonic NSC population in vivo. Pinky was also expressed in the NSCs of the subventricular zone (SVZ) of the mouse brain. In SVZ-NSCs, Pinky is normally down-regulated during neurogenesis, and shRNA-mediated depletion of this lncRNA expanded the pool of neurogenic progenitors while reducing the expression of NSC markers. Pinky-depleted cells displayed a dramatic expansion at the transit-amplifying stage, generating larger numbers of neuroblasts from single common progenitors. RNA-seq analysis of Pinky-depleted NSC cultures demonstrated significantly increased expression of cell-cycle regulators and neurogenic transcription factors, and a downregulation of genes associated with cell growth. Taken together, our work identifies a conserved long noncoding RNA that is expressed in germinal zones in the adult mouse subventricular zone and in both the human and mouse embryonic cortex. This long noncoding RNA mediates the transition from NSC to progenitor, and critically regulates their expansion in vivo and in vitro.

PROGRAM AND ABSTRACTS

FOXP2 AND NCOR REGULATE GENES ASSOCIATED WITH TOURETTE SYNDROME AND BRAIN EVOLUTION VIA A DISTAL REGULATORY ELEMENT IN NEURAL STEM CELLS

Gaudenzi, Giulia[1], Heldring, Nina[2], Islam, Saiful[3], Månsson, Robert[2], Linnarsson, Sten[3], Hermanson, Ola[1]
[1]Neuroscience, Karolinska Institutet, Stockholm, Sweden, [2]LabMed, Karolinska Institutet, Stockholm, Sweden, [3]MBB, Karolinska Institutet, Stockholm, Sweden

The transcription factor FOXP2 is crucially involved in the neurogenetic mechanisms facilitating human spoken language. Rare mutations or low FOXP2 dosage yields abnormal synaptic plasticity and impaired motor-skill learning in mice as well as disrupting vocal learning and imitation in songbirds. While all four FOXP family members seem to function as transcriptional repressors, the molecular mechanism of this repression is unknown. A functional interaction between FOXP1 and the well-known corepressor NCOR2 (SMRT) has been shown to be required for cardiac growth as well as gene regulation in monocytes (e.g. Genes Dev, 2008). We have previously shown that NCOR2 as well as NCOR1 are important for proper brain development and for the epigenetic control of the differentiation progress of cortical progenitors (Nature 2002, 2007; submitted, 2014). We hypothesized that FOXP2-mediated regulation of gene expression programs in neural development depends on NCOR1 and/or NCOR2. We took a genome wide approach to identify FOXP2 as well as NCOR2 and NCOR1 DNA binding sites in neural progenitors from the developing neural cortex (rat) and human induced pluripotent cells (hIPSCs) in a self-renewing neuroepithelial-like stem (NES) cell state. We identified a significant overlap between NCOR1 and FOXP2 target genes including a known FOXP2 target essential for speech development, CNTNAP2 (neurexin). Mammalian two-hybrid experiments validated that FOXP2 interacted with NCOR1 rather than NCOR2. We further noted that FOXP2 and NCOR1 co-occupied a gene cluster previously linked to Tourette Syndrome (TS) and recently to the evolution of the brain (Prüfer, 2014). Knockdown of NCOR1 in human NES cells entailed an increase in mRNA levels of all genes in this gene cluster indicating a functional regulatory repressive site. The histone marks in the region were characteristic of active regulatory elements as confirmed by ENCODE data. Chromosome conformation capture (3C) was applied and visualized the interaction between the gene cluster promoters and the FOXP2/NCOR-occupied distal regulatory element. We are currently characterizing the vocal and motor-skill learning in a mouse strain where NCOR1 or NCOR2 is lacking in excitatory projection neurons of the cortex. Taken together, our data obtained hitherto strongly support our hypothesis of FOXP2/NCOR mediated gene regulation as a mechanism underlying correct development and possibly evolution of vocal and motor skills.

Fundings: VR, BCF, CF.

VEGFR3 CONTROLS NEURAL STEM CELL ACTIVATION IN THE ADULT MOUSE HIPPOCAMPUS

Han, Jinah[1], Calvo, Charles-Felix[2], Baker, Kasey[1], Kang, Tae-Hyuk[1], Levittas, Marine[2], Parras, Carlos[2], Nurmi, Harri[3], Alitalo, Kari K.[3], Duman, Ronald[1], Eichmann, Anne[1], Thomas, Jean-Leon[1]
[1]Yale University School of Medicine, New Haven, CT, USA, [2]Université Pierre and Marie Curie–Paris 6, Paris, France, [3]Haartman Institute, University of Helsinki, Helsinki, Finland

Background: Neural stem cells (NSCs) persist in the adult hippocampus of all mammalian species. Decline of these NSCs during aging has been correlated to defects in cognitive function and mood. The molecular mechanisms that activate quiescent NSCs to generate progenitor cells in vivo remain poorly understood. We focused on Vascular Endothelial Growth Factor Receptor 3 (VEGFR3), a key regulator of angiogenesis and lymphangiogenesis, which is also expressed in NSCs in adult subventricular zone. Purpose: We aimed to investigate the role of VEGFR3 in hippocampal NSCs, specifically, to determine if VEGFR3 acts as a regulator of cell cycle entry and conversion to progenitor cells upon stimulation by VEGFR3 ligand VEGF-C and physical activity.Methodology: Vegfr3::YFP reporter mouse was used to characterize VEGFR3-expressing cells in adult hippocampus. Immunostaining and gene expression analyses (quantitative PCR) were performed to characterize Vegfr3YFP cells. FACS-sorted Vegfr3YFP cells were subjected to in vitro neurosphere assays as well as to high-throughput screening (RNA sequencing) following ligand VEGF-C stimulation. In vivo functional analyses included intra-hippocampal stereotaxic injection of AAV-VEGF-C (gain-of-function) and inducible NSC-specific Vegfr3 deletion by intercrossing GlastCreERT2 and Vegfr3floxed mice (loss-of-function). Experiments were carried out on sedentary and free-running mice to determine VEGFR3 role in running-induced neurogenesis. Mutant animals were tested for their locomotory performances and their anxiety state, to explore VEGFR3 role in hippocampal neurogenesis-dependent behaviors. Results: Vegfr3 expression is specifically enriched in NSCs of the hippocampal niche. VEGF-C stimulation increases the pool of neural progenitor cells, both in vitro and in vivo, in a VEGFR3-dependent manner. VEGF-C/VEGFR3 signaling in NSCs increases the expression of genes controling G1-S transition, with a concomitant decrease in the expression of stem cell markers and increase of progenitor cell markers. VEGF-C/VEGFR3 signaling thus promotes activation and conversion of quiescent cells into progenitor cells.Conditional deletion of Vegfr3 in NSCs (Glast iΔR3) leads to an abnormal

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decline of hippocampal neurogenesis and middle-aged Glast iΔR3 mice show anxiety-related behaviors, indicating that VEGFR3 signaling may regulate the mood state through its primary action on hippocampal neurogenesis.VEGF-C stimulation in vivo upon intra-hippocampal delivery of AAV-VEGF-C increases the pool of NSPCs in a VEGFR3-dependent manner. VEGFR3 is moreover mandatory for the response of hippocampal NSCs to physical exercise and running-induced NSC activation is inhibited in Glast iΔR3 mice.Conclusions: These findings establish Vegfr3 expression as a hallmark of NSCs in the mouse adult brain and demonstrate a necessary and novel role for VEGFR3 in hippocampal neurogenesis. VEGFR3 signaling controls hippocampal NSC activation and conversion to progenitor cells upon environmental stimuli and physical activity.

POSTER TEASERS:

T-2042 COMBINED SMALL MOLECULE INHIBITION ACCELERATES GENERATION OF FUNCTIONAL CORTICAL NEURONS FROM HUMAN PLURIPOTENT STEM CELLS

Qi, Yuchen, Zhang, Xinjun, Studer, Lorenz
Sloan Kettering Institute for Cancer Research, New York, NY, USA

T-2135 GENERATION OF INDUCED NEURAL PRECURSOR CELLS FROM HUMAN CORD BLOOD

Evers, Daniela[1], Kesavan, Jaideep[1], Koegler, Gesine[2], Peitz, Michael[1], Bruestle, Oliver[1]
[1]Institute of Reconstructive Neurobiology, Bonn, Germany, [2]Heinrich-Heine University, Institute for Transplantation Diagnostics and Cell Therapeutics, Duesseldorf, Germany

T-3009 MODELING DISEASE CAUSING DEFECTS IN LIPID METABOLISM IN MOUSE AND HUMAN NEURAL STEM CELLS

Bowers, Megan, Vidmar, Mojca, Jessberger, Sebastian
Brain Research Institute, University of Zurich, Zurich, Switzerland

USING THE FUNCTIONAL IDENTITY OF HUMAN GENOMES

McKay, Ronald D.
Lieber Institute for Brain Development, USA

The mammalian brain is formed from a small group of founding pluripotent stem cells that rapidly generate the regionally distinct neural stem cells that form the central nervous system. The establishment of cell culture strategies for generating many different kinds of neuron from pluripotent stem cells is a major research achievement of the stem cell field. The hope of developing new cell and pharmaceutical therapies has generated significant investment in technologies that make use of the developmental potential of human pluripotent stem cells. In contrast to animal models that utilize inbred strains to reduce experimental variability, the successful use of human pluripotent stem cells would ideally embrace the genetic variation found in the human population. To achieve this we have established a simple experimental condition where different human embryonic (ES) and induced pluripotent (iPS) stem cells can be precisely compared as they self-renew and differentiate to neur-ectodermal or mes-endodermal fates. Bio-informatic analysis identified transcriptional differences between self-renewing cell lines that predict their differentiation efficiency. To explore the validity of this approach, we particularly focus on two transcription factors, SOX21 and OTX2, found in a transcriptional signature that predicts efficient neur-ectodermal differentiation. Cell imaging and reduced expression, achieved by either genetic or pharmacological perturbation, shows that these transcription factors are dynamically regulated and co-operate to promote neur-ectodermal differentiation. High-content imaging was used to show that human genomes carrying different types of genetic risk for psychiatric disorders are functionally distinct in this early step in brain development. The finding that common alleles conferring disease risk act from the earliest stages of development opens new strategies to define the developmental origins of risk and to optimize new pharmacological interventions.

CONCURRENT IIB: TRANSDIFFERENTIATION

WEST MEETING ROOM 211-214

DIRECTED DIFFERENTIATION OF HUMAN PLURIPOTENT CELLS TO KIDNEY PROGENITOR POPULATIONS RESULTS IN FORMATION OF A SELF-ORGANISING EMBRYONIC KIDNEY

Little, Melissa H., Takasato, Minoru, Er, Pei X., Becroft, Melissa, Vanslambrouck, Jessica M., Stanley, Ed G., Elefanty, Andrew G., Glass, Nick, Sun, Jane, Cooper-White, Justin J., Wolvetang, Ernst
The University of Queensland, Australia

The directed differentiation of human pluripotent stem cells has successfully been applied to the generation of a variety of cell types including derivatives of endoderm (pancreas, liver), ectoderm (neurons) and mesoderm (cardiac muscle, blood). However, while there is considerable demand for sources of renal cells for bioengineering, drug screening and cellular therapy, to date there

has been little progress in the generation of renal tissue using this approach. The mammalian kidney is a mesodermal organ, arising from intermediate mesoderm. During normal embryogenesis, the kidney is formed from two cellular compartments, the ureteric epithelium (UE) and metanephric mesenchyme (MM) that interact with each other via a series of cell-cell and ligand-receptor driven interactions. Signals from the nephron progenitors drive dichotomous branching of the ureteric epithelium to form the collecting duct system of the organ. Conversely, signals from the epithelium promote both nephron progenitor self-renewal (and hence continued support of epithelial branching) as well as commitment to nephron formation. Drawing from our understanding of the embryonic processes involved in specifying posterior primitive streak (phase 1) , intermediate mesoderm (phase 2) and metanephric kidney (phase 3) in the mouse, we have now successfully directed the differentiation of hESCs to simultaneously form both of these key kidney progenitor populations in vitro. This was achieved using a fully chemically-defined monolayer culture with stepwise induction of each phase of development. By day 14 of differentiation, we observed synchronous induction of elongating epithelial PAX2+/GATA3+/ECAD+ UE together with a surrounding mesenchymal PAX2+/SIX2+/WT1+ MM. Given the evidence for the presence of both progenitor populations in the dish, cultures were dissociated and then reaggregated to form a pellet and grown as an organoid culture. Within these cultured aggregates, self-organizing events were observed, generating renal vesicles, proximal tubules and collecting ducts. The capacity to transfer this protocol from hESC to hiPSC has now been established. This opens up the possibility of generating patient derived iPSC for disease modeling. While this approach is very promising, it is likely that it can be further optimized with variations in the concentration and duration of growth factors used for differentiation. To investigate this further, we have developed a microbioreactor based factorial screen. The functional maturation of the nephrons being formed is also being investigated. In conclusion, the capacity for such populations to undergo self-organization in vitro provides the potential for disease modeling using patient-derived iPS cell lines, the generation of cells for tissue/organ bioengineering and in the longer term the possibility of cellular therapies.

INDUCTION OF MULTIPLE GROUPS OF INSULIN+ BETA CELLS FROM THE ADULT GASTROINTESTINAL TRACT

Zhou, Qiao[1], Ariyachet, Chaiyaboot[2], Tovaglieri, Alessio[3], Breault, David[4]

[1]Harvard University, Cambridge, MA, USA, [2]Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [3]Division of Endocrinology, Harvard Medical School, Boston, MA, USA, [4]Department of Endocrinology, Harvard Medical School, Boston, MA, USA

We used inducible mouse genetic models to investigate epigenetic plasticity of adult tissues in beta-cell conversion and discovered that distinct groups of insulin+ cells can be induced from different regions of the GI track in vivo.

We constructed and tested multiple knock-in and transgenic Teto-M3cherry mouse lines where three beta-cell reprogramming factors (Ngn3, Pdx1, and Mafa, referred to as M3 factors) are driven off the TetO inducible promoter. QPCR screening of major adult organs showed that upon Doxycycline treatment of Rosa-rtTA::TetO-M3cherry animals, insulin is strongly induced in the GI track, in addition to other organs. Immunohistochemistry revealed large numbers of insulin+ cells in the pyloric region of the stomach. These gastric beta cells express a full spectrum of critical beta-cell genes including prohormone convertase 1/3 (PC1/3), glucose transporter 2 (Glut2), Nkx2.2, and Nkx6.1. They intermingle with resident gastrin+ enteroendocrine cells as single cells or clusters. Within the intestine, insulin+ cells are concentrated in duodenum epithelium and Brunner's glands (duodenal glands). Induced beta cells from the Brunner's gland also express a full spectrum of beta cell genes. In contrast, beta cells of the duodenal epithelium lack Nkx6.1, a gene critical for beta cell function. In pulse-chase experiment, we determined that beta cells residing in duodenal epithelium have an in vivo lifespan of less than 10 days whereas beta cells in the stomach and Brunner's gland have a lifespan of around 30 days. Glucose-stimulated insulin secretion (GSIS) analyses showed that beta cells from stomach and Brunner's gland are glucose-sensitive whereas the ones from duodenal epithelium are not. Thus, among the different groups of induced GI beta cells, stomach and Brunner's gland beta cells more closely resemble endogenous pancreatic beta cells. We assessed the cellular origin of the induced GI beta cells by genetic lineage tracing, using multiple cell type-specific lines including Lgr5-CreER, Ngn3-CreER, Prom1-CreER, and Villin-CreER. The induced GI beta cells arise from the stem cell and endocrine progenitor compartments. In addition, we show that GI beta cells can be continuously produced from enteroendocrine progenitors in Ngn3-Cre::Rosa-floxed-rtTA::Teto-M3cherry animals, which allows physiological rescue of diabetic animals for extended time.

To further explore the therapeutic potential of the GI reprogramming

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approach, we established gastric and intestinal organoids from the mouse transgenic models, which yielded insulin+ beta cells upon transient M3 expression. We also established organoid cultures from human GI tract biopsies and showed that the human intestinal cells can be induced to form insulin+ cells with genetic factors and chemical compound treatment. This work, together with others, suggests that generating beta cells from gastrointestinal tissues in vivo and in vitro is a promising strategy to supply new beta cells for diabetes studies and treatment.

REDEFINING THE IN VIVO ORIGIN OF NEPHRON PROGENITORS ENABLES GENERATION OF THREE-DIMENSIONAL KIDNEY STRUCTURES FROM PLURIPOTENT STEM CELLS IN VITRO

Taguchi, Atsuhiro, Nishinakamura, Ryuichi
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Generation of the kidney *in vitro* is a challenge for developmental biology and regenerative medicine, because reconstitution of the three- dimensional nephron structures including glomeruli and nephric tubules is a prerequisite for the kidney functions. Adult kidney derives from caudally located embryonic metanephros which develops by the reciprocal interaction of the metanephric mesenchyme (MM) and the ureteric bud (UB), both of which are reportedly derived from common intermediate mesoderm (IM). Most nephron components are derived from metanephric nephron progenitors in the MM. However, how the IM differentiates from nascent mesoderm and how the anteroposterior axis is formed along the IM, so that finally gives rise to the posteriorly located MM are largely unknown. We first evaluated the functional and molecular differences between the early stage renal precursors using Osr1-GFP knock-in mice. We also tried to identify the origin of metanephric mesenchyme by lineage trace experiments utilizing T-GFPCreER mice. We identified that the MM is originated from posteriorly located T+ precursors at embryonic day (E) 8.5, which may correspond to the so-called "axial progenitor", and that developmentally distinct from Osr1+ anteriorly located IM, namely the UB progenitors. Next, we examined the combinations of factors which are required for metanephric nephron progenitor specification from embryonic nascent mesoderm. T+ cells sorted from mouse embryos differentiate into the metanephric mesenchyme in vitro by posteriorization with a high concentration of Wnt agonist, followed by its graded attenuation and stage-specific growth factor addition. Finally, by applying this protocol to the mouse and human pluripotent stem cells, metanephric nephron progenitors were obtained. When the induced metanephric nephron progenitors were cocultured with Wnt4 expressing feeder cells or embryonic spinal cords, they formed the three-dimensional structures of the kidney, including glomeruli with podocytes and renal tubules with proximal and distal regions. Furthermore, the glomeruli were efficiently vascularized upon transplantation. In conclusion, we have succeeded in inducing the metanephric nephron progenitors from both mouse embryonic stem (ES) cells and human induced pluripotent stem (iPS) cells, *in vitro.* The resultant progenitors readily "self-organized" the three-dimensional structures of the kidney, comprising renal tubules and glomeruli with podocytes, which has not been achieved in previous reports. Thus, by re-evaluating the developmental origins of metanephric progenitors, we have provided key insights into kidney specification *in vivo* and taken important steps toward kidney organogenesis *in vitro.*

DYNAMIC DEVELOPMENTAL SIGNALING LOGIC UNDERLYING LINEAGE BIFURCATIONS DURING HUMAN ENDOERM INDUCTION AND PATTERNING FROM PLURIPOTENT STEM CELLS

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Pluripotent stem cells (PSCs) can access myraid lineage opportunities and can generate over more than 200 distinct cell types. Unilateral differentiation of PSCs into a pure population of given lineage amidst multiple cell fate choices is critical for regenerative medicine, but has proven challenging. This difficulty is compounded by the imcomplete knowledge of how to direct PSCs to one cell type whilst excluding other lineages. Furthermore, it has been difficult to differentiate diverse PSC lines with uniformly high efficiencies. Here, we met these challenges by understanding the signals exclusively differentiating human PSCs into the definitive endoderm germ layer, and signals that drive differentiation to parallel fates. Definitive endoderm is the precursor to valuable cell types such as the lung, liver, pancreas, stomach and intestines. To generate a pure population of definitive endoderm, we systematically screened for the growth factors and small molecules that induce definitive endoderm, while concommitantly blocking the differentiation into other mutually exclusive cell fate (mesoderm and ectoderm). Together, this enabled highly efficient (94%) endodermal differentiation of, not only one, but also nine diverse human PSC lines. We continue to understand the signals that drive foregut versus midgut/hindgut specification during anteroposterior patterning, and subsequently the signals that direct pancreatic versus hepatic bifurcation from the foregut. Together these analyses of signaling effects on lineage segregation provided a detailed understanding of precise extrinsic control of cell fate specification at multiple stages. Next, comprehensive transcriptional and chromatin mapping of highly

pure endodermal populations revealed that endodermal enhancers existed in a surprising diversity of "pre-enhancer" state before activation, reflecting the establishment of a permissive chromatin landscape as a prelude to differentiation. Finally, we find that H2AZ marks an endoderm "pre-enhancer" state prior to activation during endoderm differentiation.

POSTER TEASERS:

T-2156 SUCCESSIVE IPSC REPROGRAMMING INTERMEDIATES IDENTIFIED BY PROSPECTIVE ISOLATION AND SINGLE CELL MASS CYTOMETRY

Lujan, Ernesto
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T-2043 SINGLE CELL TRACKING AND MOLECULAR ANALYSIS REVEALS DISTINCT MESENDODERM PROGENITORS

Yang, Dapeng[1], Burtscher, Ingo[1], Schwarzfischer, Michael[2], Irmler, Martin[3], Marr, Carsten[2], Lickert, Heiko[1]
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T-3004 P53 INHIBITION PROVOKES THE DIRECT CONVERSION OF HUMAN FIBROBLASTS INTO MULTIPLE NEURONAL SUBTYPES

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DIRECT REPROGRAMMING OF FIBROBLASTS TO FUNCTIONAL HEPATOCYTE-LIKE CELLS

Hui, Lijian
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Generating functional hepatocytes independent of donor liver organs is of great interests for regenerative medicine to cure liver diseases. Induced hepatic differentiation was achieved using embryonic stem cells or induced pluripotent stem (iPS) cells. However, induction of hepatocytes from iPS cells still composes complex steps, which can be replaced by improved technology. On the other hand, the generation of large numbers of functional human hepatocytes for cell-based approaches to liver disease is an important and unmet goal. We have previously induced mouse tail-tip fibroblasts (TTFs) into functional hepatocyte-like (iHep) cells by transduction of Gata4, Hnf1a and Foxa3 and inactivation of p19Arf. Lately, we generated human induced hepatocyte-like (hiHep) cells from fibroblasts by forced expression of human FOXA3, HNF1A, and HNF4A. HiHep cells express hepatic gene programs, can be expanded in vitro, and display functions characteristic of mature hepatocytes including cytochrome P450 enzyme activity and biliary drug clearance. Upon transplantation into mice with concanavalin A-induced acute liver failure and fatal metabolic liver disease due to fumarylacetoacetate dehydrolase (Fah) deficiency, hiHep cells restore the liver function and prolong survival. Collectively, our results demonstrate successful lineage conversion of non-hepatic human cells into mature hepatocyte-like cells with potential for biomedical and pharmaceutical applications.

CONCURRENT IIC: CANCER PLASTICITY

WEST BALLROOM C/D

MOUSE MODELS OF MALIGNANT GBM: CANCER STEM CELLS AND BEYOND

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Glioblastoma Multiforme (GBM) is an incurable cancer with a rapid progression and a prognosis of month from the time of diagnosis. Given the resistance to all known therapies, new paradigms to understand this disease and identify novel therapeutic targets are sorely needed. We have used genetically engineered models to ablate GBM relevant tumor suppressors in brain cells. Our fully penetrant mouse models indicate that adult stem cells and progenitors are preferential sites of tumor initiation. As such, further study of these cells, and how they transform may provide unique insights into tumor development and progression. Our efforts to understand whether additional cell types can give rise to GBM indicate that fully differentiated brain cells are considerably more resistant to tumor suppressor mediated transformation than are stem cells, but in contrast, OPC progenitor cells are also able to give rise to GBM that, while pathologically similar to stem cell derived tumors, also have unique growth and molecular properties that distinguish them clearly. I will discuss the state of understanding of these tumors and the implications for cancer stem cells and therapeutic opportunities.

PROGRAM AND ABSTRACTS

EVIDENCE FOR PERIVASCULAR MSC-LIKE CELLS AS POTENT MEDIATORS OF MALIGNANT METASTASES IN XENOGRAFT MODELS OF OVARIAN CANCER, CORRELATED WITH EARLIER RELAPSE AND MORTALITY IN HIGH-GRADE SEROUS OVARIAN CANCER PATIENTS

Kaur, Pritinder[1], Sinha, Devbarna[1], Chong, Lynn[1], George, Joshy[1], Schlueter, Holger[1], Moenchgesang, Susann[1], Mills, Stuart[1], Parish, Christopher[2], Australian Ovarian Cancer Study Group[3], Bowtell, David D. L.[1]

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Pericytes are mesenchymal stem cell-like cells found around microvessels and promote survival of the tumour through continuous stabilization and remodelling of the tumour vasculature. However, here we show that pericytes can accelerate both primary tumour growth and metastasis in a xenograft model of ovarian cancer without altering tumour vasculature as determined by microvessel density or pericyte coverage index. Notably, pericytes have a gene expression profile that significantly overlaps with cancer-associated fibroblasts/CAFs isolated from patient samples suggesting homology with the ovarian tumour microenvironment. More importantly, interrogation of a gene expression dataset of 215 serous ovarian cancer patients revealed that patients carrying a pericyte-specific gene expression signature bore a significantly (p=0.000195) higher risk of relapse and a lower overall chance of survival, indicating that pericyte activity is a strong predictor of cancer recurrence and mortality. Further, this high-risk patient group was distinct from that identified by an angiogenic signature. In silico analysis of the molecular profile of patients with earlier relapse associated with the pericyte signature, showed that ECM remodelling, cell adhesion and migration were the primary pathways overexpressed in that patient subset. This was experimentally validated in histological analyses of the xenografted tumours, where increased tumour invasion accompanied by epithelial mesenchymal transition (EMT) was observed in the presence of pericytes. This study is the first concrete clinical and experimental evidence for pericytes being a potential source of CAFs in the tumour microenvironment and presents the possibility of pericyte-specific genes being used at the protein level as prognostic markers for ovarian cancer progression and survival.

THE FLT3 INTERNAL TANDEM DUPLICATION HAS AGE DEPENDENT EFFECTS ON HEMATOPOIETIC STEM CELL SELF RENEWAL AND LEUKEMOGENESIS

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The genetic landscapes of human leukemias change with age. This affects prognosis and treatment, yet we have little insight into why leukemias have different mutation profiles at different ages. One possibility is that mutations require specific, permissive developmental contexts to induce malignancy. Since leukemia cells often ectopically activate stem cell self-renewal mechanisms and these mechanisms change with age, the mutations that are competent to induce leukemogenesis could change concordantly. Consistent with this idea, we have recently shown that Pten mutations induce hematopoietic stem cell (HSC) proliferation and leukemogenesis during adult, but not neonatal stages of life. This is due to age-dependent changes in mTORC2 regulation. The findings raise the question of whether other mutations also have context dependent effects on self-renewal. If so, temporal changes in self-renewal mechanisms may generally explain changes in the leukemia mutation spectrum.

We tested whether the function of the FLT3-Internal Tandem Duplication (FLT3-ITD) mutation changes with age. FLT3-ITD mutations occur commonly in adolescent and adult acute myeloid leukemias (AML), and they convey a poor prognosis. FLT3-ITD mutations occur much less commonly in infants and young children with AML. We hypothesized that the mutation has different effects on self-renewal during fetal, neonatal and adult stages of development. To test this, we analyzed HSC frequency in embryonic day (E)14.5 fetal, post-natal day (P)14 neonatal and 8-10 week old adult FLT3-ITD expressing mice. Adult FLT3-ITD mice had significantly reduced HSC frequencies and myeloproliferative neoplasms, consistent with prior studies. Similar, though less severe phenotypes were evident in P14 mice. In contrast, E14.5 fetal FLT3-ITD mice had normal HSC frequencies, and the livers were grossly normal without evidence of a myeloproliferative disorder. Restricted progenitor frequencies and myelopoiesis increased in adult, but not fetal FLT3-ITD expressing mice. In limiting dilution transplants FLT3-ITD expression impaired adult, but not fetal HSC function. Both fetal and adult progenitors expressed the FLT3 protein so temporal changes in FLT3-ITD function were not caused by changes in FLT3 expression. Unlike Pten mutations, FLT3-ITD phenotypes were mTORC2 independent. The data suggest that multiple mutations can have heterochronic effects on self-renewal and that these mutations regulate self-renewal via distinct mechanisms. Since developmental context may shape the effects of many mutations, re-programming may offer a novel and widely effective strategy for treating leukemia patients.

PROGRAM AND ABSTRACTS

ZEB2 DRIVES T-CELL LYMPHOBLASTIC LEUKEMIA DEVELOPMENT VIA ALTERED IL-7 RECEPTOR SIGNALING AND ENHANCED TUMOR-INITIATING POTENTIAL

Haigh, Jody Jonathan[1], Goossens, Steven[2], Tagon, Tom[3], Blanchet, Odile[4], Speleman, Frank[5], Soulier, Jean[4], Meijerink, Jules[6], Van Vlierberghe, Pieter[7]

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Zeb2 is a member of the ZEB family of transcriptional regulators. Its expression has been correlated with the formation and/ or function of cancer stem cells and metastatic spread in solid tumors. We have previously demonstrated that Zeb2 is highly expressed and is essential for normal hematopoiesis and evidence from mouse retroviral mutagenesis screens point to a role for Zeb2 in leukemia. Here, we examined the roles of Zeb2 in the hematopoietic system and in leukemia formation through a conditional gain-of-function approach. Zeb2 expression from the ROSA26 locus resulted in altered T cell development and a partial block in differentiation observed at the DN3 pre-T cell stage. In addition, Zeb2 overexpressing mice spontaneously develop T-ALL starting at 5 months of age, indicating that Zeb2 can act as a driver in T cell malignancies. Breeding these mice onto a tumor-prone background (using conditional p53 knock-outs) we have observed a significant decrease in tumor latency and an increase of the stem/ progenitor markers c-Kit and CD44, suggesting an increase in leukemic stem cells. Using a minimal dilution series of tumor cells into NOD/SCID mice we could demonstrate a 10-100-fold increase in leukemia-initiating cells in the Zeb2 overexpressing tumors. To assess the relevance of these findings with human disease, we screened a cohort of T-ALL patients and found increased expression of ZEB2 predominantly associated with the immature/ETP-ALL patient group. Early T-cell precursor leukemia (ETP-ALL) is a high-risk subtype of human leukemia that is poorly understood at the molecular level. Here, we report translocations targeting Zeb2 as well as decreased miR200 family expression in ETP-ALL that can result in increased Zeb2 expression. Zeb2 driven mouse leukemia recapitulates important features of human ETP-ALL, including enhanced leukemia-initiation potential and activated JAK/STAT signaling through transcriptional activation of IL7R. This study therefore reveals ZEB2 as a novel oncogene in immature T-ALL.

POSTER TEASERS:

T-1112 TRACING THE ORIGINS AND EVOLUTION OF CLONAL HETEROGENEITY IN A SHH-SUBTYPE MEDULLOBLASTOMA MOUSE MODEL

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T-2147 THE RB TUMOR SUPRESSOR RESTRICTS REPROGRAMMING BY DIRECTLY SILENCING PLURIPOTENCY GENES

Kareta, Michael[1], Gorges, Laura[2], Hafeez, Sana[1], Zmoos, Anne-Flore[1], Cecchini, Matthew J.[3], Spacek, Damek[1], Batista, Luis[1], O'Brian, Megan[1], Ng, Yi-Han[1], Ang, Cheen Euong[1], Vaka, Dedeepya[1], Artandi, Steven[4], Dick, Frederick A.[3], Sage, Julien[4], Wernig, Marius[1]

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F-1094 EPIGENOMIC CHARACTERIZATION OF GENE REGULATORY NETWORKS IN HUMAN OVARIAN CANCER STEM CELLS

Battle, Stephanie L.[1], Larjo, Antti[2], Lahdesmaki, Harri[2], Lieber, Andre[3], Hawkins, David[3]

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PROGRAM AND ABSTRACTS

RARE QUIESCENT TUMOR INITIATING CELL (TIC) CLONES IN COLORECTAL CANCER ARE CHEMOTHERAPY RESISTANT AND ACTIVATED TO DRIVE POST TREATMENT PROGRESSION

Hartinger, Eva-Maria[1], Ball, Claudia R.[1], Dieter, Sebastian M.[1], Hoffmann, Christopher M.[1], Weichert, Wilko[2], Heger, Ulrike[1], Stenzinger, Albrecht[2], Schneider, Martin[3], Weitz, Juergen[4], Koch, Moritz[4], Schmidt, Manfred[1], von Kalle, Christof[1], Glimm, Hanno[1]

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Quiescence of tumor-initiating cells (TIC) has been implicated in chemotherapy resistance even though direct evidence for TIC dormancy in human solid cancers is missing. Using genetic clonal marking of serially transplanted human colorectal cancer TIC we have previously demonstrated that rare delayed contributing TIC do not immediately contribute to tumor-formation but only after secondary or tertiary transplantation. Here, we analyzed whether TIC dormancy underlies the observed clonal dynamics in vivo and how these clonal dynamics respond to chemotherapeutic treatment. To address whether tumor-initiating activity is restricted to certain cell cycle phases, TIC enriched primary spheroid cultures (n=2) were stained with Hoechst/PyroninY and sorted according to their cell cycle phase. The majority of spheroid cells cycled actively (G1: 69% and 81%, S/G2/M: 26% and 16%), and only a small proportion (0.3% and 0.5%) was in G0. Cells in all cell cycle fractions equally well formed serially transplantable tumors in immunodeficient NSG mice, demonstrating that self-renewing long-term TIC (LT-TIC) activity was present in all cell cycle phases in vitro. To assess whether TIC differ in their proliferative activity in vitro, we stained patient derived spheroids (n=3) with CFSE, whose fluorescence is equally distributed with each cell division allowing to discriminate cells according to their proliferative history. After 8 days in vitro, a majority of fast dividing cells (57-97%) lost all detectable CFSE fluorescence, a slowly dividing fraction (3-42%) maintained less than 90% and a small proportion of rarely dividing (<0.1-1%) cells retained the original CFSE intensity. In vitro limiting dilution and serial replating demonstrated equal sphere forming activity across all proliferative subfractions. Moreover, all fractions formed serially transplantable tumors after transplantation into NSG mice. To examine whether TIC quiescence occurs in established tumors in vivo, we tracked intra-tumoral cell divisions by genetic label retention(n=2). Spheroid cells were transduced with a lentiviral vector encoding atet-off regulated expression system of human histone H2B fused to GFP and transplanted into NSG mice. After tumor formation,tetracycline addition to the drinking water resulted in halving of fluorescence with each cell division. Interestingly, a very small fraction of tumor cells was detectable that retained the original GFP intensity. Serial transplantation demonstrated equal TIC and self-renewal activity in fast, slow and rarely dividing cell subfractions. Importantly, clonal analysis of viral integration sites by highly sensitive LAM-PCR strongly indicated that dormant TIC were enriched in the rarely dividing fraction. Moreover, upon chemotherapy by 5-FU,label retaining cells were enriched from <0.1 to 0.5% and previously dormant TIC clones drove secondary tumor formation after serial transplantation. Our results provide experimental evidence that mitotic quiescence of TIC exists within established CRC tumors and that quiescent TIC clones can survive chemotherapy and drive disease progression after treatment, thereby pointing out the urgent need to develop novel treatment strategies directed against mitotically inactive TIC in CRC.

CONCURRENT IID: EPITHELIAL AND MESENCHYMAL STEM CELLS

WEST BALLROOM A

LGR5+ STEM/PROGENITOR CELLS CONTRIBUTE TO THE DEVELOPMENT AND MAINTENANCE OF THE OVARY AND TUBAL EPITHELIA

Barker, Nick and Ng, Annie

Institute of Medical Biology, Singapore

The ovary surface epithelium (OSE) undergoes ovulatory tear-and-remodelling throughout life. Resident stem cells drive such tissue homeostasis in many adult epithelia, but their existence in the ovary has yet to be definitively proven. Lgr5 marks stem cells in multiple epithelia. Here we use reporter mice and Single Molecule Florescent-in-Situ-Hybridization (FISH) to document candidate Lgr5+ stem cells within the mouse ovary and associated structures. Lgr5 is broadly expressed during ovary organogenesis, but becomes limited to the OSE in early neonate life. In adults, Lgr5 expression is predominantly restricted to proliferative regions of the OSE and the fimbria-mesovarian junction. Using conditional in vivo lineage tracing we identify embryonic and early neonate Lgr5+ populations as stem/progenitor cells contributing to the development of adult OSE and granulosa cell lineages, as well as the epithelia of the mesovarian and oviduct, including its distal opening, the fimbria. Long-term lineage tracing reveals that adult OSE-resident Lgr5+ populations contribute to epithelial homeostasis and OSE regenerative repair in vivo. We conclude that Lgr5 is a marker of stem/progenitor cells of the ovary and tubal epithelia.

PROGRAM AND ABSTRACTS

INTRINSIC AND EXTRINSIC CONSTRAINTS ON NEUROMESODERMAL AND LATERAL MESODERM PROGENITORS

Wymeersch, Filip J.[1], Huang, Yali[1], Skylaki, Stavroula[2], Economou, Constantinos[1], Marek, Carylyn J.[1], Wong, Frederick CK[1], Cambray, Noemí[1], Wilson, Valerie[1]

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Elongation of the vertebrate rostrocaudal (head-to-tail) axis depends on stem cell-like neuromesodermal progenitors in the primitive streak and tail bud regions. We have undertaken a transcriptome analysis of the mouse primitive streak and tail bud over the period of axial elongation and show that, despite their stem cell properties, temporal differences in the transcriptome predominate over regional differences between stem cell and non-stem cell-containing populations. The largest temporal expression changes occur between E8.5 and E9.5 and include prominent upregulation of members of the Wnt, Fgf and Notch signalling pathways and many Hox genes, which plateau at E9.5-10.5 and thereafter gradually decline until the end of elongation. This sequence correlates well with a peak and subsequent decline in the number of progenitors, identified by Sox2/T(bra) coexpression. We have also carried out homotopic grafts and subsequent 48 hour whole-embryo culture to refine the E8.5 fate map. We show that the relative levels of Sox2/T(bra) provide a sensitive readout of neural (N) versus mesodermal (M) fate. Loss of Wnt/β-catenin signalling drastically reduces the number of these Sox2/T(bra)-positive progenitors, showing that β-catenin is necessary for NM progenitor maintenance. Furthermore, we demonstrate that Wnt/β-catenin signalling is crucial in neuromesodermal progenitors to direct them towards mesodermal fates. Heterotopic grafts show that NM potency extends beyond regions of NM fate and the choice between N and M fates is exquisitely sensitive to the cells' position in the neuromesodermal progenitor zone. The caudal-most part of the ectoderm does not express Sox2, and is entirely fated for lateral mesoderm. Although these caudal-most progenitors can divert to paraxial mesoderm fate on heterotopic grafting, they cannot produce neurectoderm, even on ectopic Sox2 expression or β-catenin deletion, and thus constitute a committed mesoderm progenitor type separate distinct from NM progenitors. By precisely defining the signalling pathways and transcription factors in these two distinct in vivo progenitor populations, we provide a conceptual framework for design of in vitro differentiation protocols from pluripotent stem cells.

SUCCESSFUL ENGRAFTMENT OF CULTURED SMALL INTESTINAL EPITHELIAL STEM CELLS ONTO DAMAGED COLONIC MUCOSA BY HETEROTOPIC TRANSPLANTATION

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With the advent of long-term culture technologies to expand intestinal stem cells in vitro, there has emerged a growing interest in the use of cultured adult stem cells in replacement therapy for intestinal epithelial injuries. We have previously demonstrated that the cultured colonic stem cells are able to regenerate normal epithelia when transplanted onto the damaged colon in mice. To extend such approach to small intestinal (SI) diseases, it is imperative to test whether the SI stem cells in culture retain their tissue regeneration capabilities. In this study, we aimed at investigating how SI stem cells would behave in vivo when cultured in vitro and then heterotopically transplanted onto the damaged colon in mice. SI epithelial cells were isolated from EGFP-transgenic mice, cultured as stem cell-containing organoids, and used as donor cells. Meanwhile, we developed a mouse recipient model of distal colonic mucosal injury by topical chelation and mechanical epithelial abrasion. The cultured EGFP+ donor cells were transplanted by intra-colonic infusion, and the recipients' colons were histologically analyzed. We found that, shortly after the transplantation, EGFP+ cells covered the denuded colonic mucosa as a flat lining of single-layered epithelial cells. At 2 weeks post-transplantation, EGFP+ cells displayed deeply invaginated structures that contained Ki-67-positive cells, indicating that the heterotopically transplanted SI cells actively proliferated within the colon. At four weeks, within some but not all areas of the grafts, there emerged structures reminiscent of the typical architecture of the SI epithelium that contained villus-like projections and crypt-like invaginations. Interestingly, the engrafted epithelium showed higher expression of CDX2, an intestine-specific transcription factor that plays a role in region-specific control of gastrointestinal epithelial maintenance, than the surrounding colonic epithelium of the recipient origin. Moreover, the grafts contained all types of terminally differentiated cells of the SI epithelium as well as the cells positive for OLFM4, a gene that is expressed in stem cells of the SI but not in the colon. Collectively, we here show that the SI stem cells are able to reconstitute the epithelial tissues of SI phenotype in vivo, even after in vitro culture and the following transplantation.

PROGRAM AND ABSTRACTS

Our study provides the first evidence that the cultured SI stem cells could be a source for the cell therapy for various intestinal diseases in humans. In addition, it is suggested that the SI stem cells of adult mice retain their segmental identity along the gastrointestinal tract through an epithelium-intrinsic mechanism.

IDENTIFICATION OF AN EPITHELIAL STEM CELL HIERARCHY IN THE MOUSE ESOPHAGUS

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The esophageal epithelium is a rapidly self-renewing tissue comprised of a basal cell layer and more differentiated suprabasal layers. Proliferation is restricted to the basal cell layer, which contains cells that self-renew and differentiate over the lifespan of the tissue. Opposing theories have questioned whether the basal cells in the adult esophagus adhere to a classical stem cell hierarchy or if all basal epithelial cells are functionally equivalent. In the intestine, multipotent LGR5+ stem cells are found in readily identifiable structures called crypts and regenerate all epithelial lineages of the intestine. On the other hand, the basal epithelium of the esophagus is more uniform morphologically and gives rise to a single cell lineage that makes up the suprabasal layer. This simple structure has led to questions about the presence or necessity of a separate stem cell population in the basal epithelium, similar to the questions that have arisen regarding the interfollicular epidermis. In this study, we found that basal cells in the mouse esophagus contain stem cell heterogeneity. We identified a combination of cell surface markers to separate distinct cell populations from primary esophageal tissue, and observed differences in stem cell potential using an in vitro 3-D organoid assay. Furthermore, cell cycle profiles and proliferation kinetics were different among the basal epithelial cell populations in vivo. Our results show that the basal epithelium in the mouse esophagus supports a hierarchical stem cell model consisting of activated stem cells, transit amplifying cells, and early differentiating cells. These results have important implications for disease, since it is thought that an esophageal stem cell may be the cell of origin for Barrett's metaplasia and esophageal cancer.

POSTER TEASERS:

T-1044 SPATIAL IDENTITY CONTROLS MOLECULAR PROPERTIES AND STEM CELL BEHAVIOUR IN MURINE EPIDERMIS

Page, Mahalia E.[1], Andersen, Marianne S.[2], Sendrup, Sarah[2], **Jensen, Kim B.**[2]
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T-3078 IDENTIFICATION OF FUNCTIONALLY DISTINCT DIFFERENTIATION-COMPETENT AND IMMUNOMODULATORY MESENCHYMAL STROMAL CELL SUBPOPULATIONS

Knight, Charlotte Anne, James, Sally R., Clough, Sally L., Lee, Jennifer, Afsari, Farinaz, Ashmore, James, Ashton, Peter, Genever, Paul
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T-1042 LGR6+ CELLS CONSTITUTE TWO INDEPENDENT STEM CELL POPULATIONS IN MURINE EPIDERMIS AND GIVE RISE TO MULTICLONAL SKIN TUMORS

Füllgrabe, Anja[1], Are, Alexandra[1], Joost, Simon[1], Haegebarth, Andrea[2], Clevers, Hans C.[2], Toftgård, Rune[1], Kasper, Maria[1]
[1]Karolinska Institute, Stockholm, Sweden, [2]Hubrecht Institute, Utrecht, Netherlands

NICHE APPROPRIATION BY DROSOPHILA INTESTINAL STEM CELL TUMORS

Edgar, Bruce, Dutta, Devanjali, Kohlmaier, Alexander, Jin, Yinhua, Xiang, Jinyi, Petersson, Monika, Korzelius, Jerome, Patel, Parthive
German Cancer Research Center-Center for Molecular Biology Heidelberg Alliance, Germany

Cells in intestinal epithelia turn over rapidly due to wear and tear from digestion. Gut homeostasis is maintained by intestinal stem cells (ISC) that divide to replenish the epithelium. Using the Drosophila intestine, or midgut, we find that when enterocytes (ECs) in the gut epithelium are subjected to stress or damage the epithelium and supporting visceral muscle respond by producing leptin/interleukin-like cytokines (Upd2, Upd3) and EGF-like growth factors (Vn, Krn, Spi). These activate Jak/Stat and EGFR/Ras/MAPK signaling in intestinal stem- and progenitor-cells, and thereby promote ISC division, progenitor cell differentiation, and

gut epithelial renewal. We are currently investigating the biology of stem cell-derived tumors generated by altering factors that affect differentiation (Notch) or cell growth and proliferation (Ack, Src, Ras). In each of these cases transformed stem cells stimulate surrounding enterocytes and visceral muscle to produce the same growth factors that mediate normal regeneration. In the case of Notch-depleted stem cell tumors the tumor initiating cells produce an autocrine, progenitor cell-specific EGFR ligand (Spitz), which supports early tumor growth. Neighboring enterocytes initially restrict tumor growth but after achieving a critical mass, the tumors induce JNK and YAP/Yki activity, apoptosis, and cytokine (Upd2,3) expression in these enterocytes, and another EGFR ligand (Vein) in visceral muscle. These paracrine signals, normally used within the niche to support regenerative growth, are also required to propel tumor growth. Consistent with this requirement Notch-defective ISC tumors support rapid invasive growth if transplanted to sites outside the intestine, but only when provided with activated Ras/MapK signaling. Finally, tumor initiation rates are increased under conditions that stimulate normal stem cell activation, such as infection stress. We propose that niche appropriation by differentiation-defective stem cells may be a common mechanism of tumor initiation.

CONCURRENT IIE: STEM CELLS IN MODEL ORGANISMS

WEST MEETING ROOM 301-305

STEM CELL SURVIVAL PROGRAM

Ruohola-Baker, Hannele
University of Washington, USA

Apoptosis is a vital component of various processes including normal cell turnover, proper development and function of the immune system, embryonic development and stress-induced cell death. Stem cells share high similarity with cancer stem cells, including the resistance to drug/irradiation induced caspase activation. We will discuss the mechanism that protects the stem cells from apoptosis.

A HISTOCOMPATIBILITY GENE THAT REGULATES PREDATORY STEM CELLS

Voskoboynik, Ayelet[1], Newman, Aaron M.[1], Corey, Daniel M.[1], Pushkarev, Dmitry[3], Neff, Norma F.[3], Passarelli, Benedetto[3], Koh, Winston[3], Ishizuka, Katherine J.[1,2], Palmeri, Karla J.[1,2], Dimov, Ivan K.[1], Keasar, Chen[4], Fan, Christina[3], Mantalas, Gary L.[3], Sinha, Rahul[1], Penland, Lolita[3], Quake, Stephen R.[3], Weissman, Irving L.[1,2]
[1]Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, CA, USA, [2]Department of Developmental Biology, Stanford University, Hopkins Marine Station, Pacific Grove, CA, USA, [3]Departments of Applied Physics and Bioengineering, Stanford University, Stanford, CA, USA, [4]Department of Computer Science, Ben-Gurion University of the Negev, Beer-Sheva, Israel

Botryllus schlosseri is a colonial urochordate that follows the chordate plan of development following sexual reproduction, but invokes a stem cell-mediated budding program during subsequent rounds of asexual reproduction. B. schlosseri exhibits a genetically determined natural transplantation reaction, whereby self-recognition between colonies leads to formation of parabionts with a common vasculature (fusion), whereas rejection occurs between incompatible colonies. Fusion/rejection in the colonies is controlled by a single gene: colonies fuse if they share one or both alleles, rejection occurs if there are no alleles in common. Following vasculature fusion, stem cells from each B. schlosseri colony compete to overtake germline and/or somatic lineages. Stem cell competition may lead to elimination of the other colony's genome, or may produce a chimeric colony with mixed genotypes. Using genetically defined lines, whole-transcriptome sequencing, and genomics, we analyzed the recently completed B. schlosseri genome (Voskobotnik et al., 2013; eLife) and identified a single gene, BHF, that not only encodes self/non-self recognition, but is the primary determinant of predatory stem cell activity by restricting fusion partners to kin (Voskoboynik/Newman et al., 2013; Science).

ECDYSONE AND MEDIATOR TRIGGER A METABOLIC SWITCH UNCOUPLING CELL CYCLE FROM CELL GROWTH TO END PROLIFERATION IN DROSOPHILA NEURAL STEM CELLS

Homem, Catarina C. F.[1], Steinmann, Victoria[1], Burkard, Thomas[1], Jais, Alexander[2], Esterbauer, Harald[2], Knoblich, Juergen A.[1]
[1]IMBA-Institute of Molecular Biotechnology, Vienna, Austria, [2]Department of Laboratory Medicine, Medical University Vienna, Vienna, Austria

The majority of stem cells disappear during development and

PROGRAM AND ABSTRACTS

only small populations remain in the adult animal. Thus stem cell number has to be tightly regulated during development, but the molecular mechanisms causing stem cells to exit proliferation at a specific time are not well understood. To address the mechanism triggering stem cell exit during development we used Drosophila neural stem cells, the neuroblasts. Neuroblasts proliferate rapidly during development but all exit cell cycle and disappear before adulthood. Our data indicates that changes in energy metabolism induced by the steroid hormone Ecdysone together with transcription regulator Mediator initiate an irreversible cascade of events leading to cell cycle exit in Drosophila neural stem cells. We find that a change in the levels of oxidative phosphorylation in neuroblasts leads to an uncoupling between cell cycle from cell growth. This results in a progressive reduction in neuroblast cell size and ultimately in terminal differentiation. Neuroblasts isolated from brain tumors fail to undergo this shrinkage process and this may explain why they are immortalized. We are able to show that cell size and stem cell proliferation control can be modified by systemic hormonal signaling and reveal a connection between metabolism and proliferation control in stem cells. Our data further indicates that energy metabolism is a causal regulator of cell fate.

IMAGING LIVE CELL DYNAMICS OF THE MUSCLE PROGENITOR CELL NICHE DURING ZEBRAFISH DEVELOPMENT

Nguyen, Phong Dang, Currie, Peter
Australian Regenerative Medicine Institute, Monash University, Melbourne, Australia

Vertebrate muscle is derived from the dermomyotome. In the zebrafish, the equivalent structure is known as the external cell layer (ECL). It is an environment where progenitors reside in to provide progenitors for muscle growth both during and after embryogenesis. Due to this, the balance between self-renewal and supplying progenitors must be highly controlled. It remains to be elucidated how this balance occurs within the ECL niche. We used live time-lapse imaging to show that the establishment of the ECL at the end of somitogenesis (1 day post-fertilization) involves a dynamic and diverse set of proliferation modes. These proliferation modes can be classified according to the orientation of the resulting daughter cells relative to the myosepta. Additionally, in vivo label retention studies show that the brightest ECL cells concentrate at the myosepta suggesting the presence of a quiescent niche within the ECL. The myosepta is an extracellular matrix (ECM) rich structure that provides attachment sites for muscle fibres. When we surveyed a number of mutants deficient in ECM proteins along the myosepta, we found that loss of integrin linked kinase caused the formation of exclusion zones along the vertical myosepta. This was accompanied with a loss of label retaining cells at the myosepta suggesting integrin signaling may play a role in maintaining quiescence at the ECL. By observing live cell dynamics of the stem cell niche during myogenesis, we are able to examine the dynamic behaviors of muscle progenitors, and aid in understanding how progenitors maintain their numbers during development.

POSTER TEASERS:

T-1022 RNA EXPRESSION PROFILING OF DROSOPHILA INTESTINAL CELL POPULATIONS REVEAL COMPARTMENTALIZATION AS A CONSEQUENCE OF DISTINCT REGIONAL STEM CELL SIGNATURES IN THE DROSOPHILA MIDGUT

Dutta, Devanjali[1], Buchon, Nicolas[2], Edgar, Bruce A.[1]
[1]Cell growth and proliferation, DKFZ-ZMBH Alliance, Heidelberg, Germany, [2]Department of Entomology, Cornell University, Ithaca, NY, USA

T-2008 GAP JUNCTION-MEDIATED SIGNALLING REGULATES PROLIFERATION AND DIFFERENTIATION OF SOMATIC CYST STEM CELLS IN THE DROSOPHILA TESTIS

Smendziuk, Chris, Islam, Fayeza, Messenberg, Anat, Tanentzapf, Guy
University of British Columbia, Vancouver, BC, Canada

T-2011 LINEAGE TRACING DEMONSTRATES THE EXISTENCE OF MULTI-FATED NEURAL CREST CELLS IN THE MOUSE EMBRYO

Baggiolini, Arianna[1], Varum, Sandra[1], Mateos, José María[2], Bettosini, Damiano[1], John, Nessy[1], Joyner, Alexandra L.[3], Ziegler, Urs[2], Goetz, Magdalena[4], Clevers, Hans C.[5], Furrer, Reinhard[6], Sommer, Lukas[1]
[1]Institute of Anatomy, University of Zürich, Zürich, Switzerland, [2]Center for Microscopy and Image Analysis, University of Zürich, Zürich, Switzerland, [3]Memorial Sloan-Kettering Cancer Center, New York, NY, USA, [4]Institute of Stem Cell Research, Helmholtz Zentrum Muenchen, Neuherberg/Munich, Germany, [5]Hubrecht Institute, Utrecht, Netherlands, [6]Institute of Mathematics, University of Zürich, Zürich, Switzerland

PROGRAM AND ABSTRACTS

CARDIAC REGENERATION VS FIBROTIC REPAIR: LESSONS FROM THE ZEBRAFISH

Huber, Nadia Mercader[1], Sánchez, Héctor[1], Marques, Ines[1], González-Rosa, Juan Manuel[2], Santamaría, Jose González[3], Rodríguez-Pascual, Fernando[3]

[1]Centro Nacional de Investigaciones Cardiovasculares, Spain [2]Cardiovascular Research Center, Massachusetts General Hospital/Harvard Medical School, USA, [3]Centro de Biología Molecular CBMSO-CSIC, Spain

Over a decade ago, the zebrafish was shown to be able of regrow the heart upon ventricular resection. Cardiomyocytes have been described to derive form pre-existent cardiomyocytes.During the postresection healing process, only minor collagen depositions are observed. Similarly, genetic ablation of up to 60 % of cardiomyocytes is also followed by complete regeneration. Again, in this injury model cardiac fibrosis does not precede regeneration. Is thus, cardiac regeneration in the zebrafish scarless? Our recent reports revealed that this is not the case. We and others described the use of cryoinjury (CI) as an alternative method for inducing cardiac injury in zebrafish. We found that, in contrast to the resection model, heart CI induced massive cell death and fibrotic scar formation, through the accumulation of myofibroblasts and ECM deposition. Importantly, in contrast to adult mammals, cardiac fibrosis in the zebrafish is reversible. We will present our findings on the origin and fate of myofibroblasts as well as the role of the extracellular matrix during cardiac regeneration. We believe that deciphering the sources, types and mechanisms of regression of myofibroblasts present during heart regeneration in the zebrafish, that allow the degradation of fibrotic tissue and its replacement by newly formed cells could have important implications for cardiac fibrosis reversion in humans.

FRIDAY, JUNE 20, 9:00 AM - 11:20 AM

PLENARY IV: BIOENGINEERING

PLENARY HALL

Supported By Burroughs Wellcome Fund

TISSUE ENGINEERING AND REGENERATIVE MEDICINE: CURRENT CONCEPTS AND CHANGING TRENDS

Atala, Anthony

Wake Forest University, USA

Patients with diseased or injured organs may be treated with transplanted tissues. There is a severe shortage of donor organs and tissues which is worsening yearly due to the aging population. Regenerative medicine and tissue engineering apply the principles of cell transplantation, material sciences, and bioengineering to construct biological substitutes that may restore and maintain normal function in diseased and injured tissues. Stem cells may offer a potentially limitless source of cells for tissue engineering applications and are opening new options for therapy. Recent advances will be reviewed. Clinical applications of these new technologies that may offer novel therapies for patients with tissue injury and organ failure will be described.

ENGINEERING SYNTHETIC MICROENVIRONMENTS TO GUIDE STEM CELL BEHAVIOR

Burdick, Jason A.

University of Pennsylvania, USA

Stem cells (e.g., mesenchymal stem cells, MSCs) respond to many cues from their microenvironment, which may include chemical signals, mechanics, and topography. Importantly, these cues may be incorporated into scaffolding to control stem cell differentiation and optimize their ability to produce tissues in regenerative medicine. Despite the significant amount of work in this area, the materials have been primarily static and uniform. To this end, we have developed a sequential crosslinking process that relies on our ability to crosslink functional biopolymers through numerous steps, including with light. With light exposure comes control over the material in space (via masks and lasers) and time (via intermittent light exposure). We are applying this technique for numerous applications, including towards the spatiotemporal control of stem cell fate through either the patterning of mechanical properties or controlling mechanical properties with time. As we move to more 3-dimensional environments, the influence of this range of signals becomes more complex. Specifically, features such as mechanical properties and the ability of cells to respond to these cues are dependent on the specific material formulation, such as the ability of a stem cell to degrade their environment and exert traction on their surroundings. In model systems, whether a cell can degrade and spread in a matrix or where cell spreading is restricted has led to osteogenesis or adipogenesis, respectively, through changes in the cell/material interface. Most recently, we are developing 3-dimensional fibrous systems that better mimic the organization of the extracellular matrix, where features such as fiber mechanics and degradation can also be controlled. Overall, these advanced hydrogels provide us the opportunity to investigate diverse and controlled material properties for a range of biomedical applications.

PROGRAM AND ABSTRACTS

EXPLORING AND ENGINEERING THE CELL-MATERIAL INTERFACE

Stevens, Molly
Imperial College London, UK

Bio-responsive nanomaterials are of growing importance with potential applications including drug delivery, diagnostics and tissue engineering. A disagreeable side effect of longer life-spans is the failure of one part of the body - the knees, for example - before the body as a whole is ready to surrender. The search for replacement body parts has fuelled the highly interdisciplinary field of tissue engineering and regenerative medicine. This talk will describe our research on the design of new materials to direct stem cell differentiation for regenerative medicine. This talk will also cover progress in state of the art materials analysis to better understand regenerated and native tissue properties. By applying multivariate analysis techniques to micro-Raman spectra of mineralized nodules, we reveal cell-source-dependent differences in interactions between multiple bone-like mineral environments. Understanding the biological mechanisms of bone formation that contribute to cell-source-specific materials differences may facilitate the development of clinically successful engineered bone. I will also discuss the application of nano-analytical electron microscopy techniques to bone and mineralisation in tissues to yield unique insights into these tissues.

DISTRIBUTED REGULATORY CONTROL OF STEM CELL IDENTITY AND FATE

Zandstra, Peter W.
University of Toronto, Canada

Functional tissue emerges from complex spatial-temporal interactions between heterogeneous cell populations. In this presentation I will review our efforts to establish an integrated understanding of the effects of cell type heterogeneity, spatial organization and multi-scale regulatory network engagement on defined and measurable stem cell fate transitions. Specific examples from somatic (blood) and pluripotent stem cell fate control will be highlighted.

Anne McLaren Memorial Lecture
SEX, STEM CELLS, PHYSIOLOGY AND POLICY

Lovell-Badge, Robin
MRC National Institute for Medical Research, UK

Understanding cell fate choice is a common goal in both developmental biology and stem cell research. Sex determination is a paradigm for understanding how such choices are made, where supporting cell precursors can become either granulosa cells typical of an ovary or Sertoli cells, which define and promote testis differentiation. These cells are essential to both nurture and direct differentiation of germ cells into oocytes and sperm, respectively. I will discuss our recent attempts to apply knowledge gained about how the supporting cell lineage develops and then makes a choice of fate to obtain Sertoli cells in vitro by both direct reprogramming of somatic cells and by directed differentiation from pluripotent cells in culture, which may allow efficient spermatogenesis in vitro. This will be a challenge, not only because it may be necessary to recapitulate aspects of the 3-D structure of the seminiferous tubule, but also because systemic factors that normally regulate the process will be missing. We have recently shown the importance of systemic factors acting on stem cells in the pituitary. The pituitary shows considerable plasticity, modulating hormone output according to demand, which can change significantly with "life-changing events", such as puberty, pregnancy, lactation, castration, and other types of trauma. The output can be modulated by hypothalamic control of hormone secretion by differentiated cells in the pituitary, by replication of these cells, or through the activation and differentiation of multipotent pituitary stem cells into the appropriate endocrine cell type according to systemic influence from a target organ, such as the adrenals or gonads. Recent data on how changes in physiology and systemic signals act on pituitary stem cells will be presented. Cell fate choices during development depend on a combination of intrinsic factors and external influences. The same is true for a scientist's career, and I was fortunate to have been influenced by Anne McLaren during a critical period of my scientific development. I am so grateful to Anne for encouraging me to study sex determination, and supporting my stem cell research, but also for introducing me to the value of engagement with issues of science policy. I will finish with a brief description of some of my involvement, and the importance of public dialogue, to help establish and maintain an appropriately regulated environment favourable for research on stem cells and embryos, which we largely have in the UK.

FRIDAY, JUNE 20, 1:15 PM - 3:05 PM

CONCURRENT IIIA: SENSORY SYSTEMS REPAIR
WEST MEETING ROOM 211-214

Schwartz, Steven
Jules Stein Eye Institute, USA

Not available at time of printing.

PROGRAM AND ABSTRACTS

RETINAL REGENERATION BY LGR5+ AMACRINE CELLS IN ADULT MAMMALS

Liu, Hongjun[1], Chen, Mengfei[2], Tian, Shenghe[1], Glasgow, Nathan[3], Gibson, Gregory[4], Yang, Xiaoling[1], Shiber, Christen[3], Nasonkin, Igor[1], Funderburgh, James[1], Watkins, Simon[4], Johnson, Jon[3], Schuman, Joel[1]

[1]Department of Ophthalmology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [2]Johns Hopkins University School of Medicine, Baltimore, MD, USA, [3]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA, [4]Center for Biologic Imaging, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Like other regions of the central nervous system, the retina is subject to degenerative diseases. Current common knowledge suggests that the retina of adult mammals lacks regenerative capacity. However, the retina of non-mammalian vertebrates, like fish and amphibians, possesses remarkable capacity of regeneration. Two major cell types in these lower vertebrates have been demonstrated to contribute to continuous retinal regeneration: cells of the ciliary marginal zone (CMZ) and Müller glial cells within the neuroretina. However, the CMZ is evolutionarily lost in mammals. Müller cells in mammalian retinas do not proliferate under normal physiological conditions, and they only possess limited regenerative potential in response to injury. Based on the anatomical similarity between the mammalian ciliary body and the lower vertebrate CMZ, a population of pigmented epithelial cells from the ciliary body was identified as the mammalian retinal stem cell a few years ago. Initial observations suggested these cells possess retinal stem cell properties, yet further analysis demonstrated that they could not differentiate into retinal neurons in vitro and in vivo. Therefore, whether the mammalian retina possesses regenerative capacity under normal physiological conditions still remains undetermined and if so, the cellular source that serves as the precursors for retinal regeneration in adulthood is also unknown.Using a genetic lineage tracing approach, we demonstrated that Lgr5, a marker of adult stem cells identified in high turnover tissues and organs, is expressed in a subgroup of retinal cells in adult mice. Despite exhibiting features of differentiated retinal amacrine interneurons, these Lgr5+ retinal cells can re-enter the cell cycle, proliferate and generate other retinal lineages, beginning in early adulthood and continuing as the animal ages. Together, these findings suggest that the retina in adult mammals is not devoid of regeneration as previously thought. Rather, it is plastic and Lgr5+ amacrine cells contribute to its homeostatic maintenance, functioning as the putative mammalian adult retinal stem cell. The identification of such cells provides novel insight into neuronal regeneration and new therapeutic strategies for degenerative retinal diseases.

DEVELOPING AUTOLOGOUS CELL THERAPY FOR MACULAR DEGENERATION USING IPS CELL DERIVED RPE TISSUE: A MODEL FOR PUBLIC-PRIVATE PARTNERSHIP

Bharti, Kapil[1], Davis, Janine[1], Maminishkis, Arvydas[1], Hartford, Juliet[1], Khristov, Vladimir[1], Silver, Jason[2], Wan, Qin[1], Miyagishma, Kiyoharu[1], Lotfi, Mostafa[1], Sharma, Ruchi[1], Amaral, Juan[1], **Miller, Sheldon S.[1]**

[1]National Eye Institute, Bethesda, MD, USA, [2]Boulder Medical School, Boulder, CO, USA

The recent success with embryonic stem (ES) cell derived retinal pigment epithelium (RPE) has provided hope for a treatment for degenerative eye diseases. Induced pluripotent stem (iPS) cells are an alternate and an autologous source of stem cells with fewer immune-challenges as compared to ES cells. Using a developmentally guided differentiation protocol that involves manipulation of RPE primary cilium, we have developed protocols to generate fully polarized RPE tissue using iPS cells at a high efficiency. The RPE monolayer along with its secreted ECM and the scaffold form a tissue that well mimics native tissue. This tissue has been functionally authenticated in vitro for its ability to perform several key RPE functions and is being tested in animal models. We have begun developing an Phase I Investigational New Drug (IND) to transplant autologous iPS cell derived RPE in patients in advanced Geographic Atrophy stage of age-related macular degeneration (AMD), one of the leading blinding diseases in the US. We propose to develop National Institutes of Health Clinical Center as an "alpha-stem cell clinic" with the capability to recruit patients, manufacture clinical-grade autologous iPS cell derived RPE tissue, perform transplantation, do patient care, and be able to transfer technology to academic and private sectors. We suggest that our open access model with complete access to the entire IND package will reduce redundant efforts in the field, foster public-private partnerships, and help move ocular regenerative medicine field forward.

PROGRAM AND ABSTRACTS

TRANSCRIPTIONAL CONTROL OF SENSORY VERSUS NON SENSORY PROGENITOR SPECIFICATION IN THE INNER EAR

Cheah, Kathryn[1], Leung, Keith[1], Kwong, Michael[1], Niu, Ben[1], Pelling, Anna[1], Jahan, Israt[2], Fritzsch, Bernd[2], Lovell-Badge, Robin[3]

[1]Department of Biochemistry, Li Ka Shing Faculty of Medicine, University of Hong Kong, Hong Kong, [2]Department of Biology, University of Iowa, Iowa City, IA, USA, [3]Division of Stem Cell Biology and Developmental Genetics, National Institute for Medical Research, London, United Kingdom

Development of the inner ear requires coordination of early specification, in the correct location, of specific cell types: sensory hair cells, non-sensory supporting cells and sensory neurons that innervate the hair cell. These cells are essential for hearing and balance, acting as mechanosensors for the detection of sound (cochlear region), gravity and acceleration (vestibular region) which are transmitted to the central nervous system. Sensory and non-sensory structures in the functional inner ear are specified early in development, before any overt structure can be seen, according to the spatial location of progenitors within the epithelium of an initial sphere of cells (otocyst). It is thought that the six sensory organs in the inner ear develop from common progenitors in the otic epithelium.

We previously discovered that Sox2 is essential for hearing and balance through studying two allelic mouse mutants with recessive deafness and balance-impairment, Light coat and circling (Lcc/Lcc, completely deaf) and Yellow submarine (Ysb/Ysb, severely hearing impaired). We showed that Sox2 is essential for the prosensory and sensory precursors in the inner ear starting from the otocyst stage. In Lcc/Lcc inner ears, all six sensory regions were absent, neither hair cells nor supporting cells differentiate, while the sensory epithelium was severely disrupted in Ysb/Ysb. These phenotypes are due to the severely reduced (Lcc/Lcc) or reduced (Ysb/Ysb) expression of Sox2, specifically within the developing inner ear. We asked whether Sox2 is also essential for specifying the progenitors for the sensory neurons that innervate the hair cells. We found a temporal and dose-dependent requirement for Sox2 in the specification of and/or maintenance of the otic neuroblasts during neurogenesis. Our studies implicate Sox2 as the master specifier for progenitors of the three lineages (sensory neurons, hair cells and supporting cells). We also asked how sensory versus non-sensory fate was controlled in the inner ear. We found Sox2 and BMP/TGFβ signaling function antagonistically to coordinate development of sensory and non-sensory structures in the correct location in the inner ear.

POSTER TEASERS:

F-3006 DECIPHERING THE SPATIAL AND DYNAMIC GENETIC REGULATION OF THE MOUSE OLFACTORY BULB NEUROGENESIS

Beclin, Christophe[1], Wild, Stefan[2], Mahnoun, Yann[1], Bosio, Andreas[3], Cremer, Harold[1]

[1]CNRS-IBDM, Marseille, France, [2]Miltenyi Biotec, Bergisch Gladbach, Germany, [3]Miltenyi Biotec GmbH, Bergisch Gladbach, Germany

F-1039 MICROARRAY ANALYSES OF COCHLEA-DERIVED OTOSPHERES REVEAL PUTATIVE TRANSCRIPTION FACTORS WHICH REGULATE CHARACTERS OF THE OTOSPHERES

Iki, Takehiro, Tanaka, Michihiro, Saito, Megumu, Fujibuchi, Wataru, Nakahata, Tatsutoshi

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

F-2042 INDUCTION OF INNER EAR HAIR CELL LIKE CELLS FROM TRANSCRIPTION FACTOR MATH1-TRANSFECTED MOUSE EMBRYONIC STEM CELLS

Yoshikawa, Masahide, Ouji, Yukiteru, Nakamura-Uchiyama, Fukumi, Wanaka, Akio

Nara Medical University, Kashihara, Japan

COCHLEAR HAIR CELL GENERATION FROM LGR5-POSITIVE SUPPORTING CELLS

Edge, Albert

Massachusetts Eye and Ear Infirmary, USA

The vestibular and auditory organs have a limited ability to replace damaged cells, but our laboratory has recently identified cells in the cochlear sensory epithelium with stem cell properties. Located in the organ of Corti, this epithelium consists of hair cells, the receptor cells for sound, and surrounding supporting cells. In contrast to the lack of regeneration in untreated ears, cochlear cells showed a capacity for hair cell replacement when treated with a gamma-secretase inhibitor. Inhibition of Notch signaling within the epithelium by the drug following damage to the cochlea resulting from exposure to noise increased expression of transcription factor, Atoh1. New hair cells were seen after damage. This is the first time that hair cell regeneration has been seen in vivo in postnatal animals. The cells that gave rise to the hair cells were identified by lineage tracing studies, following in vitro Notch inhibition, as supporting cells that expressed Lgr5, a downstream target of the Wnt pathway and a protein that marks intestinal epithelial stem

cells. Whereas all supporting cells express Sox2, a specific subset expresses Lgr5. Cochlear Lgr5-expressing supporting cells after isolation by flow cytometry gave rise to self-renewing neurospheres that could be induced to differentiate to hair cells. Lgr5-positive cells had distinct phenotypes from other supporting cells and differentiated to hair cells at a higher rate than the total Sox2-positive supporting cells, consistent with these cells playing a role as hair cell progenitors. Hair cells did not differentiate from Lgr5-negative cells. Upregulation of Wnt signaling specifically targeted the Lgr5-expressing cells, leading to proliferation in the postnatal ear, and the cells transdifferentiated to hair cells. Thus, in response to manipulation of signaling pathways, Lgr5-expressing cells of the cochlear epithelium have a unique capacity to proliferate and differentiate and can lead to hair cell replacement and hearing restoration.

CONCURRENT IIIB: MODELING DISEASE WITH IPSCS

WEST BALLROOM C/D

Supported By Cellular Dynamics International

CARDIAC AND VASCULAR DISEASE MODELED BY (ISOGENIC PAIRS OF) HUMAN PLURIPOTENT STEM CELLS

Mummery, Christine L.[1], Atsma, D.[1], Bezzina, C.[2], Casini, S.[1], Davis, R.[1], Laugwitz, K.[3], Orvola, V.[1], Verkerk, A.[1]

[1]Leiden University Medical Center, Netherlands, [2]Amsterdam Medical Centre, The Netherlands, [3]University of Munich, Germany

Cardiomyocytes and vascular endothelial cells can now be derived efficiently from human pluripotent stem cells under defined culture conditions providing new opportunities for modeling disease and determining relevant drug responses. We have created isogenic pairs of hPS cell lines, either as hiPSC from patients with mutations in cardiac ion channels in which the defect has been repaired, or by introducing targeted mutations into healthy hESC. The phenotype is evident as altered electrophysiological and drug responses and the underlying mechanism revealed as a problem of protein trafficking to the cell surface. Nevertheless, the phenotypic differences between cardiomyocytes with and without the mutation are surprisingly small, illustrating the potential impact of genetic background on correctly attributing phenotypes to specific mutations. In addition, more than one cells type may be required to reveal disease phenotypes. As an example, vascular endothelial cells (ECs) derived from patients with a vascular disease caused by mutations in endoglin, a gene expressed in ECs but not smooth muscle cells, we show that the additional presence of smooth muscle cells is required to reveal the phenotype. Together, these examples show that both genetic background and the presence of other relevant cell types may be necessary to reveal subtle cardiac and vascular disease phenotypes in cells which may be relatively immature in culture.

HUMAN IPSC-BASED MODELLING OF ENDOTHELIAL DYSFUNCTION

Patsch, Christoph[1], Urich, Eduard[1], Thoma, Eva[1], Challet Meylan, Ludivine[2], Heckel, Tobias[1], Christensen, Klaus[1], Prummer, Michael[1], Jakob-Roetne, Roland[1], Dernick, Gregor[1], Burcin, Mark[1], He, Wei[1], Huang, Paul[3], Freskgård, Per-Ola[1], Kling, Dorothee[1], Cowan, Chad[2], Graf, Martin[1], Iacone, Roberto[2]

[1]Hoffmann - Roche, Basel, Switzerland, [2]HSCRB, Harvard University Cambridge, MA, USA, [3]Harvard Medical School, Boston, MA, USA

The use of human pluripotent stem cells (PSCs) for in vitro disease-modeling and clinical applications is limited by the lack of robust and efficient protocols for the differentiation of relevant adult cell types.

Herein, we report a scalable monolayer protocol to induce vascular cells in chemically defined conditions utilizing a new GSK3beta inhibitor. Within six days we generated large cell populations that are highly enriched for endothelial cells (VE-Cadherin+ >=85%). We isolated VE-cadherin+ cells by magnetic activated cell sorting (MACS) to ensure pure and homogenous endothelial cell cultures (>=98%). Time-resolved whole-genome expression and selective qRT-PCR analysis revealed a gene expression pattern closely resembling early embryonic vasculogenesis. Overall the purified VE-Cadherin+ cells present an endothelial-specific expression pattern; positive for PECAM-1+, CD34+, VE-Cadherin+, vWF+, CXCR4+, VEGFR2+, VEGFR3+ and negative for the hematopoetic lineage markers CD45-, CD43- and for the smooth muscle cell markers PDGFRβ-, SMA- The endothelial cell population maintained their cellular identity over the period of cultivation.

Further characterizations of VE-Cadherin+ cells, confirm a functional endothelial phenotype. Stem cell-derived endothelial cells give rise to continuous endothelium with dynamic barrier function properties, form vascular network-like structures in angiogenesis assays, and convert into activated endothelium after treatment with pro-inflammatory cytokines. Activated endothelium facilitated the recruitment of co-cultured leukocytes and secreted several mediators associated with impaired endothelial function/inflammation such as pro-inflammatory cytokines, Endothelin1, Plasminogen activator inhibitor-1, soluble Cellular Adhesion Molecules and Selectins.

This novel and robust method allowed us to reproducibly generated large numbers of homogenous endothelial cells from more than 20 different PSC lines including disease-specific lines from patients

PROGRAM AND ABSTRACTS

that have vascular complication associated with Type 2 Diabetes. Interestingly, in comparative transcriptome and secretome assays of stem cell-derived ECs from different iPS clones clustered according to their genetic background. Implying that the cell-specific expression pattern is due to the individual genetic background and not caused by process variability of cellular reprogramming and directed endothelial cell differentiation. With the growing need for defined protocols, our differentiation system may become the standard for deriving endothelial cells at relevant scales appropriate for drug discovery campaigns and regenerative therapies.

DIRECTED DIFFERENTIATION OF FUNCTIONAL CHOLANGIOCYTES FROM HUMAN PLURIPOTENT STEM CELLS

Ogawa, Shinichiro[1], Ogawa, Mina[2], Bear, Christine[3], Ahmadi, Saumel[3], Chin, Stephanie[3], Kamath, Binita M.[4], Ghanekar, Anand[5], Keller, Gordon M.[2]

[1]McEwen Centre for Regenerative Medicine, Toronto, ON, Canada, [2]McEwen Centre for Regenerative Medicine Ontario Cancer Institute, Toronto, ON, Canada, [3]Molecular Structure and Function, The Hospital for Sick Children, Toronto, ON, Canada, [4]Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children and the University of Toronto, Toronto, ON, Canada, [5]Division of General Surgery, University Health Network, Toronto, ON, Canada

The development of protocols for the efficient generation of hepatic cell types from human embryonic and induced pluripotent stem cells (pluripotent stem cells; PSCs) has paved the way for establishing in vitro models of liver development and disease and for designing new platforms for drug discovery and predictive toxicology. Disorders involving the biliary tract including cystic fibrosis (CF) and Alagille syndrome are common causes of chronic liver disease that result in significant morbidity and often require whole organ transplantation for definitive management. To be able to model such diseases in vitro, we developed a strategy for the efficient generation of hPSC-derived cholangiocytes, the cells that form the biliary system. The cholangiocyte lineage derives from a bipotential fetal progenitor known as the hepatoblast and is specified through a Notch dependent signaling event. To identify the hPSC-derived hepatoblast stage of development, we monitored differentiating populations induced with our recently described hepatic protocol (Ogawa et al, Development, 2013) for markers indicative of these bi-potential progenitors including (ALB), alpha fetoprotein (AFP) and cytokeratin 19 (CK19). At day 25 of culture, the majority of the cells (>90%) in the differentiating population were found to express these markers indicating that they represent hepatoblasts. To promote cholangiocyte development, the day 25 progenitors were cultured in a 3D-gel together with OP9 stromal cells as a source of Notch signaling. These conditions promoted cholangiocyte specification and the formation of cysts consisting of CK19+ALB- epithelial cells surrounding a central lumen, indicative of the early stages of duct formation. Mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) result in CF that affects the function of many different tissues including the biliary epithelium. Analyses of the hPSC-derived cysts revealed that the cells express CFTR, and that protein is predominantly restricted to the apical side of the structures, a pattern similar to that in the mature bile duct. Treatment of the cysts with the combination of Forskolin and IBMX (F/I) resulted in CFTR-mediated transport of fluid and a measurable swelling of the cysts, indicating that the CFTR protein was functional. In contrast to those from wild-type hPSCs, cysts generated from a CF patient (deltaF508 mutation) iPSCs did not show the same degree of swelling following F/I treatment, consistent with the interpretation that this response is dependent on functional CFTR protein. Addition to the culture of two chemical correctors of CFTR, VX-809, currently in clinical trials for the treatment of CFTR patients and Corr-4a increased the amount of detectable protein at the cell surface and significantly increased the extent of F/I induced swelling. Taken together, these findings demonstrate that it is possible to generate functionally mature human cholangiocytes and biliary ductal-like structure from hPSCs and to use these derivative cell types to model a biliary disease such as that caused by cystic fibrosis.

IPSC-BASED MODELING OF HUMAN NOTCH1 MUTATIONS REVEALS NOVEL PATHWAYS REGULATING AORTIC VALVE DISEASE

Theodoris, Christina V., White, Mark P., Li, Molong, Liu, Lei, He, Daniel, Pollard, Katherine S., Bruneau, Benoit, Srivastava, Deepak

Gladstone Institute of Cardiovascular Disease and University of California, San Francisco, San Francisco, CA, USA

In humans, NOTCH1 mutations result in congenital heart defects including valve malformations and severe valve calcification in adults. To understand the mechanisms by which NOTCH1 mutations in endothelial cells (ECs) cause disease, we generated episomally induced pluripotent stem cell (iPSC) lines from fibroblasts of four individuals from two families affected with aortic valve disease due to heterozygous non-sense mutations in NOTCH1. We differentiated control and mutant iPSC lines into ECs using a differentiation protocol developed in our lab. We exposed the ECs to either static or fluid shear stress conditions to model the aortic or ventricular side of the valve, respectively. NOTCH1 mRNA levels were decreased in the NOTCH1+/- ECs in both static and shear stress conditions. Of the NOTCH1 transcripts sequenced in heterozygote ECs, 86-93% were transcribed from the wild-type copy of NOTCH1, suggesting that the mutant mRNA was likely degraded by nonsense-mediated decay. RNA-seq results

indicated that 165 genes were differentially expressed in static conditions and 193 genes responded abnormally to shear stress in NOTCH1+/- ECs compared to NOTCH1+/+ ECs. Differentially expressed genes included canonical NOTCH1 targets HRT2 and EFNB2 as well as novel targets involved in vascular development, inflammation, and endochondral ossification. Overall, gene ontology terms significantly overrepresented in differentially expressed genes included cardiovascular development and response to wounding, suggesting that the NOTCH1+/- ECs were unable to mount the normal developmental and protective response to shear stress in the valve. Generating genetically matched NOTCH1+/+ and NOTCH1+/- cell lines using TALen genome editing identified genes specifically dysregulated due to NOTCH1 heterozygosity rather than differentially expressed due to genetic background and showed rescue of this dysregulation in TALen-corrected NOTCH1+/+ ECs. We have mapped the gene networks dysregulated in NOTCH1+/- ECs as determined by NOTCH1 ChIP-seq, differentially methylated regions of DNA, and genome-wide differences in the progression of activating and repressive chromatin states that begin to explain the mechanisms by which heterozygosity of a transcription factor leads to disease-specific changes. Determining the consequence of NOTCH1 heterozygous mutations in human patient-specific ECs will greatly increase our understanding of the role NOTCH1 plays in aortic valve calcification and may reveal novel targets for intervention.

POSTER TEASERS:

F-2243 THE DISCUSS PROJECT: INDUCED PLURIPOTENT STEM CELL LINES FROM PREVIOUSLY COLLECTED RESEARCH BIOSPECIMENS AND INFORMED CONSENT

Isasi, Rosario[1], Lomax, Geoffrey[2], Hull, Sara Chandros[3], Lowenthal, Justin[4], Rao, Mahendra[5]

[1]Centre of Genomics and Policy, McGill Univ, Montreal, QC, Canada, [2]CIRM, San Francisco, CA, USA, [3]NHGRI Bioethics Core, National Institutes of Health, Bethesda, MD, USA, [4]Department of Bioethics, National Institutes of Health, Bethesda, MD, USA, [5]NIH Center for Regenerative Medicine, Bethesda, MD, USA

POSTER TEASERS (cont'd):

F-2222 USING INDUCED PLURIPOTENT STEM CELL TECHNOLOGY TO MODEL AND TREAT IDIOPATHIC PULMONARY FIBROSIS

Vijayaraj, Preethi[1], Mehrabi, Mehrsa[2], Chung, Katherine[1], Kuo, Alan[1], Zhang, Kelvin[3], Darmawan, Kelly[3], Manze, Chase[1], Karumbayaram, Saravanan[4], Damoiseaux, Robert[1], Malone, Cindy[2], Gomperts, Brigitte[5]

[1]Pediatrics, University of California, Los Angeles, CA, USA, [2]Biology, California State University, Northridge, CA, USA, [3]University of California, Los Angeles, CA, USA, [4]Broad Stem Cell Research Center at UCLA, Los Angeles, CA, USA, [5]Mattel Children's Hospital UCLA, Los Angeles, CA, USA

MODELING HUMAN NEUROLOGICAL AND PSYCHIATRIC DISEASE IN VITRO

Gage, Fred H.[1], Boyer, Leah F.[1], Mertens, Jerome[1], Wright, Rebecca[1], Kim, Hyung Joon[1], Kim, Yongsung[1], Brennand, Kristen J.[2], Bardy, Cedric[1], Erwin, Jennifer A.[1], Paquola, Apua C.[1], Kerman, Bilal[1], Narvaiza, Inigo[1], Marchetto, Maria C.[1]

[1]Salk Institute for Biological Studies, USA; [2]Icahn School of Medicine at Mount Sinai, USA

Most of the studies of human brain and neuronal function in neurological and psychiatric patients have been performed on postmortem tissues that were not always well preserved and often represented the end-stage of the disease. In addition, mouse models available to study neurological diseases are limited and usually do not fully recapitulate the human neural phenotype. The advent of iPSCs provided an important tool for the study of human neurodegenerative and neurodevelopmental diseases in live human neurons in a controlled environment. Researchers are just beginning to grasp the many implications of studying developing neurons from patients. For example, reprogramming cells from patients with neurological diseases allows the study of molecular pathways particular to specific subtypes of neurons (ex: Hippocampal neurons in Autism); such an experiment can only be done using neurons differentiated from programed or reprogrammed somatic cells, as it is too invasive to isolate these neurons from patients' brains. In addition, because reprogramming technology allows for the study of human neurons during development, disease-specific pathways can be investigated prior to and during disease onset. Detecting disease-specific molecular signatures in live human neurons, as opposed to late stage post-mortem tissues, opens possibilities for early intervention therapies and new diagnostic tools. Importantly, it is now feasible to obtain neurons that capture the genetic material from the patient, which includes not only the mutated gene(s) - if the gene is known - but

PROGRAM AND ABSTRACTS

also the genetic modifiers that play an important but yet largely unknown role in the pathology of neurological and Psychiatric diseases. We will present examples of recent insights gained from this approach.

CONCURRENT IIIC: DIABETES

WEST BALLROOM A

Supported By Sanofi US

EPIGENOMIC PRINCIPLES OF PANCREATIC LINEAGE COMMITMENT AND BETA-CELL DIFFERENTIATION

Sander, Maike
University of California San Diego, USA

Converting human pluripotent stem cells (hPSCs) into functional pancreatic insulin-producing β-cells has proven difficult. Likewise, methodology for direct reprogramming of fibroblasts into β-cells is still lacking. To gain a comprehensive understanding of the cell-intrinsic mechanisms that underlie programming of the pancreatic lineage and β-cells, we generated genome-scale maps of gene transcription and chromatin modifications during the stepwise differentiation of hPSCs toward the β-cell lineage. Building on these maps, we investigated epigenetic mechanisms of gene activation associated with pancreatic lineage commitment and β-cell differentiation. We found that chromatin patterns are highly informative for identifying functionally related genes and that epigenetic information facilitates the identification of novel regulators of pancreatic endocrine cell development. We further observed that chromatin remodeling at distal gene regulatory elements precedes the activation of associated target genes and show that specific histone modifications serve as predictors for the cell's ability to respond to extrinsic differentiation cues. The mapping of active distal gene regulatory elements during pancreatic lineage progression also provided novel insight into transcription factors that drive pancreatic endocrine lineage specification. These novel insights will be used to guide the design of improved hPSC differentiation and direct reprogramming strategies toward the β-cell lineage.

IN VITRO GENERATION OF PANCREATIC BETA CELLS FROM HUMAN PLURIPOTENT STEM CELLS

Millman, Jeffrey Robert, Pagliuca, Felicia W., Gurtler, Mads, Segel, Michael, Van Dervort, Alana, Ryu, Jennifer H., Peterson, Quinn, Melton, Douglas A.
Harvard Stem Cell Institute, Harvard University, Cambridge, MA, USA

Numerous reports by us and others have shown that insulin-producing cells differentiated from human pluripotent stem cells in vitro are similar to fetal cells and lack many of the hallmarks of β cells, in particular secretion of appropriate amounts of insulin to high glucose stimulation, appropriate gene expression, and rapid function after transplantation. We have developed a scaleable, suspension-based differentiation protocol using defined factors and are tackling this challenge in human embryonic and induced pluripotent stem cells. Here I report our progress on making β cells in vitro that can respond to multiple high glucose challenges, support my findings with multiple assays, including animal studies, and show proof-of-concept experiments in drug screening.

CHEMICAL GENETIC IDENTIFICATION OF SIGNALS THAT CONTROL LATE-STAGE PANCREATIC BETA CELL DIFFERENTIATION

Kume, Shoen
Stem Cell Biology, Institute of Molecular Embryology and Genetics, Kumamoto Univ, Kumamoto, Japan

Embryonic stem (ES) cells and induced pluripotent stem (iPS) cells have virtually unlimited replicative capacity and the potential to differentiate into most cell types, including pancreatic cell lineages. Although many researchers have reported differentiation procedures for pancreatic cell lineages from ES cells or iPS cells, it is still challenging to efficiently guide ES into functionally mature insulin-secreting cells.

Recently, we performed a high-throughput screening of low molecular weight chemical compounds and identified candidate chemical compounds that potentiated differentiation into pancreatic beta cells. I would like to introduce our assay system and discuss our results using shRNA to identify the candidate target molecules of the hit compounds. We identified vesicular monoamine transporter 2 (VMAT2) -monoamines as negative regulators of late-stage differentiation of Pdx1-positive pancreatic progenitor cells into Neurog3-positive endocrine precursors. The VMAT2 inhibitors acted additively with a cell-permeable cAMP analog, dBu-cAMP, to potentiate differentiation of ES cells into beta cells that exhibited glucose-stimulated insulin secretion. Upon engraftment into AKITA diabetic mice, the ES cell-derived cells reversed hyperglycemia. Our results indicate that molecular

compounds are useful tool to identify unknown mechanism underlying the differentiation into endocrine beta cells.

IPSC-DERIVED ENDOTHELIAL CELLS REPRODUCE INSULIN RESISTANCE AND ENDOTHELIAL DYSFUNCTION IN VITRO

Carcamo-Orive, Ivan[1], Cundiff, Paige[2], D'Souza, Sunita[2], Shahbazi, Mohammad[1], Huang, Qi[1], Lancero, Hope[1], Hendry, Carolin[2], Sevilla, Ana[2], Abassi, Fahim[1], Reaven, Gerald M.[1], Whalen, Sean[3], Pandey, Gaurav[3], Schadt, Eric[3], Lemischka, Ihor R.[2], Knowles, Josh[1], Quertermous, Thomas[1]

[1]Cardiovascular Medicine, Stanford School of Medicine, Stanford, CA, USA, [2]Department of Developmental and Regenerative Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA, [3]Department of Genetics and Genomics, Institute of Genomics and Multiscale Biology, Icahn School of Medicine at Mount Sinai, New York, NY, USA

Insulin resistance (IR) is a major health issue in western countries and a risk factor for the development of cardiovascular disease. The vasculature of insulin resistant individuals shows a set of common features, mainly defined by a reduction in the bioactivity of nitric oxide, an increase in reactive oxygen species production and a chronic pro-inflammatory state. However, the role of insulin resistance at the level of the endothelial cell in vascular pathophysiology is unclear and the molecular pathways that drive the appearance of IR are still elusive. Through the GENESIPS project we have established a cohort of iPSC lines (97 patients, 3 to 6 lines per patient) from individuals that reflect all the array of insulin response in the general population. In addition, genome-wide genotyping data previously obtained from those patients is available. In the present study we aim to validate our *in vitro* model and study the molecular pathways that define both insulin resistance appearance and its relationship to endothelial dysfunction.

In a preliminary study, we have analyzed the RNA profile of insulin resistant vs. insulin sensitive (IS) iPSCs. By means of RNAseq technology we have performed a differential expression analysis with SAM (FDR<5%) in 99 lines from 27 patients (13 IR, 14 IS). We have discovered a set of 467 genes up-regulated in IR iPSCs vs. 627 genes up-regulated in IS iPSCs. Interestingly, some of the enriched pathways in IS iPSCs include for insulin signaling pathway, insulin receptor signaling and diabetes associated genes. On the other hand IR iPSCs show an up-regulation in pathways related to glucose and carbohydrate metabolism, gluconeogenesis and lipid and fatty acid metabolism, among others. We plan to extend this analysis to iPSC-derived endothelial cells.

We have successfully generated endothelial cells from several iPSC lines from multiple individuals (4 IR, 4 IS) with varying degrees of insulin sensitivity as measured by the insulin suppression test. iPSCs and endothelial cells (but not primary fibroblasts) from insulin resistant individuals have a decreased response to insulin compared to insulin sensitive individuals as assessed by phospho-AKT activation. Additional signaling molecules (insulin receptor, ERK1/2) demonstrate a defective activation in IR iPSCs when exposed to insulin. Moreover, iPSC-derived endothelial cells (but not fibroblasts or iPSCs) from insulin resistant individuals show an increased response to pro-inflammatory signals (TNF-α), reflecting a potential endothelial cell dysfunction. Taken together, our results suggest that both iPSCs and their differentiated progeny reproduce the insulin sensitivity profile of the patient to allow the *in vitro* modeling of a multifactorial disease like insulin resistance. Our work highlights the differential insulin and pro-inflammatory signal response in distinct cell types (fibroblasts-iPSCs-endothelial cells) from IS vs. IR patients and paves the way for a deep understanding of the insulin resistance mediated endothelial dysfunction.

POSTER TEASERS:

T-1086 ANTI-OBESE HORMONE ADIPONECTIN REGULATES EMERGENCY HEMATOPOIESIS AND ANTIBACTERIAL RESPONSE THROUGH SUPPRESSION OF TNF-ALPHA PRODUCTION IN BONE MARROW AND DOWNREGULATION OF SOCS3 IN HEMATOPOIETIC STEM/PROGENITOR CELLS

Masamoto, Yosuke[1], Arai, Shunya[1], Sato, Tomohiko[1], Yoshimi, Akihide[1], Takamoto, Iseki[2], Kubota, Naoto[2], Kadowaki, Takashi[2], Kurokawa, Mineo[1]

[1]University of Tokyo Hospital, Department of Hematology/Oncology, Tokyo, Japan, [2]University of Tokyo Hospital, Department of Diabetes and Metabolic Diseases, Tokyo, Japan

F-2022 ENDOCRINE SPECIFICATION AND MATURATION OF HUMAN PLURIPOTENT STEM CELL-DERIVED PANCREATIC PROGENITORS

Sackett, Sara Dutton, Li, Grace, Tremmel, Dan, O'Brien, Cori, Nair, Gopika, Xu, Xiaofang, Odorico, Jon S.

Surgery, University of Wisconsin, Madison, WI, USA

F-3094 CHARACTERIZATION OF MICRORNAS EXPRESSION PROFILING OF IN VITRO DE-DIFFERENTIATED HUMAN PANCREATIC ISLET CELLS

Sebastiani, Guido, Ventriglia, Giuliana, Nigi, Laura, Mancarella, Francesca, Valentini, Marco, Dotta, Francesco

Diabetes Unit, Fondazione Umberto Di Mario ONLUS - University of Siena, Siena, Italy

PROGRAM AND ABSTRACTS

GENERATION OF PANCREATIC PROGENITOR CELLS FROM HUMAN PLURIPOTENT STEM CELLS

Nostro, M. Cristina
McEwen Centre for Regenerative Medicine, Canada

The destruction of pancreatic β-cells by the immune system leads to type I diabetes. The current treatment for this devastating disease is insulin injection. While effective, it is not a perfect substitute to continuous insulin release by one's own β-cells. Recent improvements and successes in islet transplantation for the treatment of type I diabetes demonstrate that cell therapy could become a reality in the management of this disease. However, the low number of islets obtainable from donors limits their therapeutic use. The generation of β-cells from human embryonic and induced pluripotent stem cells (hESCs, hiPSCs) differentiated in culture offers a potential novel and unlimited source of insulin-producing cells for transplantation for the treatment of this disease. I will present our recent data elucidating the signaling pathways leading to the generation of multi-potent pancreatic progenitors from human pluripotent stem cells and their capacity to generate functional beta cells in vivo.

CONCURRENT IIID: EPIGENETICS

WEST BALLROOM B

Supported by Nature Publishing Group

TRANSCRIPTIONAL REGULATION OF CARDIAC CELL FATE

Boyer, Laurie
Massachusetts Institute of Technology, USA

Heart development depends critically on precise spatial and temporal control of gene expression patterns, and disruption of transcriptional networks underlies congenital heart disease (CHD). We currently lack a detailed understanding of the epigenetic control mechanisms that coordinate gene expression programs during mammalian developmental transitions. To this end, we interrogated the transcriptome and several histone modifications across the genome during several defined stages of in vitro cardiomyocyte (CM) differentiation. We find that distinct chromatin patterns are coordinated with stage-specific expression of functionally related genes, including many cardiac disease-associated genes. Using chromatin modification patterns, we also identify thousands of stage-specific distal enhancer elements and find enriched DNA binding motifs within these regions that predict sets of transcription factors that orchestrate cardiac differentiation. Long non-coding RNAs (lncRNAs) have recently emerged as an additional regulatory layer of gene expression in part through interaction with chromatin modifiers. We show that lncRNAs display stage specific expression during CM differentiation and identify Braveheart, a novel lncRNA that is necessary for activation of a core network of cardiovascular transcription factors through interaction with Polycomb group proteins. Together, our work demonstrates the diverse transcriptional mechanisms that cells employ to regulate cell fate and forms a basis for improving methods for stem cell derived cardiomyocytes for replacement therapy.

EPIGENETIC STATE REGULATING COMPETENCE OF THE IN VIVO POST-IMPLANTATION MOUSE EPIBLAST

Zylicz, Jan Jakub[1], Dietmann, Sabine[2], Lee, Caroline[1], Nichols, Jennifer[2], Surani, Azim[1]
[1]Gurdon Institute and Stem Cell Institute, University of Cambridge, Cambridge, United Kingdom, [2]Stem Cell Institute, University of Cambridge, Cambridge, United Kingdom

TCell fate decisions of the embryonic lineages occur shortly after implantation at the onset of gastrulation at embryonic day (E)~6.5 soon after the primed pluripotent epiblast cells acquire competence for the somatic and germ cell fates. The precise transcriptional and epigenetic mechanisms leading to the formation of this short-lived competent state are yet to be fully elucidated. Amongst the candidates possibly involved in this process are chromatin marks that accumulate during implantation: DNA methylation and H3 lysine 9 dimethylation (H3K9me2). Genetic experiments revealed that the polycomb mark, H3K27me3, is also involved in regulating the onset of gastrulation. To examine the role these epigenetic modifications in vivo, we optimised a protocol for low cell-number chromatin immunoprecipitation followed by next generation sequencing (lcChIP-seq). We have combined the data for H3K9me2 and H3K27me3, with that for DNA methylation and gene expression. In doing so, we have generated a comprehensive epigenetic and transcriptional characterisation of the in vivo E6.25 epiblast and in vitro epiblast stem cells (EpiSCs). This study has revealed not only the mutually exclusive character of H3K9me2 and H3K27me3 but also their correlation with DNA methylation levels. Importantly, H3K9me2 in the epiblast marks regulatory elements and precedes the acquisition of DNA methylation during the derivation of EpiSC. Furthermore, a number of pluripotency, germline and apoptosis associated genes were targets of H3K9me2 including Esrrb, Blimp1, Nr5a2 and Bclx. To gain further insight into the functions of these modifications in vivo, we focused on transcriptionally characterising epiblasts deficient in G9a or Ezh2, the enzymes responsible for methylating H3K9 and H3K27 respectively. The RNA-seq from single E6.5 G9a knockout epiblasts has confirmed this protein to be involved in directly regulating apoptosis and the exit from pluripotency. This investigation shows that the acquisition of competence of the epiblast is associated with,

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regulated and limited by G9a-dependent deposition of H3K9me2 followed by de novo DNA methylation.

REORGANIZATION OF ENHANCER PATTERNS IN TRANSITION FROM NAÏVE TO PRIMED PLURIPOTENCY

Buecker, Christa, Wysocka, Joanna
Stanford University School of Medicine, Stanford, CA, USA

Naïve and primed pluripotency is characterized by distinct signaling requirements, transcriptomes and developmental properties, but both cellular states share key transcriptional regulators, Oct4, Sox2 and Nanog. Here we demonstrate that transition between these two pluripotent states is associated with widespread Oct4 relocalization, mirrored by global rearrangement of enhancer chromatin landscapes. Our genomic and biochemical analyses identified candidate mediators of primed state-specific Oct4 binding, including Otx2 and Zic2/3. Even in the absence of other differentiation cues, premature Otx2 overexpression is sufficient to exit the naïve state, induce transcription of a large subset of primed pluripotency-associated genes and redirect Oct4 to thousands of previously inaccessible sites. However, ability of Otx2 to engage new enhancer regions is determined by its levels, cis-encoded properties of the sites and signaling environment. Our results illuminate regulatory mechanisms underlying pluripotency and suggest that capacity of transcription factors such as Otx2 and Oct4 to function as pioneers is highly context-dependent.

NANOG AND SALL1 REGULATE CHROMATIN ORGANISATION IN EMBRYONIC STEM CELLS

Rugg-Gunn, Peter J.[1], Novo, Clara[1], Morgan, Natasha[1], Hayre, Jasvinder[1], Tang, Calvin[2], Ahmed, Kashif[2], Fussner, Eden[2], Djuric, Ugljesa[2], Ellis, James[2], Bazett-Jones, David[2]
[1]The Babraham Institute, Cambridge, United Kingdom, [2]The Hospital for Sick Children, Toronto, ON, Canada

Mouse embryonic stem cells have an unusual nuclear architecture, characterized by decondensed open chromatin that is largely devoid of compact heterochromatin domains. Cells acquire an open chromatin configuration upon reprogramming to pluripotency, and remodelling of chromatin is an impediment to the reprogramming process. These observations have led to the idea that an open chromatin organisation may contribute to stem cell behavior in general, potentially by creating an unrestricted and accessible genome. It remains important to determine, however, how chromatin organisation is connected functionally to the regulatory network of pluripotent cells. We have identified new roles for the transcription factors Nanog and Sall1 as regulators of chromatin organisation. Extensive analyses of nuclear organisation revealed that deletion of either transcription factor in embryonic stem cells leads to chromatin condensation and remodelling of heterochromatin domains. Disruption of nuclear architecture occurred independently of alterations in cell state or major transcriptional changes. Furthermore, forced expression of Nanog in more differentiated cell types is sufficient to decondense chromatin, and Sall1 is a necessary co-factor for this remodelling process. We found that Nanog and Sall1 regulate the localization and transcriptional activity of pericentric heterochromatin in embryonic stem cells, thereby contributing to chromatin decondensation and organisation. Mis-regulation of pericentric heterochromatin caused by Nanog or Sall1 deletion is associated with chromosome segregation defects, leading to the accumulation of cells with an abnormal number of chromosomes. Our studies establish a direct molecular connection between the pluripotency regulatory network and nuclear organisation, and suggest that decondensed chromatin may have an unanticipated role in maintaining genetic stability in embryonic stem cells.

POSTER TEASERS:

F-2237 EVOLUTIONALLY DYNAMIC KAP1-MEDIATED CONTROL OF LINE-1 ENDOGENOUS RETROELEMENTS IN HUMAN EMBRYONIC STEM CELLS

Castro-Diaz, Nathaly, Turelli, Priscilla, Kapopoulou, Adamandia, Yazdan-Panah, Benyamin, Marzetta, Flavia, Friedli, Marc, Raclot, Charlene, Trono, Didier
Swiss Federal Institute of Technology (EPFL), Lausanne, Switzerland

F-2048 ACETATE LINKS GLYCOLYSIS TO HISTONE ACETYLATION AND PLURIPOTENCY IN HUMAN EMBRYONIC STEM CELLS

Aberdam, Daniel[1], Moussaieff, Arieh[1], Shen-Orr, Shai[2], Amit, Michal[3], Elena-Herrmann, Benedicte[4], Meshorer, Eran[5], Itskovitz-Eldor, Joseph[6], Nahmias, Yaakov[7]
[1]INSERM, Paris, France, [2]TECHNION, Haifa, Israel, [3]Technion, Haifa, Israel, [4]CNRS, Lyon, France, [5]The Hebrew University of Jerusalem Institute of Life Sciences, Jerusalem, Israel, [6]Rambam Health Care Campus, Haifa, Israel, [7]Hebrew University of Jerusalem, Jerusalem, Israel

PROGRAM AND ABSTRACTS

POSTER TEASERS (cont'd):

F-1095 CHROMATIN ORGANIZATION AND EPIGENETIC MODIFICATIONS ASSOCIATED WITH PLURIPOTENCY AND SELF-RENEWAL IN CANCER STEM CELLS

Biran, Alva Ada[1], Scaffidi, Paola[2], Meshorer, Eran[1]
[1]The Hebrew University of Jerusalem, Jerusalem, Israel, [2]Cancer Research UK London Research Institute, London, United Kingdom

THE ROUTES OF REPROGRAMMING TO ALTERNATIVE STATES OF PLURIPOTENCY

Nagy, Andras[1] and PG Consortium
[1]Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Canada

The ability to reprogram somatic cells to a pluripotent state is paradigm shifting for both biology and medical research. Reprogramming continues to challenge many of our assumptions about the specification of cellular phenotypes and yet, despite major efforts, we still lack a complete molecular characterization of the process. To address this gap we generated a comprehensive molecular description of the reprogramming cascade toward two distinct pluripotent states. We explored alternative outcomes of somatic reprogramming by fully characterizing reprogrammed cells independent of preconceived definitions of reprogrammed iPSC states. We demonstrate that manipulating the expression level of the reprogramming factor influences cells arrival to a non-ES cell-like or ES cell like pluripotent state. This bifurcated process has been characterized with multiple "omic" platforms, consisting of the transcriptome (microRNA, lncRNA and mRNA), CpG methylation, ChIP-sequencing (for chromatin marks: H3K4me3, H3K27me3 and H3K36me3), in addition to quantitative mass spectrometry profiling of the global and cell surface proteome. This dataset enables cross-referencing between "omic" platforms, which facilitates deeper understanding of the cascade of molecular events driving the generation of pluripotent cells.

CONCURRENT IIIE: ASYMMETRIC CELL DIVISION

WEST MEETING ROOM 301-305

WNT SIGNALING AND STEM CELL CONTROL

Nusse, Roeland
Stanford University School of Medicine, USA

Our laboratory is interested in the growth, development and integrity of animal tissues. We have identified stem cells in tissues by marking the Wnt-responsive cells and their descendants. For example, the stratified epithelia of the epidermis turn over rapidly and are maintained by progenitor cells residing in the basal epidermis. The origin and nature of these cells and the signaling mechanisms that control their activity remain poorly understood. We could show that Wnt marks long-lived adult murine non-follicular epidermal progenitors that cycle actively. These progenitor cells require Wnt/beta-catenin signaling to function, repair skin wounds. We found unexpectedly that self-renewing Wnt signals arise from the stem cells themselves and not separate niche cells. At the same time, the stem cells produce Wnt inhibitors, which influence epidermal stem cells in vivo. The net effect is that Wnt signaling is restricted to the basal epidermal layer, and suggests an autocrine signaling mechanism of stem cell regulation there.
We have also asked whether Wnt signals could operate in a directional, oriented manner on stem cells to orchestrate their asymmetric division. We have developed a novel technology that includes immobilized Wnt proteins on small beads and the application of these to single stem cells in culture. By this method, we were able to activate one specific side of the cell by the locally acting Wnt, follow by time-lapse imaging. Our data show that a local source of Wnt proteins sets up the orientation of cell division and the mitotic spindle. The oriented Wnt signal induces asymmetric division of stem cells: the daughter cell in contact with the Wnt source maintains pluripotency, whereas the distal cell differentiates.

PAR3-INSC AND G-ALPHA-I3 COOPERATE TO PROMOTE ORIENTED EPIDERMAL DIVISIONS

Williams, Scott E.[1], Ratliff, Lyndsay[1], Postiglione, Maria Pia[2], Knoblich, Juergen A.[2], Fuchs, Elaine[3]
[1]Pathology and Laboratory Medicine, University of North Carolina - Chapel Hill, Chapel Hill, NC, USA, [2]IMBA-Institute of Molecular Biotechnology, Vienna, Austria, [3]Rockefeller University, New York, NY, USA

Asymmetric cell divisions allow stem cells to balance proliferation and differentiation. During embryogenesis, murine epidermis expands rapidly from a single layer of unspecified progenitors to

a stratified, differentiated epithelium. Both in development and in adulthood, mitotically active progenitor cells of the interfollicular epidermis reside in the innermost basal layer, while differentiating suprabasal cells are positioned above them, providing the mechanical and barrier function of the skin. Two mechanisms have been proposed to promote epidermal stratification: 1) "delamination" or detachment of basal cells from the underlying basement membrane, 2) oriented asymmetric cell divisions which result in the production of one basal and one suprabasal daughter. Our previous studies have shown that such perpendicular (asymmetric) divisions involve the spindle orientation protein LGN (Gpsm2), the coiled-coil microtubule-binding protein NuMA, and the motor protein dynactin (Dctn1/p150glued), as loss of each of these proteins results in a pronounced bias toward parallel (symmetric) divisions and defects in differentiation and barrier function. However, less is known about how the apical localization of LGN is regulated, or whether delamination may also contribute to epidermal differentiation.

By combining conventional genetics and lentiviral-mediated in vivo RNAi, we explore the functions for the LGN-interacting proteins Par3, mInsc and Gαi3. Loss of each gene alone leads to partially penetrant errors in the ability of LGN to properly localize to the apical cortex. This results in randomized division angles, and subtle differentiation defects. We find these phenotypes are consistent for both Pard3 and mInsc regardless of whether the genes are knocked out by either transgenic Krt14-Cre or lentiviral Cre, or knocked down by RNAi. On the other hand, combined loss of Gnai3 and mInsc leads to a near complete failure of LGN to polarize. These double mutants/knockdowns display an LGN-like phenotype of mostly parallel divisions, leading to severe differentiation defects. Together, these findings lend experimental support for the hitherto untested model that Par3/mInsc and Gαi act cooperatively to polarize LGN and promote perpendicular divisions.

In the course of these studies, we discovered that the requirement for spindle orientation genes is not obligate throughout development. In agreement with previous studies, we find that in the single-layered epithelium (E12-E13), most divisions are planar, while during the peak of stratification (E16-E17), perpendicular divisions outnumber planar divisions by ~2:1. However, between E14-E15, when stratification commences, division angles are randomized. Neither early ectopic overexpression of mInsc nor loss of LGN, Pard3, mInsc or Gnai3 has any effect on division orientation or differentiation at this stage. Using a lentiviral tamoxifen-inducible CreER and a Rosa26-confetti reporter, we perform short-term genetic lineage tracing to show that delamination is the predominant driver of stratification at this stage. Thus, we uncover a developmental switch between spindle orientation-independent and dependent differentiation that occurs around E15, revealing a two-step mechanism underlying epidermal maturation.

SISTER CHROMATID SEGREGATION IN ASYMMETRICALLY DIVIDING HUMAN HEMATOPOIETIC STEM CELLS

Sanders, Ashley D.[1], Falconer, Ester[2], Naumann, Ulrike[2], Hills, Mark[2], Knapp, David JHF[2], Eaves, Connie J.[2], Lansdorp, Peter[3]

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How cellular heterogeneity is created during development and differentiation is a long-standing question in biology. One mechanism involves asymmetric cell division (ACD), where selective segregation of cell fate determinants (e.g. RNAs and proteins) differentially programs daughter cells during mitosis. Another potential mechanism involves selective DNA segregation, where functionally distinct sister chromatids and any associated epigenetic modifications direct sister cells toward different fates. Both ACD and selective DNA segregation have been reported in several model organisms and systems, suggesting they are evolutionary conserved phenomena; however, whether they contribute to the cellular complexity seen in humans is not clear. As stem cells undergo divisions that simultaneously replenish the stem cell pool and generate downstream progenitors, they offer an ideal system to investigate how cellular diversity is established during mitosis. To investigate mechanisms driving cellular heterogeneity, we developed a single-cell model using human hematopoietic stem cells (HSCs). We single-sorted and cultured highly-purified (CD34+ CD45RA- CD38+ Thy1+ α6-integrin+) human HSCs derived from cord blood or bone marrow to perform a paired sister cell analysis. After a single cell division, we assayed each sister cell simultaneously for signs of diversification by measuring fluorescence of specific cell surface markers that distinguish primitive (CD34+, or CD133+) and lineage-restricted (CD45RA+) progeny using a live-cell imaging system. We found that cell diversity was generated during the first mitosis in vitro. For instance, whereas some sister pairs display little difference in marker fluorescence, others show clear asymmetry in CD34 and CD45RA-fluorescence. This suggests subsets of HSCs undergo ACD to generate daughter cells directed towards different cell fates. To also test DNA segregation in these sister pairs, we isolated the nuclei of each individual cell and built directional genomic libraries using the Strand-seq protocol, which were analyzed with B.A.I.T. software. This allowed us to track DNA segregation patterns in each daughter cell and test whether specific sister chromatids are selectively segregated in specific cell types. Finally, this system offers an opportunity to explore differential gene expression patterns in paired sisters, using a targeted qPCR approach, to test transcriptional networks in divergent cells. This multi-layered single-cell approach aims to better define pathways

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that differentially program daughter cell fates and generate cellular heterogeneity in the human hematopoietic system.

SPATIOTEMPORAL CONTROL OF CANCER STEM CELL ASYMMETRIC DIVISION BY VERSATILE MICRORNA MECHANISMS

Shen, Xiling[1], Bu, Pengcheng[2], Chen, Kai-Yuan[3]
[1]Biomedical Engineering, Cornell University, Ithaca, NY, USA, [2]Cornell University, Ithaca, NY, USA, [3]Electrical and Computer Engineering, Cornell University, Ithaca, NY, USA

Colon cancer stem cells (CCSC) undergo both symmetric and asymmetric division, which balance differentiation versus self-renewal in the tumor cell population. This decision is determined by the microRNA miR-34a, whose spatial segregation generates a bimodal Notch response that determines cell fate outcomes. This bimodal response is caused by kinetic mutual sequestration between miR-34a and Notch mRNA. However, three questions remain after we reported the above findings in Cell Stem Cell last May. First, what is the relationship between miR-34a and the canonical cell fate determinant Numb, which also targets Notch to regulate cell fate symmetry? Second, what is the upstream regulator of miR-34a that causes it to be asymmetrically segregated? And third, does miR-34a generate bimodal responses from all of its target genes?
Here, we report a new mechanism in which miR-34a targets Numb to generate a bimodal Numb response during asymmetric division. Furthermore, miR-34a and Numb form an incoherent feedforward loop (IFFL), which synergistically enhance Notch and cell fate asymmetry by orders of magnitude. Dynamically, the IFFL exhibits adaptive behavior to offset interference from other miR-34a target genes, hence buffering asymmetric cell fate outcomes from fluctuations in miR-34a levels. Next, we report a novel, p53-independent mechanism that regulates miR-34a distribution during cell division, This upstream complex can asymmetrically localize to one of the daughter cells and inactivate miR-34a, hence initiating asymmetric cell fate determination. Lastly, we performed a systematic study of miR-34a regulation kinetics on its many target genes. Quantitative single-cell analysis revealed that miR-34a generates bimodal responses from a small subset of genes that are involved in cell fate determination, but regulating the majority of genes (e.g., metabolic and growth genes) in a graded, continuous manner. These data suggest that a microRNA can regulate its many target genes in a context-dependent manner based on their cellular functions.

POSTER TEASERS:

F-3037 ABVENTRICULAR STEM CELLS IN THE DEVELOPING HUMAN VENTRAL FOREBRAIN

Nicholas, Cory[1], Wang, Xiaoqun[2], Harwell, Corey[3], Chen, Jiadong[1], Rubenstein, John[4], Alvarez-Buylla, Arturo[5], Kriegstein, Arnold R.[1]
[1]Department of Neurology, University of California San Francisco, San Francisco, CA, USA, [2]Institute of Biophysics, Chinese Academy of Sciences, Beijing, China, [3]Department of Neurobiology, Harvard University, Boston, MA, USA, [4]Department of Psychiatry, Univ of California San Francisco, San Francisco, CA, USA, [5]Department of Neurological Surgery, University of California San Francisco, San Francisco, CA, USA

F-3053 MOLECULAR REGULATION OF SATELLITE STEM CELL FATE DETERMINATION

Chang, Natasha C.[1], Rudnicki, Michael A.[2]
[1]Sprott Centre for Stem Cell Research, Ottawa Hospital Research Institute, Ottawa, ON, Canada, [2]Ottawa Hospital Research Institute, Ottawa, ON, Canada

F-1086 ASYMMETRIC DIVISION OF MOUSE FETAL AND ADULT HEMATOPOIETIC STEM CELLS

Koechlein, Claire Steeves[1], Reya, Tannishtha[2]
[1]Pharmacology, University of California, San Diego, La Jolla, CA, USA, [2]University of California San Diego School of Medicine, La Jolla, CA, USA

MECHANISM OF ASYMMETRIC MEIOTIC CELL DIVISION IN MOUSE OOCYTES

Li, Rong
Stowers Institute for Medical Research, USA

Maturation of mouse oocytes involves two rounds of extremely asymmetric cell division, each generating the egg and a small polar body. Symmetry breaking occurs during meiosis I (MI) when the MI spindle migrates from a central location to a subcortical location. The meiotic chromatin elicits a Ran GTPase-dependent signal to induce cortical polarity characterized by an actomyosin domain that establishes the site for the first polar body extrusion. After MI completion, the meiosis II (MII) spindle forms at a nearby subcortical location and establishes a new actomyosin cortical domain, poising the oocyte to immediately complete MI upon sperm entry. Our recent work has shed light on the mechanisms by which the chromatin signal-regulated actin dynamics drive spindle migration and maintain an asymmetric spindle position. In particular, an Arp2/3-complex nucleated treadmilling actin network produces cytoplasmic streaming that generates a dynamic

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force pushing and maintaining the spindle at the cortex. However, this force is only activated once the spindle is approaching the cortex, whereas the initiation of spindle migration requires spindle periphery organelles and an associated actin nucleator - formin2 (FMN2). New mechanistic insights into the actin-based forces and a mechanical model accounting for the symmetry breaking process will be presented.

FRIDAY, JUNE 20, 4:00 PM - 5:50 PM

CONCURRENT IVA: MONITORING AND MODULATING THE NICHE

WEST MEETING ROOM 211-214

LYMPHOID NEOGENESIS AND LYMPHANGIOGENESIS IN NICHE FORMATION: LESSONS FROM CANCER

Swartz, Melody
Ecole polytechnique federale de Lausanne, Switzerland

Lymphoid neogenesis and lymphangiogenesis occur in areas of chronic inflammation and cancer, and lymph node lymphangiogenesis precedes cancer metastasis to sentinel lymph nodes. However, the functional roles of these processes remain unclear. We hypothesize that lymphoid neogenesis and lymphangiogenesis promotes niche environments that support cancer cells as well as adult stem cells. We have recently shown that some tumors can drive lymphoid-like stromal transformation via secretion of the lymphoid chemokine CCL21, which attracts lymphoid tissue inducer cells as well as CCR7+ leukocytes. In turn, this transformed stroma supports immune suppressive cells and matrix proteins, and can drive anergy and tolerance of naïve T cells. We have also recently shown that lymphatic endothelial cells (LECs) can scavenge and cross-present antigens locally for T cell deletion, which help tumors escape host immunity. VEGF-C is a growth factor secreted by macrophages and tumor cells that drives lymphangiogenesis, and we find that VEGF-C-activated LECs secrete CCL21 and TGF-b to drive these stromal changes. When VEGF-C signaling is blocked, lymphoid-like stromal changes are prevented and immune suppressive features are lessened; in turn, anti-tumor immunotherapy is more effective. Together, these data suggest a new role of lymphangiogenesis in niche formation.

CORRELATIVE LIGHT AND ELECTRON MICROSCOPY REVEALS THE ULTRASTRUCTURE OF AN ENDOGENOUS HEMATOPOIETIC STEM CELL IN ITS NICHE AND A SURROUNDING POCKET OF ENDOTHELIAL CELLS

Tamplin, Owen[1], Durand, Ellen M.[2], Carr, Logan A.[1], Childs, Sarah J.[3], Zon, Leonard I.[1]
[1]Hematology/Oncology and Stem Cell Program, Boston Children's Hospital, Boston, MA, USA, [2]Biological and Biomedical Sciences, Harvard University, Cambridge, MA, USA, [3]Biochemistry and Molecular Biology, University of Calgary, Calgary, AB, Canada

Stem cells are found in a highly structured microenvironment that provides physical support and important signals for maintenance and fate determination. The rarity of stem cells in their niche can often make them difficult to identify and locate. Even if a suitable combination of cell type-specific antibodies and/or transgenics can be found that enable visualization by confocal microscopy, there is a limit to the resolution that can be achieved by this light-based imaging technique. Electron microscopy (EM) can be used to acquire much higher resolution images, and together with serial block-face scanning, can generate three-dimensional images from small tissues. A combined approach is called correlative light and electron microscopy (CLEM), and involves identification of cells in a tissue by confocal microscopy, followed by fixation of the same sample for EM scanning. To begin addressing the challenge of locating a stem cell and observing it at high resolution in its niche, we have developed a transgenic reporter in zebrafish that marks endogenous hematopoietic stem cells (HSC). We generated this line by using the previously described mouse Runx1 +23 kb intronic enhancer to drive GFP or mCherry expression. We confirmed the purity of the stem cell population by adult-to-adult limiting dilution transplantation with as few as one Runx1+23 positive cell. Based on long-term multi-lineage engraftment, we estimated a stem cell purity of approximately 1/35, which is similar to the well-characterized KSL (Kit+Sca1+Lin-) population in mouse. Using embryo-to-embryo transplantation, we estimated an even higher stem cell purity of 1/2. Together these experiments have defined the most pure HSC population in the zebrafish system. To visualize these HSC in their microenvironment, we tracked their migration in the embryo using time-lapse live imaging, and confirmed their lodgement in a new site of hematopoiesis. We fixed and processed embryos for scanning EM. The entire caudal hematopoietic tissue (or fetal liver equivalent in the zebrafish) was serially sectioned at 100 nanometer steps and scanned at 10 nanometers/pixel resolution, allowing us to recreate a high resolution three-dimensional model of the HSC niche. Using vessels as anatomical markers, we correlated the position of a lodged Runx1+23 positive HSC tracked

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during live imaging, with a cell identified in sections of EM data. The ultrastructure revealed a large round HSC with its distinctive large nucleus, scant cytoplasm, and ruffled membrane. The HSC was almost completely surrounded by endothelial cells, which we have observed in confocal images, but at this high resolution we could see that the HSC was not tightly wrapped as predicted. Instead the HSC was loosely held by finger-like protrusions from the endothelial cells that created gaps and spaces between the two cell types. These reconstructions have also allowed us to identify other cell types in close proximity to the HSC, such as stromal cells and myeloid progenitors. Combined confocal microscopy and serial scanning EM of a transgenic zebrafish reporter has enabled us to create the first high resolution 3D image of an endogenous stem cell in its niche.

MODELING THE THYMIC MICROENVIRONMENT TO SUPPORT T CELL MATURATION AND THE CULTURE OF FUNCTIONAL THYMIC EPITHELIAL CELLS

Piccinini, Elia[1], Shukla, Shreya[1], Ireland, Ronnie[2], Tam, Roger[1], Mahmood, Mohtashami[3], Shoichet, Molly[1], Zuniga-Pflucker, Juan Carlos[3], Simmons, Craig[2], Zandstra, Peter W.[1]

[1]University of Toronto Institute of Biomaterials and Biomedical Engineering, Toronto, ON, Canada, [2]University of Toronto, Toronto, ON, Canada, [3]Department of Immunology University of Toronto, Toronto, ON, Canada

The thymus is the primary lymphoid organ where T cell progenitors mature into competent immune cells. The newly generated T cells play a central role in the establishment of a functional adaptive immune system by maintaining balance of immunity and tolerance. Occurrence of conditions such as thymic aplasia, AIDS, and total ablation therapies can lead to reduced numbers of T cells and hence to increased susceptibility to infections, tumors, and autoimmune diseases. Generating functional T cells in vitro is envisioned as a valuable strategy to address life threatening T cell deficiencies. However, the complex interactions that occur between developing T cells and the thymus remain partially unknown, thus affecting our comprehension and ability of producing mature T cells in controlled conditions. At this regard, one of the limiting factors is the lack of functional models recapitulating the thymic microenvironment and one of its main constituents, the thymic epithelial cells (TEC). In fact, TEC lose their functional competence when exposed to traditional culture conditions, resulting in their inability to support ex vivo T cell development and hindering the investigation of T cell maturation mechanisms.

To address the current limitations, we are developing new engineering strategies that integrate (i) the generation of T cell precursors from stem cells, and (ii) the establishment of an ex vivo thymic organoid able to recapitulate the cross-talk between developing T cells and TEC. First, we established serum and feeder free conditions on immobilized Notch ligand Delta-like 4 that generate and expand pro T cell (CD45+CD90+CD25+) from fetal liver HSC with a yield comparable to serum- containing media (52.4+/-6.3 proT/HSC in serum free, 44.8+/-4.9 proT/HSC with serum). Then, culture conditions were moved to a scalable 3D hydrogel system based on functionalized methylcellulose (MC) able to display DL4 in an orientation-controlled manner. A dual-luciferase reporter assay that was used to determine activation of Notch signaling in 3T3 cell line displayed comparable activity in monolayer control and in the functionalized MC. In parallel, TEC were cultured on an array of different extracellular matrix proteins patterned on hydrogels with defined mechanical properties. Variations of protein composition and concentration affected number and frequency of CD45- EpCAM+ MHCII+ TEC. Moreover, arranging the proteins in a hydrogel-based 3D scaffold confirmed the crucial role of a complex architecture for TEC culture as assessed by phenotype analysis. Functional assays like in vivo and in vitro generation of T cells will be carried out after optimizing the culture conditions, and microarray technology will be exploited to investigate how different parameters affect TEC functionality.

These results suggest that we can recapitulate crucial aspects of the thymic environment that are essential for an in vitro development of T cells and of a functional thymic stroma. Our approach will provide a comprehensive platform for the generation of both progenitor and mature T cells and for investigating unknown aspects of thymus development and function that are central for the translation of bioengineering approaches into clinical applications. In combination with emergent differentiation technologies of PSC, the proposed methodology can prospectively be used in designing customized therapies and modeling T cell-related diseases.

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MICROENVIRONMENTAL REGULATION OF LUNG STEM CELL DIFFERENTIATION

Lee, Joo-Hyeon[1], Bhang, Dong Ha[2], Beede, Alexander[1], Stripp, Barry[3], Bloch, Kenneth D[4], Wagers, Amy[5], Tseng, Yu-Hua[6], Ryeom, Sandra[2], Kim, Carla[7]

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Lung stem cells are instructed to produce lineage-specific progeny through unknown factors in their microenvironment. We used clonal three-dimensional (3D) co-cultures of endothelial cells and distal lung stem cells, bronchioalveolar stem cells (BASCs), to probe the instructive mechanisms. Single BASCs had bronchiolar and alveolar differentiation potential in 3D co-culture with lung endothelial cells (LuMECs) and subcutaneous co-injection (S.C.) of single colonies from BASCs with LuMECs also generated bronchiolar- and alveolar-like structures in vivo. Importantly, whereas LuMECs induced bronchiolar and alveolar differentiation of BASCs, liver endothelial cells (LiMECs) fail to support substantial BASC alveolar differentiation indicating organ-specific regulation of BASC differentiation specifically to the alveolar lineage; BASC/LiMEC co-cultures yielded 91.9% bronchiolar colonies and 2.7% alveolar colonies, corresponding to 3.5-fold increased bronchiolar and 21.5-fold diminished alveolar colony yield per well compared to BASC/LuMEC cultures ($p<0.001$). Thrombospondin1 (Tsp1) was identified as a crucial regulator of BASC differentiation in LuMECs. BASCs co-cultured with Tsp1-/- LuMECs produced 3.2-fold more bronchiolar colonies and 3.5-fold less alveolar colonies than BASC/Tsp1+/+ LuMEC ($p<0.01$). Adding purified TSP1 in BASC/ Tsp1-/- LuMEC restored defective alveolar differentiation of BASCs suggesting the sufficiency of endothelial derived TSP1 in driving alveolar differentiation of BASCs. Subcutaneous transplantation of single BASC colonies with Tsp1-/- LuMECs increased bronchiolar-like structure formation (2.6-fold) at the expense of alveolar-like structures (4.1-fold) compared to BASC/Tsp1+/+ LuMEC ($p<0.01$). In response to bronchiolar injury using naphthalene, Tsp1-/- mice exhibited enhanced injury repair, however Tsp1-/- mice showed impaired regeneration of alveolar epithelia after bleomycin treatment. Injection of conditioned medium (CM) from Tsp1+/+ LuMECs into Tsp1-/- mice following bleomycin treatment rescued impaired alveolar regeneration. BMP4 treatment in BASC/ Tsp1+/+ LuMEC increased alveolar differentiation of BASCs (1.6-fold, $p<0.01$ vs. control) by induction of Tsp1 expression in LuMECs, whereas adding BMP4 in BASC/LiMEC, BASC/Bmpr1a-/- LuMEC or BASC/ Tsp1-/- LuMEC showed no discernable changes. BMP4 activates Calcineurin which triggers NFATc1 nuclear translocation following binding the promoter of Tsp1 to induce Tsp1 expression in LuMECs through Bmpr1a. Treatment of NOG or cyclosporin A in BASC/LuMEC significantly abrogated the increase of alveolar differentiation of BASCs and up-regulation of Tsp1 expression in LuMECs after BMP4 treatment; 93.3% alveolar colony formation seen in BMP4-treated cultures was diminished to 57.1% with NOG addition (1.6-fold less, $p<0.01$) and to 66.1% with CsA addition (1.4-fold less, $p<0.01$). These experiments reveal an organ-specific, Bmp4-Calcineurin/NFATc1-Tsp1 axis in endothelial cells regulating lineage-specific stem cell differentiation. Elucidation of this pathway points to methods to direct the derivation of specific lung epithelial lineages from multipotent cells. These findings provide new ways to study mechanisms of respiratory disease and potential therapeutics.

POSTER TEASERS:

F-1084 HOMOZYGOUS EXPRESSION OF JAK2V617F DRIVES RAPID HEMATOPOIETIC STEM CELL PROLIFERATION AND DIFFERENTIATION AT THE EXPENSE OF SELF-RENEWAL AND IS ACCOMPANIED BY STARK CHANGES IN HOMING ABILITY

Kent, David[1], Li, Juan[1], Fink, Juergen[1], Prick, Janine CM[1], Hawkins, Edwin D.[2], Lo Celso, Cristina[2], Green, Anthony R.[3]

[1]Stem Cell Institute, University of Cambridge, Cambridge, United Kingdom, [2]Imperial College London, London, United Kingdom, [3]University of Cambridge, Cambridge, United Kingdom

F-2098 GROWING MULTIPLE VASCULARIZED ORGAN BUDS FROM DISSOCIATED MIXED PROGENITORS THROUGH SELF-DRIVEN DYNAMIC AGGREGATION

Takebe, Takanori, Enomura, Masahiro, Yoshizawa, Emi, Kimura, Masaki, Koike, Hiroyuki, Takahashi, Yoshinobu, Koike, Naoto, Sekine, Keisuke, Taniguchi, Hideki

Yokohama City University, Yokohama, Japan

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POSTER TEASERS (cont'd):

F-2153 PASSING THROUGH A PRIMITIVE STREAK-LIKE MESENDODERM STATE AND MAKING A RESISTANT FOR REVERSION BACK TO A SOMATIC CELL FATE ARE HURDLES IN A MATURATION OF HUMAN REPROGRAMMING TOWARD PLURIPOTENCY

Tanabe, Koji[1], Takahashi, Kazutoshi[2], Ohnuki, Mari[2], Nakamura, Michiko[2], Narita, Megumi[2], Aki, Sasaki[2], Yamamoto, Masamichi[3], Sutou, Kenta[4], Osafune, Kenji[5], Yamanaka, Shinya[2]

[1]Stanford University Institute of Stem Cell Biology and Regenerative Medicine, Palo Alto, CA, USA, [2]Kyoto University, Center for IPS Cell Research and Application, Kyoto, Japan, [3]Development Unit, Gunma University, Gunma, Japan, [4]Department of Reprogramming Science, Kyoto University, Center for IPS Cell Research and Application, Kyoto, Japan, [5]Kyoto University, Kyoto, Japan

STEM CELL NUCLEAR PROPERTIES IN RELATION TO THE NICHE

Discher, Dennis and Swift, Joe

University of Pennsylvania, USA

Tissues can be soft like fat, which bears little stress, or stiff like bone, which sustains high stress, but whether there is a systematic relationship between tissue mechanics and differentiation is unknown. Our proteomics analyses has revealed that levels of the nucleoskeletal protein lamin-A scaled with tissue elasticity, E, as did levels of collagens in the extracellular matrix that determine E. Stem cell differentiation into fat on soft matrix was enhanced by low lamin-A levels, whereas differentiation into bone on stiff matrix was enhanced by high lamin-A levels. Matrix stiffness directly influenced lamin-A protein levels, and, although lamin-A transcription was regulated by the vitamin A/retinoic acid (RA) pathway with broad roles in development, nuclear entry of RA receptors was modulated by lamin-A protein. Tissue stiffness and stress thus increase lamin-A levels, which stabilize the nucleus while also contributing to lineage determination.

CONCURRENT IVB: LARGE SCALE ANALYSIS OF CELL FATE DECISIONS

WEST BALLROOM A

HORMONAL REGULATION OF SELF-RENEWAL IN HESCS

Reversade, Bruno

Institute of Medical Biology, Singapore

A disproportionate emphasis has been placed on the role of transcription factors to maintain pluripotency and self-renewal of hESCs. But these two defining properties are mainly driven by an upstream cocktail of extracellular growth factors which are either added exogenously or secreted by hESCs. Here, we report a novel peptide hormone that is endogenously secreted by hESCs and required for their growth and maintenance through activation of the PI3K/AKT pathway. Strikingly, this 32-amino acid hormone is sufficient to replace insulin in hESC media, and exerts potent anti-apoptotic and growth promoting effects through an as-yet unidentified cell surface receptor.

EPIGENETIC PRIMING TO PROMOTE PLURIPOTENT STEM CELL DIFFERENTIATION

Chetty, Sundari[1], Ziller, Michael[1], Lui, Kathy[2], Gifford, Casey[2], Meissner, Alexander[3], Melton, Douglas A.[2]

[1]Stem Cell and Regenerative Biology, Harvard University, Cambridge, MA, USA, [2]Harvard University, Cambridge, MA, USA, [3]Harvard University/Broad Institute, Cambridge, MA, USA

Pluripotent stem cells have great therapeutic potential because they can in theory differentiate into any specialized cell type of the body. However, unlocking this vast potential of stem cells has proven to be challenging in practice. Prior work has found that only certain stem cell lines have the ability to generate cells of a particular type, limiting the prospects of cell replacement therapy for regenerative medicine. Moreover, generating terminally differentiated cells with functional capacity in a robust and efficient manner has proven challenging. Here, we investigate the underlying mechanisms that regulate the competency for differentiation into functional cell types of human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs). Specifically, we investigate the role of epigenetics on the cell cycle and differentiation in an effort to understand the mechanism by which pluripotent stem cells differentiate. Using chromatin immunoprecipitation (ChIP) sequencing technology, we identify specific histone modifications that are associated with stem cells becoming primed to differentiate. These modifications show enriched acetylation (e.g. H3K27ac) in regions associated

with genes involved in early development and differentiation that occur prior to gene activation. Regions associated with genes involved in early development (such as Sox1, Sox2, FoxA2, BMP2, HOX genes, etc) have enriched acetylation at H3K27 prior to gene activation, suggesting a potential priming mechanism. In "primed" pluripotent stem cells, H3K27ac is not differentially regulated at the pluripotency genes (e.g. Nanog, Oct4), but is reduced at many of the cell cycle-related genes (e.g. Cdk4, Cdc6). Further investigation of additional histone modifications (H3K4me3, H3K27me3) along with whole-genome bisulfite sequencing and RNA sequencing show unique events associated with the "primed" pluripotent state and that of the cell cycle. Furthermore, inducing the transition of pluripotent stem cells into a "primed" state subsequently improves their capacity to differentiate into all germ layers following directed differentiation. Improvements of more than 100-fold in differentiation rates are observed in low propensity cell lines. Thus, this study provides a comprehensive epigenetic profiling associated with the transition of a pluripotent stem cell into a state amenable for differentiation. We also identify small molecules and chemicals to epigenetically prime pluripotent stem cells into a state competent for differentiation. More generally, the mechanist insights highlighted here demonstrate that repressive epigenetic modifications can be overcome to enable one to more effectively and efficiently direct stem cells into desired cell types.

COMPREHENSIVE CLONAL MAPPING OF HEMATOPOIESIS IN VIVO IN HUMANS BY RETROVIRAL VECTOR INSERTIONAL BARCODING

Biasco, Luca[1], Calabria, Andrea[1], Dionisio, Francesca[1], Scala, Serena[1], BassoRicci, Luca[1], Baricordi, Cristina[1], Scaramuzza, Samantha[1], Giannelli, Stefania[1], Neduva, Victor[2], Dow, David[2], Pellin, Danilo[3], Di Serio, Clelia[3], Vicard, Paola[4], Naldini, Luigi[5], Montini, Eugenio[6], Aiuti, Alessandro[6]

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Hematopoietic stem cells (HSC) are endowed with the unique role of generating an adequate and efficient pool of blood cells throughout human life. Data derived from clonal tracking of HSC activity and hematopoietic dynamics in vivo in humans would be of paramount importance for the design of therapies for hematological disorders and cancers. Our gene therapy (GT) clinical trials for adenosine deaminase (ADA) deficient-SCID and Wiskott-Aldrich Syndrome (WAS) based on the infusion of genetically engineered HSC, constitute unique clinical settings where each vector-marked progenitors and its blood cell progeny is traceable being univocally barcoded by a vector integration site (IS). To study early dynamics of hematopoietic reconstitution in humans, we collected by LAM-PCR + Illumina-Miseq sequencing 14.807.407 sequence reads corresponding to 71.981 IS tagging clones belonging to 13 different cell types purified from the bone marrow and the peripheral blood of 4 WAS patients up to 36 months after GT. We firstly identified and quantified identical IS shared among CD34+ progenitors, and mature Myeloid/Lymphoid cells as marker of the real-time clonal output of individual vector-marked HSC clones in vivo. We unraveled the timing and nature of short, intermediate and long term HSC output showing that CD34+ clones active at 3-6 months after GT are not detectable at later follow up and that early reconstitution is markedly skewed towards myeloid production. By the study of clonal entropy through the Shannon Diversity Index we found that progenitor output occurs in distinct waves during the first 6-9 months after transplantation reaching a "homeostatic equilibrium" only by 12 months after GT. At steady state we estimated by mark-recapture mathematical approaches that 1900-7000 transduced HSC clones were stably contributing to the progenitor repertoire for up to 3 years after infusion of gene corrected CD34+ cells. To evaluate the long-term preservation of activity by transplanted HSC we exploited data derived from the IS-based tracking of 4.845 clones in ADA-SCID patients performed for up to 6 years after GT. We showed that identical IS are consistently detected at multiple lineages level even several years after GT. Strikingly, by semi-quantitative PCRs on specific vector-genome junctions we tracked a fluctuating but consistent output of marked HSC over a period of 5 years without the manifestation of clonal quiescence phases. Additionally, since the gammaretroviral vector used in this trial is able to transduce only actively replicating cells, we provided the first evidence that in vitro activated HSC, "awaken" from dormancy, can still, once infused, retain in vivo long-term activity in humans. We are exploiting IS similarities among the lineages for both WAS and ADA-SCID datasets to reconstruct the hematopoietic hierarchy by combining conditional probability distributions and graphical models of dependencies. Notably, preliminary data unveiled a link between myeloid progenitors and mature lymphoid cells that supports the recently suggested model of hematopoiesis based on a delayed branching of myeloid and lymphoid lineages. Overall our data constitute the first molecular tracking of individual hematopoietic clones in humans providing an unprecedented detailed analysis of HSC activity and dynamics in vivo. The information gathered will be crucial for the design of therapeutic approaches for a broad spectrum of diseases and tumors.

PROGRAM AND ABSTRACTS

ORDERED HALLMARKS AND REGULATORY COORDINATION POINTS OF HUMAN B CELL DEVELOPMENT VIA TRAJECTORY DETECTION

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A challenge exists to devise approaches that can analyze and order cells of complex tissues so as to reveal their developmental relationships, behavior, and ultimately the mechanisms that govern their differentiation and expansion. A case in point is the early development of human B lymphocytes, a process which initiates in the adult bone marrow. Early B cells, like all immune cells, originate from the hematopoietic stem cell, followed by a common lymphoid progenitor cell, pro-B cell, pre-B cell, and finally an immature B cell, which migrates out of the. While these early developmental hallmarks have been described in the mouse, the exact nature of cell types and timing of critical events such as required regulatory signaling (IL7/STAT5), IgH rearrangement and clonal expansion remains elusive in human B lymphopoiesis.

B cell centric, 44 parameter, single cell mass cytometry data was collected from human bone marrow simultaneously measuring multiple cellular features including: phenotypic proteins (CD34, CD38, CD10, CD19, CD20, CD24, CD179a/b, CD117, CD127, CD79b, HLA-DR, CXCR4, CD40, CD72, CD22, IgHs, IgHi, IgD, kappa, lambda, CD45, CD45RA, CD43), transcription factors, regulatory enzymes, cell state indicators (Pax5, RAG, TdT, cleaved PARP, Ki67), and activation of regulatory signaling molecules (phosphorylation of STAT5, STAT3, PLC gamma, Akt, Btk, Syk, Creb, Erk, Src, P38, S6). Sufficient cells were measured to encompass a complete spectrum of B cell lymphopoiesis that could be reassembled into a continuous progression from within a single sample. The resulting high dimensional data was ordered using a graph-based trajectory detection algorithm (termed Wanderlust) that orders cells based on their maturity to a unified trajectory, thus predicting the developmental path de novo, which was subsequently validated.

Wanderlust generated remarkably consistent trajectories across multiple individuals, starting with progenitor populations and ending at naive B cells, with results that were largely congruent with prior knowledge. By using the trajectory as a framework, we determined the timing and order of key molecular and cellular events across development, including identifying previously unrecognized subsets of B cell progenitors that pinpoint the timing of DJ and V(D)J recombination of the immunoglobulin heavy chain (IgH). Surveying the dynamic changes in cellular expression across the Wanderlust trajectory, we identified 'coordination points', where re-wiring of the signaling network occurs concurrently with the rise and fall of multiple proteins. These coordination points and their characteristic signaling could be further aligned with cell cycle status, apoptosis, and germline IgH locus rearrangement, together forming a deeply detailed map of human B lymphopoiesis. Using this map, emerging human B-lymphocytes could be predictably stalled in ex vivo bone marrow culture by targeting the signaling network governing the earliest coordination point identified here. Overall, this constructed trajectory offers an unprecedented view into a human maturational system, previously limited to inquiry by the rarity of cells and an inability to perform in vivo manipulations. Instead, by exploiting the cellular heterogeneity of the human system while monitoring both single-cell identity and behavior, a holistic model ordered by developmental chronology could be created to infer functional relationships.

POSTER TEASERS:

F-2063 THE CIRCADIAN CLOCK IN PLURIPOTENT STEM CELLS AND DIFFERENTIATION

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F-2170 DEEP RNA-SEQUENCING OF DIFFERENTIATING HUMAN CARDIOMYOCYTES REVEALS NOVEL LNCRNA, SPLICING, MIRNA AND TRANSCRIPTIONAL REGULATORY NETWORKS

Salomonis, Nathan[1], Spindler, Matthew[2], Nguyen, Trieu[2], Russell, Caitlin[2], Lizarraga, Paweena[2], Truong, An[2], So, Po-Lin[2], Conklin, Bruce R.[2]
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F-1085 THE GLOBAL RNA AND PROTEIN LANDSCAPE OF HEMATOPOIETIC STEM CELLS AND THEIR IMMEDIATE PROGENY

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PROGRAM AND ABSTRACTS

IMPACT OF CELL TYPE OF ORIGIN AND REPROGRAMMING METHOD ON HUMAN INDUCED PLUTIPOTENT STEM CELLS

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Human induced pluripotent stem cells (hiPSCs) are conventionally derived from somatic cells by overexpression of pluripotency factors. hiPSCs have the unique characteristic to self renew in vitro while maintaining the capacity to differentiate into a broad number of cell types. Thus, they represent a unique in vitro platform for the generation of large quantities of cells for disease modelling, drug screening and ultimately cell based therapy. The rapid adoption of hiPSC technology has resulted in derivation of an exponential growing number of cell lines. However, the current lack of standardized criteria for evaluating hiPSC quality could obscure cell line specific limitations that diminish their utility in future clinical applications. This study aims to address several of these limitations including the influence of the cell type of origin and the impact of the reprogramming method.A panel of 45 hiPSC lines were derived from the same patients (n=5) from blood cells or skin fibroblasts using the two most common non-integrative methods of reprogramming, Sendai virus and episomal plasmids. The resulting hiPSCs were then characterised using rigorous genome-wide assays including RNA-seq, CHIP-seq, exome sequencing, 450K-methylation array and by karyotyping. Additionally, the capacity for differentiation into three primary tissue layers (endoderm, neuroectoderm and mesoderm) was analysed using chemically defined two dimensional protocols. Finally, the resulting hiPSC lines were differentiated further by patterning them into insulin secreting pancreatic progenitors cells to access their suitability for the production of clinically relevant cells.Taken together these analyses revealed that cell types of origin and method of reprogramming have an important impact on the properties of the resulting hiPSC lines. This insight will be essential for the establishment of GMP grade HLA-matched hiPSC lines and also for the future development of personalised regenerative medicine. Accordingly our results represent the first step in establishing robust standards for characterising hiPSCs for research and clinical applications.

CONCURRENT IVC: STEM CELLS AND CANCER

WEST BALLROOM B

THE ROLE OF RNA EDITING IN MALIGNANT REPROGRAMMING

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Enhanced RNA editing, mediated by inflammatory niche-responsive adenosine deaminase acting on RNA (ADAR), has emerged as an important epigenetic driver of malignant progenitor reprogramming. Malignant reprogramming contributes to therapeutic resistance and relapse in a number of recalcitrant human malignancies, including blast crisis chronic myeloid leukemia (BC CML; Jamieson PNAS), lobular breast cancer and hepatocellular cancer. To elucidate niche-specific mechanisms of malignant reprogramming of human progenitors into self-renewing leukemia stem cells (LSC), whole transcriptome RNA sequencing (RNA Seq), lentiviral human-JAK2 transduction, microRNA PCR array, quantitative RT-PCR (qRT-PCR), ADAR reporter, and serial LSC transplantation studies were performed. In human BC CML progenitors, RNA seq revealed extensive upregulation of inflammation-responsive genes that trigger both ADAR activity and JAK/STAT signaling. Notably, lentiviral human JAK2 overexpression in normal cord blood progenitors enhanced ADAR1 expression and activity of an ADAR reporter. In CML progenitors, JAK2/STAT5 overexpression and BCR-ABL amplification triggered ADAR1 and CDKN2a senescence gene expression leading to the emergence of self-renewing LSC. Overexpression of the inflammatory mediator responsive form of ADAR1, p150, reduced let7 microRNA family member expression in a pattern similar to that seen in CML BC progenitors that harbored high levels of ADAR1 expression. These observations provided the impetus for testing if a combined reduction in BCR-ABL and JAK2 signaling could inhibit LSC self-renewal. In a humanized RAG2-/-γc-/-mouse model of BC CML, a potent BCR-ABL inhibitor, dasatinib, combined with a selective JAK2 inhibitor, SAR302503, reduced LSC serial transplantation potential in concert with phospho-JAK2 mediated ADAR1 expression and RNA editing activity. Increased inflammatory stimuli emanating from the malignant microenvironment combined with heightened BCR-ABL oncogene-mediated sensitivity to TNF, IFN and JAK2 signaling promotes RNA editing of self-renewal regulatory transcripts and altered expression of microRNAs involved in reprogramming. Notably, aberrant RNA recoding can be effectively reduced in CML progenitors with a combination of BCR-ABL and JAK2 inhibition that expunges malignant self-renewal capacity in vivo. Targeted reversal of RNA recoding and malignant

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reprogramming in inflammatory microenvironments that promote progenitor senescence may enhance cancer stem cell (CSC) eradication in a broad array of human malignancies and provides a strong rationale for reducing JAK2 triggered ADAR triggered activity as a vital component of CSC targeted clinical trials.

MSI1 INTEGRATES APC LOSS AND MTORC1 ACTIVATION TO PROMOTE INTESTINAL STEM CELL TRANSFORMATION

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Loss of the APC tumor suppressor in the intestinal epithelium initiates the majority of human colorectal adenocarcinomas. Constitutive β-catenin activation is thought to underlie tumorigenesis induced by loss of APC, however β-catenin activation alone does not recapitulate all APC-loss phenotypes, suggesting that additional pathways are required. We demonstrate that aberrant activation of the Msi1 RNA binding protein occurs upon APC loss and that Msi1 activation alone is sufficient to phenocopy APC loss in the intestinal epithelium. Msi1 elicits these effects through binding of mRNAs encoding pleiotropic tumor suppressors resulting in promiscuous activation of quiescent intestinal stem cells, proliferative expansion of the stem cell compartment, crypt fission, and blocked differentiation. Further, these phenotypes are largely dependent on mTORC1 activity, and we demonstrate that loss of Msi activity is sufficient to abrogate tumorigenesis in both murine and human systems. These findings implicate Msi1 as a central coordinator of APC loss-induced intestinal stem cell transformation and adenocarcinoma progression.

HEMATOPOIETIC STEM CELL ORIGIN OF A MATURE B CELL NEOPLASM

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Hairy cell leukemia (HCL) is a chronic lymphoproliferative disorder characterized by somatic BRAFV600E mutations. The malignant cell in HCL has immunophenotypic and functional features of a mature B-cell, but no normal counterpart along the continuum of developing B-lymphocytes has been delineated as the cell of origin. Here we find that the BRAFV600E mutation is present in hematopoietic stem cells (HSCs) in HCL patients, and that these patients exhibit marked alterations in hematopoietic stem/progenitor cell (HSPC) frequencies, including a marked progenitor B-cell expansion. Quantitative sequencing analysis revealed a mean BRAFV600E mutant allele frequency of 4.97% in HSCs from HCL patients. Moreover, transplantation of BRAFV600E mutant HSCs from an HCL patient into immunodeficient mice resulted in stable engraftment of human hematopoietic cells harboring the BRAFV600E mutation, confirming the preserved self-renewal capacity of mutant HCL HSCs. Consistent with the human genetic data, expression of BRafV600E in murine HSPCs resulted in a lethal hematopoietic disorder characterized by splenomegaly, anemia, thrombocytopenia, increased circulating soluble CD25 (sCD25), and increased clonogenic capacity of B-lineage cells- all classic features of human HCL. In contrast, restricting expression of BRafV600E to the B-cell compartment did not result in disease. Treatment of HCL patients with vemurafenib, an inhibitor of mutated BRAF, resulted in normalization of HSPC frequencies and increased myeloid and erythroid output from HSPCs. These findings link the pathogenesis of HCL to somatic mutations that arise in HSPCs and further suggest that neoplasms of mature B cells may initiate in aberrant hematopoietic stem cells.

ROLE OF SOX2 IN MOUSE GLANDULAR STOMACH HOMEOSTASIS AND TUMORIGENESIS

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Sox2 is an SRY-related HMG box transcription factor that maintains the pluripotency of early embryonic cells and regulates the formation of several epithelia during fetal development including the primordia of tissues such as the trachea, esophagus, stomach and lungs. Although Sox2 is widely expressed in foregut endoderm during development, we have found that Sox2 expression becomes restricted to a rare stem cell population in the adult glandular stomach epithelium capable of continuous self-renewal and differentiation throughout the life-time of a mouse. Given the importance of Sox2+ stem cells in replenishing stomach tissue, we went on to test if the transcription factor itself may play a critical role in maintaining glandular stomach homeostasis. Using a conditional Sox2 knockout allele($Sox2^{fl/fl}$) to delete Sox2 in adult mice, we surprisingly found that loss of Sox2 is dispensable for normal stomach homeostasis as well as for stomach derived organoid growth, suggesting that Sox2 may play an alternative role and become functionally important during times of tissue stress or tumorigensis. Sox2 has been described as an amplified oncogene in several types of human cancers derived from the foregut endoderm including lung and esophageal squamous cell carcinomas. However, its role in stomach cancer is still undefined. Since Sox2 expression is limited to a rare population of cells in the adult stomach, we hypothesized that the dysregulation of Sox2 or Sox2+ stem cell activity may lead to tumorigenesis in the stomach as well. We tested this by several means. First we generated mice

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containing a doxycycline-inducible Sox2 allele to conditionally overexpress Sox2 in adult mice. Overexpression of Sox2 lead to disruption of stomach tissue composition in the glandular stomach with ectopic expression of the squamous cell epithelial marker p63, suggesting that dysregulation of Sox2 during homeostasis can change stomach cell identity but does not lead to tumorigenesis. Second, we inactivated the tumor suppressor Apc specifically in Sox2-expressing by crossing Apc conditional null mice ($Apc^{fl/fl}$) to a strain expressing inducible Cre recombinase in Sox2+ positive cells($Sox2^{CreER}$) to determine if tumors can arise from Sox2+ stem cells. Sox2+ stem cells gave rise to adenomas, indicating that Sox2+ stem cells are a potent cell of origin in gastric tumorigenesis. Third, we directly tested the function of Sox2 in tumorigenesis by conditionally deleting both Apc and Sox2 in Sox2+ stem cells by inducing $Sox2^{CreER/fl/fl}$; $Apc^{fl/fl}$ mice. However, contrary to the observed amplification of Sox2 found in other cancers, deletion of Sox2 in Sox2+ stomach stem cells lead to an increase in adenoma formation, when Apc was inactivated, indicating that Sox2 my act as a tumor suppressor in stomach tumor initiation. Furthermore, Sox2 negative adenomas grew more quickly than Sox2 positive adenomas and eventually invaded the stomach muscle layer, suggesting that loss of Sox2 may be a prerequisite for development of stomach cancer. In conclusion, our genetic studies provide some of the first findings suggesting a novel role for Sox2 as tumor suppressor.

POSTER TEASERS:

F-3001 HUMAN ES CELL-BASED MODELING OF PEDIATRIC GLIOMAS BY K27M MUTATION IN THE H3.3 HISTONE VARIANT

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F-1032 DUAL ROLES FOR ID4 IN THE REGULATION OF ESTROGEN SIGNALING IN THE MAMMARY GLAND AND OVARY

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POSTER TEASERS (cont'd):

F-1089 BALANCE OF P53 AND E2F1 MAINTAINS CHRONIC MYELOID LEUKAEMIA STEM/ PROGENITOR CELL QUIESCENCE

Pellicano, Francesca[1], Park, Laura[1], Hopcroft, Lisa[1], Sinclair, Amy[1], Scott, Mary[1], Aspinall-O'Dea, Mark[1], Susan, Graham[1], Leone, Gustavo[2], Kranc, Kamil[3], Whetton, Anthony[4], Holyoake, Tessa[1]

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NRAS SIGNALING IN PRE-LEUKEMIC STEM CELL TRANSFORMATION

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Accumulating evidence suggests that LSCs initiate and maintain leukemia and are the cellular reservoir responsible for the high frequency of AML relapses. Genetic mutations sequentially transform normal hematopoietic stem cells and progenitors (HSC/Ps) first into pre-LSCs and then to LSCs in a multi-step process. The presence of pre-leukemic clones has been implied in whole genome sequencing studies of leukemia patients at the time of initial diagnosis and relapse, and was recently demonstrated in AML patients who have achieved remission. "Pre-leukemic" mutations are thought to promote clonal expansion of HSCs by increasing self-renewal and competitiveness; however, mutations that increase HSC proliferation tend to reduce competitiveness and self-renewal potential, raising the question of how a mutant HSC can sustainably outcompete wild-type HSCs. Activating mutations in NRAS are prevalent in human myeloproliferative neoplasms and leukemia. Our recent studies showed that a single allele of oncogenic $Nras^{G12D}$ increases HSC proliferation but also increases reconstituting and self-renewal potential upon serial transplantation in irradiated mice, all prior to leukemia initiation. $Nras^{G12D}$ also confers long-term self-renewal potential upon multipotent progenitors. To explore the mechanism by which $Nras^{G12D}$ promotes HSC proliferation and self-renewal we assessed cell cycle kinetics using H2B-GFP label retention and short- and long-term BrdU incorporation. $Nras^{G12D}$ had a bimodal effect on HSCs, increasing the rate at which some HSCs divide and reducing the rate at which others divide. This mirrored bimodal

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effects on reconstituting potential as rarely dividing $Nras^{G12D}$ HSCs outcompeted wild-type HSCs while frequently dividing $Nras^{G12D}$ HSCs did not. $Nras^{G12D}$ had these effects by promoting the non-canonical effector STAT5 signaling, inducing different transcriptional responses in different subsets of HSCs. One signal can therefore increase HSC proliferation, competitiveness, and self-renewal through bimodal effects on HSC gene expression, cycling, and reconstituting potential. We are currently investigating the mechanism underlying $Nras^{G12D}$ induced bimodal effect on HSCs.

CONCURRENT IVD: HEMATOPOIESIS

WEST BALLROOM C/D

Supported By The Hospital for Sick Children Research Institute

INTEGRATION OF CELL INTRINSIC AND EXTRINSIC SIGNALS IN LINEAGE CHOICE OF HEMATOPOIETIC STEM CELLS

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It is of central importance for stem cell biology and the production of specific sell types to understand the principles of lineage specification. In this context hematopoietic stem cells (HSC) have served as a central model to decipher the underlying mechanisms. More specifically we have studied the role of transcription factors and haematopoietic cytokines to analyze the specific contribution of cell intrinsic and extrinsic factors in cell fate choice of HSC. Whereas cytokines are known to increase output of specific mature cells by affecting survival, expansion and differentiation of lineage committed progenitors, it has been long questioned whether long-term haematopoietic stem cells (HSC) are susceptible to direct lineage-specifying effects of cytokines. Previously it has been widely assumed that the initiation of HSC commitment is triggered by stochastic fluctuation in cell intrinsic regulators, leaving cytokines the task of simply ensuring survival and proliferation of the progeny cells after the choice has been made. We could recently show, however, that M-CSF, a myeloid cytokine released during infection and inflammation, can act directly on HSC in vitro and in vivo to instruct a change of cell identity. Using various single cell assays we observed that this cytokine could directly induce the myeloid master regulator PU.1 and instruct myeloid myeloid differentiation preference of HSC, independently of selective survival or proliferation. We show that high levels of M-CSF can induce a rapid but transient burst of mature myeloid cell production that can protect the host from both fungal and bacterial infection during stem cell transplantation without affecting long term stem cell activity. Our data show that stress-induced cytokines can directly instruct a functionally important change in lineage output of HSC to produce new blood cells that are adapted to the specific challenge. Finally we observed that endogenous levels of the transcription factor MafB affect both the timing and extent of cell cycle entry in response to M-CSF and this way indirectly impact on the rate of myeloid commitment of HSC. Thus both the strength of the external signal and the setting of the intrinsic signal processing machinery determine lineage choice of stem cells.

GPI80 DEFINES SELF RENEWAL ABILITY IN HEMATOPOIETIC STEM CELLS DURING HUMAN DEVELOPMENT

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Advances in pluripotent stem cell and reprogramming technologies have provided hope of generating transplantable hematopoietic stem cells (HSC) in culture. However, greater understanding of the identity and regulatory mechanisms that define the self-renewing HSC during human development is required to reach this goal. We discovered that the glycophosphatidylinositol-anchored surface protein GPI-80 (Vanin-2), previously implicated in neutrophil migration, distinguishes the subpopulation of human fetal hematopoietic stem and progenitor cells (HSPC) that possess self-renewal ability. CD34+CD90+CD38-GPI80+ HSPCs were the only population that could undergo self-renewing cell divisions and maintain proliferative potential and undifferentiated state in co-culture on supportive mesenchymal stem cell stroma, and displayed engraftment potential in sublethally irradiated, immune-deficient NSG mice. GPI-80 expression also enabled tracking of human HSC during development after they have emerged from hemogenic endothelium and migrate between human fetal hematopoietic niches (e.g. the placenta, fetal liver and fetal bone marrow). Microarray analysis comparing fetal liver CD34+CD90+CD38-GPI80+ HSPC to their immediate progeny (CD34+CD90+CD38-GPI80-) demonstrated remarkable molecular similarity of the two functionally distinct hematopoietic populations, yet identified novel candidate self-renewal regulators enriched in GPI-80 HSPC. The two most highly enriched transcripts were transcription factor HIF3alpha and ITGAM, an integrin that co-operates with GPI-80 to enable leukocyte adhesion and diapedesis. Image-stream analysis evidenced co-localization of GPI-80 and ITGAM on the surface of fetal HSC, as shown in neutrophils. Knockdown of GPI-80, ITGAM or HIF3alpha documented the necessity of all three molecules in sustaining human fetal HSC self-renewal. These findings provide new insights to the poorly understood regulation of human HSC development and suggest that human fetal HSCs utilize common mechanisms with leukocytes to enable cell-cell interactions critical for HSC self-renewal. Our studies also showed that while GPI-80 is not expressed in hemogenic endothelial precursors isolated from

embryoid bodies (EB) during human ES cell differentiation, GPI-80 expression can be induced in a subset of EB derived CD34+CD38-CD90+CD45+ cells during their developmental maturation on mesenchymal stroma. The finding that GPI-80 expression can be detected in pluripotent stem cell (PSC) derived HPC that are defective in self-renewal implies that GPI-80 expression is necessary, but not sufficient, for self-renewal ability. GPI-80 can now be used to track the migration of self-renewing human fetal HSC in their in vivo niches as well as investigate the appearance and developmental maturation of PSC-derived HSC precursors, thereby helping to define the pre-requisites for generating self-renewing HSC for therapeutic use.

REGULATION OF HEMATOPOIETIC STEM CELLS BY THEIR MATURE PROGENY: MPL EXPRESSION ON MEGAKARYOCYTES AND PLATELETS IS DISPENSABLE FOR THROMBOPOIESIS BUT ESSENTIAL FOR PREVENTION OF MYELOPROLIFERATION

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Thrombopoietin (TPO) is the major cytokine regulator of steady state platelet production and is required for rapid responses to platelet loss. TPO is produced primarily in the liver at a rate largely independent of platelet number. The circulating level of TPO is thought to be regulated by internalization and degradation of TPO via a specific receptor, the Mpl protein, on platelets and megakaryocytes. In general, the circulating concentration of TPO depends on the number of Mpl-expressing cells, providing an effective feedback regulatory mechanism whereby the availability of TPO to stimulate megakaryopoiesis is inversely proportion to platelet number and appropriate to the need for cellular production. TPO binding its specific receptor Mpl controls megakaryocyte number by stimulating megakaryocyte progenitor cells. TPO is also an important regulator of hematopoietic stem cell (HSC) number and activity. However, whether Mpl expression on megakaryocytes is required for efficient production of platelets, once megakaryocytes are formed, is unclear.

To define the role of Mpl/TPO in megakaryocytes and platelets for thrombopoiesis and to definitively assess the importance of Mpl expression on these cells in control of circulating TPO concentration, we generated a conditional cre-dependent knockout Mpl allele that included the ability to detect transcriptional activity of the locus via a green fluorescent protein (GFP) reporter. As expected, mice with whole-body cre-mediated inactivation of Mpl were thromobocytopenic and failed to make sufficient megakaryocytes, identical in phenotype to our previously published Mpl-/- mice. However, specific inactivation of Mpl in megakaryocytes and platelets, using a platelet factor 4 cre-recombinase (PF4cre) transgene, resulted in an unexpected and a dramatic megakaryocytosis and thrombocytosis, with platelet numbers approximately 10-fold in excess of controls. We confirmed the specific absence of Mpl expression on megakaryocytes and platelets, with expression maintained within HSCs and on specific progenitor cells with megakaryocytic potential. Moreover, the thrombocytosis in MplPF4cre/PF4cre mice was accompanied by myeloproliferation - a remarkable expansion of stem and progenitor cells accompanied by significant skewing of bipotential erythroid-megakaryocytic progenitors in favor of megakaryocyte production. Thus our work provides important advances in understanding the roles of TPO and Mpl in HSC regulation and thrombopoiesis. The data establish the novel discovery that that Mpl expression on megakaryocytes is dispensable for platelet production and that the key role for TPO signaling in maintaining platelet numbers is via stimulation of megakaryopoiesis via effects on stem and progenitor cells. Moreover, Mpl expression on megakaryocytes and platelets is a critical means of communication between the mature hematopoietic cell compartment and HSCs, preventing myeloproliferation via regulation of available TPO to the stem cell pool. The previous observation in human myeloproliferative neoplasms of low Mpl expression on megakaryocytes and platelets accompanied by normal or increased TPO levels - despite thrombocytosis - suggests that subversion of feedback communication between megakaryocytes/platelets and HSCs may contribute to human disease.

MITOCHONDRIAL ACTIVITY DETERMINES HEMATOPOIETIC STEM CELL POTENTIAL

Vannini, Nicola, Girotra, Mukul, Naveiras, Olaia, Campos, Vasco, Williams, Evan, Roch, Aline, Auwerx, Johan, Lutolf, Matthias P.
Ecole polytechnique federale de Lausanne, Switzerland

Cellular metabolism is emerging as a crucial regulator of the hematopoietic stem cell (HSC) pool in the adult bone marrow. Accordingly, the low oxygen tension found in some niches imposes a distinct metabolic phenotype that protects these long-lived and rare cells from high levels of reactive oxygen species (ROS). Although HSC quiescence has for long been associated with low mitochondrial activity, as testified by the low rhodamine stain that marks primitive HSC, we hypothesized that mitochondrial activation could be an HSC fate determinant in its own right. We examined the mitochondrial activation profile of each murine hematopoietic stem and progenitor compartment in adult mice. We found that long-term HSC (LT-HSC; Lin-cKit+Sca1+ (LKS) CD150+CD34-), short-term HSC (ST-HSC; LKS CD150+CD34+), multipotent progenitors (MPP; LKS CD150-) and committed progenitors (Lin-cKit+Sca1-) display highly distinct mitochondrial

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activity profiles, increasing with each commitment step. Strikingly, we found that overall function of the hematopoietic progenitor and stem cell compartment can be resolved by mitochondrial activity alone, as illustrated by the fact that LKS cells having low mitochondrial activity (LKS:TMRMlow) can provide efficient long-term engraftment, while those having high mitochondrial activity (LKS:TMRMhigh) cannot engraft in lethally irradiated mice. Moreover, low mitochondrial activity can also predict efficiency of engraftment within the LT-HSC and ST-HSC compartments, opening the field to a novel method of discriminating a population of transitioning ST-HSC that retain long-term engraftment capacity. Furthermore, transcriptome analysis revealed that loss of self-renewal activity is tightly linked to upregulation of important metabolic pathways such as the TCA cycle and pyruvate metabolism. Finally, with our new approach we were able prospectively identify stem cell activity of HSC cultured in vitro, where the standard surface marker repertoire fails to predict in vivo function. Collectively, our data show that low mitochondria activity is a key feature of HSC and suggest that regulation of mitochondrial metabolism is crucial for HSC maintenance.

POSTER TEASERS:

F-1081 SPI IS ESSENTIAL AT EARLY STAGES OF DEVELOPMENT FOR NORMAL HAEMOPOIETIC DIFFERENTIATION

Gilmour, Jane[1], Assi, Salam A.[1], Kulu, Divine[2], van de Werken, Harmen[2], Westhead, David[3], Philipsen, Sjaak[2], Bonifer, Constanze[1]

[1]University of Birmingham, Birmingham, United Kingdom, [2]Erasmus University Department Cell Biology and Genetics, Rotterdam, Netherlands, [3]Leeds University, Leeds, United Kingdom

F-1069 ASYMMETRY IN SKELETAL DISTRIBUTION OF MURINE HEMATOPOIETIC STEM CELL CLONES AND THEIR EQUILIBRATION BY MOBILIZING CYTOKINES

Bystrykh, Leonid, Verovskaya, Evgenia, Broekhuis, Mathilde J.C., Zwart, Erik, Weersing, Ellen, Ritsema, Martha, van Poele, Theo, Bosman, Lisette J., De Haan, Gerald

European Research Institute for the Biology of Ageing, Laboratory of Ageing Biology and Stem Cells, University Medical Centre Groningen, Groningen, Netherlands

POSTER TEASERS (cont'd):

F-1088 MONOPOTENT MEGAKARYOPOIETIC PATHWAY BRIDGING HEMATOPOIETIC STEM CELLS AND MEGAKARYOCYTES

Nishikii, Hidekazu[1], Goltsev, Yury[2], Kanazawa, Yosuke[3], Umemoto, Terumasa[4], Matsuzaki, Yu[4], Matsushita, Kenji[3], Nolan, Garry[2], Negrin, Robert S.[1], Yamato, Masayuki[5], Chiba, Shigeru[3]

[1]Division of BMT, Stanford University, Stanford, CA, USA, [2]Baxer Laboratory in Stem Cell Biology, Department of Microbiology and Immunology, Stanford University, Stanford, CA, USA, [3]Department of Hematology, University of Tsukuba, Tsukuba, Ibaraki, Japan, [4]Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Shinjuku-Ku, Japan, [5]Institute of Advanced Biomedical Engineering and Science, Tokyo Women's Medical University, Tokyo, Japan

GENETIC AND EPIGENETIC CONTROL OF HEMATOPOIETIC GENE EXPRESSION

Orkin, Stuart H.

Boston Children's Hospital, Dana-Farber Cancer Institute and Harvard Medical School, USA

Hematopoietic cell gene expression and development are controlled by lineage-affiliated transcription factors in concert with more general transcription factors and epigenetic regulators. Previously we have established how lineage-affiliated factors drive commitment and differentiation. More recently, we have addressed how stage-specific gene expression is determined within a lineage. Using erythroid development from primary fetal or adult-type human CD34 progenitors, we have asked how fetal versus adult stage expression is determined. By an integrative approach we have observed that stage-specific transcription is largely dependent on stage-selective enhancers, rather than promoters. The activity of enhancers is rendered stage-selective by stage-selective cofactors acting together with the canonical lineage-specific transcription factors. Using motifs within the stage-selective enhancers as a discovery tool, we have found that interferon response factors (IRFs) favor adult-type expression. The finding that stage-selective gene expression is largely determined by enhancer sequences is consistent with large-scale genomic data correlating genetic variation in distal regulatory sequences, often identified in GWAS, with changes in gene expression during evolution or upon mutation. In this presentation the contribution of epigenetic control through polycomb repressive complex 2 (PRC2) will also be addressed. More recent findings point to distinct differences in the function of PRC2 complexes in different cellular contexts. The integrative

approaches used in this studies form the basis for a comprehensive understanding of regulatory networks in hematopoietic cells.

CONCURRENT IVE: GERMLINE BIOLOGY

WEST MEETING ROOM 301-305

DNA METHYLATION AND GENE EXPRESSION PROFILES IN MOUSE GERM CELL DEVELOPMENT

Sasaki, Hiroyuki
Kyushu University, Medical Institute of Bioregulation, Japan

The epigenetic profile of germ cells, which is defined by modifications of DNA and chromatin, changes dynamically during their development. We are interested in the roles of DNA methylation in genomic imprinting, silencing of retrotransposons, and regulation of germ cell differentiation and development. Using a whole-genome bisulfite shotgun sequencing approach applicable to small amount of DNA, we are studying the DNA methylation profiles of mouse germ cells at various developmental stages. In the male germline, the bulk genome is initially hypomethylated in primordial germ cells and becomes de novo methylated in fetal prospermatogonia (or gonocytes). After birth, the cells start to differentiate into spermatogonia, which include the stem cell population that supports continuous spermatogenesis throughout adulthood. We have determined the base-resolution DNA methylation maps and gene expression profiles of prospermatogonia, undifferentiated spermatogonia and differentiating spermatogonia in neonatal mouse testis, and found the following. Firstly, we revealed large partially methylated domains (PMDs) coincident with AT-rich, nuclear lamina-associated domains, similar to those found in cultured cell, cancer cells and placenta. PMDs have not been reported in somatic tissues and stem cells. Second, we found extremely high levels of non-CG methylation in prospermatogonia, which could be attributed to the high levels of de novo DNA methylatransferase activity in this cell type. The non-CpG methylation disappeared after the resumption of mitosis, most likely due to the lack of maintenance mechanism for asymmetric methylation. Third, we identified stage-specific differentially methylated regions closely associated with genes that regulate stem cell properties, spermatogonial differentiation and spermatogenesis. This suggests that DNA methylation plays an important role in spermatogenesis. Finally, we found an enrichment of 5-hydroxymethylcytosine in satellite repeats of neonatal prospermatogonia. Our findings reveal dynamic DNA methylation changes associated with spermatogonial stem cell generation and differentiation and suggest the critical function of this epigenetic modification in male gametogenesis.

HIGH TELOMERASE LEVELS DEFINE THE SPERMATOGONIAL STEM CELL COMPARTMENT

Pech, Matthew F.[1], Garbuzov, Alina[2], Benayoun, Berenice A.[2], Sukhwani, Meena[3], Brunet, Anne[4], Orwig, Kyle E.[3], Artandi, Steven[4]
[1]Cancer Biology, Stanford University, Stanford, CA, USA, [2]Genetics, Stanford University, Stanford, CA, USA, [3]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, [4]Stanford University School of Medicine, Stanford, CA, USA

Homeostasis of renewing tissues, including the male germline, requires efficient maintenance of telomeres by telomerase, a process impaired in patients with telomere diseases. Although telomerase is enriched in stem cells and progenitor cells, reliable detection of telomerase-positive cells in vivo has been elusive. Here, we show that high levels of telomerase reverse transcriptase (TERT) define the spermatogonial stem cell compartment by using a knock-in mouse strain in which the TERT promoter directs expression of a fluorescent reporter protein. Unexpectedly, we identify a gradient of TERT promoter activity that allows delineation of each major step in spermatogenesis and enables discrimination between spermatogonial stem cells and committed progenitor cells by fluorescence activated cell sorting. Molecular characterization of purified spermatogonial stem cells using RNA-SEQ reveals important signaling pathways, new potential stem cell regulators and links to genes required for male fertility and for male germ cell tumorigenesis. Our data suggest that elevated levels of telomerase in spermatogonial stem cells contribute to telomere maintenance and immortality of the mammalian germline and provide a molecular framework for understanding spermatogonial stem cell self-renewal and differentiation.

DNMT3L PROMOTES QUIESCENCE IN POSTNATAL SPERMATOGONIAL PROGENITOR CELLS

Liao, Hung-Fu[1], Chen, Wendy SC[1], Kao, Tzu-Hao[1], Cheng, Winston TK[1], Sasaki, Hiroyuki[2], Wu, Shinn-Chih[1], Huang, Yen-Hua[3], Ho, Hong-Nerng[4], Yen, Pauline[5], **Lin, Shau-Ping[1]**
[1]Institute of Biotechnology, National Taiwan University, Taipei, Taiwan, [2]Kyushu University, Medical Institute of Bioregulation, Fukuoka, Japan, [3]Taipei Medical University Sch of Medicine, Taipei, Taiwan, [4]Medical College, National Taiwan University, Taipei, Taiwan, [5]Institute of Biotechnology, Academia Sinica, Taipei, Taiwan

The ability of adult stem cells to reside in a quiescent state is crucial for preventing premature exhaustion of the stem cell pool. However, the intrinsic epigenetic factors that regulate spermatogonial stem cell quiescence are largely unknown. Here, we investigated how DNA methyltransferase 3-like (DNMT3L), an

PROGRAM AND ABSTRACTS

epigenetic regulator important for interpreting chromatin context and facilitating de novo DNA methylation, sustains the long-term male germ cell pool. We demonstrated that stem cell-enriched THY1+ spermatogonial stem/progenitor cells (SPCs) constituted a DNMT3L-expressing population in postnatal testes. DNMT3L influenced the stability of promyelocytic leukemia zinc finger (PLZF), potentially by downregulating Cdk2/CDK2 expression, which sequestered CDK2-mediated PLZF degradation. Reduced PLZF in Dnmt3l KO THY1+ cells released its antagonist, Sal-like protein 4A (SALL4A), which is associated with overactivated ERK and AKT signaling cascades. Furthermore, DNMT3L was required to suppress the cell proliferation-promoting factor SALL4B in THY1+ SPCs and to prevent premature stem cell exhaustion. Our results indicate that DNMT3L is required to delicately balance the cycling and quiescence of SPCs. These findings reveal a novel role for DNMT3L in modulating postnatal SPC cell fate decisions.

PERSISTENCE OF DNA METHYLATION IN EMBRYONIC STEM CELLS DEPENDS ON THE HISTONE METHYLTRANSFERASE SETDB1

Leung, Danny[1], Du, Tingting[1], Wagner, Ulrich[1], Wei, Xie[1], Lee, Ah Young[1], Goyal, Preeti[2], Li, Yujing[3], Szulwach, Keith E.[3], Jin, Peng[3], Lorincz, Matthew[2], Ren, Bing[4]
[1]Ludwig Institute for Cancer Research, La Jolla, CA, USA, [2]University of British Columbia, Vancouver, BC, Canada, [3]Emory University School of Medicine, Atlanta, GA, USA, [4]Department of Cellular and Molecular Medicine, UCSD School of Medicine, La Jolla, CA, USA

During mammalian development DNA methylation patterns need to be reset in primordial germ cells (PGC) and preimplantation embryos. However, many LTR retrotransposons and imprinted genes are impervious to such global epigenetic reprogramming via hitherto undefined mechanisms. We found that a subset of such genomic regions are resistant to widespread erasure of DNA methylation in mouse embryonic stem cells (mESCs) lacking the de novo DNA methyltransferases Dnmt3a and Dnmt3b. Intriguingly, these loci are enriched for H3K9me3 in mESCs, implicating this mark in DNA methylation homeostasis. Indeed, deletion of the H3K9 methyltransferase Setdb1 results in reduced H3K9me3 and DNA methylation levels at specific loci, concomitant with an increase in 5-hydroxymethylation (5hmC) and Tet1 binding. Taken together, these data reveal that Setdb1 promotes the persistence of DNA methylation in mESCs, likely reflecting the mechanism by which DNA methylation is maintained at LTR retrotransposons and imprinted genes in vivo during key developmental stages.

POSTER TEASERS:

F-2012 HIRA-MEDIATED H3.3 INCORPORATION IS REQUIRED FOR DNA REPLICATION AND RIBOSOMAL RNA TRANSCRIPTION IN THE MOUSE ZYGOTE

Lin, Chih-Jen[1], Koh, Fong Ming[2], Wong, Priscilla[1], Conti, Marco[1], Ramalho-Santos, Miguel[2]
[1]Center for Reproductive Sciences, University of California San Francisco, San Francisco, CA, USA, [2]University of California San Francisco, San Francisco, CA, USA

F-2006 POLAR BODY GENOME TRANSFER TO PREVENT THE TRANSMISSION OF INHERITED MITOCHONDRIAL DNA DISEASES

Wang, Tian[1], Sha, Hongying[1], Zhu, Jianhong[2]
[1]State Key Laboratory for Medical Neurobiology, Fudan University, Shanghai, China, [3]Fudan University Huanshan Hospital, Shanghai, China

F-2002 GERMLINE STEM CELL DIFFERENTIATION IS DEPENDENT ON THE FORMATION OF A DIFFUSION BARRIER BY THE SOMA IN THE DROSOPHILA TESTES

Fairchild, Michael John, Tanentzapf, Guy
Cellular and Physiological Sciences, University of British Columbia, Vancouver, BC, Canada

ARGININE METHYLATION IS REQUIRED FOR GROUND STATE NAÏVE PLURIPOTENCY AND GERM LINE POTENTIAL

Clark, Amander T., Li, Ziwei, Yu, Juehua, Feng, Youyou, Patel, Sanjeet, Hosohama, Linzi, Chaudhari, Sonal, Cass, Ashley, Clarke, Steven, Xiao, Xinshu
University of California, Los Angeles, USA

High quality pluripotent stem cell lines for research or clinical applications require an ability to self-renew and the capacity to differentiate into the four major embryonic lineages (ectoderm, mesoderm, endoderm and germ line). In recent years three pluripotent stem cell states have been described, ground state, naïve, and primed. Although we know a lot about naïve and primed pluripotency, the foundational mechanisms that govern ground state pluripotency remain to be fully established. In the current study we evaluated the role of symmetrical dimethylation of arginine (SMDA) by protein arginine methyltransferase 5 (Prmt5) in regulating both ground state pluripotency and germ line formation. In naïve pluripotent stem cells it was established

that Prmt5 is highly enriched in the cytoplasm where it promotes SMDA at arginine 3 of histone H2A (H2AR3). In ground state pluripotent stem cells we also found that Prmt5 was highly enriched in the cytoplasm, yet cytoplasmic SMDA of H2AR3 was not detected. This suggests that Prmt5's mechanism of action in ground state pluripotency may be different from its mechanism in naïve. To address this we developed Prmt5fl/fl and Prmt5fl/+ 4-hydroxytamoxifen (4OHT) inducible Cre-ERT2 embryonic stem cell (ESC) lines maintained under ground state conditions. Creation of a null or heterozygote mutation in Prmt5 after induction with 4OHT caused loss of self-renewal, increased cell size, cellular senescence, decreased survival and loss of germ-line potential in the null mutant ESC lines in vitro. Given the role of Prmt5 in splicing we used paired end RNA-Seq and discovered that Prmt5 functions to prevent exon skipping in ground state pluripotent ESC lines. Furthermore, genes with skipped exons (FDR <0.01) were enriched in gene ontology groups associated with splicing, chromatin modifications and chromosome organization. Using Western blot, immunfluorescence and mass spectrometry we revealed that Prmt5 null mutant ESCs exhibit significant changes to covalent histone modifications at lysine rather than arginine amino acids and we speculate these changes are occurring downstream of abnormally spliced chromatin writers and erasers. Finally, in order to evaluate the role of Prmt5 in germ line development in vivo we generated a conditional loss of function mutation using Blimp1-Cre, and similar to ESCs we find that loss of Prmt5 in the germ-line leads to PGC senescence, increased heterochromatization and apoptosis at the time when Prmt5 becomes enriched in the cytoplasm.

SATURDAY, JUNE 21, 9:00 AM - 11:20 AM

PLENARY V: INFLAMMATION AND TISSUE REPAIR

PLENARY HALL

TYPE 2 INNATE SIGNALS REGULATE MUSCLE REGENERATION

Chawla, Ajay
University of California, San Francisco, USA

In vertebrates, activation of innate immunity is an early response to injury, implicating it in the regenerative process. However, the mechanisms by which innate signals might regulate stem cell functionality are unknown. Here we demonstrate that type 2 innate immunity is required for regeneration of skeletal muscle after injury. Muscle damage results in rapid recruitment of eosinophils, which secrete IL-4 to activate the regenerative actions of muscle resident fibro/adipocyte progenitors (FAPs). In FAPs, IL-4/IL-13 signaling serves as a key switch to control their fate and functions. Activation of IL-4/IL-13 signaling promotes proliferation of FAPs to support myogenesis, while inhibiting their differentiation into adipocytes. Surprisingly, type 2 cytokine signaling is also required in FAPs, but not myeloid cells, for rapid clearance of necrotic debris, a process that is necessary for timely and complete regeneration of tissues.

INFLAMMATION CONTROLLED CELL PLASTICITY AND STEMNESS IN COLON CANCER

Greten, Florian
Georg-Speyer-Haus, Germany

Over the last years we were able to obtain in vivo evidence highlighting the functional importance of IKK/NF-κB in inflammation-associated intestinal carcinogenesis. Using different genetic mouse models of sporadic colon cancer that allow functional analysis specifically of tumor initiation, promotion and progression, we have now identified novel distinct regulatory functions of IKK signaling during different tumor stages. These comprise dedifferentiation of epithelial cells into tumor stem cells, epithelial-mesenchymal transition as well macrophage polarization. Interestingly, the two catalytical subunits of the IKK complex mediate diverse and context dependent functions.

Geissmann, Frederic
King's College, London, UK

Not available at time of printing.

EPITHELIAL DYNAMICS IN THE GUT OF DROSOPHILA IN RESPONSE TO INDIGENOUS AND PATHOGENIC MICROBES

Buchon, Nicolas
Cornell University, USA

The midgut of Drosophila is a highly compartmentalized organ and a major site of interaction between the fly and microbes, both benign and pathogenic. In response to infection, the midgut relies on two complementary mechanisms for survival: a potent immune response to eliminate bacteria and repair mechanisms to cope with infection-induced damage. The immune response incorporates the production of reactive-oxygen species by NADPH-oxidases and the induced expression of antimicrobial peptides by the Imd pathway. Upon infection, both the virulence of the pathogen ingested and the immune response itself inflict damage to the gut epithelium. This damage is repaired by an acceleration of epithelium renewal that combines increased delamination of enterocytes with reprogramming of intestinal stem cells to proliferate and regenerate

the gut epithelium. The proper regulation of epithelium renewal, as well as its coordination with immune effector mechanisms, is required to maintain intestinal homeostasis and organismal health. However, it remains unclear how epithelium renewal is quantitatively regulated upon infection, and restored to basal renewal afterwards. In addition, it is yet to be determined whether epithelial dynamics vary in different regions of the gut upon infection. In this talk, we will present new data on the mechanisms that control cell dynamics upon infection, and how epithelium renewal is quantitatively regulated along the gut. In addition, we will discuss how both indigenous and pathogenic microbes alter stem cell activity in the gut.

ISSCR - BD Biosciences Outstanding Young Investigator Lecture

UNCOVERING CELLULAR AND SIGNALING MECHANISMS OF SKIN REGENERATION USING TWO-PHOTON MICROSCOPY

Greco, Valentina, Rompolas, Panteleimon, Zito, Giovanni, Deschene, Elizabeth, Myung, Peggy, Mesa, Kailin, Gonzalez, David, Haberman, Ann, Saotome, Ichiko
Yale University School of Medicine, USA

Since starting my lab, our goal has been to understand how stem cells and their environment, also called niche, contribute to organ regeneration, and how dysregulation of growth signals leads to cancer. The major challenge in studying these questions has been the inability to follow the same cells in vivo and to understand how their interactions with neighboring cells contribute to tissue growth. To overcome this challenge, my lab has established the ability to visualize and manipulate stem cells and their environment in an intact mammal using two-photon microscopy and laser ablation.
Using the hair follicle as a stem cell model system, we have thus far 1) elucidated the cellular behaviors driving hair regeneration, including novel migratory epithelial behaviors which exemplify the power of live imaging over static analysis. 2) Demonstrated that the niche is required for tissue regeneration whereas stem cells are dispensable. These unexpected findings indicate that an intact niche provides a robust compensatory mechanism, whereby other cell types can adopt specialized stem cell function to drive tissue regeneration. 3) Shown that stem cells are not all equal in fate and their fate decision depends on the position they inhabit in their environment. This discovery revealed the fundamental importance of the environment in stem cell fate and overall tissue regeneration. 4) Demonstrated that an evolutionarily conserved pathway, Wnt/β-catenin, promotes growth non cell-autonomously. These findings provide a novel understanding of β-catenin-mediated tissue growth and it identifies a novel signaling mechanism by which cells can co-opt their neighbors to participate in tissue growth. 5) Identified mechanisms of skin tumor regression via activation of Retinoic Acid (RA) by utilizing a unique skin tumor capable of self-regressing, called Keratoacanthoma. Importantly, we show that applied RA can also induce regression of the malignant Squamous Cell Carcinoma.
Taken together, by visualizing stem cells in vivo and identifying signaling pathways that regulate normal skin and skin cancer growth, we have made key contributions to our understanding of organ growth and cancer regulation. Our work has provided important insights into tissue regeneration, which relies upon the coordinated activation of resident stem cells and their environment, and into key signaling pathways controlling dynamic stem cell behaviors and decisions.

SATURDAY, JUNE 21, 1:15 PM - 3:00 PM

PLENARY VI: MESENCHYMAL STROMAL CELLS

PLENARY HALL

Supported by Mesoblast Ltd.

"MESENCHYMAL" STEM CELLS BETWEEN COMMERCE AND PATHOPHYSIOLOGY

Bianco, Paolo
Sapienza University of Rome, Italy

Our understanding of the biology of stem/progenitor cells for the skeleton and for extraskeletal, solid-phase mesoderm derivatives has been hindered by the creation and dissemination of commerce-oriented definition of biological nature and properties of an otherwise unique system. Defining the biology of "MSCs" in an unbiased fashion has however major implications for the understanding of physiology and disease. Stem cells in the bone marrow stroma critically contribute to the HSC niche, while at the same time acting as self-renewing progenitors for bone and fat cells. In this way, they represent the central relais of adaptive reponses of the entire bone environment and of hematopoiesis. Human stromal stem cells are best explored by current versions of the classical heterotopic transplantation approach; in these systems, human stromal progenitors can establish HSC niches and capacitors in the absence of all the cell types that have been implicated with a "niche" function in the mouse bone marrow; they can also establish a unique metastatic niche sought by blood borne human cancer cells, resulting in humanized models of cancer metastasis. In addition, organoids that result from heterotopic transplantation reveal unique aspects of skeletal morphogenesis, including, notably, phenotype reversibility as one of the unique features of the stromal system. For example, establishing a stromal HSC niche can be done by transplanting ex vivo generated chondrocytes, which can revert

to a stromal phenotype in vivo. Marrow fat cells, which represent a local modulation of marrow perivascular progenitors, actually represent a compartment of cAMP-sensitive "beige" fat, recruitable to a thermogenic function. Expression of constitutively active, mutated Gs-alpha, which couples signals from the beta2-adrenergic receptor, in marrow fat cells further convert "beige" marrow adipocytes to an aberrant osteoblastic phenotype, noted for ectopic expression of adipocyte genes in osteoblasts, causing osteoblast dysfunction. This reveals the cause of one crippling skeletal disease, Fibrous Dysplasia (OMIM174800), the role of the stromal system in bone disease, and specific druggable mechanisms centered in the biology of stromal progenitors and dependent system of lineages. As SNS inputs are the prime feeder of Gsa signaling in the stromal system, neural control of the stromal cell system in bone marrow is a central regulator of the integrated physiology of hematopoiesis and the skeleton.

IMMUNE REGULATION BY MESENCHYMAL STEM CELLS

Shi, Yufang
Institute of Health Sciences, China

Mesenchymal stem cells (MSCs), also known as multipotent mesenchymal stromal cells, exist in most tissues and are a key cell source for tissue repair and regeneration. When tissue is damaged, these cells are mobilized to the site of injury. As tissue injury is often accompanied by inflammation, the recruited MSCs are subject to the influence of inflammatory factors and cells. This is a bidirectional interaction: while the MSCs respond to inflammatory factors, the MSCs also affect the immune microenvironment. We have reported that MSCs become potently immune modulatory in response to IFNγ and TNFα (or IFNγ and IL-1), which together provoke MSCs to express large amounts of immune cell specific-chemokines, as well as iNOS (in mice) or IDO (in humans). These chemokines attract immune cells into close proximity with MSCs, where high levels of NO or IDO metabolites then suppress the immune cells. The relationship between MSCs and the immune microenvironment confers upon MSCs a unique function: the ability to generate immunosuppression in response to normally proinflammatory factors (such as IFNγ, TNFα, IL-1 or IL-17), and enhanced immune responses from typically immunosuppressive factors (TGFβ or glucocorticoids). Indeed, we have shown that MSCs that are normally curative in liver cirrhosis can actually promote inflammation in the presence of dexamethasone. We will focus on the crosstalk between MSCs and immune responses and their potential clinical applications especially in inflammation-mediated diseases.

PATHOGENESIS RECAPITULATES ONTOGENESIS: LESSONS FROM THE HEMATOPOIETIC STEM CELL NICHE IN THE BONE MARROW

Mendez-Ferrer, Simon
Centro Nacional de Investigaciones Cardiovasculares, Spain

Lineage and functional relationships among non-hematopoietic cells have remained largely unclear, contrasting with the knowledge accumulated regarding their hematopoietic neighbors in the bone marrow. Among other cell types, neural and glial cells, mesenchymal stem cells and osteochondral cells have been proposed as key elements of the hematopoietic stem cell niche in the bone marrow. However, the developmental and functional relationships of these cells have remained poorly characterized. We previously showed that bone marrow nestin+ mesenchymal stem cells innervated by sympathetic nerve fibers regulate normal hematopoietic stem cells. Our recent data has demonstrated the relevance of this circuitry in human pathology; damage to this regulatory network is required for the manifestation of myeloproliferative neoplasms, diseases that were previously considered to be autonomously driven by mutated hematopoietic stem cells. Nestin+ mesenchymal stem cells negatively regulate the expansion of mutated hematopoietic stem cells but they do not give rise to the excessive fibroblasts and osteoblasts characteristic of these diseases. Also, physiological skeletal turnover seems to depend mostly on nestin- mesenchymal precursors. These data suggested a potential segregation of skeletal and hematopoietic stem cell maintenance in different mesenchymal progenitors. We have addressed this question from a developmental point of view. Our recent data shows that different mesenchymal stem cells have distinct functions in the developing bone marrow of the axial skeleton. While mesoderm-derived nestin- mesenchymal stem cells proliferate quickly and participate in fetal skeletogenesis, they lose stem cell activity soon after birth. In contrast, neural crest-derived nestin+ cells proliferate slowly, do not generate fetal chondrocytes and retain mesenchymal stem cell activity over longer time periods. Perineural migration of these neural crest-derived cells to the bone marrow is required for the formation of the hematopoietic stem cell niche. Therefore, our data shows that organismal control of a peripheral stem cell niche through a master regulator of vertebrates, the autonomic nervous system, is relevant in pathogenesis and builds upon an ontogenic relationship of their components. This is evidenced by multiple contributions of the neural crest to a peripheral stem cell niche: nerves, supporting Schwann cells and mesenchymal stem cells with specialized niche functions.

PROGRAM AND ABSTRACTS

MESENCHYMAL STROMAL CELLS IN TISSUE HOMEOSTASIS AND REGENERATION

Underhill, T. Michael
University of British Columbia, Canada

Adult stem and progenitor cells play fundamental roles in tissue homeostasis, renewal and regeneration, and when these cells become dysfunctional they contribute to a myriad of diseases including cancer, fibrosis, accelerated aging and degenerative disorders. Mesenchymal stromal cells (MSCs) represent one type of adult progenitor cell and can be found to varying extents in most tissues. In homeostasis, MSCs are mostly in an inactive, or quiescent, state and become "activated" in response to various signals. Activation is typically associated with MSC re-entry into the cell cycle where they produce an environment to support tissue regeneration. To better understand the role of MSCs in tissue renewal and regeneration, we have developed mouse models that involve knock-in of LacZ or CreERT2 into a gene largely restricted to quiescent MSCs. Lineage and marker analysis shows that these cells generally reside in a perivascular location and commonly express a cluster of markers associated with MSCs, such as Nestin, Platelet derived growth factor alpha (PDGFRA), Sca-1 and CD34. To better understand the contribution of MSCs to tissue renewal and growth, long-term lineage analysis was performed that involved characterization of tdTomato reporter gene +ve cells 90 - 180 days post-tamoxifen injection in ~ 8 week old mice. TdTomato +ve cells were found to make a significant contribution to multiple mesenchymal lineages including adipocytes (both beige and white), chondrocytes, osteocytes, marrow stromal cells, as well as alpha-SMA +ve myofibroblasts. Under these conditions we observed no appreciable contribution to the myogenic lineage. To more rigorously assess the contribution of this identified population of MSCs to myogenesis, a notexin-induced muscle regeneration model was used to follow their fate after injury. Shortly after notexin-induced damage, tdTomato +ve cells re-enter the cell cycle and are disseminated throughout the damaged region. TdTomato-expressing cellular processes can be found enveloping the regenerating myofibres as well as the vasculature. In this regard, these "activated" cells appear to play fundamental roles in both stabilizing the damaged region and in potentially providing trophic support for regeneration. As the damage is resolved, MSCs (LacZ knock-in allele) return to their normal frequency and distribution. Interestingly, at 28-days post notexin-injection, tdTomato +ve cells can be found throughout the regenerated muscle, however, no tdTomato+ myofibres were found, indicating that these labelled MSCs do not directly contribute to the myogenic lineage. These two mouse models are currently being used to better understand the nature, fate and function of MSCs in tissue homeostasis and regeneration.

SATURDAY, JUNE 21, 3:40 PM - 6:00 PM

PLENARY VII: EPIGENETICS AND PLURIPOTENCY

PLENARY HALL

Supported By Fate Therapeutics

REPROGRAMMING TO PLURIPOTENCY

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

We are interested in the epigenetic mechanisms that maintain the pluripotent state and govern reprogramming to the iPSC state, as the generation of iPSCs presents a powerful tool for dissecting mechanisms that stabilize the differentiated state and are required for the establishment of pluripotency. Particularly for therapeutic applications, it is vital that basic issues surrounding reprogrammed cells are settled, the limits of reprogramming understood, and the epigenetic stability of the pluripotent state is carefully dissected. We also believe that understanding these questions at a mechanistic level is integral to our ability to modulate expression states and cell identities. Our approach is two-fold: First, we are studying how the reprogramming transcription factors induce pluripotency in somatic cells. We have mapped where the reprogramming factors bind at various stages of reprogramming genomically, and how binding is associated with transitions in chromatin states and transcription. These studies inform us on the mechanisms by which transcription factors control the cell fate transitions during reprogramming. Second, we are examining the dynamics of X chromosome-inactivation in pluripotent cells and during reprogramming, to understand how heterochromatin is reset during reprogramming to pluripotency and assess its stability in pluripotent cells. Our findings on the dynamics of the inactive X chromosome in female human pluripotent stem cells have important implications for the use of these cells in disease modeling and other translational studies.

DNA OXIDATION TOWARDS TOTIPOTENCY IN MAMMALIAN DEVELOPMENT

Xu, Guo-liang
Institute of Biochemistry and Cell Biology, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences, China

Mammalian development begins with a single cell resulted from the fertilization of a sperm and an oocyte. The early embryonic genome undergoes profound epigenetic reprogramming to prepare for development. The biological significance and mechanisms

of epigenetic reprogramming are poorly understood. We find that 5-methylcytosine (5mC), the most abundant type of base modification in DNA, is oxidized to 5-hydroxymethylcytosine (5hmC) as well as 5-carboxymethylcytosine (5caC) in mouse zygotes. In vitro, the Tet family of dioxygenases oxidize 5mC to 5caC under physiologically relevant conditions (e.g. in the presence of 1mM ATP). In zygotes, the Ten-eleven-translocation protein Tet3 is responsible for the genome-wide oxidation of 5mC to 5hmC and 5caC. Deficiency of zygotic Tet3 impedes demethylation at the paternal Oct4 and Nanog genes and delays the reactivation of Oct4 in early embryos. The heterozygous mutant embryos lacking maternal Tet3 suffer increased developmental failures. Importantly, oocytes lacking Tet3 also show impaired reprogramming of injected somatic cell nuclei. In addition, MEFs deficient in all Tet genes were unable to be reprogrammed by Yamanaka factors. We conclude that Tet-mediated oxidation is important for DNA demethylation and gene activation in the early embryo following natural fertilization, as well as for the reprogramming in somatic cell nuclear transfer and factor-based iPSC generation.

Deng, Hongkui
College of Life Sciences at Peking University, China

Not available at time of printing.

Keynote Address

FROM YEAST CELLS TO HUMAN NEURONS-MODELING COMPLEX PROTEIN FOLDING DISEASES

Lindquist, Susan
Whitehead Institute for Biomedical Research, USA

Many neurodegenerative diseases result from basic problems in protein folding and homeostasis. These disorders appear to have little in common besides their devastating effects on patients and their families. However, they share the occurrence of complexes of misfolded, aggregated proteins in affected neurons. In Parkinson's disease (PD) the protein is alpha-synuclein (α-syn) and in Alzheimer's disease (AD) Aβ and tau are involved. Exploiting the highly conserved nature of eukaryotic cell biology and protein homeostasis mechanisms, we have developed yeast models for the pathologies caused by these proteins. Yeast cells offer unmatched opportunities for systematic, high throughput combinatorial analyses of causative factors and the discovery of pathology modifiers. Remarkably, each of the models exhibits cellular toxicity by a different mechanism and each yields a discovery platform directly relevant to human disease.

Yeast cells overexpressing human α-syn or Aβ allow genetic and chemical screens, which would only be possible in yeast at such high throughput. Our α-syn screens yielded genes and compounds that rescued dopaminergic neurons in nematode, fruit fly and rat primary midbrain cultures as well as cortical human neurons differentiated from the iPS cells of patients with PD. Our Aβ screens revealed genes and compounds that specifically rescue neurons from Aβ, and other AD risk factors. Combining these discovery platforms with state-of-the art chemical genetics allowed the identification of compounds with high therapeutic potential as well as insight into their mechanisms of action.

INNOVATION SHOWCASES

THURSDAY, JUNE 19, 8:00 AM - 8:30 AM

AN INTEGRATED WORKFLOW FOR THE ISOLATION, EXPANSION, AND CHARACTERIZATION OF HEMATOPOIETIC PROGENITORS AND THEIR CONVERSION TO INDUCED PLURIPOTENT STEM CELLS IN DEFINED CULTURE CONDITIONS

Wing Chang, PhD, Scientist and
Steve Szilvassy, PhD, Director, Hematopoietic Products
STEMCELL Technologies
WEST BALLROOM A

Hematopoietic stem and progenitor cells are undoubtedly the most well studied tissue-specific precursor cells and now are commonly used for generating iPSCs. This presentation will describe the isolation, expansion, and characterization of human blood-derived CD34+ progenitors and erythroid cells, and methods for subsequent reprogramming of these cells to iPSCs using defined culture conditions. The tutorial will highlight STEMCELL Technologies integrated workflow for manipulating hematopoietic development in vitro and the generation of iPSCs from these precursors.

THURSDAY, JUNE 19, 8:00 AM - 8:30 AM

DIFFERENTIATING STEM CELL POPULATIONS WITH SUCCESS

Joy Aho, PhD
R&D Systems
WEST BALLROOM B

The utility of stem cells resides in their ability to differentiate into a multitude of cell types, providing powerful tools for regenerative medicine and drug toxicity testing. Differentiation protocols can be fraught with unknown variables and are time- and reagent-consuming. We present tools and protocols to reduce experimental variability and drive efficient stem cell differentiation. We will discuss methods to simultaneously measure protein levels of established markers and investigate functional characteristics of derivative cells.

THURSDAY, JUNE 19, 8:00 AM - 8:30 AM

LARGE PARTICLE FLOW CYTOMETRY PROVIDES HIGH THROUGHPUT ANALYSIS AND AUTOMATION FOR CELL CLUSTERS (EBS, SPHEROIDS) AND ENCAPSULATED 3D CELL CULTURES

Rock Pulak, Ph.D.
Union Biometrica
WEST MEETING ROOM 211-214

Embryonic stem cells (embryoid bodies), neural stem cells (neurospheres), certain solid tumors (tumorspheres) and other cell types all tend to form cell clusters. These clusters are a more natural arrangement, where cell-cell interactions and cell-substrate contacts can be established and maintained. Union Biometrica discusses the use of their Large Particle Flow Cytometers for automating the multiparametric analysis and gentle intact dispensing of these types of cell clusters to wells of multi-well plates.

THURSDAY, JUNE 19, 8:00 AM - 8:30 AM

USING STEM CELLS TO STUDY NEURODEGENERATIVE DISEASE

Prof. Lee Rubin, Harvard University
Nikon Corporation
WEST MEETING ROOM 301-305

The general idea of using stem cells to discover new treatments for serious neurodegenerative diseases, especially, "in vitro clinical trial" using the live cell imaging system is described. Nikon has been provided the live cell imaging system (BioStation CT) and it has been well accepted in the stem cell research field. This advanced system has the capability of the long term observation and measuring cell behavior with image analysis technology.

THURSDAY, JUNE 19, 11:30 AM - 12:30 PM

INDUCTION OF A NATIVE STATE IN HUMAN PLURIPOTENT STEM CELLS

Huck-Hui Ng, PhD, Executive Director,
Genome Institute of Singapore
STEMCELL Technologies
WEST BALLROOM A

In contrast to traditional hPSC cultures, native or naïve hPSCs are more primitive, resembling cells of the pre-implantation blastocyst. Beyond their importance for studying early development, naïve cells may accelerate pluripotent cell therapies, owing to their single-cell

INNOVATION SHOWCASES

passaging compatibility, robust growth and amenability to genetic manipulation. Dr. Ng will discuss his ground-breaking research on induction and maintenance of a novel state in established human embryonic stem cell lines using mTeSR™1 medium and small molecules.

During the second half-hour, from 12:00-12:30pm, Erik Hadley, PhD, Senior Scientist will present *Scalable Enzyme-Free Protocols for the Isolation and Maintenance of Human Induced Pluripotent Stem Cells (hiPSCs) Without Mechanical Colony Scraping.* This tutorial focuses on fibroblast reprogramming and hiPSC maintenance protocols which use ReLeSR™, an enzyme-free passaging reagent that eliminates manual removal of differentiated cells, colony scraping and complicated techniques to obtain uniform cell aggregates. When used with mTeSR™1 or TeSR™-E8™, ReLeSR™ enables the use of closed vessels, thus facilitating scale-up and automation. Applicability of ReLeSR™ in a complete workflow from fibroblast reprogramming to the establishment of a new hiPSC line will be discussed.

THURSDAY, JUNE 19, 11:30 AM - 12:30 PM

BRIDGING RESEARCH TO THERAPY: NOVEL IPSC TOOLS AND TECHNOLOGIES

Behnam Ahmadian Baghbaderani, Ph.D., Lonza Cell Therapy Development Services

LONZA

WEST BALLROOM B

Dr. Yamanaka's Nobel Prize winning discovery has spurred scientific advancements in basic research, disease modeling, drug development, and regenerative medicine. We have assembled three speakers that describe how Lonza is working to help stem cell researchers overcome their challenges.

From the Nobel Prize to the Clinic: One Step Closer to iPSC-based Therapies
Behnam Ahmadian Baghbaderani, Ph.D., Lonza Cell Therapy Development Services

Lonza L7™ Reprogramming and Cell Culture System - A Case Study
Yu-Chieh Wang, Ph.D., Center for Regenerative Medicine, The Scripps Research Institute

Highly Efficient and Specific Human Genome Editing in iPSCs Using CRISPR-Cas9 System
Linzhao Cheng, Ph.D., Professor of Medicine and Oncology, Stem Cell Program, Johns Hopkins School of Medicine

Dr. Baghbaderani will introduce Lonza's L7™ Reprogramming and Culture System outlining the benefits for the generation and maintenance of iPSCs for research and clinical applications. Dr. Wang will review the potential challenges in cell reprogramming and how the L7™ System helps researchers overcome these hurdles. Lastly, Professor Cheng will present the latest results on human genome editing in iPSCs using CRISPR-Cas9 system and address issues related to the level of off-target rates in human iPSCs. Collectively, these timely presentations will showcase the latest innovative technologies and tools to empower scientists conducting human stem cell research.

THURSDAY, JUNE 19, 11:30 AM - 12:30 PM

POWERING DISCOVERY THROUGH SINGLE-CELL BIOLOGY: UNRAVELING CELL FATE, DIFFERENTIATION AND LINEAGE

Nianzhen Li, Senior Scientist, Fluidigm Corporation

Fluidigm

WEST BALLROOM C/D

THURSDAY, JUNE 19, 11:30 AM - 12:30 PM

CELL SURFACE MARKER SCREENING & ANALYSIS OF STEM CELL POPULATIONS

Robert Balderas and Christian Carson

BD Biosciences

WEST MEETING ROOM 211-214

The first half-hour will be dedicated to how cell surface marker analysis of stem cells allows for phenotypic characterization as wll as cell purification. This tutorial will include the disscussion of the following topics:

- Designing and performing cell surface marker screens to identify unique surface signatures for the isolation of stem cells and their derivatives
- Effective sorting of pluripotent and neural lineages
- Flow Cytometry panel design and instrument optimization for stem cell populations

The second half-hour, from 12:00-12:30 PM, will focus on the *Use of Intracellular Flow Cytometry to Monitor Lineage Differentiation and Potency in Stem Cells*. Presenters Robert Balderas and Nil Emre will demonstrate how intracellular flow cytometry enables the quantitative measurement of stem cell populations and their derivatives. Applications discussed will include:

- Effective cell preparation and procedural considerations when performing intracellular flow cytometry
- Analysis of neural, cardiac, and endodertm differentiation of hESCs using intracellular flow cytomety
- Assays to measure immunomodulation by MSCs

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THURSDAY, JUNE 19, 11:30 AM - 12:30 PM

REPROGRAMMING SOMATIC CELLS USING THE SENDAI VIRUS TECHNOLOGY

Laurence Daheron, Harvard University
Life Technologies
WEST MEETING ROOM 301-305

In recent years, non-integrating reprogramming technologies have been developed to efficiently generate safer iPS lines. One of them uses the Sendai virus as a vector to introduce the four Yamanaka factors into somatic cells. The Sendai virus is a single stranded RNA virus that can effectively transduce a variety of cells. At the HSCI iPS core, we've widely used this method to derive induced pluripotent stem cells. We will discuss the advantages of this method.

In the second half-hour from 12:00-12:30pm, Dr. Dhruv Sareen, Director, iPSC Core at Cedars-Sinai Medical Center will present, *From bland to grand: iPSC technology and its applications*. A significant bottleneck in drug development is reproducible and unlimited supply of physiologically-relevant human cells that bear patient-specific genetics. Human iPSC technology promises to circumvent this and support development of more predictive high-content cellular assays. I will highlight reprogramming and differentiation technologies used in the CSMC iPSC core with emphasis on:

- Platforms for high-content screening/imaging (HCS/HCI)
- Developing predictive cellular assays with iPSCs
- iPSC disease modeling with HCI
- Challenges for translating iPSC-derivatives from lab-scale to high-content

FRIDAY, JUNE 20, 8:00 AM - 8:30 AM

INTRODUCING A NOVEL, ANIMAL COMPONENT-FREE (ACF) CULTURE SYSTEM FOR EFFICIENT ISOLATION, EXPANSION AND CRYOPRESERVATION OF HUMAN MSCS DERIVED FROM BONE MARROW AND ADIPOSE TISSUE

Ravenska Wagey, PhD, Senior Scientist
STEMCELL Technologies
WEST BALLROOM A

This tutorial will describe MesenCult™-ACF, a novel animal component-free culture system optimized for efficient isolation, expansion and cryopreservation of human MSCs (hMSCs) derived from primary tissues. Clonogenic characteristics, phenotype and long-term expansion of hMSCs under strict ACF culture conditions will be discussed. The application of three robust and versatile differentiation kits to characterize these hMSCs will also be introduced, providing a complete and integrated workflow for efficient isolation, expansion, differentiation and cryopreservation of hMSCs.

FRIDAY, JUNE 20, 8:00 AM - 8:30 AM

NEXT-GENERATION TECHNOLOGIES FOR STEM CELL RESEARCH

Sebastian Knoebel, PhD,
Senior Project Manager R&D Stem Cells
Miltenyi Biotec GmbH
WEST BALLROOM B

The development of clinically compliant technologies is key in transitioning from basic stem cell research to clinical applications. We will introduce workflows for the integration-free reprogramming and modulation of stem cells using modified mRNAs. Furthermore, we will present a novel xeno-free culture system that guarantees robust, feeder-free cultivation of human pluripotent stem cells. Lastly, the microchip-based MACSQuant® Tyto enables gentle, multiparameter flow sorting in a sterile, closed system complementing our MACS® Separation Technology.

FRIDAY, JUNE 20, 8:00 AM - 8:30 AM

THE LAMININ PROTEIN FAMILY – THE KEY TO PRIMARY CELL CULTURE DIFFICULTIES

Kristian Tryggvason, PhD, MBA
BioLamina
WEST BALLROOM C/D

Primary cell culture has four major problems. First, expansion of pluripotent cells has been considered difficult. Second, keeping adult differentiated cells in their differentiated state in vitro for prolonged periods was previously impossible. Third, differentiating primary cells on biorelevant matrices is a large challenge. And fourth, it has been considered impossible to culture adult cells or tissue samples. With the help of the Laminin protein products, we have solved all these problems.

FRIDAY, JUNE 20, 8:00 AM - 8:30 AM

OPTIMIZING THE CULTURE OF PPSC USING NOVEL XENO AND INSULIN FREE LOW PROTEIN MEDIA

Rick I. Cohen, Ph.D., Rutgers
PeproTech
WEST MEETING ROOM 211-214

This tutorial will introduce Animal Free PeproGrow-hESC, a new Pluripotent Stem Cell Media with companion products and the

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proper techniques to optimize the growth iPSC or hESC. Our presentation will include, but not limited to; the use of this novel media during iPSC generation; Cryopreservation and Thawing, Growth VitroGrow-hESC (recombinant full length human Vitronectin), and ability to passage cells at wildly high dilution factors.

FRIDAY, JUNE 20, 8:00 AM - 8:30 AM

THERMO-STABLE FGF-BASIC (APPLICATIONS & FUTURE)

Dr. Mark Azam
HumanZyme, Inc.
WEST MEETING ROOM 301-305

FGF-basic is a critical component of stem cell culture medium; the growth factor is necessary for the cells to remain in an undifferentiated state. However, FGF-basic is not stable at 37°C requiring daily media change. Humanzyme, Inc. has a proprietary thermo-stable FGF-basic that will allow for media add or changes every 2-3 days.

FRIDAY, JUNE 20, 11:30 AM - 12:30 PM

A NOVEL XENO-FREE CULTURE SYSTEM FOR ISOLOTATION AND EXPANSION OF HMSC FROM VARIOUS SOURCES TOWARD CELL THERAPY APPLICATIONS

David Fiorentini
Biological Industries Israel Beit Haemek Ltd.
WEST BALLROOM A

hMSC serves as a new, promising tool for regenerative medicine and cell therapy with advantages over other stem cells types, mainly due to their multipotent characteristic, broad variety of tissue sources and immuno-privilege. The presentation addresses the ability of MSC Nutristem XF culture medium as well as auxiliary solutions for attachment, dissociation, and cryopreservation to isolate hMSC from various tissue sources and to support long-term expansion of multipotent hMSC suitable for cell therapy applications.

FRIDAY, JUNE 20, 11:30 AM - 12:30 PM

ADVANCED TECHNOLOGIES FOR IN VITRO CULTURE OF CELL TYPES RELEVANT FOR CLINICAL RESEARCH

Zara Melkoumian, PhD
Corning Incorporated
WEST BALLROOM B

Today's complex cell culture techniques, such as stem cell culture and tissue engineering, require in vitro environments with expanded capabilities. These include xeno-free and human-origin component-free culture conditions and scalable closed vessel design. Corning brings together a comprehensive, innovative line of vessels, media and surfaces designed and characterized to meet the needs of these advanced applications, enabling researchers with the right environment for every cell. This tutorial will focus on technologies available for expansion and functionality of clinically relevant cell types including, mesenchymal stem cells (MSCs), human keratinocytes (HKN), endothelial colony forming cells (ECFCs), neural progenitor cells (NPCs) and other attachment dependent cell types.
In the second half-hour from 12:00-12:30pm, Deepa Saxena, PhD will present *Surface Applications for Feeder-free Culture of Human Pluripotent Stem Cells (HPSC).* Human pluripotent stem cells have an infinite capacity of self-renewal and differentiation into all derivatives of the three germ layers. A great deal of hope is associated with the potential application of these cells in functional genomics, cell therapy, and regenerative medicine. Conventionally, hpsc have been cultured on mitotically inactivated murine embryonic fibroblast (MEF) cell feeder layers. Robust, easy to use, reproducible and scalable culture systems are desired for undifferentiated expansion of these cells. Corning® offers several matrices that support feeder-free hPSC expansion. Tutorial will provide an overview of natural and recombinant/synthetic matrices for hPSC culture.

FRIDAY, JUNE 20, 11:30 AM - 12:30 PM

VIRUS-FREE, EFFICIENT REPROGRAMMING USING A SINGLE TRANSFECTION OF A SYNTHETIC, POLYCISTRONIC SELF-REPLICATING RNA

Vi Chu, Ph.D. Manager II, R&D, Stem Cells/Cell Biology, EMD Millipore
EMD Millipore Corporation
WEST BALLROOM C/D

Drawbacks of current iPSC generation methods, involving virus or multiple transfections, include experimental variability, questions of biosafety, and known and unknown effects of introducing viruses into experimental systems. We describe a simple, non-integrating reprogramming system in which a single transfection of a synthetic, polycistronic (OKS-Glis), self-replicating RNA species was sufficient to generate high numbers of human iPSCs. The efficiency of this new RNA-Replicon Reprogramming Technology ranged from 0.3% to 1.1%, depending on fibroblast proliferation rate.

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FRIDAY, JUNE 20, 11:30 AM - 12:30 PM

EX VIVO EXPANSION, DIFFERENTIATION AND CRYOPRESERVATION OF MESENCHYMAL STROMAL/ STEM CELLS

Ning Liu, PhD
Irvine Scientific
WEST MEETING ROOM 211-214

Mesenchymal stromal/ stem cells (MSCs) are capable of self-renewal, differentiation into various cell lineages, and immunomodulation, which make them a valuable source of cells for clinical applications. This workshop will illustrate the development of a portfolio of serum-free, ready-to-use and customizable media for *ex vivo* expansion, differentiation and cryopreservation of human MSCs. It will demonstrate the superior performance of our cGMP grade medium and how it can facilitate consistent and high quality clinical research of MSCs.

FRIDAY, JUNE 20, 11:30 AM - 12:30 PM

RNA-MEDIATED GENERATION OF INTEGRATION-FREE IPS CELL LINES FROM CELLS ISOLATED FROM HUMAN BLOOD

Brad Hamilton, Director of Research and Development
Stemgent-Asterand
WEST MEETING ROOM 301-305

Stemgent-Asterand's non-integrating mRNA reprogramming platform utilizes microRNA to facilitate fast and efficient establishment of iPS cell lines from diseased human fibroblasts that often times can be refractory to other reprogramming methods. Here we present data highlighting the application of novel RNA reprogramming technologies that, in combination with microRNA, enable the generation of stable, fully reprogrammed iPS cell lines from late-outgrowth endothelial progenitor cells (L-EPCs) isolated from human peripheral blood.

SATURDAY, JUNE 21, 8:00 AM - 8:30 AM

LIFEMAP DISCOVERY® - THE ROADMAP FOR STEM CELL RESEARCH

Idit Livnat, PhD
LifeMap Sciences Inc.
WEST BALLROOM A

LifeMap Discovery (http://discovery.lifemapsc.com) is a powerful stem cell research platform that provides comprehensive mapping of embryonic development along with substantial information about stem and progenitor cells, their differentiation protocols and cell therapy applications. We will showcase our platform and demonstrate its value for stem cell research and the development of therapeutic products. GeneAnalytics, our novel tool for classification and identification of derived stem cells, will also be presented.

SATURDAY, JUNE 21, 8:00 AM - 8:30 AM

EXPANSION AND HARVEST OF ADULT STEM CELLS SUPPORTS LARGE SCALE MANUFACTURING

Julie R. Murrell
EMD Millipore Corporation
WEST BALLROOM B

As more stem cell therapeutics progress through clinical testing, current in vitro culture methods are cumbersome to scale. In this case study, we verified that cells expanded in the single use stirred tank bioreactor and subsequently harvested were identical in phenotypic profile in comparison to flat culture and maintained the desired cell characteristics of hMSCs, thereby confirming the consistency, quality and reproducibility of large scale in vitro systems for stem cell expansion.

Over **90 scientific sessions**, including Life and Death in the Cell; Cell Division and Cell Cycle Control; New Ways for Probing and Interrogating Cells; Cell Dysfunction in Cancer and other Diseases; Stem Cells, Tissues and Organs; Optical Microscopy and Superresolution Imaging

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