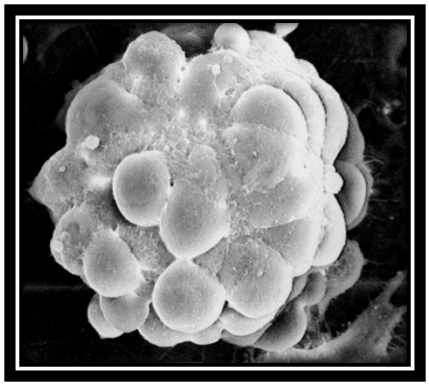
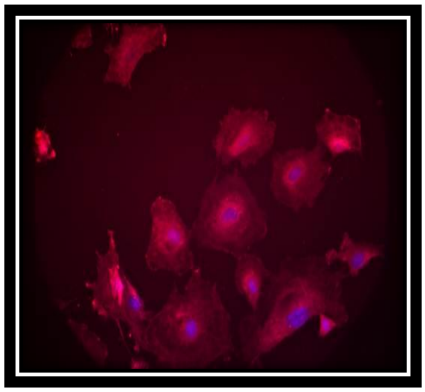
The Second Midwest Conference on Stem Cell Biology and Therapy

Human Health Building

Oakland University, Rochester, MI
October 5-7, 2012





Conference Program

OAKLAND UNIVERSITY

Beaumont HEALTH SYSTEM

Oakland University | Beaumont Health System
ISCRM
Institute for Stem Cell and Regenerative Medicine

www.oakland.edu/scbt

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Welcome

The Second Midwest Conference on Stem Cell Biology and Therapy

Statement:

The SCBT Conference provides an opportunity to bring together scientists and clinicians from across the globe to share the latest advancements in stem cell research.

Conference Topics Included:

- Special Topics in Translational Research and Stem Cell Therapy
- Stem Cell Biology
- Cancer Stem Cell Biology
- Stem Cell Business and Entrepreneurial Opportunities: Panel Discussion
- Stem Cell Differentiation
- *In Vivo* Image-based Stem Cell Analysis
- Adult Stem Cell Development
- Bio-engineering
- Development and Regeneration
- Drug Discovery and Therapy
- Programming and Differentiation
- Epigenetic Regulation
- Tissue Engineering
- Biomaterials and Stem Cell Maintenance
- Disease Models
- Biobanking
- Political, Ethical, and Regulatory: Panel Discussion

Organization Committee

Chair

G. Rasul Chaudhry, Ph.D.

Members

Genetics Policy Institute (GPI), **Florida:** Bernard Siegel, J.D.

Georgia Institute of Technology: Dong Yao, Ph.D. (Eng)

University of Illinois at Chicago: Thomas Diekwisch, D.M.D., Ph.D. (sc.), Ph.D. (phil.)

University of Michigan: Sue K. O'Shea, Ph.D., Marty Fischhoff, B.A, Gary Hammer, M.D., Ph.D., and Elizabeth Lawlor, M.D., Ph.D.

Michigan State University: Jose Cibelli, D.V.M, Ph.D., Vilma Yuzbasiyan-Gurkan, Ph.D., and Jim Trosko, Ph.D.

Wayne State University: Graham Parker, Ph.D., Jim Eliason, Ph.D., and Zhengqing Hu, M.D., Ph.D.

University Research Corridor: Jeff Mason **MichBio:** Stephen Rapundalo, Ph.D.

Oakland County: David Schreiber

St. Johns Health System: David Svinarich, Ph.D.

Kansas State University: Mark Weiss, Ph.D.

Case Western University: Michael Gilkey, MBA

University of Minnesota: Dan Kaufman, M.D., Ph.D.

University of Wisconsin-Madison: Craig Atwood, Ph.D., and John Lough, Ph.D.

Beaumont Health System: David Felten, M.D., Ph.D., George Wilson, Ph.D., Mick Perez-Cruet, M.D., Kenneth Peters, M.D., and Charles Shanley, M.D.

Oakland University: Brad Roth, Ph.D., Dorothy Nelson, Ph.D., Gerard Madlambayan, Ph.D. (Eng), Anne Mitchell, R.N., Ph.D., Sumi Dinda, Ph.D., M. Siadat, Ph.D. (Eng), and Ferman Chavez, Ph.D.

STATE OF MICHIGAN
EXECUTIVE OFFICE
LANSING

RICK SNYDER
GOVERNOR

BRIAN CALLEY
LT. GOVERNOR

October 5, 2012

Dear Friends:

It gives me great pleasure to welcome you to the Second Midwest Conference on Stem Cell Biology and Therapy.

As governor, I'm dedicated to building a healthier Michigan, and committed to preparing students for the technological age of today and jobs of tomorrow by developing the best minds in science, technology, engineering and math. As you gather for discussion and learning, I hope you enjoy the many conference activities planned, including various workshops and lectures from both nationally and internationally known stem cell research experts.

Thank you to Oakland University, Beaumont Health System and the many coordinators and volunteers for organizing and hosting this outstanding conference.

On behalf of the Great Lakes State, please accept my very best wishes for a productive and enjoyable gathering.

Sincerely,

Rick Snyder
Governor

OAKLAND COUNTY MICHIGAN

L. BROOKS PATTERSON, OAKLAND COUNTY EXECUTIVE

October 5, 2012

Dear Stem Cell Researchers:

As the chief elected official of Oakland County, I welcome you to Oakland University's second Midwest Conference on Stem Cell Biology and Therapy.

This collaborative endeavor between Oakland University and the Beaumont Health System is being held in the heart of Oakland County's Medical Main Street – a unique alliance of world-class hospitals, universities, medical device and bio-pharma companies as well as some of the country's top medical professionals. This alliance collaborates to commercialize innovative medical technologies that will heal human ailments and is working to change the face of health care and the life sciences.

Oakland County is a world-class center for health care and the life sciences. We are home to over 100,000 health care workers – more than the Mayo Clinic and the Cleveland Clinic combined. Nearly 4,900 active clinical trials occur here every year. In just the three years, Medical Main Street has been in existence, 26 life science companies have located or expanded into Medical Main Street, investing over $220 million while creating over 1,900 new life science jobs in our community. Our future is bright.

Please take advantage of all our county has to offer. I hope you have a successful and productive Stem Cell Conference and an enjoyable stay in Oakland County, Michigan.

Sincerely,

ROCHESTER HILLS
MICHIGAN

innovative by nature

October 5, 2012

Dear Participants,

It is my great privilege and honor to welcome you to the Second Midwest Conference on Stem Cell Biology and Therapy. This event offers an opportunity to discuss developments in stem cell and regenerative medicine research with experts and leaders in the field from around the world.

I am certain that their presentations and discussions on the issues and opportunities for developing biomedical knowledge and treatments for debilitating diseases using stem cells and application of regenerative medicine will benefit us all.

As the mayor of the City of Rochester Hills, where Oakland University is located, I welcome you to the conference and to our city. I would like to applaud the Oakland University William Beaumont Institute for Stem Cell and Regenerative Medicine for taking the lead to host this important event. I also commend the participants and presenters of the conference for promoting education and helping to prepare our future leaders of biomedical sciences, especially stem cell biology and regenerative medicine.

Please accept my sincere wishes for the informative and productive interaction and enjoyable stay during your visit.

Sincerely,

Bryan K. Barnett, Mayor
City of Rochester Hills

1000 Rochester Hills Dr. | Rochester Hills, MI 48309 | 248.656.4600 | rochesterhills.org

City of
AUBURN HILLS
Honoring The Past. Building The Future.

October 2, 2012

Dear Friends,

It is my great pleasure to welcome you to the Second Midwest Conference on Stem Cell Biology and Therapy. This event offers an opportunity to discuss developments in stem cell and regenerative medicine research with experts and leaders in the field from around the world. I am certain that their presentations and discussions on the burning issues and opportunities for developing biomedical knowledge and treatments for debilitating diseases using stem cells and application of regenerative medicine will benefit us all.

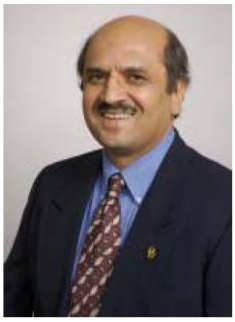
As Mayor of the City of Auburn Hills, where Oakland University is located, I welcome you to the conference and to our city. It is my please to acknowledge the work of the Oakland University William Beaumont Institute for Stem Cell and Regenerative Medicine in hosting this ambitious and important conference. This conference promises to promote education and help prepare our future leaders in the biomedical sciences, especially stem cell biology and regenerative medicine.

Again, welcome, and please accept my sincere wishes for the informative and productive interaction and enjoyable stay during the course this event.

James D. McDonald
Mayor

1827 N. Squirrel Rd., Auburn Hills, MI 48326
www.auburnhills.org

OU-WB Institute for Stem Cell and Regenerative Medicine



Rochester, Michigan 48309-4476
(248) 370-3350 Fax: (248) 370-3586

October 5, 2012

A Personal Message from the SCBT Conference Chair

It is with great pleasure that I extend my sincere greetings to those attending the Second Midwest Conference on Stem Cell Biology and Therapy hosted by Oakland University William Beaumont Institute for Stem Cell and Regenerative Medicine (OU-WB ISCRM), Oakland University and Beaumont Health System in cooperation with the Genetic Policy Institute. Several other institutions such as St. John Providence Health System, A. Alfred Taubman Medical Research Institute, Michigan State University, Organogenesis, and Michigan University Research Corridor, have generously provided support for the conference. In addition, a number of biotech companies including Bioinvision, Cell Guidance Systems Ltd, Fisher BioServices, Orthofix, MTI-GlobalStem Inc. and SPOT Imaging Solutions, contributed to the conference.

This conference offers a tremendous opportunity for networking with stem cell researchers, experts, and leaders, who lead the innovations in biomedical and life sciences, and serves as an excellent source of motivation for students, residents, clinicians and investigators alike. Oakland University is rapidly expanding and improving the quality of its educational programs. It has recently launched the Oakland University William Beaumont School of Medicine, the newest medical school in the state of Michigan. OU prides itself in providing an excellent education for both graduate and undergraduate students and encourages them to participate in high level, creative research projects, gaining hands-on experience.

The conference would have not been possible without the active participation of the faculty and staff from a number of academic and professional institutions as represented on the conference organizing committee. I am particularly thankful to the representatives from the following institutions: Genetics Policy Institute, Georgia Institute of Technology, University of Illinois at Chicago, University of Michigan, Michigan State University, Wayne State University, University, Research Corridor, Oakland County, St. Johns Health System, Kansas State University, Case Western University, University of Minnesota, University of Wisconsin-Madison, Beaumont Health System and Oakland University.

I wish to applaud all the speakers and attendees for adding to the success of this intensive educational event. I hope we will all have an enjoyable and productive experience during the course of this 3-day conference at Oakland University's historic campus.

Please accept my warmest appreciation for your participation in this educational conference.

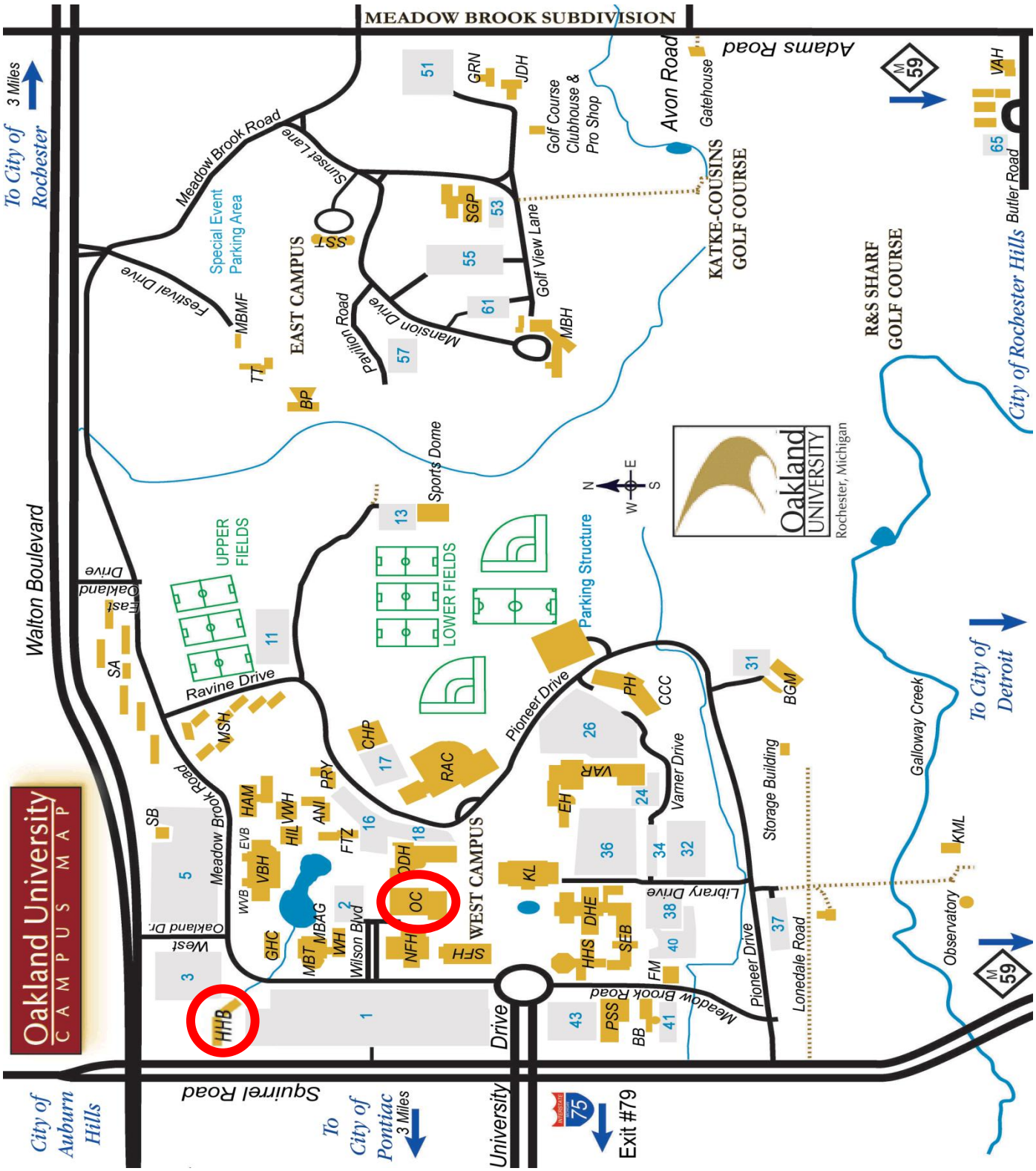
Sincerely,

G. Rasul Chaudhry, Ph.D.
Professor of Molecular Biology
Co-Director, OU-WB ISCRM
Chair, Organizing Committee

Campus Map & Conference Map

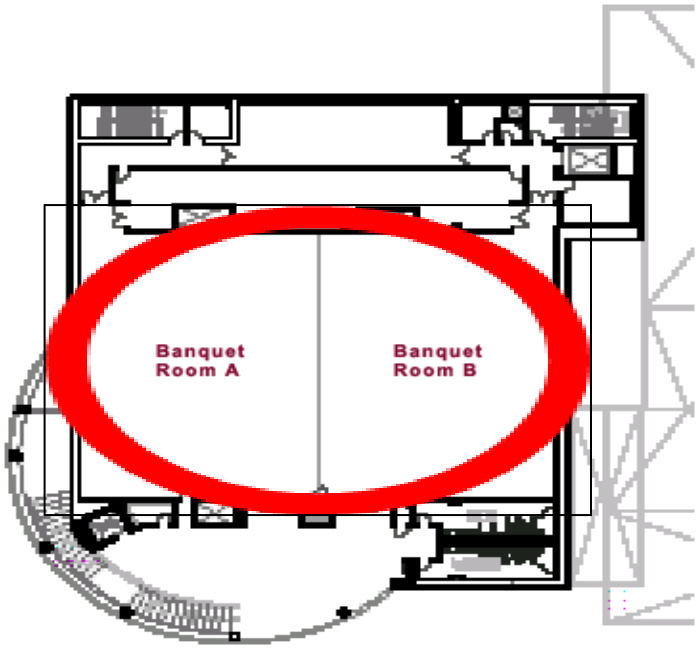
Campus Map

Circled Areas Indicate Conference Areas: HHB-Human Health Building; OC-Oakland Center

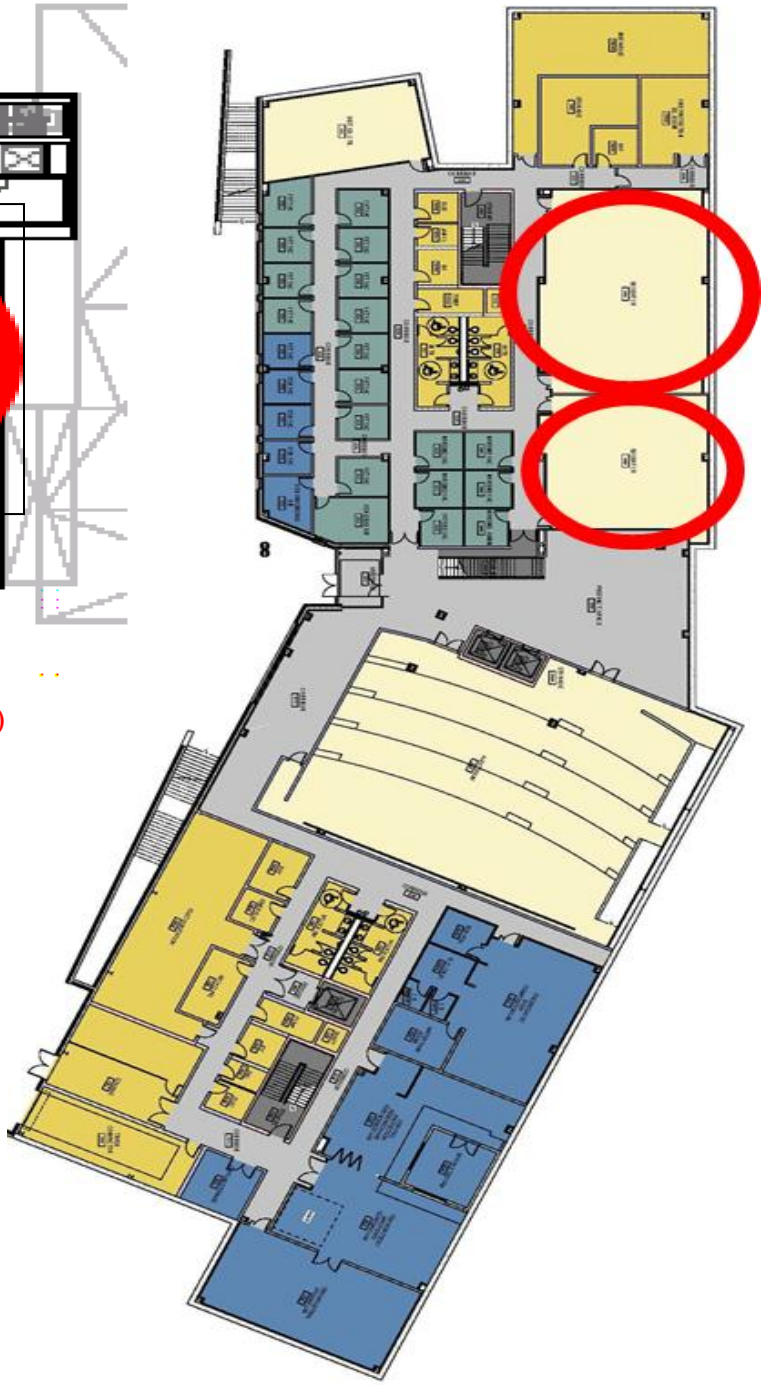


Conference Map

Circled Areas Indicate Conference Areas: OC-Oakland Center Banquet Rooms; HHB-Human Health Building level 1 (1005-1006)

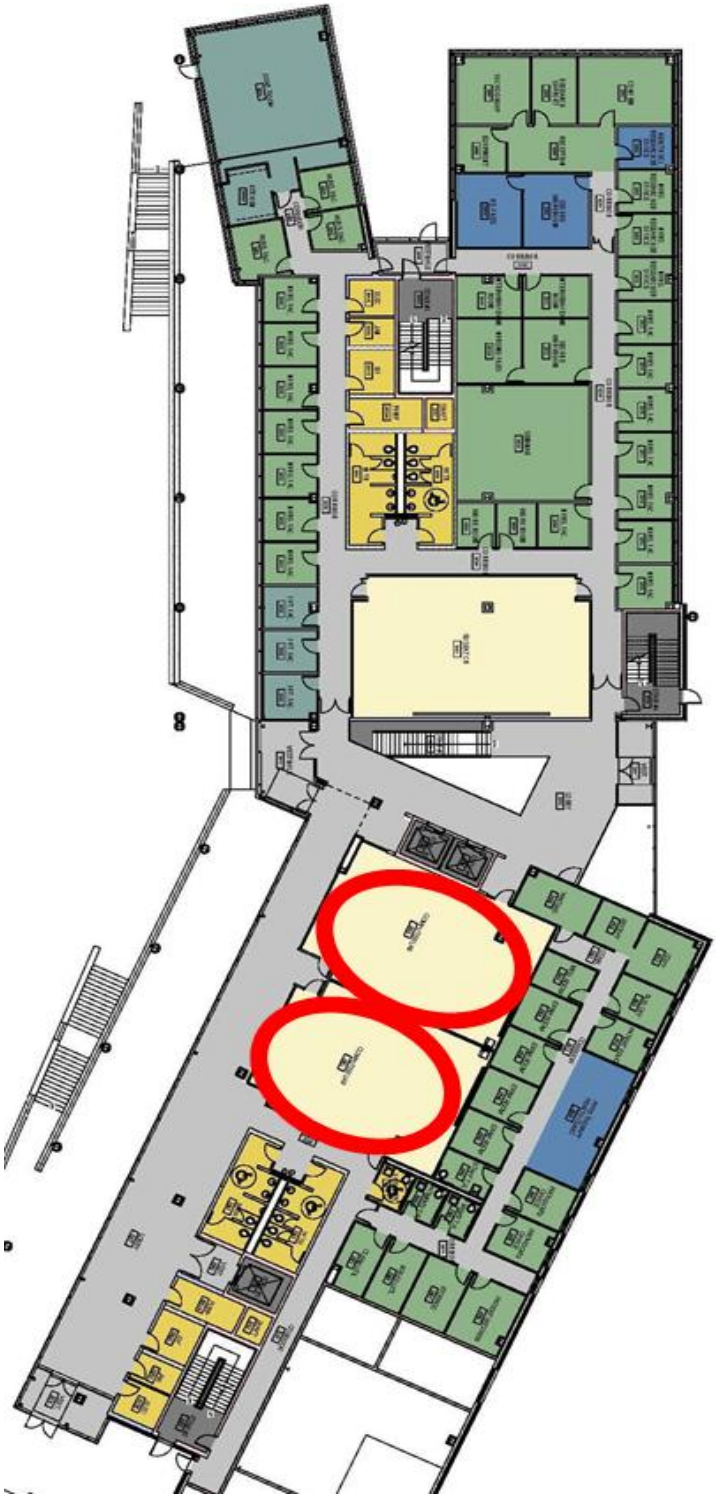


Upper Level (above Café O'Bear's)



Conference Map

Circled Areas Indicate Conference Areas: HHB-Human Health Building level 2 (2085-2086)



Speaker Presentation List

Speaker Presentation List

Presentations will be given by:
(*Speakers in alphabetical order)*

Bradly Alicea, Doctoral Candidate, Michigan State University

Ali S. Arbab, M.D., Ph.D., Henry Ford Health System

Craig S. Atwood, Ph.D., University of Wisconsin Medical Center

Frank Baaijens, Ph.D., Eindhoven University of Technology

Ronnda L. Bartel, Ph.D., Aastrom Biosciences, Inc.

Naimisha Reddy Beeravolu M.S., Oakland University

Nissim Benvenisty, M.D., Ph.D., Hebrew University

Dean H. Betts, Ph.D., University of Western Ontario

Kapil Bharti, Ph.D., NIH

G. Rasul Chaudhry, Ph.D., OU-WB ISCRM, Oakland University

Ferman Chavez, Ph.D., Oakland University

Chien-Wen Chen, M.D., Ph.D., University of Pittsburgh

Jose Cibelli, Ph.D., Michigan State University

Sarah Conley, Ph.D., University of Michigan

Thomas Diekwisch, D.M.D., Ph.D. (sc.), Ph.D. (phil.), University of Illinois at Chicago

Sumi Dinda, Ph.D., Oakland University

Gregory Dressler, Ph.D., University of Michigan Health System

Paul Dyce, Ph.D., University of Western Ontario

James Eliason, Ph.D., Wayne State University

Richard Fessler, M.D., Ph.D., Northwestern University Feinberg School of Medicine

Erik J. Forsberg, Ph.D., WiCell Research Institute and the University of Wisconsin-Madison

Katrina Fox, M.S., Kansas State University, College of Veterinary Medicine

Judith Fulton, Ph.D., Akron General Medical Center

Jose L. Garcia-Perez, Ph. D., Pfizer-University of Granada-Junta de Andalucía Center for Genomics and Oncological Research

Michael Gilkey, MBA, MS, National Center for Regenerative Medicine

Gokul Gopinathan, Ph.D., University of Illinois at Chicago

Jason A. Hamilton, Ph.D., Athersys, Inc.

Gary Hammer, M.D., Ph.D., University of Michigan Medical School

Ales Hampl, D.V.M., Ph.D., Masaryk University

Zhengqing Hu, M.D., Ph.D., Wayne State University

Ralf Huss, M.D., Ph.D., Apceth GmbH in Munich, Germany

Branislava Janic, Ph.D., Henry Ford Health System

Jan Jensen, Ph.D., Cleveland Clinic

Quan Jiang, Ph.D., Henry Ford Health System

Dan Kaufman, M.D., Ph.D., University of Minnesota

Paul H. Krebsbach, DDS, Ph.D., University of Michigan

Sarah Krueger, Ph.D., Beaumont Health System

Ernest F. Krug, III, M.Div., M.D., FAAP, OUWB School of Medicine

Hillard Lazarus, M.D., Case Western University

Senator Carl Levin, D-Michigan

Chunying Li, Ph.D., Wayne State University School of Medicine

Linheng Li, Ph.D., Stowers Institute for Medical Research

Qi Li, Ph.D., University of Illinois at Chicago

Feng Lin, Ph.D., Case Western University School of Medicine

Xianghong Luan, M.D., University of Illinois at Chicago

Domenico Luongo, M.S., C.H.M.M., Oakland University

Gerard Madlambayan, Ph.D., Oakland University

Tristan Maerz, M.S., Beaumont Health System

Ivan Maillard, M.D., Ph.D., University of Michigan Medical School

Martin Marsala, M.D., University of California -San Diego

Melvin McInnis, M.D., University of Michigan

Christina McKee, M.S., Oakland University

Anne Mitchell, Ph.D., R.N., C.R.N., Oakland University

Jack T. Mosher, Ph.D., University of Michigan Center for Stem Cell Biology

Ying Nie, Ph.D., Lonza Walkersville, Inc.

Dan O'Donnell, Fisher Biosciences

Jon Odorico, M.D., University of Wisconsin-Madison

Suresh Selvaraj Palaniyandi, Ph.D., Henry Ford Health System

Graham Parker, Ph.D., Wayne State University School of Medicine

Mick Perez-Cruet, M.D., M.S., OU-WB SOM and Beaumont Hospital

Kenneth Peters, M.D., Beaumont Health System

Xu Qian, Doctoral Candidate, University of Michigan

Diana L. Ramírez-Bergeron, Ph.D., Case Western Reserve University School of Medicine

Mahendra Rao, M.D., PhD., NIH

Daniel Rappolee, Ph.D., Wayne State University

Stacey A. Sakowski, Ph.D., University of Michigan

Peter Sartipy, Ph.D., Cellartis AB Sweden

Bernard Siegel, J.D., Genetics Policy Institute

Gary Smith, Ph.D., University of Michigan

Anna Sonstegard, University of Minnesota

Irene Spanos, Oakland County

David M. Svinarich, Ph.D., M.S., St. John's Health System

Shuichi Takayama, Ph.D., University of Michigan

Dean Tantin, Ph.D., University of Utah School of Medicine

Andrew M. Tidball, Doctoral Candidate, Vanderbilt University

Vince Tropepe, Ph.D., University of Toronto

Saba Valadkhan, Ph.D., Case Western Reserve University School of Medicine

Luis G. Villa-Diaz, Ph.D., University of Michigan

Chenran Wang, Ph.D., University of Michigan

Q. Tian Wang, Ph.D., University of Illinois at Chicago

Mark Weiss, Ph.D., Kansas State University

George Wilson, Ph.D., OU-WB ISCRM, Beaumont Health System

Donggang Yao, Ph.D., Georgia Institute of Technology

Mervin Yoder, M.D., University of Indiana

Vilma Yuzbasiyan-Gurkan, Ph.D., Michigan State University

Conference Schedule

Conference Schedule

Location: Human Health Building (HHB) Auditorium

3:00pm – 3:10pm: **Introductory Remarks** by **Rasul Chaudhry, Ph.D.**, and **George Wilson, Ph.D**., Oakland University William Beaumont Institute for Stem and Regenerative Medicine (OU-WB ISCRM)

Welcome by **Dorothy Nelson, Ph.D.**, Vice Provost for Research, Oakland University; **David Felten, M.D., Ph.D.**, Vice President for Research, Beaumont Health System

Location: HHB 1050 (Auditorium)
3:10pm – 5:15pm: **Plenary Session I**: Special Topics in Translational Research and Stem Cell Therapy I
Moderators: **Mick Perez-Cruet, M.D., M.S.**, OU-WB School of Medicine, Beaumont Health System; **Jeff Mason, Ph.D.**, Executive Director, Michigan's University Research Corridor

3:10pm – 3:30pm: **Mick Perez-Cruet, M.D., M.S.**, OU-WB School of Medicine, Beaumont Health System, "Stem Cell Based Treatment of Spinal Degenerative Disorders"

3:35pm – 3:55pm: **Martin Marsala, M.D.,** University of California-San Diego, "The Utilization of the Pig Model for Spinal and Brain Grafting (as a Safety Preclinical model) of Human Neural Precursors as well as Porcine iPS-derived Neural Precursors"

4:00pm – 4:20pm: **Richard Fessler, M.D., Ph.D.**, Northwestern University Feinberg School of Medicine, "Transplantation of GRNOPC-1 into the Injured Human Spinal Cord: Results in Five Patients"

4:25pm – 4:45pm: **Jon Odorico, M.D.**, University of Wisconsin-Madison, "Generating Functional Beta Cells from Human Pluripotent Stem Cells: Progress and Challenges"

4:50pm – 5:10pm: **Kenneth Peters, M.D.**, Beaumont Health System, "Autologous Muscle Derived Cells for Treatment of Stress Urinary Incontinence: Dose Escalation Study of Safety and Potential Effectiveness"

Location: HHB (2nd Floor)
5:15pm – 5:30pm: **Coffee Break**

Location: HHB 1050 (Auditorium)
5:30pm – 7:00pm: **Keynote Forum**

5:30pm – 5:40pm: **Welcome by Rasul Chaudhry, Ph.D**., OU-WB ISCRM, Oakland University

Welcoming Remarks by **Gary D. Russi, Ph.D**., President, Oakland University; **Ronald E. Robinson**, Member Board of Trustees, Oakland University; **Susan Awbrey, Ph.D**., Provost, Oakland University; **Ananias Diokno, M.D**., Chief Medical Officer, Beaumont Health System; **Matt Gibb**, Deputy County Executive, Oakland County

5:45pm – 5:50pm: Remarks by Honorable **Senator Carl Levin**, D-Michigan

FRIDAY, OCTOBER 5th

Location: HHB (1st Floor)
10:00am – 6:00pm: On-site Registration

Location: Oakland Center Banquet Rooms
1:00pm – 3:00pm Poster and Exhibit Set-up

Location: HHB 5037
Workshop (Registration- HHB)

11:00am – 12:00pm: Regulatory (**Domenico Luongo, M.S., C.H.M.M.**, Oakland University; **David Svinarich, Ph.D.,** Vice President of Research, St. John Providence Health System)

12:00pm – 1:00pm: Basic Science (**Naimisha Reddy Beeravolu,** Doctoral Candidate, Oakland University; **Christina McKee,** Doctoral Candidate, Oakland University)

1:00pm – 1:30pm: Lunch

1:30pm – 2:15pm: Clinical (**Kenneth Peters, M.D.**, Beaumont Health System)

5:50pm – 6:10pm: **Bernard Siegel, J.D**., Executive Director, Genetics Policy Institute, "The Power of Stem Cell Advocacy"

6:15pm – 6:55pm: Keynote Speaker, **Mahendra Rao, M.D., Ph.D.**, Director, Center for Regenerative Medicine, NIH, "NIH CRM- An Update on Efforts in Translational Science"

Location: Oakland Center Banquet Rooms
7:00pm – 9:00pm: **Reception** (OU Jazz Combo)

Remarks by **Louay Chamra, Ph.D.,** Dean, School of Engineering and Computer Science, Oakland University; **Tamara Jhashi, Ph.D.,** Acting Dean, College of Arts & Sciences, Oakland University

SATURDAY, OCTOBER 6th

Location: HHB (1st Floor)
7:00am – 5:00pm: Registration

Location: Oakland Center
7:00am – 7:50am: **Continental Breakfast**
Students and residents meet the experts: (**Nissim Benvenisty, M.D., Ph.D**., **Craig Atwood, Ph.D.**, **Ales Hampl, D.V.M., Ph.D.**, **Mark Weiss, Ph.D.**)

Conference Schedule

Location: HHB 1050 (Auditorium)
8:00am – 9:15am: **Plenary Session II**: Stem Cell Biology I

Welcoming Remarks by **Brad Roth, Ph.D.**, Director, Center for Biomedical Research, Oakland University; **Kenneth Hightower, Ph.D,** Dean, School of Health Sciences, Oakland University

Moderators: by **Brad Roth. Ph.D.,** Oakland University**; Mark Weiss, Ph.D.**, Kansas State University

8:00am – 8:20am: **Craig Atwood, Ph.D.**, University of Wisconsin Medical Center, "Human Embryonic Stem Cells as a Model System for Understanding Early Human Embryogenesis: Human Chorionic Gonadotropin Induction of the Proliferation and Differentiation of hESC into Neural Precursor Cells"
8:25am – 8:45am: **Nissim Benvenisty, M.D., Ph.D**., Hebrew University, "The Role of Pluripotent Stem Cells in Modeling Human Disorders"
8:50am – 9:10am: **Mervin Yoder, M.D.**, University of Indiana, "Challenges to the Stem Cell Theory of Hematopoiesis"

Location: HHB (2nd Floor)
9:15am – 9:30am **Coffee Break**

Location: HHB 2085
9:30am – 11:00am **Focus Session A**: Cancer Stem Cell Biology

Moderators: **Gerard Madlambayan, Ph.D.**, Oakland University; **Sumi Dinda, Ph.D.**, Oakland University

9:30am – 9:50am: **Sarah Krueger, Ph.D.**, Beaumont Health System, "Recruitment and Retention of Bone Marrow–derived Progenitor Cells Following Radiation-induced Lung Damage"
9:52am – 10:12am: **Sarah Conley, Ph.D.**, University of Michigan, "Cancer Stem Cells: Attacking Cancer at its Roots"
10:15am – 10:35am: **George Wilson, Ph.D.**, Beaumont Health System, "The Role of CD44-associated Stem Cells in Recovery of Head and Neck Squamous Cell Carcinoma Following Radiation"
10:38am – 11:00am: **Gerard Madlambayan, Ph.D.**, Oakland University, "Migration of Hematopoietic Stem and Progenitor Cells (HSPCs) to Tumors Following Radiation: A Role of HSPCs in Tumor Re-growth Following Treatment"

Location: HHB 1005
9:30am – 11:00am **Focus Session B**: Stem Cell Business and Entrepreneurial Opportunities: Panel Discussion

Remarks by Mohan Tanniru, Ph.D., Dean, School of Business, Oakland University

Moderators: **Wayne Blizman**, **MBA**, Oakland University

9:30am – 9:50am: **Michael Gilkey, MBA, M.S.**, National Center for Regenerative Medicine, "Commercialization of Regenerative Medicine Products Through State Funding"
9:52am – 10:12am: **Irene Spanos**, Director, Economic Development and Community Affairs, Oakland County, "Medical Main Street"
10:15am – 11:00am: Discussion
Panel members: **James Eliason, Ph.D.,** Wayne State University and **Stephen Rapundalo, Ph.D.,** MichBio

Location: HHB 2086
9:30am – 11:00am **Focus Session C**: Stem Cell Differentiation

Moderators: **Paul Dyce, Ph.D.**, University of Western Ontario; **TBA**

9:30am – 9:50am: **Dan Rappolee, Ph.D.**, Wayne State University, "Hypoxia and Other Stresses that Diminish Growth Cause Imbalanced Stem Cell Differentiation, Stress Enzymes and Mitochondria are Critical"
9:52am – 10:12am: **Paul Dyce, Ph.D.**, University of Western Ontario, "Can *In Vivo* Conditions Improve Oocyte Development from Somatic Stem Cells?"
10:15am – 10:35am: **Xianghong Luan, M.D.**, University of Illinois at Chicago, "SCF/C-kit Promotes Dental Pulp Cell Migration Through Rapid Activation of PI3K and MEK/ERK Pathways - Potential Applications in Pulp Regeneration"
10:37am – 11:00am: **Dean Tantin, Ph.D.**, University of Utah School of Medicine, "Transcriptional Mechanism of the Reprogramming Factor Oct4"

Location: HHB 1006
9:30am – 11:00am **Focus Session D**: *In Vivo* Image-based Stem Cell Analysis

Moderators: **Mohammad Siadat, Ph.D.**, Oakland University; **Naimisha Reddy Beeravolu**, Doctoral Candidate, Oakland University

9:30am – 9:55am: **Ali S. Arbab, M.D., Ph.D.**, Henry Ford Health System, "Tracking of Stem Cells by *In Vivo* Magnetic Resonance Imaging"
10:00am – 10:25am: **Quan Jiang, Ph.D.**, Henry Ford Health System, "Imaging in Stem Cell Therapy of Brain Injury"
10:30am – 11:00am: **Branislava Janic, Ph.D.**, Henry Ford Health System, " Long Term *In Vitro* Expanded Cord Blood Derived AC133+ Endothelial Progenitor Cells in MCAo Rat Model for Cerebral Ischemia"

Conference Schedule

Location: HHB
11:00am –11:05am **Break**

Location: HHB 2085
11:05am – 12:35pm **Focus Session E**: Adult Stem Cell Development

Moderators: **Vince Tropepe, Ph.D.**, University of Toronto; **Jan Akervall, M.D., Ph.D.**, Beaumont Health Systems

11:05am – 11:25am: **Vince Tropepe, Ph.D.**, University of Toronto, "FGF Dependent Zfhx1b Gene Expression Promotes Definitive Neural Stem Cell Development"
11:27am – 11:47am: **Jose Luis Garcia-Perez, Ph.D.**, Pfizer-University of Granada-Junta de Andalucía Center for Genomics and Oncological Research, "LINE-1 Retrotransposition in Somatic Stem Cells"
11:49am – 12:09pm: **Diana L. Ramírez-Bergeron, Ph.D.**, Case Western Reserve University School of Medicine, "Hypoxic Responses in the Bone Marrow's Vascular Stem Cell Niche"
12:11pm – 12:35pm: **Feng Lin, Ph.D.**, Case Western University School of Medicine, "Mesenchymal Stem Cells are Injured by Complement After their Contact with Serum"

Location: HHB 1005
11:05am – 12:35pm **Focus Session F**: Bio-engineering

Moderators: **Gary Smith, Ph. D.**, University of Michigan; **Donggang Yao, Ph.D.**, Georgia Institute of Technology

11:05am – 11:25am: **Gary Smith, Ph. D.**, University of Michigan, "Integration of Bioengineering to Improve Stem Cell Culture"
11:27am – 11:47am: **Shuichi Takayama, Ph.D.**, University of Michigan, "Microfluidic Stem Cell Manipulations"
11:49am – 12:09pm: **Ferman Chavez, Ph.D.**, Oakland University, "Potential Bio-engineering Applications of Self-Assembling Scaffold"
12:11pm – 12:35pm: **Donggang Yao, Ph.D.**, Georgia Institute of Technology, "Hierarchically Functional Porous Structures for Tissue Engineering Applications"

Location: HHB 1006
11:05am – 12:35pm **Focus Session G**: Development and Regeneration

Moderators: **Gregory Dressler, Ph.D.**, University of Michigan Health System; **Graham Parker, Ph.D.**, Wayne State University School of Medicine

11:05am – 11:25am: **Gregory Dressler, Ph.D.**, University of Michigan Health System, "Stem Cells in Kidney Development and Regeneration"
11:27am – 11:47am: **Zhengqing Hu, M.D., Ph.D.**, Wayne State University, "A Stem Cell-Based Strategy for Inner Ear Regeneration"
11:49am – 12:09pm: **Suresh Palaniyandi, Ph.D.**, Henry Ford Health System, "Activation of Aldehyde Dehydrogenase in Cardiac Stem/Progenitor Cells: A Novel Approach to Boost Regeneration?"
12:11pm – 12:35pm: **TBA**

Location: HHB 2086
11:05am – 12:35pm **Focus Session H**: Drug Discovery and Therapy

Moderators: **Peter Sartipy, Ph.D.**, Cellartis AB Sweden; **Frank Giblin, Ph.D.**, Eye Research Institute, Oakland University

11:05am – 11:25am: **Peter Sartipy, Ph.D.**, Cellartis AB Sweden, "Derivation and Use of Cardiomyocytes from Human Pluripotent Stem Cells"
11:27am – 11:47am: **Ralf Huss, M.D., Ph.D.**, Apceth GmbH in Munich, Germany, "Clinical Development of Pharmaceutical Grade Cellular Therapeutics"
11:49am – 12:09pm: **Jason A. Hamilton, Ph.D.**, Athersys, Inc., "Pre–Clinical Development of MultiStem for Treatment of Multiple Sclerosis"
12:11pm – 12:35pm: **Ronnda Bartel, Ph.D.**, Aastrom Biosciences, Inc., "Patient Specific Stem Cell Therapies"

Location: HHB
12:35pm – 1:30pm: **Lunch**

Location: HHB 1050 (Auditorium)
1:30pm – 3:30pm **Plenary Session III**: Stem Cell Biology II

Remarks by **David Svinarich, Ph.D.,** St. John's Health System; **Vilma Yuzbasiyan-Gurkan, Ph.D.,** Michigan State University

Moderators: **Jose Cibelli D.V.M., Ph.D.**, Michigan State University, TBA

1:30pm – 1:50pm: **Ales Hampl, D.V.M., Ph.D.**, Masaryk University, "Human Embryonic Stem Cells – Strong or Vulnerable?"
1:55pm – 2:15pm: **Jose Cibelli D.V.M., Ph.D.**, Michigan State University, "Egg to Reprogram Cell"
2:20pm – 2:40pm: **Paul Krebsbach, D.D.S., Ph.D.**, University of Michigan, "The Role of mTOR Signaling in Balancing Self-renewal and Differentiation in Pluripotent Stem Cells"
2:45pm – 3:05pm: **Thomas Diekwisch, D.M.D., Ph.D. (sc.), Ph.D. (phil.).**, University of Illinois at Chicago, "Learning from Development: Cellular, Molecular, and Topographical Clues for Periodontal Tissue Regeneration and Tooth Replantation"

Conference Schedule

3:10pm – 3:30pm: **Hillard Lazarus, M.D., FACP**, Case Western University, "Novel Applications of Multipotent Mesenchymal Stromal Cells"

Location: HHB (2nd Floor)
3:30pm – 3:45pm: **Coffee Break**

Location: HHB 2085
3:45pm – 5:30pm **Focus Session I**: Programming and Differentiation

Moderators: **Kapil Bharti, Ph.D.**, NIH; **Christina McKee,** Doctoral Candidate, Oakland University

3:45pm – 4:05pm: **Kapil Bharti, Ph.D.**, NIH, "Generating Authentic RPE from iPS Cells: Lessons from Mouse Eye Development"
4:06pm – 4:26pm: **Melvin McInnis, M.D.**, University of Michigan, "Induced Pluripotent Stem Cell (iPSC) Models to Study Bipolar Disorder"
4:27pm – 4:47pm: **Jan Jensen**, **Ph.D.**, Cleveland Clinic, "Differentiation of ESCs into Islet Cells"
4:48pm – 5:08pm: **Stacey A. Sakowski, Ph.D.**, University of Michigan, "Outcomes of the First Completed FDA Phase 1 Intraspinal Stem Cell Transplantation Trial for ALS"
5:09pm – 5:30pm: **Saba Valadkhan, Ph.D.**, Case Western Reserve University, "Long Non-coding RNA-mediated Trans-differentiation of Adult Cells into Neurons"

Location: HHB 2086
3:45pm – 5:30pm **Focus Session J**: Epigenetic Regulation

Moderators: **Ivan Maillard, M.D., Ph.D.**, University of Michigan Medical School; **Shailesh Lal, Ph.D.**, Oakland University

3:45pm – 4:05pm: **Linheng Li, Ph.D.**, Stowers Institute for Medical Research, "Niche, Signaling, and Epigenetic Regulation of Stem Cells"
4:06pm – 4:26pm: **Gokul Gopinathan , Ph.D.**, University of Illinois at Chicago, "High Throughput Histone Modification Profiling of Multipotent Odontogenic Stem Cells Reveals Distinct Epigenetic Signatures for Individual Neural Crest Derived Subpopulations"
4:27pm – 4:47pm: **Dean Betts, Ph.D.**, University of Western Ontario, "Alternative Splicing of Telomerase Reverse Transcriptase (Tert) in Human Embryonic Stem Cells"
4:48pm – 5:08pm: **Ivan Maillard, M.D., Ph.D.**, University of Michigan Medical School, "Cooperative Effects of Trithorax Group Histone Methyltransferases in the Regulation of Hematopoietic Stem Cell Homeostasis"
5:09pm – 5:30pm: **Q. Tian Wang, Ph.D.**, University of Illinois at Chicago, "Epigenetic Regulation of Cardiac Development and Regeneration"

Locaion: HHB 1005
3:45pm – 5:30pm **Focus Session K**: Tissue Engineering

Moderators: **Mervin Yoder, M.D.**, University of Indiana; **Joe Guettler, M.D.**, Beaumont Health System

3:45pm – 4:05pm: **Mervin Yoder, M.D.**, University of Indiana, "Engineering Blood Vessel Formation and Repair"
4:10pm – 4:30pm: **Judith Fulton, Ph.D.,** Akron General Medical Center Medical Center, "Wound Healing Using Progenitors, Natural Matrices and Cold Plasma"
4:35pm – 4:55pm: **Qi Li, Ph.D.**, University of Illinois at Chicago, "Lyophilization of PRF as a Strategy to Improve Cell Proliferation, Osteogenic Differentiation, and Tissue Integration for Craniofacial Tissue Engineering"
5:00pm – 5:30pm: **TBA**

Location: HHB 1006
3:45pm – 5:30pm **Focus Session L**: Biomaterials and Stem Cell Maintenance

Moderators: **Chenran Wang, Ph.D.**, University of Michigan; **Ferman Chavez, Ph.D.**, Oakland University

3:45pm – 4:05pm: **Luis G. Villa-Diaz, Ph.D.**, University of Michigan, "Derivation of Transgene Integration-free Human Induced Pluripotent Stem Cells in Xeno-free and Synthetic Conditions"
4:10pm – 4:30pm: **Chenran Wang, Ph.D.**, University of Michigan, "FIP200 is Required for Maintenance and Differentiation of Postnatal Neural Stem Cells Through Regulation of Oxidative State"
4:35pm – 4:45pm: **Xu Qian**, Doctoral Candidate, University of Michigan, "Effects of Surface Thickness on the Ability of Synthetic Polymer Coatings to Support Human Embryonic Stem Cell Self-renewal"
4:50pm – 5:00pm: **Katrina Fox, M.S.,** Kansas State University, College of Veterinary Medicine, "Comparing Methods for Cryopreservation of Rat Sperm with Intrauterine Insemination"
5:05pm – 5:15pm: **Bradly Alicea**, Doctoral Candidate, Michigan State University, "Simulating the Dynamic Regulation of a Cell: Relevance to Cell Reprogramming"
5:20pm – 5:30pm: **Ying Nie, Ph.D.**, Lonza Walkersville, Inc., "A Novel cGMP-compliant Method for Passaging of Human Pluripotent Stem Cells"

Conference Schedule

Location: Oakland Center Banquet Rooms
3:00pm – 6:30pm: **Poster Presentation**
Presenters will be at the posters from 5:30pm - 6:30pm

Location: Oakland Center Banquet Rooms
6:30pm – 8:30pm: **Dinner**

Welcoming Remarks by Ananias Diokno, M.D., Chief Medical Officer, Beaumont Hospital; **Gary Moore, Ph.D., RN,** Associate Dean, School of Nursing, Oakland University

Introduction by **Rasul Chaudhry, Ph.D.**, OU-WB ISCRM, Oakland University

6:30pm – 7:10pm: Dinner Lecture, **Mahendra Rao, M.D., Ph.D.**, Director, Center for Regenerative Medicine, NIH, "Regenerative Medicine – An International Perspective"
7:15pm – 7:30pm: Poster Awards
7:30pm – 8:30pm: Dinner

SUNDAY, OCTOBER 7th

Location: Oakland Center
7:00am – 7:50am: **Continental Breakfast**
Students and residents meet the experts: (**Mahendra Rao, M.D., Ph.D.**, **Mark Weiss, Ph.D.**, **Mervin Yoder, M.D.**, **Dan Kaufman, M.D., Ph.D**)

Location: HHB 1050 (Auditorium)
8:00am – 10:00am **Plenary Session IV**: Special Topics in Translational and Stem Cell Therapy II

Welcoming Remarks by **TBA**

Moderators: **Rasul Chaudhry, Ph.D.**, OU-WB ISCRM, Oakland University; **Gary Hammer, M.D., Ph.D.**, University of Michigan Medical School.

8:00am – 8:20am: **Gary Hammer, M.D., Ph.D.**, University of Michigan Medical School, "Translation of Adrenal Stem Cells"
8:25am – 8:45am: **Mark Weiss, Ph.D.**, Kansas State University, "PiggyBac Transposon Mutagenesis in Rat Embryonic Stem Cells"
8:50am – 9:10am: **Dan Kaufman, M.D., Ph.D.**, University of Minnesota, "Human Pluripotent Stem Cell-derived Natural Killer Cells to Treat Cancer and HIV/AIDS"
9:15am – 9:35am: **Rasul Chaudhry, Ph.D.**, OU-WB ISCRM, Oakland University, "Retinal Regeneration"
9:40am – 10:00am: **Vilma Yuzbasiyan-Gurkan, Ph.D.,** Michigan State University, "Evaluation of OCT4 Expression as a Cancer Stem Cell Marker in Canine and Human Osteosarcoma: Insights and Challenges"

Location: HHB (2nd Floor)
10:00am – 10:15am: **Coffee Break**

Location: HHB 2085
10:15am – 12:00pm **Focus Session M**: Disease Models

Moderators: **Graham Parker, Ph.D.**, Wayne State University School of Medicine; **Craig Atwood, Ph.D.**, University of Wisconsin Medical Center,

10:15am – 10:35am: **Jack Mosher, Ph.D.**, University of Michigan Center for Stem Cell Biology, "Modeling Ewing's Sarcoma with Neural Crest Stem Cells"
10:38am – 10:58am: **Graham Parker, Ph.D.**, Wayne State University School of Medicine, "Advancing Spinal Muscular Atrophy Interventions Using Stem Cell Research"
11:01am – 11:21am: **Craig Atwood, Ph.D.**, University of Wisconsin Medical Center, "Human Embryonic Stem Cells as a Model System for Understanding Alzheimer's Disease: The Role of the amyloid-beta Precursor Protein in the Differentiation of Neurons"
11:24am – 11:44am: **Sumi Dinda, Ph.D.**, Oakland University, "Differentiation and Proliferation of Embryonic Stem Cells by Hormonal Regulation."
11:47am – 12:00pm: **Andrew M. Tidball**, Doctoral Candidate, Vanderbilt University, "Selective Metal Sensitivity in hiPSC–derived Neural Progenitors from a Preclinical Parkinson's Disease Patient"

Location: HHB 1005
10:15am – 12:00pm **Focus Session N**: Biobanking

Moderators: **George Wilson, Ph.D.**, OU-WB ISCRM, Beaumont Hospital, **Anne Mitchell, Ph.D., R.N., C.R.N.**, Oakland University

10:15am – 10:35am: **Erik Forsberg, Ph.D.**, WiCell Research Institute and the University of Wisconsin-Madison, "Challenges of Making, Banking and Distributing Pluripotent Stem Cells"
10:40am – 11:00am: **George Wilson, Ph.D.**, Beaumont BioBank, "Multidisciplinary Translational Research Facility"
11:05am – 11:25am: **Dan O'Donnell**, Fisher Biosciences, "Logistical Considerations for Biologic Product Storage and Transport"
11:30am – 12:00pm: **TBA**

Location: HHB 2086
10:15am – 12:00pm **Focus Session O**: Political, Ethical, and Regulatory: Panel Discussion

Moderators: **Kenneth Hightower, Ph.D.**, Dean, Health Sciences, Oakland University; **Pat Piskulich, Ph.D.**, Oakland University

10:15am – 10:35am: **Bernard Siegel, J.D.**, Genetics Policy Institute
10:40am – 11:00am: **Ernest F. Krug, III, M.Div., M.D.,**

Conference Schedule

FAAP, OU-WB School of Medicine, "Stem Cell Research: What Does Our Humanity Require of Us"

11:00am – 11:30pm: Discussion
Panel Members: **Bernard Siegel, J.D.**, Genetics Policy Institute, **Ernest F. Krug, III, M.Div., M.D., FAAP,** OU-WB School of Medicine**, Domenico Luongo, M.S., C.H.M.M.,** Oakland University; **Anne Mitchell, Ph.D., R.N., C.R.N.**, Oakland University; **David Svinarich, Ph.D.**, Vice President of Research, St. John's Health System

Location: HHB 1006
10:15am – 12:00pm **Focus Session P**: Applications of Stem Cell Therapy

Moderators: **Chien-Wen Chen, M.D., Ph.D.**, University of Pittsburgh; **Lan Jiang, Ph.D.,** Oakland University

10:15am – 10:35am: **Chunying Li, Ph.D.**, Wayne State University School of Medicine, "A Critical Role of CXCR2 PDZ–mediated Interactions in Endothelial Progenitor Cell Neovascularization"

10:40am – 11:00am: **Chien-Wen Chen, M.D., Ph.D.**, University of Pittsburgh, "Human Pericytes: The Anti–fibrotic, Anti–inflammatory, and Angiogenic Roles for the Treatment of Myocardial Infarction"

11:05am – 11:15am: **Anna Sonstegard**, **B.S.**, University of Minnesota, "Intra–arterial Infusion of Human UCSCs in Rats 48 Hours after Middle Cerebral Artery Stroke"

11:20am – 11:30am: **Tristan Maerz, M.S.**, Beaumont Health System, "Tissue Engineering of the Intervertebral Disc: In Vitro and *In Vivo* Studies of Combinations of a Natural Hydrogel, Morphogenic Growth Factors, a Proteinase Inhibitor, and Allogenic Mesenchymal Stem Cells"

11:35am – 11:45am: **Christina McKee,** Doctoral Candidate, Oakland University, "Self-assembling Scaffold Supports Pluripotent Growth of Embryonic Stem Cells"

11:50am – 12:00pm: **Naimisha Reddy Beeravolu,** Doctoral Candidate, Oakland University, "The Effect of Arsenite on Cord Blood Stem Cells"

Location: HHB 1050 (Auditorium)
12:00pm: **Closing Remarks and Acknowledgements** by **Rasul Chaudhry, Ph.D.**, and **George Wilson, Ph.D**., Oakland University William Beaumont Institute for Stem and Regenerative Medicine (OU-WB ISCRM)

12:15pm: **Business Meeting**

Biosketches & Research Interests

Biosketches & Research Interests

Bradly Alicea (doctoral candidate), is a graduate researcher in Animal Science at Michigan State University. His work focuses on the computational, dynamic, and bioengineering approaches to cellular reprogramming.

> **Research Interests:** The research focuses on biotechnology and systems biology, including the transgenic and computational models of cells, tissues, and living systems as well as virtual worlds, telerobotics, and biomimetic technologies, the applications of microsystems/sensor technologies and neurotechnology/neural engineering. Experimental, theoretical, and measurement-based approaches to complex systems: dynamical/evolutionary systems, self-assembly, critical and emergent phenomena. Alternative models for research funding/web-based academia, entrepreneurship.

Ali S. Arbab, M.D., Ph.D., received his M.D. from the Institute of Post-graduate Medicine and Research in Bangladesh and his Ph.D. in radiological science from Yamanashi Medical University in Japan. He served as senior medical officer at the Institute of Nuclear Medicine in Bangladesh and was in charge of the Nuclear Medicine Division at Yamanashi Medical University. Dr. Arbab completed a research fellowship in cellular magnetic resonance imaging at the National Institutes of Health. He is currently associate scientist and the director of the Cellular and Molecular Imaging Laboratory, Department of Radiology, at Henry Ford Health System in Detroit, MI.

> **Research Interests:** Differentiation of glioma from radiation injury: Despite advancement in the CT, MRI and PET technologies, early differentiation of recurrent glioblastoma multiforme (GBM) from radiation necrosis in patients is still a problem. We hypothesize that based on active angiogenesis or immunogenicity recurrent GBM can be differentiated from radiation necrosis/injury. Active sites of angiogenesis or accumulation of immunogenic cells can be detected by in vivo MRI using magnetically labeled endothelial progenitor cells or cytotoxic T-cell, respectively. The magnetic labeling technique is developed by our group at NIH and optimized in our laboratory (CMIL).

Craig S. Atwood, Ph.D., is an Associate Professor of Medicine at the University of Wisconsin and a Health Science Specialist with the Geriatric Research, Education and Clinical Center at the William S. Middleton Memorial Veterans Administration Hospital in Madison. Dr. Atwood received his Ph.D. in Biochemistry from the University of Western Australia in Perth, Australia prior to post-doctoral fellowships at the National Cancer Institute, NIH, Bethesda, and Massachusetts General Hospital, Charlestown. He has held faculty positions at Harvard Medical School and Case Western Reserve University prior to his current appointment where he directs the research program of the Laboratory for Endocrinology, Aging and Disease in the Department of Medicine at the University of Wisconsin-Madison. He also holds the position of Research Director of the Wisconsin Alzheimer's Institute, and of the Wisconsin Comprehensive Memory Program, and is a Health Science Specialist with the Geriatric Research, Education and Clinical Center at the William S. Middleton Memorial Veterans Administration Hospital, Madison.

Research Interests: Dr. Atwood is renowned for his research utilizing human embryonic stem cells (hESCs) as a model for identifying the physiological hormonal signals that drive cell proliferation and differentiation during early human embryogenesis. Additionally, his laboratory has utilized hESC as a model system for understanding the neurodegeneration associated with Alzheimer's disease. He has broad research interests related to the endocrinology of embryogenesis, adulthood and senescence as elaborated upon in 'The Reproductive-Cell Cycle Theory of Aging'. He has published over 200 scientific articles, has served on numerous review boards and is an Editor of more than 30 scientific journals including the *Journal of Biological Chemistry*. In 2006 he received the Zenith Fellows Award from the Alzheimer's Association in recognition of his research.

Frank Baaijens, Ph.D., is full professor in Soft Tissue Biomechanics & Tissue Engineering. He received his PhD degree from the Eindhoven University of Technology in 1987 with professor J.D. Janssen as his supervisor. In 1985 he joined Philips Research Laboratories in Eindhoven to work on Computational Mechanics. Since 1990 he has been a part time professor in the Polymer Group of the division of Computational and Experimental Mechanics of the Eindhoven University of Technology, in the area of Computational Rheology. In July 1995, he was appointed full professor in the Department of Mechanical Engineering. In October 2002, he was appointed full professor in the Department of BioMedical Engineering (division of Biomechanics and Tissue Engineering). From 2003-2007 he was Dean of the Department of Biomedical Engineering, and he is currently Scientific Director of the national research program on BioMedical Materials (BMM).

Research Interests: His current research focuses on soft tissue biomechanics and tissue engineering.

Naimisha Reddy Beeravolu, M.S., (doctoral candidate), graduated with a Master of Science degree from New Jersey Institute of Technology in Biomedical Engineering in 2011. She wrote her master's thesis on the "Fabrication of 3D scaffolds with Soy protein and Polyvinyl Alcohol," at which time, she became interested in tissue engineering and stem cell regeneration. After graduation she worked as a research scientist at Bristol Myer's Squibb in the development of cell culture lab for six months. Currently she works in Dr. Chaudhry's lab at Oakland University and is a second year Ph.D. student.

Research Interests: Her current research focuses on differentiating cord blood stem cells into chondrogenic derivatives, specifically, into nucleus pulposus for the regeneration of degenerated intervertebral discs. She is interested in studying the properties of endothelial progenitor cells (EPCs) isolated from human umbilical cord blood. She also studies the effects of arsenite on stem cells.

Ronnda L. Bartel, Ph.D., joined Aastrom in 2006 and is responsible for the scientific direction of the company, including research, development and technical operations. She has more than 20 years of research and product development experience and most recently was executive director, biological research at MicroIslet and vice president, scientific development at StemCells Inc. Earlier in her career, she was senior principal scientist and director of research at Advanced Tissue Sciences and was involved in the development and approval of some of the first cell-based products approved by the FDA. She has also worked as senior director, science

and technology at SRS Capital, LLC evaluating life science investments and has held positions in clinical development, drug delivery, business development and manufacturing. Ronnda holds a PhD in biochemistry from the University of Kansas, has completed postdoctoral work at the University of Michigan and received a BA in chemistry and biology from Tabor College.

> **Research Interests:** Dr. Bartel is responsible for the product development and manufacturing of Aastrom's TRC-based cell products, as well as the Company's discovery and research efforts. Her broad experience and leadership in the biotechnology and pharmaceutical industries, along with experience in the manufacturing and marketing of new cell-based products, strongly support and complement the Company's progress in moving its tissue regeneration products through the commercialization process.

Nissim Benvenisty M.D., Ph.D., is the Herbert Cohn Chair in Cancer Research and the director of the Stem Cell Unit at the Hebrew University. He earned his M.D. and Ph.D. degrees from the Hebrew University, and conducted postdoctoral studies at Harvard University. He published numerous original and review papers on human pluripotent stem cells, and serves on the editorial board of various stem cell related journals. He is a member of the steering committee of the International Stem Cell Initiative, and the Board of Directors of the ISSCR. Professor Benvenisty presents the issue of human embryonic stem cells in many international conferences, and gave testimonies before the US Senate and the European Union. He was awarded several prizes among them the Foulkes Prize (London), the Hestrin Prize, the Teva Prize, and the Kaye Prize.

> **Research Interests:** Professor Benvenisty's research projects focus on stem cell biology, tissue engineering, human genetics, and cancer research.

Dean H. Betts, Ph.D., is internationally recognized for his contributions to our current understanding of early embryo development and as one of the first research groups to generate and characterize numerous canine embryonic stem cell lines and mesenchymal stromal cells from umbilical cord blood of foals. He received degrees from the University of Western Ontario (BSc, MSc), and the University of Guelph (Ph.D.). Following a post-doctoral fellowship at Case Western Reserve University, Dr. Betts joined the faculty at the Ontario Veterinary College as an Assistant Professor in 2001. Dr. Betts' research, which has resulted in 50 peer-reviewed publications, has focused on characterizing and understanding the molecular and cellular mechanisms of early mammalian development using cattle embryos as his main experimental model. Notably, his studies on telomere length regulation presented evidence of a telomere-lengthening event during the first week of embryogenesis and that some healthy and fertile cloned animals and their offspring exhibit variant telomere lengths compared to their reproductively bred counterparts suggesting that epigenetic alterations could be passed through the germ line. Dr. Betts was one of the first to apply RNA interference technology to study gene function in early mammalian embryos. Using live cell imaging and embryo microinjections his lab revealed that the stress adaptor protein p66Shc is mechanistically involved in the ROS signaling pathway of permanent embryo arrest. Applying global gene expression analyses to stably transfected cell lines, his research has discovered alternative function(s) for the catalytic subunit of telomerase (TERT) that changes the cell state towards a progenitor stem cell-like condition. This information explains the utility of ectopically expressed TERT as a potent reprogramming factor in the production of induced pluripotent stem cells (iPSCs). In November 2008, he moved his lab to Western University where his research is focused on characterizing the

role of various telomerase splice variants in pluripotency maintenance and induction. Dr. Betts has a strong interest in developing clinically relevant animal models for stem cell-based transplantation therapies.

> **Research Interests**: Our research program is aimed at understanding the cellular and molecular basis of pluripotency and self-renewal and to elucidate the reprogramming events necessary to reverse cellular aging and differentiation processes that will facilitate the production of induced pluripotent stem cells in humans and dogs.

Kapil Bharti Ph.D., holds a bachelor's degree in Biophysics from the Panjab University in Chandigarh, India, a master's degree in biotechnology from the M.S. Rao University in Baroda, India, and a diploma in molecular cell biology from the Johann Wolfgang Goethe University in Frankfurt, Germany. Supported by an international Ph.D. student fellowship, he obtained his Ph.D. from the same institution, graduating summa cum laude. His Ph.D. work involved research in the areas of heat stress, chaperones, and epigenetics. He did his postdoc at the National Institutes of Health, where he published numerous papers in the areas of transcription regulation, pigment cell biology, and developmental biology of the eye. Dr. Bharti has successfully gotten grants in three out of three cycles from the NIH Center for Regenerative Medicine. He has won several awards, including, most recently, being a finalist in the prestigious trans-NIH Earl Stadtman Tenure-Track Symposium.

> **Research Interests**: His current work as the head of the Unit on Ocular Stem Cells and Translational Research involves developing cell-based therapy for retinal degenerative diseases using induced pluripotent stem cell technology.

G. Rasul Chaudhry, Ph.D., is Professor of Molecular Biology in Department of Biological Sciences and Co-Director, Oakland University William Beaumont Institute for Stem Cell and Regenerative Medicine (OU-WB ISCRM), Oakland University. He received his Ph.D. in Microbiology with Professor Howard Lees from the University of Manitoba, Canada. In 1980, he joined the Department of Microbiology at Georgetown University School of Medicine. After which he worked as a Sr. Staff Fellow in Molecular Biology Lab, NINCDS, National Institutes of Health from 1982-1985. He was Assistant Professor of Environmental Microbiology at University of Florida for five years before joining Oakland University as Associate Professor in 1989. In 2004 he was appointed full professor and since 2010 he is serving as the founding Co-Director of the OU-WB ISCRM.

> **Research Interests**: His research focuses on the molecular mechanisms of stemness and differentiation of embryonic, cord blood and adult stem cells. He is also interested in tissue bioengineering, the regulation of gene expression and stem cell-based therapeutic and biotechnological applications.

Ferman Chavez, Ph.D., is an Associate Professor in the Chemistry department at Oakland University, and specializes in bioinorganic chemistry.

> **Research Interests:** Dr. Chavez's current research aim is to develop synthetic models for active sites of metalloenzymes. Such models will be used to probe enzymatic mechanisms and as catalysts for organic transformations and bioremediation. He has

recently become interested in developing MRI contrast agents for imaging hypoxia and the development of hydrogel scaffolds for regenerative medicine applications.

Chien-Wen Chen, M.D., Ph.D., recently earned his Ph.D. in bioengineering from the University of Pittsburg where he is continuing to do his postdoctoral research. For his doctoral research he studied the application of human blood vessel derived stem cells to treat ischemic heart disease.

Research Interests: Dr. Chen's research is focused on the identification and characterization of potential stem/progenitor cell populations in the heart.

Jose Cibelli, Ph.D., currently holds the position of Professor of Animal Biotechnology at Michigan State University. He heads the Cellular Reprogramming Laboratory in the Departments of Animal Science and Physiology. From October 1999 until December 2002 he was the vice president for research of Advanced Cell Technology, a stem cell company in Worcester, Massachusetts. He has testified about nuclear transfer and stem cells in public forums sponsored by the US Food and Drug administration, the USA National Academy of Sciences, Canadian House of Commons, the USA Department of Agriculture and the United Nations Commission for Human Rights. Dr. Cibelli also serves as the Associate Scientific Director of the 'Program for Cell Therapy and Regenerative Medicine of Andalucía', Seville, Spain; the International Committee of the 'International Stem Cell Research Society', the Ethics Committee of the 'American Society of Gene Therapy' and the Scientific and Medical Accountability Standards Working Group of the 'California Institute for Regenerative Medicine'.

Research Interests: Dr. Cibelli is one of the pioneers in the area of cloning with transgenic somatic cells for the production of animals and embryonic stem cells. Dr. Cibelli together with his colleagues, were responsible for the generation of the world's first transgenic cloned calves, the first embryonic stem cells by nuclear transfer and the first embryonic stem cells by parthenogenesis in primates. This was followed by publications in Science, Nature Biotechnology, Nature Medicine, PNAS and JAMA.

Sarah Conley, Ph.D., received her bachelor's degree in Biology from Alma College (Alma, MI) and her Ph.D. in Cell and Molecular Biology from Michigan State University (East Lansing, MI), where she studied the endocrine regulation of mammary gland development. As a postdoctoral fellow in Max Wicha's lab at the University of Michigan.

Research Interests: She has focused her research on the regulation of breast cancer stem cells by oxygen levels. She is now continuing this work as a Research Investigator at the University of Michigan.

Thomas Diekwisch, D.M.D., Ph.D. (sc.), Ph.D. (phil.), was born in Bielefeld, Germany, and he holds degrees in dental medicine (1986, D.M.D.), Anatomy (1988, Ph.D. with "*summa cum laude*"), and philosophy (2005, Ph.D. with "*magna cum laude*"), all from the Philipps-University of Marburg/FRG. From 1986-1990, Dr. Diekwisch worked as a lecturer, clinical instructor, and research associate in the Departments of Anatomy and Periodontics at the Philipps-University. After postdoctoral training at the University of Southern California he joined the faculty of Baylor College of Dentistry in Dallas/TX in 1994, where he created an award-winning community science education outreach program entitled "Habitat for Science". In 2001, Dr.

Diekwisch was recruited to the University of Illinois at Chicago to become the first Director of the Brodie Laboratory for Craniofacial Genetics and the Allan G. Brodie Endowed Chair. Two years later, he was appointed Professor and Head of the Department of Oral Biology at UIC. Besides Oral Biology, Dr. Diekwisch holds appointments in Anatomy and Cell Biology, Bioengineering, Orthodontics and Periodontics.

> **Research Interests**: The Brodie Laboratory for Craniofacial Genetics is a multidisciplinary molecular research environment supported by the Brodie Endowment, the University of Illinois, and the National Institute for Dental and Craniofacial Research. Research in the Brodie Laboratory for Craniofacial Genetics focuses on stem cells and epigenetic control of pluripotency by the chromatin remodeling factor CP27. Other areas include craniofacial tissue engineering as well as development and evolution of tooth enamel and periodontal attachment.

Sumi Dinda, Ph.D., is an Associate Professor of Biomedical Diagnostic and Therapeutic Sciences in the School of Health Sciences and a founding member of the Institute for Stem Cell and Regenerative (ISCRM). Dr. Dinda's laboratory has been conducting research on the molecular mechanism of steroid hormones on tumor suppressor proteins in breast cancer cells. This research will aid in understanding the mechanism of tumor suppression and designing better approaches in the hormonal management of breast cancer. Dr. Dinda's laboratory, in collaboration with Dr. Rasul Chaudhry, professor of Biological Sciences and Dr. Donald Taylor from Obstetrics and Gynecology department of William Beaumont Hospital is also investigating the effects of estrogen and progesterone hormones on the induction of steroid hormone receptors in embryonic stem cells (ESCs) and how they influence the differentiation and proliferation of stem cells in women. This work was presented in the annual meetings of the International Society of Stem Cell Research. The stem cell research project will provide better understanding of the molecular mechanism of hormonal regulation on the ESC differentiation, which may lead to develop new strategies for treating breast, ovarian or uterine cancer and other related applications in biomedical research. Dr. Dinda's research is supported by the Research Excellence Fund, OU-Beaumont research funds and other organizations.

> **Research Interests:** Molecular mechanism of steroid action on breast cancer cells and tumor suppressor genes, hormone action on stem cell differentiation and proliferation.

Gregory Dressler, Ph.D., is a Collegiate Professor of Pathology Research at the University of Michigan Medical School. He received a B.S.E. and a Ph.D. from the University of Pennsylvania and was a post-doctoral fellow in the laboratory of Peter Gruss at the Max Planck Institute of Biophysical Chemistry in Goettingen. Upon returning to the US, he was a Senior Staff Fellow at the National Institutes of Health in Bethesda before coming to Michigan. For the past 15 years, Dr. Dressler's has lab has studied the role of transcription factors and cell signaling pathways in renal development and disease. The lab has made numerous discoveries including: the Pax2 gene, the function of GDNF/c-ret in kidney development and chemotaxis, the function of KCP, the first enhancer of BMP signaling, in renal fibrosis, and the function of the epigenetic co-factor PTIP in histone methylation.

> **Research Interests:** The body of work most relevant to this grant includes the discovery of Pax2, one of the earliest genes expressed in the renal and urogenital epithelial lineage.

Pax2 is essential for kidney development and has been linked to cancer in both kidney and uterine epithelia. More recently, we discovered PTIP, a protein that is essential for histone H3K4 methylation in development and stem cells. PTIP is an adaptor protein that links Pax2, and other serine phosphorylated proteins, to the histone H3K4 methylation machinery. This changed the model for how developmental DNA binding proteins may act to restrict cell lineage progression along certain pathways and unified the idea of developmental competence with epigenetic imprinting of the genome. The focus on epigenetic determination during development and disease utilizes genetic and biochemical models developed in the lab specifically to understand how renal epithelial cells are generated and how they remain phenotypically stable in the adult.

Paul Dyce, Ph.D., completed his B.Sc., M.Sc. and Ph.D. degrees at the University of Guelph. He is currently a postdoctoral fellow in Dr. Gerald Kidder's laboratory at Western University in Ontario Canada.

Research Interests: His research focuses on the germline potential of somatic skin derived stem cells as well as the roles of intercellular signaling pathways, including gap junctional intercellular communication (GJIC), in ovarian and follicular development.

James Eliason, Ph.D., has worked in stem cell research for over 40 years at institutions around the world. Dr. Eliason received his Ph.D. in biochemistry from the University of Chicago in the laboratory of Dr. Eugene Goldwasser at the time erythropoietin was purified. His postdoctoral training was done at the Paterson Laboratories, Christie Hospital and Holt Radium institute in Manchester, England and the Radiobiological Institute, TNO in Rijswijk, the Netherlands. He was an Associate Researcher at the Swiss Institute for Experimental Cancer Research (ISREC) in Lausanne, where he headed up a program to study human tumor stem cells from tumor biopsy samples. He established a high throughput screening program for modifiers of multidrug resistance with cancer cells at Hoffmann-La Roche in Basel, Switzerland. When Roche closed preclinical the drug discovery program in their Swiss laboratories, he was responsible for transferring the oncology research projects from Basel to the Nippon Roche Research Center in Kamakura, Japan.

Research Interests: He returned to Detroit in 1995 to join the Karmanos Cancer Institute and the stem cell research program. He was a founder and Chief Scientific Officer of Asterand, the human tissue research services company. James Eliason is Executive Director of the Great Lakes Stem Cell Innovation Center located in TechTown, Wayne State University's business incubator. He is also adjunct faculty at the Karmanos Cancer Institute and is CEO of MitoStem a startup stem cell research technology company.

Richard Fessler, M.D., Ph.D., serves as Professor of Neurosurgery at the Feinberg School of Medicine of Northwestern University. Prior to assuming this position he was the John Harper Seeley Professor and Chief of Neurosurgery at the University of Chicago Hospitals and Clinics. He previously founded and directed the Institute for Spine Care at the Chicago Institute of Neurosurgery and Neuroresearch (CINN) and was Professor of Neurological Surgery at Rush Medical College in Chicago, after serving as Director of Clinical Services and Education at the University of Florida Brain Institute. Additionally, at the University of Florida, he held the Dunspaugh-Dalton Chair of Brain and Spinal Surgery and served as Professor in the Department

of Neurological Surgery. Dr. Fessler completed his Medical Doctorate with honors, and Surgical and Neurosurgical residencies at the University of Chicago. In addition to surgical training, Dr. Fessler completed a Doctorate of Philosophy in Pharmacology and Physiology, and a Master's of Science in Psychology. Continuing education after earning doctoral degrees, Dr. Fessler held research Fellowships at the University of Chicago Medical Center in Neurological Surgery and Psychiatry. The Chicago Surgical Society honored Dr. Fessler with the Excellence in Surgical Research award.

> **Research Interests:** Dr. Fessler's research focuses primarily clinical applications of stem cell therapies for treatment of spinal cord injuries.

Erik J. Forsberg, Ph.D., studies the development of novel biotechnologies directed towards treating human diseases. At Infigen, Inc. and subsequently Pharming Group, NV, his work was instrumental in the generation of genetically engineered animals targeted to produce human proteins and 'humanized' organs for treating conditions including hereditary angioedema, organ failure, organ rejection following transplant, and uncontrolled bleeding. His is also contributing to the development of new a gene therapy approach to treat type I diabetes as a senior scientist in the Department of Surgery at the UW-Madison. After graduating from Kalamazoo College, he earned a Ph.D. in pharmacology and physiology from the University of Chicago and did his postdoctoral work at the NIH. He was subsequently appointed Assistant Professor of physiology at the University of Wisconsin-Madison where he elucidated several signal transduction pathways in the adrenal gland

> **Research Interests:** In his current position as the executive director of WiCell, Dr. Forsberg is working to build WiCell's collaborative R&D efforts with universities, non-profit organizations and companies to promote the translation of basic stem cell research into new therapies and diagnostics for unmet medical needs.

Katrina Fox, M.S., is a research student working in the Weiss laboratory.

> **Research Interests:** Her research focus is on various stem cell lines such as rat embryonic stem cells and cells derived from umbilical cord or other tissues with the intent of using this technology to advance cellular therapy and regenerative medicine. She also has an interest towards the mechanisms of pluripotency in rat embryonic stem cells and new rat models of human disease using gene targeting in rat embryonic stem cells. The lab is focused upon producing promising cellular therapeutics for regenerative medicine.

Judith Fulton, Ph.D., is the Director of Wound Research in the Wound Healing and Limb Preservation Center at Akron General Medical Center in Akron, Ohio. She is responsible for integrating research (basic science and clinical) into wound care, education and outreach. She is also an administrator for the Heal Ohio Collaborative™, a voluntary multi-disciplinary and multi-institutional collaborative dedicated to research, education and commercialization activity focused on all aspects of wound healing and prevention. She is a member of the Akron Entrepreneurial Network, works closely with the Akron Global Business Accelerator, and serves on the advisory board of Sterionics, Inc. She holds adjunct faculty positions at Kent State University and Northeast Ohio College of Medicine.

Research Interests: She is primarily focused on wound healing research, wound healing education, skin tissue engineering, animal wound models, and emerging wound technologies.

Jose L. Garcia-Perez, Ph.D., is an emerging Principal Investigator that studies how Transposable Elements impact the genome of human stem cells. He has worked in this field for more than 10 years and has published over 30 articles (the total includes articles, reviews, book chapters, perspectives, and a thesis). He received his Ph.D. in Molecular Biology from the University of Granada-Spanish Research Council (CSIC) in 2003, where he studied under Dr. Manuel Carlos Lopez the mobilization of repeated DNA in *Trypanosomes*. In late 2003, he joined the University of Michigan Medical School (Department of Human Genetics, Lab of Dr. John V. Moran) as a post-doctoral fellow. In 2007, he was promoted to Research Investigator in the University of Michigan, and since late 2008 he is a Group Leader in Spain (at Genyo, Pfizer-University of Granada-Andalusian Government Center for Genomics and Oncological Research, Granada). In January 2012, the Howard Hughes Medical Institute appointed him as an International Early Career Scientist.

Research Interests: Our lab studies the impact and control of L1s in the genome of hESCs and other derived stem cell types like Neuronal Stem Cells (NSCs), and iPSCs. We recently demonstrated that hESCs are a bona fide model to study the accumulation of new L1 insertions in humans, as newly inserted L1s would be transmitted to new generations. *In vitro,* we have demonstrated that engineered L1s can insert into genes in hESCs and that some insertions can be accompanied by genomic deletions at the site of insertion. Furthermore, hESCs are characterized for the expression of L1 mRNA and proteins, and preliminary data from our lab indicate that endogenous L1s are retrotransposing in hESCs, contributing to their genomic fluidity. In addition, and very recently, we have analyzed L1 expression and mobilization in iPSCs, and our data revealed that with regards to L1 expression, hESCs and iPSCs are indistinguishable as both over-express L1 retrotranspositon intermediates and support L1 retrotransposition. Similarly, we described L1 mobilization in other stem cells like NSCs, although the biological meaning, if any, remains to be determined as L1 insertions in somatic genomes break the paradigm of TEs as "selfish DNA".

Michael Gilkey, MBA, M.S., is the Marketing and Operations Manager for both the National Center for Regenerative Medicine (NCRM) and the Center for Stem Cell and Regenerative Medicine (CSCRM). He reports directly to the Executive and Technical Directors of both organizations and assists in the development and execution of organizational strategy, planning and execution of both external and internal marketing efforts, and provides administrative and operational support. Michael Gilkey earned two degrees from Case Western Reserve University. The first was a Master's of Science in Biomedical Engineering and the second was a Master of Business Administration with concentrations in Bioscience Entrepreneurship and Marketing. He also has a Bachelor's of Science in Biological Engineering from Louisiana State University.

Research Interests: Mr. Gilkey also has two start-up companies; Invenio Therapeutics, Inc. and Gilkey Biotechnology Consulting, LLC. Invenio Therapeutics was founded by Dr. William Tse, M.D., Dr. David Wald, M.D. and Mr. Michael Gilkey, M.B.A, M.S. The initial idea for the technology was submitted by Dr. Wald on August 2, 2005 and

submitted for a provisional patent on June 12, 2007. The intellectual property for this start-up consists of drug compounds that terminally differentiate leukemia cells so that they no longer have the ability to divide and replicate. Once these cells die, the disease is cured. Gilkey Biotechnology Consulting provides contract services for business planning and strategy, proforma creation, grant writing, and marketing strategy and design.

Gokul Gopinathan, Ph.D., born in Quilon, India, Gokul Gopinathan completed a Master's degree and graduated with a Ph.D. in Biotechnology (CDFD, University of Manipal, 2010). His Ph.D. thesis focused on the role of epigenetic modifications at the *DNMT3L* promoter in various cancers. Based on its innovative nature, his work was chosen for the "Scholar in Training" award at the American Association of Cancer Research conference in 2008. In 2009, he joined the University of Illinois at Chicago as a Postdoctoral Research Associate.

Research Interests: At UIC, Dr. Gopinathan is mentored by Dr. Tom Diekwisch at the Brodie Laboratory for Craniofacial Genetics. Here, he focuses on the role of epigenetics in determining the fate of neural crest cells in the craniofacial region. He is also working on the function of the CP27 gene as a novel chromatin remodeling factor. Other interests include the role of epigenetics in cancer and cancer stem cells, as well as the role of histone variants in the regulation of chromatin architecture.

Jason A. Hamilton, Ph.D., received his Ph.D. in Neuroscience from the University Of Rochester School Of Medicine, Rochester, NY, in 2006, and subsequently completed a postdoctoral fellowship in stem cell biology and neurobiology at the University of California, Irvine. He has since worked in the Regenerative Medicine department at Athersys, Inc. (Cleveland, OH), which is developing a bone marrow-derived adult stem cell therapy (MultiStem®) that is currently being tested in clinical trials for the treatment of inflammatory bowel disease and ischemic stroke. Dr. Hamilton is responsible for pre-clinical study management and biomarker assay development for their adult stem cell therapy product.

Research Interests: He has since worked in the Regenerative Medicine department at Athersys, Inc. (Cleveland, OH), which is developing a bone marrow-derived adult stem cell therapy (MultiStem®) that is currently being tested in clinical trials for the treatment of inflammatory bowel disease and ischemic stroke. Dr. Hamilton is responsible for pre-clinical study management and biomarker assay development for their adult stem cell therapy product.

Gary Hammer, M.D., Ph.D., is a highly respected researcher, clinician, teacher and mentor. He has served in leadership positions on numerous committees for the Endocrine Society and sits on the editorial board of Molecular Endocrinology receiving the 2005 Outstanding Reviewer Award. His most notable awards include the 1999 Endocrine Society Senior Fellow Award and the 2005 Jerome Conn Award from the University of Michigan, the top award given by the Department of Medicine to a junior faculty. In the same year, co-incident with tenure, Dr. Hammer was installed as the Millie Schembechler Professor of Adrenal Cancer and named Director of the Endocrine Oncology Program in the Cancer Center which incorporates diagnosis, treatment and research of adrenal cancer.

Research Interests: The long range objective of my laboratory is to understand the cellular and molecular mechanisms by which signaling pathways and downstream transcription factors coordinate the specification of adrenocortical cells within the adrenal gland in health and disease. Recent efforts examine the hypothesis that IGF and Wnt/beta-catenin signaling maintains the functional capacity of the adrenal cortex though the regulation of undifferentiated adrenocortical cell fate. Dysregulation of this system is predicted to result in abnormal adrenocortical growth and/or differentiation. Using cellular systems, mouse models together with genomic approaches with mouse and human adrenocortical carcinoma (ACC) samples, we aim to characterize the stem/progenitor cells of the adrenal cortex and uncover the mechanisms by which these cells are regulated by various signaling pathways in normal adrenal growth maintenance and cancer. In the adrenal cortex, IGF and Wnt/beta-catenin signaling are restricted to the subcapsular region. While these subcapsular undifferentiated adrenocortical cells are known to migrate centripetally into the cortical zones of the gland to populate the three zones of the adrenal cortex, the molecular mechanism underlying role of these cells in tissue homeostasis is poorly understood. We present data that support a role of IGF and Wnt/beta-catenin signaling in the selfrenewal and multipotent properties of these adrenocortical cells in vivo. We also characterize mechanisms by which gain of IGF and Wnt/beta-catenin signaling participate in the development of ACC. ACC is an incredibly rare and routinely fatal disease with few effective treatments. Understanding the role of the signaling pathways in adrenocortical cell fate will lay essential groundwork for future therapies that target this pathway and downstream genes that are found in the course of these studies to participate in adrenocortical stem/progenitor cell biology.

Ales Hampl, D.V.M., Ph.D., is an Associate Professor and Head of the Department of Histology and Embryology at the Faculty of Medicine of the Masaryk University, and Head of the Centre of Biomolecular and Cellular Engineering of the International Clinical Research Centre of the St. Anne´s University Hospital, Brno, Czech Republic, is the leading scientist in the Czech Republic in the field of human embryonic stem cells. After graduating from the Brno Veterinary University, he earned a Ph.D. in animal physiology and morphology from the Czech Academy of Sciences. Following postdoctoral training at the Jackson Laboratory, Bar Harbor, Maine, he established his laboratory in the Institute of Experimental Medicine of the Academy of Sciences of the Czech Republic. He is an author or coauthor of about 70 papers in scientific journals. He acts as a PI in international projects focusing at various aspects of biology of human embryonic stem cells, such as global International Stem Cell Initiative and EU project Platforms for Biomedical Discovery with Human ES Cells. Recently he was appointed vice-dean for research of the Faculty of Medicine of the Masaryk University.

Research Interests: In his laboratory the first lines of human ES cells in the Czech Republic were derived in 2003. He has contributed significantly to understanding molecular pathways functioning in pluripotent cells, including female gametes and mouse and human embryonic stem cells. His major focus is on mechanisms involved in a genetic instability of stem cells.

Zhengqing Hu, M.D., Ph.D., is an Assistant Professor in the Department of Otolaryngology – Head and Neck Surgery at Wayne State University School of Medicine. He received his M.D. from Shanghai Medical University, Shanghai, China in 1993. From 1993 to 1999, Dr. Hu had his

residency and fellowship training, together with a Ph.D. program focusing on neurotology and hearing research in HuaShan Hospital and EENT Hospital in Shanghai Medical University. Dr. Hu became an Attending Doctor in RenJi Hospital, Shanghai Second University, Shanghai, China in 1999-2001. He went to Karolinksa Institute, Sweden for his second Ph.D. program focusing on stem cell and cell replacement therapy for the inner ear, which was supported by the fellowships from Swedish Institute and Karolinska Institute – Chinese Academy of Medical Sciences in 2001-2005. Dr. Hu attended University of Virginia for his postdoctoral training from 2005 to 2009.

> **Research Interests**: Dr. Zhengqing Hu explores stem cell-based biological and translational strategies to replace injured sensory cells and their neural components to rescue hearing loss, and high-impact health problems. The Hu's lab focuses on inner ear developmental biology, stem cell biology and translational research for the inner ear. Dr. Hu uses *in vitro* models to understand the mechanisms of proliferation and differentiation of stem cells, intracellular pathways regulating ototoxicity and cell fate determination, and the innervation of *in vitro*-generated sensory cells. In the *in vivo* models, Dr. Hu investigates the survival, differentiation, migration, integration and function of the stem cells transplanted into the inner ear. The lab performs researches in cell culture, cell biology, molecular biology, immunocytochemistry, advanced confocal microscopy, inner ear transplantation, and functional evaluation of hearing. The long term aim of the lab is to establish a new Biological-EAR model, which will provide a novel treatment option for cases of hearing loss, tinnitus and other inner ear disorders.

Ralf Huss, M.D., Ph.D., has made significant contributions to the understanding and functional role of mesenchymal stromal cells in mammalian hematopoiesis and tissue regeneration. He received his MD from the University of Erlangen-Nuremberg and was trained in immunology and transplantation medicine at the Department of Immunology in Zurich, Switzerland and the Fred Hutchinson Cancer Research Center in Seattle. Dr. Huss completed his residency in surgical and anatomical pathology at the University of Munich, where he eventually received his Ph.D. and was appointed Professor for Pathology. In 2005, he joined Roche Diagnostics in Penzberg, Germany as the Head of Histopathology and Tissue Biomarker. There he was strongly involved in biomarker discovery to stratify cancer patients as part of a global Personalized Healthcare Strategy. Eventually, Dr. Huss was promoted VP in Pharma Research & Early Development and became the Global Head of the Roche Therapeutic Cell Initiative. In October 2011, Dr. Huss joined the apceth management team as a co-founder, managing director and chief scientific officer. He was also appointed to numerous advisory boards and is currently also an Adjunct Professor of Regenerative Medicine at the Wake Forest Institute for Regenerative Medicine in Winston-Salem.

> **Research Interests:** His research is focused on the biology, immunology and manufacturing of adult stem cells and their clinical application.

Branislava Janic, Ph.D., is a research scientist with broad experience in cellular and molecular biology, specializing in the field of immunology and stem cell biology with the particular interest in methodologies pertaining molecular and cellular imaging focusing on cellular biology and immunology. Her graduate work at The Pennsylvania State University was on investigating the role of air pollution on immunological processes in the lung by analyzing the effects of ozone on

Surfactant Protein A (SP-A)-alveolar macrophage functional interaction. During part of her postdoctoral training at the Department of Immunology and Microbiology (University of Miami), she investigated the mechanisms of Human T cell leukemia virus type I (HTLV-I)-induced transcriptional deregulation in adult T cell leukemia (ATL), with focus on the effects of HTLV-I Tax on cellular signaling pathways (NFAT and NF-kB) and CD40/CD40L transcriptional regulation and expression. By exploring the topics relevant to hematological malignancies, such as cell proliferation, cell differentiation, haematopoiesis and haematopoietic stem cell, Dr. Janic slowly made a transition to the field of stem cell biology. In particular, working on neuronal and retinal stem cells where she investigated the role of transcription factors in retinal stem cell fate determination, with focus on the effects of Math5 transcription factor on retinal stem cell differentiation.

Research Interests: Dr. Janic now works in the Cellular and Molecular Imaging Laboratory at Henry Ford Hospital focused on various types of stem cells derived from umbilical cord blood and bone marrow and acquired skills and knowledge on isolation, *in vitro* expansion, differentiation and magnetical labeling of cord blood derived endothelial progenitor cells as well as *ex vivo* and *in vivo* immunofluorescence, nuclear medicine and magnetic resonance imaging approaches. Her current work focuses on cord blood derived stem cells and their role in angiogenic processes in conditions such as stroke and tumors. The ongoing projects involve investigation of the role/s of cord blood derived AC133+ endothelial progenitor cells in angiogenic mechanisms in rat models of middle cerebral artery occlusion (MCAO) stroke and glioma. In the same *in vivo* animal model, we use these progenitor cells as MRI probes for the purpose of tracking the cell migration and accumulation at the sites of stroke/tumor.

Jan Jensen, Ph.D., is the Associate Staff Eddie J. Brandon Endowed Chair for Diabetes Research Director, Diabetes Research at the Cleveland Clinic. Dr. Jensen is a developmental biologist focusing on pancreas, and endodermal organs. His research has involved signaling pathways in development, morphogen codes, bioinformatics and, more recently, pluripotent stem cell research. Current research efforts are directed towards understanding the pancreatic progenitor and their supportive niche support cells. It also involves directed differentiation of pluripotent cells towards an insulin producing fate, applying developmental principles and automation. Recently, Dr. Jensen, as part of the National Center for Regenerative Medicine, helped in securing funding for OH-Alive; a cell therapy facilitating platform, to be established as a multi-center facility shared with collaborating for-profit companies in the cell therapy space. Dr. Jensen is also the director of the islet cell genesis project; a sub-component of the Chicago Diabetes Project; a philanthropically supported international collaboration focused on providing a functional cure for T1 diabetes. Dr. Jensen received his M.Sc. and PhD from U. Copenhagen in 1998. He became Asst. Professor at the Barbara Davis Center for Childhood Diabetes at U. Colorado Health Sciences Center in 2001. In 2007, following promotion to Associate Professor, he took at Staff position at the Cleveland Clinic. He is holding faculty appointments at the Case Western Reserve University in Pathology and in Regenerative Medicine, and is a current member of the National Center for Regenerative Medicine.

Research Interests: He is interested in developmental biology of the pancreas and endodermal development, pancreatic islets, systems biology, morphogen signaling, stem cell therapies and macroencapsulation.

Quan Jiang, Ph.D., serves as Senior Bioscientist of Neurology at Henry Ford Hospital and Professor of Neurology at Wayne State University. Dr. Jiang completed his Medical Physics Ph.D. degree in Physics Department at Oakland University.

Research Interests: His research focuses on the development of magnetic resonance imaging (MRI) methodology and image analysis for neurological diseases, especially in molecular imaging, neuronal, and vascular remodeling after brain injury. These MRI methodologies could non-invasively monitor stem cell migration, distribution, concentration, and stage neuronal and vascular reorganization during brain recovery.

Dan Kaufman, M.D., Ph.D., is an Associate Professor of Medicine in the Division of Hematology, Oncology, and Transplantation and Associate Director the Stem Cell Institute. He serves as co-Director of the Integrated Center of Cellular Therapy and Regenerative Medicine at the International Clinical Research Center, St. Anne's Hospital. Brno, Czech Republic.

Research Interests: Research in the Kaufman lab uses human pluripotent stem cells to understand the development of blood cells and related mesodermal cell populations. Specific projects investigate development of distinct cell populations from hESCs and iPSCs, including: hematopoietic stem/progenitor cells, lymphocytes, endothelial cells, cardio-vascular progenitor cells, and osteogenic (bone forming) cells. Recent studies have demonstrated the ability to use hESC and iPSC-derived natural killer (NK) cells to kill diverse types of human cancer cells both in vitro and in vivo. Other studies demonstrate these hESC and iPSC-derived NK cells can preferentially kill HIV-infected cells. We now aim to advance this work to use human pluripotent stem cells as a resource for new clinical applications against a variety of lethal diseases.

Paul H. Krebsbach , D.D.S, Ph.D., is the Roy H. Roberts Professor of Biomedical Engineering at the University of Michigan. He serves as the Chair of the Department of Biologic and Materials Sciences and Division of Prosthodontics. Dr. Krebsbach received his D.D.S. degree from the University of Minnesota and his certificate in Periodontology and Ph.D. in Biomedical Sciences from the University of Connecticut Health Center. Prior to joining the faculty at the University of Michigan, he served as a Senior Staff Fellow for three years at the National Institute of Dental and Craniofacial Research. Dr. Krebsbach has served on many local and national committees, including chairing the AADR William J. Gies Award Committee and the AADR and IADR Hatton Award Committees, a term on the AADR Constitution Committee and serving on the AADR Board of Directors for 3 years as Treasurer. He served on the American Association for the Advancement of Science Electorate Nominating Committee and completed a term as Member at Large. He currently is a chartered member of the Moss IRB Musculoskeletal Tissue Engineering study section. He is on the editorial boards of the Journal of Bone and Mineral Research and the International Journal of Oral and Maxillofacial Surgery. He has organized IADR symposia, and Chaired the Midwest Tissue Engineering Consortium and 9th International Conference on the Chemistry and Biology of Mineralized Tissues.

Research Interests: Our lab studies mechanisms of self-renewal and differentiation of human pluripotent stem cells. Studies are also directed towards understanding how to direct differentiation towards osteoblast cells for bone regeneration.

Sarah Krueger, Ph.D., studied at Wayne State University in Detroit concentrating on cellular radiobiology, particularly the effects of low-dose radiation on in vitro cellular DNA repair responses. Her project focused on measuring the survival responses of several normal and tumor cell lines following exposure to low-dose ionizing radiation in an effort to characterize the radiation survival response known as low-dose hyper-radiosensitivity. To elucidate the biological mechanism underpinning this response, she also examined the induction and repair of DNA double strand breaks and worked to define the cell cycle checkpoint response after low dose irradiation. As a result of this work, they were able to show that the progression of cells from the G2-phase of the cell cycle into mitosis with unrepaired DNA double strand breaks initiates caspase-3 dependent apoptosis, which suggests that this apoptotic response is the likely mode of cell death within the low-dose hypersensitivity dose range.

> **Research Interests:** Currently, I am working in the Department of Radiation Oncology at William Beaumont Hospital in Royal Oak, Michigan. In the course of my research at WBH I have worked on a variety of projects, including the in vitro response of prostate cells to radiation and dietary supplements, the in vivo impact of chemotherapy and radiation therapy during hypobaric oxygen treatment and the damage response pathways in hematopoietic stem cells after whole-body irradiation. Most recently, I have been examining the role of bone marrow-derived progenitor cells in vivo after radiation-induced lung damage. I have also recently undertaken the scientific oversight of the Radiation Oncology pre-clinical imaging area, which includes a MicroPET/SPECT/CT, image-guided small animal irradiator (SARRP) and small animal MRI unit. This includes the oversight of several different projects, including tracking the response of low-dose pulsed radiation treatment in an orthotopic glioma mouse model as well as utilizing PET imaging to measure the radiation response of head and neck cancer xenografts.

Ernest F. Krug, III, M.Div., M.D., FAAP, received his B.A. from Harvard College, the M.Div. from Union Theological Seminary in New York City, and M.D. from the University of North Carolina at Chapel Hill. He completed pediatric training in Boston at the Massachusetts General Hospital and the Children's Hospital Medical Center, and completed a fellowship in Developmental Pediatrics at the William Beaumont Army Medical Center in El Paso, Texas while on active duty in the U.S. Army. He is now retired from clinical practice in developmental-behavioral pediatrics and is course director for the longitudinal course in Medical Humanities and Clinical Bioethics at the Oakland University William Beaumont School of Medicine, where he is Professor of Biomedical Sciences and Pediatrics. Dr. Krug has been involved in clinical ethics for over 25 years and recently retired from his position as Corporate Director of Clinical Bioethics in the Beaumont Health System. He is also an ordained Presbyterian minister and member of the Presbytery of Detroit, serving as Parish Associate at the First Presbyterian Church of Birmingham, Michigan.

> **Research Interests:** Determining effective ways to teach professionalism and bioethical reasoning to medical students.

Hillard Lazarus, M.D., is a Professor of Medicine at Case Western Reserve University, Director of Novel Cell Therapies, University Hospitals Case Medical Center and the George and Edith Richman Professor and Distinguished Scientist in Cancer Research. He was the first Chair

the ECOG Blood and Marrow Transplant Committee and was Co-Chair of the Lymphoma Committee of the CIBMTR for 19 years. Dr. He has over 450 publications, including 320 peer-reviewed articles. He is a member of several journal editorial boards, is Deputy Editor of the journal Bone Marrow Transplantation and is an editor of 6 textbooks in the field of blood and bone marrow transplantation, hematologic malignancies, and supportive care for cancer patients.

> **Research Interests:** He is internationally recognized for his contributions in the areas of mesenchymal stem cell transplantation, autologous blood and marrow transplantation for lymphoma, and allogeneic blood and marrow transplantation for malignancies.

Senator Carl Levin (D-Michigan). In an editorial about Carl Levin, the Detroit News wrote, "He has been above reproach personally and has stuck to his principles, even when they were unpopular. Principled leadership, no matter what political ideology it comes from, is sorely needed in Washington." TIME Magazine recently named Carl Levin one of "America 's 10 Best Senators," noting that "the Michigan Democrat has gained respect from both parties for his attention to detail and deep knowledge of policy." Senator Carl Levin has proudly served in the United States Senate since 1978 earning a reputation for dogged investigations and common sense approaches to government spending, policies and legislation. He is currently the Chairman of the Senate Armed Services Committee, introducing legislation to protect our troops while providing realistic proposals to end the war. As Chairman of the Permanent Subcommittee on Investigations, Levin has focused on issues that impact the wallets of most Americans, including unfair credit card practices and sky-high oil and natural gas prices. He has also lead investigations into economy damaging foreign tax havens, money laundering schemes and corporate abuses including the most in-depth examination of the Enron collapse. In Michigan, Carl Levin has placed a high priority on constituent services, offering a wide array of casework and resources. Levin and his staff are accessible and eager to assist Michigan residents, earning him a reputation as one of the most responsive Senators in the nation.

> **Research Interests:** Senator Levin, along with other Michigan elected officials, serves on the advisory council for the Michigan Citizens for Stem Cell Research and Cure (MCSCRC), a non-profit organization established in 2006 for the purpose of educating Michigan citizens on the potential promises of embryonic stem cell research. The non-profit works with the organization that is currently pushing for a state ballot initiative which would remove the ban on embryonic stem cell research in Michigan. Senator Levin will be discussing the potential that embryonic stem cell research holds for families and individuals battling disease as well as the political implications and struggles that lie ahead.

Chunying Li, Ph.D., is an Assistant Professor, in the Department of Biochemistry and Molecular Biology. Graduated with Ph.D. from University of Tennessee Health Science Center, 2001-2005 Postdoctoral, University of Tennessee Health Science Center, 2005-2008.

> **Research Interests:** PDZ-mediated macromolecular complexes in health and diseases; CXCR2 macromolecular signaling complex in vascular diseases (ischemia, angiogenesis), inflammation (neutrophil transmigration), and cancer biology (tumor metastasis and angiogenesis); Spatiotemporal dynamics of CXCR2 macromolecular

signaling complex in living cells. Techniques used in our research: molecular cloning, protein engineering and purification, biochemical assays, mammalian cell culture, live cell imaging, animal models (for cancer and inflammation), etc.

Linheng Li, Ph.D., received a Master of Science degree in Genetics from Fudan University in Shanghai, P.R. China, and Master of Science and Doctorate degrees in Molecular and Cellular Biology from New York University Medical School.

Research Interests: We mainly focus on two systems to study stem cell development: hematopoietic and intestinal stem cell compartments. The hematopoietic system facilitates functional characterization of stem cells as bone marrow transplantation experiments can be readily performed. The intestinal system has a well-organized developmental architecture in which stem cell marking and lineage tracing can be used to investigate how stem cells are maintained by their microenvironment (niche), how stem cells undergo asymmetric division to keep the balance between self-renewal and lineage commitment, and what molecular signals are involved in this regulation. To investigate the molecular mechanisms that control stem cell properties, we use the combined approaches described as follows: To identify the location (or niche) where hematopoietic and intestinal stem cells reside, and to further investigate the interaction between stem cell and its niche and dissect the key signals emanating from the niche, such as the Wnt, BMP, and PTEN signals. To characterize the functions of the niche signals in stem cell regulation, we use genetic approaches such as transgenic or gene targeting animal models to examine their influence on stem cell development. Our goal is to understand how these signal pathways or mechanisms regulate normal development in the hematopoietic and intestinal system. This information should reveal how they may malfunction or be altered in association with human diseases, such as leukemia and colon cancer.

Qi Li, D.D.S, Doctoral Candidate, born in Hohhot, Inner Mongolia, she received her DDS degree from Jilin University Dental College in Changchun, P.R. China. After enrollment in Jilin University's Ph.D. program in 2009, she received an Outstanding Student Award from the Chinese Government and an Outstanding Student Award from Jilin University in 2010. In 2011, Dr. Li was awarded a scholarship sponsored by the Chinese Government State Scholarship Fund to pursue her studies in the United Stated of America as a joint PhD candidate. From then on, she worked in the Brodie Laboratory for Craniofacial Genetics directed by Dr. Thomas G.H. Diekwisch, Head of the Department of Oral Biology at the University of Illinois at Chicago.

Research Interests: Dr. Li's primary scientific interest focuses on the use of bone regeneration and other tissue engineering strategies to improve oral implant restoration. She is currently working on a modification of platelet concentrated fibrin graft, which may act as reservoir of growth factors and autologous scaffold for bone regeneration. Her studies focus on two aspects: (i) the modification of platelet-rich fibrin for preservation and future use by lyophilization, and (ii) the effect of modified PRF on human primary oral progenitor cells.

Feng Lin, Ph.D., received his B.S. from NanKai University, China (1992). He completed his Ph.D. at Sichuan University, China, in 1997. That year he came to Case as a Research Associate in the Institute of Pathology. He is presently holding an Associate Professor position.

Research Interests: The Complement system plays important roles in fighting pathogen invasions, and helps to maintain body homeostasis. Complement activation products promote inflammation, and help to eliminate invaded pathogen through different mechanisms. They are also important for many immunological reactions including immune complex clearance, antibody production and T cell activation. Insufficient or excess complement activation contribute to various disease states including transplant rejection, cancer, systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, myasthenia gravis and age related macular degeneration. Using gene knockout mice and transgenic mice as disease models, my lab is interested in studying complement activation and regulation in disease states, thus eventually developing novel reagents to fight against those diseases.

Xianghong Luan, M.D., received an MD from Harbin Medical University (1983) and an MS from the Chinese Academy of Medicine (1988). From 1989 to 1993, she was trained as a Research Fellow in the National Laboratory of Molecular Virology and Genetic Engineering, Department of Public Health, China. After her postdoctoral training at the University of Texas Medical Center at San Antonio, Dr. Luan worked as a Research Assistant Professor at Baylor College of Dentistry from 1998 to 2010. In 2001, she became a faculty member at the University of Illinois at Chicago. In 2009, Dr. Luan was promoted to the rank of Associate Professor in the Department of Oral Biology, University of Illinois at Chicago. Currently, Dr. Luan's research group is working on the role of the ameloblastin matrix protein in the development and homeostasis of craniofacial and mineralized tissues. Other topics in her lab are related to the epigenetics and biology of dental stem cells as well as tooth development and regeneration.

Research Interests: Tissue engineering is a process by which new tissues are generated to replace, repair, or aid existing tissues. Usually, tissue engineering is based upon biomimetic or bioinspired strategies; i.e. the tissue engineer utilizes principles found in nature to generate novel tissues. Today, tissue engineering reaches beyond merely copying or mimicking natural processes. One aspect of tissue engineering has increasingly become a synthetic science in which concepts found in biological organisms are utilized to fabricate novel, biocompatible materials, often based on nanotechnology. A second trend in tissue engineering has developed in which the bioinductive properties of molecules are exploited to induce the regeneration of lost or deficient tissues. Classic concepts of tissue engineering are founded on the "Tissue Engineering Triad" consisting of cells (usually stem cells or inducible pluripotent cells), signaling systems, and matrices (scaffolds). These concepts are based on the paradigm that in order to replace or repair a normal tissue environment, all three components of natural tissues have to be rebuilt: cells, molecules, and the extracellular matrix environment, in which cells and molecules occur.

Domenico Luongo, M.S., C.H.M.M., began his career as a research assistant in Wayne State University's Department of Internal Medicine. After seven years at the lab bench, he switched gears to the compliance side of research, utilizing his Master of Science Degree in Occupational and Environmental Health Sciences from Wayne State University's School of Pharmacy and Allied Health. Domenico is currently the Laboratory Compliance Manager for Oakland University and a senior level Certified Hazardous Materials Manager. He has been a Biosafety Officer for over eight years, with additional responsibilities as Oakland University's Radiation Safety Officer and Chemical Hygiene Officer.

> **Research Interests**: Stem cell research is governed by a myriad of regulations and guidelines that can affect a researcher's ability to be funded and approved for their research. This workshop will provide participants with a background on the institutional responsibilities associated with stem cell research and a basic understanding of the regulations and guidelines required for keeping their research in compliance.

Gerard Madlambayan, Ph.D., is an Assistant Professor of Biological Sciences at Oakland University. He received his undergraduate degree from Rose-Hulman Institute of Technology, his Master's degree from the University of Michigan and his Ph.D. degree from the University of Toronto all in the areas of Chemical and Biomedical Engineering. Prior to joining Oakland University, Dr. Madlambayan was faculty at the University of Florida in the Division of Hematology/Oncology. Dr. Madlambayan also has industry experience as the Senior Scientist and Laboratory Director of Insception Biosciences, Canada's leading stem cell research company. Through these activities he has worked in the areas of stem cell and cancer biology, tumor vasculogenesis, and signaling mechanisms responsible for controlling stem cell fate decisions. In addition to publications, Dr. Madlambayan's work has resulted in two patents, one being a bioprocess for the growth of stem cells that has been approved for use in clinical trials. His work has also lead to an active FDA IND to test a novel vascular disrupting agent in patients with relapsed and refractory acute myeloid leukemia, which is ongoing at the University of Florida. These activities demonstrate the ultimate goals of his lab, which are to identify promising cellular and molecular therapies for cancer treatment, prevention of relapse, and disease monitoring.

> **Research Interests:** Dr. Madlambayan is internationally recognized for his contributions in defining the biological mechanisms underlying the role of BM-derived stem and progenitor cells in solid tumor growth and the role of endothelial cells in the progression of leukemia.

Tristan Maerz, M.S., is a Research Engineer in Sports Medicine Research at the Department of Orthopaedic Research and an Assistant Professor for the Department of Surgery at the Oakland University William Beaumont School of Medicine

> **Research Interests:** Tissue engineering of orthopaedic soft tissue (cartilage, tendons, ligaments, and intervertebral discs), the biomechanics of orthopaedic soft tissues, novel magnetic resonance imaging for molecular analysis, and microCT of bone.

Ivan Maillard, M.D., Ph.D., is a Physician-Scientist and an Assistant Professor in the Center for Stem Cell Biology at the Life Sciences Institute, University of Michigan, Ann Arbor. Dr.

Maillard's work has been recognized by support from the Damon Runyon Cancer Research Foundation, the American Society of Hematology, the Kimmel Foundation for Cancer Research and the National Institutes of Health. Besides his research interests, Dr. Maillard continues to work as a practicing hematologist taking care of patient with hematological malignancies.

> **Research Interests:** His research includes the regulation of hematopoietic stem cell homeostasis and the immunobiology of bone marrow transplantation. In particular, Dr. Maillard has provided numerous contributions to the understanding of the Notch signaling pathway and more recently to the study of Trithorax group genes in hematopoiesis. A common focus in this work is the study of ancestral genes first identified in flies that play a critical function both in normal blood progenitors and in leukemic transformation.

Martin Marsala, M.D., is a Professor in the Anesthesiology Research Laboratory and a Safarik Medical Faculty member in Kosice.

> **Research Interests:** The primary goal of my research is focused on studying the pathophysiology of spinal ischemic and traumatic injury and identifying the role of cellular and subcellular components involved into development of neurological complications resulting from spinal injury such as muscle spasticity and rigidity (i.e. increased muscle tone). A separate line of our investigations include the characterization of a potential therapeutical role of spinally grafted neural stem cells in modulating motor dysfunction in animals after spinal injury. To identify the functional incorporation of grafted cells into spinal neuronal circuitry we use several immuhohistochemical and in vivo electrophysiological techniques which permits to study the development of local synaptic connectivity between grafted terminally differentiated neurons and the neurons of the host. We also actively collaborate with biotechnology and pharmaceutical companies and test new drugs or cell lines in spasticity studies. Majority of students and postdoctoral fellows in my laboratory are actively involved in both in vivo model preparation and molecular, eletrophysiological and immunohistological analysis.

Melvin McInnis, M.D., earned his M.D. from the University of Iceland, Reykajavik, Iceland (1983) and currently works as a Professor in the Department of Psychiatry at the University of Michigan.

> **Research Interests:** Genetics of bipolar disorder, genetics of major depression, longitudinal outcomes and translational research in mood disorders.

Christina McKee, M.S., Doctoral Candidate, graduated with a bachelor's of science degree from the University of Michigan (Ann Arbor) and with a master's of science in biology from Oakland University. She is currently working in Dr. Chaudhry's lab at Oakland University in stem cell research. She has had the opportunity to co-author and present at professional conferences including Word Stem Cell Summit, October, 2010 and the International Society for Stem Cell Research (ISSCR), June, 2011.

> **Research Interests:** Her research focuses on stem cell biology, and tissue engineering specifically the maintenance of the pluripotent stem cells using self-assembling scaffolds

via the mouse model, and also stress related effects and specific differentiation of stem cells seeded onto various biodegradable scaffolds. She also works on the isolation and differentiation of stem cell lineages isolated from umbilical cord blood.

Anne Mitchell, Ph.D., R.N., C.R.N., is an Associate Professor of Nursing and has served as a School of Nursing representative to the Faculty Assembly and University Senate and is currently a member of the Commonwealth Relations Committee. She is actively involved in a number of community-based grief and bereavement organizations offering support services to members of the community and am President of the Pittsburgh Chapter of the American Foundation for Suicide Prevention. She has received the Leadership in Nursing Practice Award from the Eta Chapter, Sigma Theta Tau International. Dr. Mitchell is certified as an advanced practice holistic nurse (AHN-BC) through the American Holistic Nurses Association and provide consultation and education services specific to holistic healthcare.

Research Interests: My scholarly interests include mental health outcomes research, bereavement following sudden, unnatural death specifically by suicide, and complicated grief. Pilot data from a recent study is being used to develop and evaluate the effectiveness of a crisis intervention program for survivors of suicide after the death of a family member or significant other. I am also working on a technology project using a phone application called COMPANION to evaluate its feasibility for use with survivors' and their social support networks. Currently I am the Project Director (PI) on a HRSA-funded grant designed to teach Emergency Department Registered Nurses (EDRNs) the evidence-based practice of screening, brief intervention, referral to treatment (EDRN-SBIRT) for patients who use or misuse alcohol and/or other drugs. I am certified as a clinical research coordinator (CCRC) through the Association of Clinical Research Professionals and provide consultation and education specific to research and evidence-based practices.

Jack T. Mosher, Ph.D., is currently an Assistant Research Scientist in the Department of Pediatrics and Communicable Disease at the University of Michigan. Previously, Dr. Mosher was a postdoctoral fellow with Dr. Sean Morrison in the Life Sciences Institute at the University of Michigan where he studied stem cell biology. He completed his Ph.D. in neurobiology at the University of North Carolina at Chapel Hill where he trained with Dr. Steve Crews in the transcriptional control of early nervous system development. He received his Bachelors of Science degree from Allegheny College and a Masters of Arts from the University of Hartford.

Research Interests: To investigate how stem cells contribute to the development and disease of the peripheral nervous system.

Ying Nie, Ph.D., is a Scientist in the Pluripotent Stem Cell Innovation Center at Lonza. Before joining Lonza, Dr. Nie worked as a Scientist at the WiCell Research Institute, where she focused on identifying solutions for growing hPSCs in suspension culture. Dr. Nie gained her expertise in stem cell bioengineering during her Ph.D. training in the Department of Biological and Chemical Engineering at the University of Wisconsin-Madison. Her multi-disciplinary background offers a unique perspective when addressing the issues that arise when translating stem cell research to clinical application.

Research Interests: His research focuses on developing cGMP-compliant tools and technologies for the scalable cultivation of human Pluripotent Stem Cells.

Dan O'Donnell, has worked extensively in the development and deployment of logistic strategies for both International and Domestic Phase II and Phase III clinical Trials. Previously, Dan served as a Vice President for Disease Management programs with both Baxter Healthcare and United Healthcare where he developed population based healthcare models and coordination of care processes to address high risk patient groups. In addition to healthcare process Dan has worked extensively in the development of reimbursement models for high cost and high risk disease states and therapies.

Research Interests: He specializes in Cyrogenic and ULT product management and distribution with an emphasis on the creation of a project specific 21 CFR part 11 compliant Chain of Custody. Dan is also versed in the validation and qualification of storage and shipping solution for complex biological applications. In addition he has an in-depth knowledge of bio-banking and cold Chain logistics.

Jon Odorico, M.D., completed his Residency, General Surgery, at the Hospital of the University of Pennsylvania, Philadelphia, PA, 1987-1994 He completed his Postdoctoral Research Fellow at the Harrison Department of Surgical Research, Hospital of the University of Pennsylvania, Philadelphia, PA, 1990-1992He was a Fellow, in Transplant Surgery at the University of Wisconsin Hospital and Clinics, Madison, WI, 1994-1996. Dr. Odorico is certified by the American Board of Surgery. He specializes in pancreatic, islet cell, and multi-organ transplants. He provides a wide range of services including Kidney Transplant and Pancreas Transplant.

Research Interests: His research focuses on stem cell biology and differentiation, developing novel stem cell-based strategies for treating diabetes, pancreas transplantation, and islet cell transplantation.

Suresh Selvaraj Palaniyandi Ph.D., is a faculty member in Division of Hypertension and Vascular Research, Department of Medicine, Henry Ford Hospital, Detroit, Michigan. He has completed his postdoctoral training from Stanford University School of Medicine, Stanford, USA and PhD from the Department of Clinical Pharmacology, Niigata University of Pharmacy and Applied Life Sciences, Niigata, Japan. He holds a Master of Pharmacy (Pharmacology) from Department of Pharmaceutical Sciences and Drug Research, Punjabi University, Patiala, India. Dr. Suresh won the many awards including Early Career Award from JMCC/ISHR, Jay N. Cohn Young Investigator Award (Basic Science) from Heart Failure Society of America meeting in Toronto, Canada 2008. One of his research papers won the best paper award for 2007 in EBM. Dr. Suresh also secured "Honors Scholarship" during his PhD course by Ministry of Education, Culture, Sports, Science and Technology of Japan. He has received Advanced Postdoctoral Fellowship from JDRF and Seed Grant from Stanford Cardiovascular Institute. Dr. Suresh published papers in peer reviewed journals like Cardiovascular Research, Journal of Molecular and Cellular Cardiology, Journal of Cellular Molecular Medicine, Experimental Biology and Medicine, Eur J Immunol, Biochem Pharmacol, American Journal of Physiology, International Journal of Cardiology, Pharmacology, Mol Cell Biochem and J Cardiovasc Pharmacol. Dr. Suresh is Life member of ISHR (Indian Section) and also the member of Society of

Experimental Biology Medicine. Dr. Suresh has worked as lecturer in the Department of Pharmacy, BBDNITM, and Affiliated to Uttar Pradesh Technical University, Lucknow, India (2002-03). Dr. Suresh has presented his work in many international conferences.

> **Research Interests:** Dr. Suresh is particularly interested in researching heart failure and cardiac remodeling. Currently, he focuses on aldehyde dehydrogenase in diabetic cardiomyopathy.

Graham Parker, Ph.D., is a research Assistant Professor in the division of Pediatric Neurology of the Carman and Ann Adams Department of Pediatrics, Wayne State University School of Medicine located at Children's Hospital of Michigan. Graham is also the Editor-in-Chief of *Stem Cells and Development*, an international peer-review journal with an impact factor over 4.

> **Research Interests:** His research interests include the therapeutic potential and vulnerability of human stem cells with a particular focus on developmental models of neuromuscular disorders, and the ethics of stem cell research. In particular, the potential of embryonic and somatic stem cells in this regard.

Mick Perez-Cruet, M.D., M.S., received his B.A. degree from Grinnell College in Iowa in 1983 and then pursued a Masters in Chemistry from the University of South Florida in Tampa. In 1991, he received his MD degree under an Air Force Health Professions Scholarship from Tufts University in Boston. He then went on to complete his neurosurgical residency at Baylor College of Medicine. As a Major in the Air Force he served as Vice-Chairman of the Department of Neurosurgery at Wilford Hall Medical Center, Lackland Air force Base, San Antonio, Texas. He then pursued a spine fellowship in Reconstructive and Minimally Invasive Spine Surgery at Rush University, Chicago, Illinois. Dr. Perez-Cruet is a neurosurgeon who practices with a multi-specialty group in metro Detroit, Michigan and is best known for his work in minimally invasive spine surgery. He is the Director of Minimally Invasive Spine Surgery and Spine Program at the Michigan Head and Spine Institute. He has edited three textbooks (Outpatient Spinal Surgery, Anatomical Approach to Minimally Invasive Spine Surgery, and Minimally Invasive Spinal Fusion: Techniques and Operative Nuances), multiple chapters and peer –review manuscripts. His work has resulted in an improved quality of life for many patients. He leads the Minimally Invasive Neurosurgical Society, a national association. Dr. Perez-Cruet is currently the Vice-Chairman, Professor, and Director of Minimally Invasive Spine Surgery and Spine Program for the Department of Neurosurgery at the Oakland University William Beaumont School of Medicine.

> **Research Interests:** Dr. Perez-Cruet is an internationally-recognized pioneer in the treatment of spinal disorders through the use of minimally-invasive surgical techniques.

Kenneth Peters, M.D., is a Distinguished Chair in Urology, graduated from the Case Western Reserve University School of Medicine and completed Urology residency and fellowship training at Beaumont Hospital. Dr. Peters specializes in the treatment of voiding dysfunction and female urology. Dr. Peters is an active member of the American Urological Association, the North Central Section of the AUA, the Society for Urodynamics & Female Urology, the Michigan Urological Society, the International Continence Society and serves on the Research

Council of the American Urological Association. Dr. Peters has won the clinical research award from the Society for Urodynamics & Female Urology on two occasions.

> **Research Interests:** He is an NIH-funded researcher and has performed innovative studies on neuromodulation to treat voiding dysfunction, lumbar to sacral nerve re-routing to restore voiding in spina bifida patients, and adult human stem cell injection for stress urinary incontinence.

Xu Qian, Doctoral Candidate, is a Graduate Student Research Assistant in Biologic and Materials Sciences in the School of Dentistry at the University of Michigan. She received her DDS, and MS from Sichuan University in China.

> **Research Interests:** She is interested in the stem cell biology as it relates to dental biology and tissue engineering.

Diana L. Ramírez-Bergeron, Ph.D., is an Assistant Professor of Medicine in the Case Cardiovascular Research Institute at Case Western Reserve University.

> **Research Interests:** Her main research interest is to understand how adaptive responses to changes in oxygen tension affect blood cells and vessels. One aspect of her laboratory is to dissect the specific biological and molecular roles of Hypoxia Inducible Factor (HIF) transcriptional complex during the emergence, growth, differentiation and maturation of blood vessels during normal development and pathological vascular injuries. A second interest in Dr. Ramirez-Bergeron's laboratory is to examine how hypoxic responses influence the generation of cardiovascular stem/progenitor cells and their differentiation into various cardiovascular cell lineages. These studies will provide a conceptual framework for understanding the pathogenesis of human hypoxic conditions and provide new directions for the development of novel therapeutic applications targeting vascular growth processes critical for tissue regeneration and repair.

Daniel Rappolee, Ph.D., is an Associate Professor and Graduate Officer of Reproductive Sciences Concentration, Ob/Gyn. He earned his Ph.D. in 1989 at the University of California, San Francisco in Cell Biology and Anatomy.

> **Research Interests:** Our labs focus is on intracellular communication during high-risk time periods of human embryonic development. One such period occurs as the embryo prepares to implant into the uterus and embryonic and placental trophoblast stem cells expand their populations. Soon after implantation subpopulations of stem cells normally undergo differentiation essential to survival. When insufficient stem cell proliferation occurs a proportional increase in differentiation occurs, we call this "*compensatory" differentiation*. At low doses of stress where no significant decrease in stem cell proliferation occurs there is no regulation of factors mediating differentiation, but at doses of stress where proliferation decreases, stress enzymes shift from stem cell survival mechanisms to organismal survival mechanisms that mediate differentiation. One example is the inactivation of an anabolic enzyme by AMP-activated protein kinase (AMPK) at low stress doses (shifting from anabolic to catabolic processes) and the

AMPK-mediated loss of the potency factor, inhibitor of differentiation (ID)2 at higher stress doses (Zhong et al, 2010, Reproduction, Xie et al, Mol Repro Dev, 2010). Although stress activated protein kinase (SAPK) has no role in stress-induced ID2 loss (Zhong et al, Reproduction, 2010) required to induce placental lactogen (PL)1 hormone, SAPK does mediate stress-induced upregulation of the transcription factors that ID2 blocks that is necessary for PL1 induction (Awonuga et al, 2011). SAPK reports the amount of stress preimplantation embryos sense in seven media used in in vitro fertilization protocols (Wang et al, 2005) and the amount of stress sensed by trophoblast stem cells when exposed to O2 levels between 0-20% (Zhou and Xie et al, 2011).

Stacey A. Sakowski, Ph.D., received her Ph.D. in Molecular Biology & Genetics from Wayne State University in 2006, where her graduate research focused on the biochemical characterization and analysis of post-translational modifications of proteins involved in serotonin biosynthesis. She then joined the laboratory of Dr. Eva Feldman in the Neurology department at the University of Michigan to pursue research focused on understanding the mechanisms of motor neuron degeneration in amyotrophic lateral sclerosis (ALS). Dr. Sakowski joined the Taubman Institute as Deputy Managing Director in 2011. In addition to providing support for cutting-edge research projects examining ALS, Alzheimer's disease, stem cells and diabetic neuropathy, her responsibilities include supporting the operation of the organization and managing scientific programs of the Taubman Institute.

Research Interests: Specifically, she examined the neuroprotective mechanisms of growth factor therapy using primary cellular models of ALS, and she developed and utilized zebrafish models of ALS to examine disease onset and progression and investigate novel therapies.

Peter Sartipy, Ph.D., is a Senior Principal Scientist and Department Head at Cellartis Stem Cells. He received his M.Sc. in Chemical Engineering in 1994 from Chalmers University of Technology (Göteborg, Sweden). He then went on to earn his Ph.D. in 2000 from the Faculty of Medicine at Göteborg University. After working as a post-doc at the Department of Cell Biology at The Scripps Research Institute (La Jolla, CA, USA) he returned to Göteborg and joined Cellartis AB in 2002. His previous responsibilities at Cellartis have included establishment and characterization of human embryonic stem cell lines.

Research Interests: His current research is mainly directed at exploring human embryonic stem cell differentiation towards cardiomyocytes and development of novel drug discovery applications based on these cells.

Bernard Siegel, J.D., is the founder and full-time Executive Director of the nonprofit Genetics Policy Institute (GPI) based in Palm Beach, Florida. He is the founder and the co-chair of the World Stem Cell Summit series of global conferences and editor-in-chief of the peer- reviewed *World Stem Cell Report*. A native of Richmond, Virginia, he received his undergraduate and law degrees from the University of Miami (BA 1972, JD 1975). He is a member of the Florida Bar since 1975.

Research Interests: At the University of Miami Miller, School of Medicine, Mr. Siegel serves on the Governance Advisory Board of the Interdisciplinary Stem Cell Institute and

as a member the Stem Cell Research Oversight (SCRO) Committee. He serves on several boards of national and international industry and patient group coalitions relating to regenerative medicine.

Gary Smith, Ph.D., is a Professor of Molecular and Integrative Physiology, and OB/Gyn and Urology. He is the Co-Director of the Reproductive Sciences Program as well as the Co-Director of the A. A. Taubman Consortium for Stem Cell Therapies. He earned his Ph.D from Washington State University, 1993.

Research Interests: Work in Dr. Smith's research laboratory focuses on regulation of mammalian gamete and embryo development and function. Specifically, investigations include intracellular regulation of oocyte meiosis, factors and forces influencing sperm function, and molecular regulators of pre- and postimplantation embryo development. Studies in his laboratory range from very basic in nature to translational research aimed at introducing new or improving existing means of preserving fertility or treating infertility.

Irene Spanos, is the Director of Economic Development & Community Affairs, Oakland County, Michigan. She is a graduate of Wayne State University, and holds a bachelor's degree in business administration with a major in marketing. She is a member of the Michigan Economic Developers Association, the Swedish American Chamber of Commerce, and Southfield's Healthcare Corridor board. Ms. Spanos also has been asked to sit on the Mechatronics advisory board for Oakland Community College.

Research Interests: Medical Main Street offers diverse services—from introducing companies that are new to the area to networking opportunities to providing information about available tax abatements and access to resources for such things as FDA consulting and more. We listen to what a company needs and bring them the right resources, whether federal, state or local. Because of Michigan's strong automotive history and abundant use of advanced technologies, we have a special blend of manufacturing expertise, top doctors and hospitals, and recognized universities and colleges that all come together in the Medical Main Street network. And, our goal is to fortify and grow this health care and life sciences hub for our community.

David M. Svinarich, Ph.D., M.S., received his bachelor's degree in Microbiology from The University of Michigan and completed his Master's degree at Wayne State University. His Doctoral degree in Immunology and Microbiology, and Postdoctoral Fellowship with the Department of Molecular Medicine and Genetics were both completed at the Wayne State University of Medicine. He served as a Senior NIH Scientist with the Extramural branch of the National Institute of Children's Health and Disease (NICHD). As an Assistant Professor in the Department of Obstetrics and Gynecology at Wayne State University, he studied the genetic regulation of inflammatory cytokines and their relationship to pre-term birth. He later became the Director of Research in the Department of Patient Care Research at Providence Hospital. Presently, Dr. Svinarich is the Vice President of Research for the St. John Providence Health System and oversees Institutional Review Boards and both clinical and basic research activities. He also directs the Department of Patient Care Research at Providence Hospital and chairs the Animal, Biosafety and Medical Simulation committees in the West Region. Dr. Svinarich's international health experience includes serving on the Preterm Birth International Collaborative

(PREBIC), in collaboration with the World Health Organization (WHO). Outside of his professional responsibilities, Dr. Svinarich is a licensed pilot, dedicated cyclist and enjoys technical mountaineering.

> **Research Interests:** He holds adjunct professorships within the departments of Immunology and Microbiology, Obstetrics and Gynecology and The Center for Molecular Medicine and Genetics, at the Wayne State University School of Medicine

Shuichi Takayama, Ph.D., is internationally renowned for development of microfluidic devices and applying their use in cell culture and handling including stem cell culture and handling. Dr. Takayama is currently a Professor in the Department of Biomedical Engineering and the Macromolecular Science and Engineering Program at the University of Michigan. He is also WCU Visiting Professor at the Ulsan National Institute of Science and Technology (UNIST) in South Korea. His interests (B.S. and M.S. from the University of Tokyo in 1994, his Ph.D. degree in chemistry from the Scripps Research Institute in 1998) started with organic synthesis of molecules that mediate biological chemical communication. Subsequently he became interested in evaluating the function of synthesized molecules in engineered bio-microsystems and pursued postdoctoral studies at Harvard University as a Leukemia and Lymphoma Society Fellow.

> **Research Interests:** His current research interests are Micro/nanofluidics, Cellular microenvironment engineering including stem cell cultures, and Epigenetics. He constructs microfluidic models of the body such as artificial oviducts for enhanced in vitro fertilization treatment, microtissue engineered models of lung injury, and models of cancer metastasis for drug testing. He also develops aqueous two phase system micropatterning technologies, self-switching fluidic circuits, and nanofluidic single molecule DNA and chromatin analysis systems.

Dean Tantin, Ph.D., is an expert in the areas of gene expression, chromatin and transcription factor function. His laboratory has made central discoveries in mechanisms of transcription factor regulation and function. Recent work has identified a mechanism for establishing and maintaining poised gene expression states, a configuration indispensable for stem cell function. After graduating from UC San Diego with a degree in Molecular Biology, he was a graduate student at UCLA where he earned a Ph.D. in Molecular Biology. Subsequently he did a postdoctoral at MIT in the laboratory of Dr. Phillip Sharp. He is currently an Associate Professor of Pathology at the University of Utah, School of Medicine, in Salt Lake City where he has been for six years.

> **Research Interests:** He is focused on gene regulation of somatic and cancer stem cells, as well as developmental biology and induced pluripotency.

Andrew Tidball, Doctoral Candidate, researches in vitro cell models including human induced pluripotent stem cells to model gene-environment interactions in neurodegenerative diseases. He aims to define underlying mechanisms of neurodegenerative disease and provide information about environmental disease modifiers. His work primarily focuses on Huntington's disease and Parkinson's disease. This proposal is a part of the overarching goal of his thesis lab to develop approaches for studying mechanisms of neurotoxicological risk and clinically relevant cellular

stress vulnerability within individual patients using differentiated neural progenitors from human induced pluripotent stem cells.

> **Research Interests:** I am interested in the use of induced pluripotent stem cells to address neuropathologies with unknown etiologies such as the majority of psychiatric disorders. Investigating these pathologies has the potential to develop therapies to help millions as well as deepen our understanding of how the cellular and molecular framework of the brain effects our conscious thought and behavior.

Vince Tropepe, Ph.D., is an Associate Professor and Director of the Human Biology Program at the University of Toronto. His research focus is on cell and developmental biology, functional genomics and genetics as well as neurobiology.

> **Research Interests:** The production of nerve cells in the brain (neurogenesis) is a life-long process with regional specializations that are critical for the development of distinct functional domains. Moreover, neurogenesis in the adult brain may contribute to the structural changes that underlie neural plasticity, which is crucial for normal brain function. My lab investigates the fundamental questions of how neurogenesis is initiated in the developing brain, and how this process contributes to the generation and maintenance of regional nerve cell diversity throughout life. We use mouse and zebrafish as complementary vertebrate model systems and employ a variety of technical approaches that range from histological and cell culture techniques to molecular biology and genetics in order to identify and characterize the molecular mechanisms that govern vertebrate neurogenesis.

Luis G. Villa-Diaz, Ph.D., is a Research Investigator studying Biology and Materials Science, in the School of Dentistry at the University of Michigan.

> **Research Interests:** He is interested in the stem cell biology as it relates to dental biology and materials science.

Chenran Wang, Ph.D., is a Research Fellow studying Internal Medicine at the University of Michigan Medical School.

> **Research Interests:** His research focuses on molecular medicine and genetics to understand the fundamental principles of cell signaling and determine how the disruption of normal signaling pathways leads to diseases such as cancer.

Q. Tian Wang, Ph.D., obtained a B.S. degree in biochemistry from Beijing University, China in 1994 and a Ph.D. degree in biochemistry, molecular biology, and cell biology from Northwestern University, IL, USA in 2000. She was a Postdoctoral Fellow, then a Research Associate, in the Departments of Biochemistry and Developmental Biology at Stanford University, NY, USA from 2000 to 2006. She joined the Department of Biological Sciences at the University of Illinois, Chicago, IL, USA as an Assistant Professor in 2007. Wang's research expertise is in transcriptional regulation, epigenetics, lineage differentiation, heart development, stem cells, and heart regeneration.

Research Interests: Our lab is interested in the roles and mechanisms of chromatin remodeling in the context of mammalian development and diseases. How is the chromatin regulated in the right place and at the right time to accommodate the differentiation and development needs of the mammalian cell? Does chromatin remodeling has gene specificity and cell-type specificity, and if yes, where does the specificity come from? How is chromatin remodeling related to human diseases? We use mouse and mouse embryonic stem cells as model systems to address these questions.

Mark Weiss, Ph.D., joined the faculty at Kansas State University in 1991. He is co-discoverer of mesenchymal stromal cells within umbilical cord Wharton's jelly, is a Founding Fellow of the Midwest Institute for Comparative Stem Cell Biotechnology and serves as Associate Director of the Terry C. Johnson Center for Basic Cancer Research.

Research Interests: The KSU Stem Cell Biotechnology Research team has been focused upon characterizing non embryonic stem cells that they have discovered in the umbilical cord matrix and rat embryonic stem cell. We lead this group and organize research efforts. To date, our published work indicates a propensity for the nonembryonic stem cells to differentiate along the neural lineage (Mitchell et al., 2003) and for these cells to engraft following xenografting into rats that are not receiving immune suppression treatment (Weiss et al., 2004; Medicetty et al. 2004). Currently, my laboratory is characterizing the role of human and animal umbilical cord matrix stem cells to reverse the behavioral deficits found in a rat model of Parkinson's disease. My laboratory has also isolated and characterized rat embryonic stem cells. These stem cells are pluripotent and will be used to generate preclinical rat models for studying a variety of diseases.

George Wilson, Ph.D., born in Edinburgh, Scotland, Dr. Wilson received his Ph.D. from the University of Liverpool in the UK in 1978 and undertook his postdoctoral training at the Universities of Birmingham and London. In 1984, Dr. Wilson joined the Gray Laboratory in London as a senior scientist and worked there for 18 years. In 2002, Dr. Wilson became Professor of Radiation Oncology at Wayne State University and the Karmanos Cancer institute. Dr. Wilson joined Beaumont in 2005 as Chief of Radiation Biology. In 2008, Dr. Wilson also became the Scientific Director of the Beaumont BioBank and the Director of the Erb Family Core Molecular Laboratory at Beaumont Research Institute. Dr. Wilson has published over 210 scientific articles and book chapters.

Research Interests: His current interests include cancer stem cells, molecular imaging and biomarkers of treatment response.

Donggang Yao, Ph.D., is an Associate Professor in the School of Materials Science and Engineering at Georgia Institute of Technology. He teaches and directs research in the broad area of polymer engineering. His ongoing research deals with polymer microfabrication, sustainable composites processing, fiber processing, viscoelastic constitutive modeling, and polymer processing modeling. He was a recipient of the 2003 Career Award from NSF for his research on rapid production of polymer-based microstructures. He was an Assistant Professor at Oakland University before he joined Georgia Tech.

Research Interests: His research focuses on the polymer microfabrication (micromolding processes), sustainable composites processing, polymer fiber processing, constitutive modeling, manufacturing process modeling and simulation.

Mervin Yoder, M.D., received his undergraduate degree from Malone College, a Master's degree from Indiana State University, and an MD from Indiana University School of Medicine. He completed a residency in Pediatrics and fellowship in Neonatal Perinatal Medicine at the University of Pennsylvania. He became an Assistant Professor in Pediatrics at Indiana University School of Medicine and rose through the ranks to achieve tenure and the rank of Professor of Pediatrics and of Biochemistry and Molecular Biology in 2000. In 2004, Dr. Yoder was named the Richard and Pauline Klingler Professor of Pediatrics. In March 2008, he was promoted to Director, Herman B Wells Center for Pediatric Research and Associate Chair for Basic Research in the Department of Pediatrics. In June 2011 he was chosen to serve as Assistant Dean for Entrepreneurial Research. Dr. Yoder has trained more than 60 students, postdoctoral fellows, and visiting scientists. He has served as past-president of the ISEH Society for Stem Cells and Hematology and is on the editorial boards of 4 stem cell and cardiovascular research journals. He serves on the Advisory Board of several small biotechnology firms and is co-founder of EndGenitor Technologies, Inc. He was recently appointed by the Governor of Indiana to the Indiana Cord Blood Bank Advisory Board. He continues to care for critically ill neonates in the Newborn Intensive Care unit.

Research Interests: Dr. Yoder is internationally recognized for major contributions to our current understanding of developmental hematopoiesis and the role of the murine yolk sac as a site of emergence for multiple hematopoietic lineages. He is also renowned for contributions that have clarified the field of endothelial progenitor cell biology through the use of novel assays and tools to better define a series of proangiogenic hematopoietic stem and progenitor cells and the identification of the endothelial colony forming cell.

Presentation Abstracts

Presentation Abstracts

Friday, October 5, 2012

3:10 pm – 5:15 pm: **Plenary Session I**: Special Topics in Translational Research and Stem Cell Therapy I

Mick Perez-Cruet, M.D., M.S., OU-WB SOM and Beaumont Hospital, "Stem Cell Based Treatment of Spinal Degenerative Disorders"

As patients grow older degenerative disc disease is often the underlying cause of back and neck pain. In the course of one's lifetime, water is lost from the intervertebral disc which causes it to collapse. This collapse leads to insufficient vertebral support and resulting nerve root compression.

Throughout the aging process, intervertebral disc degeneration occurs by the biomechanical changes of the disc, most likely through the loss of hydrophilic proteoglycans within the nucleus pulposus (NP). These molecules are structured to hold water and therefore provide the cushioning support of the intervertebral disc. Studies show that notochordal cells, which are believed to be responsible for spine intervertebral disc development, are no longer around after age 10 (Trout, 1982). These cells produce 1.5 fold more proteoglycans and extracellular matrix than terminally differentiated chondrocytes (Lipson, 1981). As notochordal cells differentiate towards chondrocytes in the NP, less water holding proteoglycan matrix is available. The loss of water over time in the intervertebral disc results in eventual disc degeneration and collapse.

Stem cell (SC) research is a growing field with the potential to alleviate symptoms and reverse pathology of a wide range of diseases, including degenerative disc disease. As of today, there is no therapy to restore a degenerated intervertebral disc, but intervertebral disc stem cell based regeneration may be a viable solution. Studies show that SC can differentiate *in vitro* towards specific cell lineages by selective culture media and adequate growth environments. We have shown that certain cell lineages have the potential to differentiate into the nucleus pulposus *in vivo.* (Sheikh, 2009)

SC represents a possible source of notochordal cells due to their ability to differentiate into multiple cells lines. Investigators have examined the use of mesenchymal stem cells for intervertebral disc regeneration (Risbud, 2004) and have shown these cells, with the proper growth environment, can differentiate towards a NP-like phenotype similar to that found in an intervertebral disc (Sheikh, 2009). Studies show SC can differentiate towards a chondrogenic lineage in the presence of selective media culture supplemented with TGF- ß, dexamethasone, and ascorbate (Facek C, 2008). It is believed that the notochordal cell line is the first seen in the development of the NP, so it is expected that the notochordal line would be the first cell line seen histiologically. This finding was validated in our studies. (Sheikh, 2009)

Success with stem cells equates to restoration of physical and biologic properties of intervertebral discs. These physiologic changes have potential to improve clinical outcomes in patients with neck, back, and leg pain where degenerative disc disease is the underlying cause.

Martin Marsala, M.D., University of California - San Diego, "The Utilization of the Pig Model for Spinal and Brain Grafting (as a Safety Preclinical model) of Human Neural Precursors as well as Porcine iPS-derived Neural Precursors"

The use of large preclinical animal models is a key component for the successful transition of cell replacement therapies into clinical practice. These models are commonly used to define the safety of a given cell grafting procedure/cell injection device and to identify the optimal cell dosing which can potentially be used in human patients. In addition, if available, large animal models of specific neurodegenerative disease (such as spinal trauma or spinal ischemic injury) can serve to define the degree of disease modifying activity (i.e., efficacy). In comparison to rodent neurodegenerative disease models, the use of large animal models in general is considered to have a high predictive value and often serve effectively in refining the clinical study protocols for perspective human clinical trials.

In our previous studies we have developed and described a porcine spinal and brain cell grafting model using miniature Gottingen-Minnesota minipigs. Using this model and human fetal spinal cord, human embryonic stem cell or porcine iPS-derived neural stem cells (NSCs), we have characterized: i) the long-term survival and differentiation of grafted NSCs, ii) the optimal cell dosing regimen which is safe and well-tolerated over an extended period of time after spinal or intra-striatal cell grafting, iii) an immunosuppression protocol which permits long-term xenograft survival, and iv) a spinal cell-injection device which effectively eliminates the effect of spinal cord pulsation and facilitates the process of repetitive spinal cell injection. The data from some of these preclinical GLP studies were used for an IND application for treatment of ALS by spinal grafting of human fetal tissue-derived neural precursors. The clinical trial is currently ongoing. In our more recent study, we have characterized a minipig chronic spinal trauma model which shows remarkable similarities in quantitative neurological deficit and spinal histopathological changes to human patients with chronic spinal injury. This model is currently being used to define the treatment efficacy after spinal parenchymal delivery of human spinal neural stem cells.

The use of this minipig model appears to represent a simple and reliable platform for testing the preclinical safety (as well as efficacy) of specific cell lines to be used in human patients with a variety of neurodegenerative disorders, including amyotrophic lateral sclerosis, brain and spinal cord ischemic injury or spinal trauma.

Richard G. Fessler, M.D., Ph.D., Northwestern University Feinberg School of Medicine, "GRNOPC1 trial for transplantation of stem cells into the injured human spinal cord"

Roughly 12-15 thousand individuals suffer injury to their spinal cord each year in the United States. Worldwide incidence is estimated to vary between 11.5-57.8/million population. The most dramatic improvements in care of these patients occurred during WWII and the Korean War when effective rehabilitation protocols were developed. This maximized mobility of the patient, and minimized complications, but return of function still remains an elusive goal.

Oligodendrocyte Progenitor Cells were derived from human embryonic stem cells, cryopreserved, and ultimately injected into the injured thoracic spinal cord of 5 patients participating in and FDA approved IDE for investigation of the safety of this as a potential treatment of subacute spinal cord injury. These cells had previously been demonstrated to contain a variety of neurotrophic factors, to survive following transplantation, to induce myelination and angiogenesis in rats and mice, and to improve ambulation. Moreover, appropriate safety had been demonstrated on all measures tested in animals.

Seven centers participated in the study, between which 5 patients met inclusion and exclusion criteria. Variables assessed included: physical examination, vital signs, neurological examination, ASIA examination, MRI, Pain assessment, hematology, CBC, immune suppression testing, evaluation of concomitant medications,lower extremity motor function, bowel and bladder function, functional ability, donor-specific immune responsiveness to GRNOPC1, and adverse events. Assessments were conducted pre-operatively, and at 30, 60, 90, 120, 180, 270, and 365 days post-operatively.

The primary endpoint of safety was met in all 5 patients. No surgical complications were noted. No serious AE's have been seen to date. No AE's related to injection or to GRNOPC1 have been noted. A few mild AE's related to immunosuppression have been seen. No unexpected neurologic changes to date. No evidence of adverse changes or cavitation on MRI have been seen. There has been no evidence of immune responses to GRNOPC1. There has been evidence of new sensory function related to B/B function in 3/5 patients. Transplantation of GRNOPC1 appears to be safe. Efficacy has been marginal, but in line with expectations given the thoracic level of injection.C

Jon Odorico, M.D., University of Wisconsin-Madison, "Generating Functional Beta Cells from Human Pluripotent Stem Cells: Progress and Challenges"

Pluripotent stem cells hold great promise for the treatment of Type 1 diabetes (T1D). Whereas islet transplantation from cadaver donors is an accepted cure for T1D, issues of availability, islet quality and islet yield limit applicability to a small number of patients (<100 in the US annually). Stem cell-derived β-like cells could function as an abundant and quality–controlled source of transplantable tissue when donor tissue is not available.

Significant progress in this field has been achieved over the last half decade. Using a variety of different protocols, multiple groups, including our own, have now demonstrated that human ESCs and iPSCs have the capacity to differentiate through key development stages into insulin^{+} β-like cells in vitro. However, the majority of published protocols designed to produce β cells from stem cells still result in either a heterogeneous population, of which only a relatively small percentage of cells are β cells, or a population of cells that are not mature (e.g. cells that express more than one hormone, revealing an immature state), or both. Whereas a reversal of chemically induced diabetes in mice can be achieved after transplantation of some of these cell populations, generation of enriched populations of functional β cells in vitro, as judged by standard assays, has not been reproducibly achieved. We have recently developed an improved differentiation protocol that combines growth factors bFGF (50 ng/ml), Activin A (100ng/ml), and BMP4 (50ng/ml)(FAB), in serum-free media with Matrigel to generate a nearly pure population of

pancreatic progenitors. These progenitors are capable of being driven toward endocrine specification by culture in the presence of media containing ITS, FGF7, INGAP, nicotinamide (Nic), and exendin 4 (Ex4) (Stage 3) and can serve as a platform for improving endocrine specification protocol conditions as the progenitor population is more homogeneous. This protocol is highly reproducible and works for multiple hESC and hiPSC lines. Comparisons to other protocols demonstrate increased gene expression of key markers at several different stages in FAB treated cells compared to cells culture by the Viacyte protocol, and more enriched populations of PDX1+ pancreatic progenitor cells than several other published protocols. Additional analysis revealed key Stage 3 components include FGF7, Nic and Ex4. Further studies are revealing conditions which can maintain PDX1+ pancreatic progenitor cells in stable culture for more than 100 days. Such conditions could practically support down stream applications, such as those aimed at improving functional beta cell differentiation for therapeutic application, or those targeting discovery of drugs which promote endogenous beta cell regeneration.

Challenges remain in the quest for direct application of stem cell-derived tissue to the clinic, and perhaps the greatest of these is still the need for deriving functionally-mature β cells in vitro. Nonetheless, tremendous progress has been made in a short period of time. As protocols improve, cells can not only be used for therapeutic purposes, but also used as in vitro disease models of human diabetes (using iPSCs derived from patients with diabetes), and as platforms for drug toxicity/drug discovery assays.

This study is supported by funding provided by the NIH, JDRF, ADA, WiCell, Regenerative Medical Solutions, Inc.

Kenneth Peters, M.D., Beaumont Health System, "Autologous Muscle Derived Cells for Treatment of Stress Urinary Incontinence: Dose Escalation Study of Safety and Potential Effectiveness"

Introduction and Objectives: This prospective, phase II, multicenter, dose escalation study assessed the 12-month safety and potential effectiveness of 4 different doses of Cook MyoSite, Inc. Autologous Muscle Derived Cells (AMDC) for treatment of stress urinary incontinence (SUI) in women.

Methods: This study enrolled 64 women (mean age 54 ± 1 yrs) who had failed prior treatment for SUI and who had no improvement in symptoms over the past 6 months. Patients received intrasphincteric injection of either 10 x 106 (n=16), 50 x 106 (n=16), 100 x 106 (n=24), or 200 x 106 (n=8) AMDC, which were derived from biopsies of the quadriceps femoris. The primary outcome measure was safety determined by the incidence and severity of adverse events (AEs). Secondary outcomes of clinical effectiveness were based on 3-day diaries, 24-hour pad weight tests, and quality of life (QOL) scores (e.g., UDI-6, IIQ 7) at baseline and 12 months.

Results: Fifty-nine patients completed 12-month follow-up; 1 patient was lost to follow-up and 4 patients withdrew from the study. No serious treatment-related AEs occurred. AEs related to muscle biopsy included hematoma (2/64) and bleeding requiring sutures (1/64). Genitourinary AEs within 30 days of AMDC injection were limited to dysuria (3/64), pelvic/abdominal pain or

cramping (3/64), vaginal and/or urethral itching (3/64), hematuria (2/64), increased frequency/urgency (1/64), and sensation of a foreign object in the urethra (1/64). The effectiveness analysis assessed a subset of 48 patients with moderate to severe SUI (i.e., ≥ 3 stress leaks and ≥ 3 g pad weight at baseline). The percentage of patients who experienced ≥ 50% reduction in baseline stress leaks and pad weight increased with increasing dose (Table 1). At 12 months, 100% (6/6) of the 200 x 106 group had ≥ 50% reduction in stress leaks and 83% (5/6) had ≥ 50% reduction in pad weight. Additionally, the 200 x 106 group had the highest percentage of patients with 0-1 leaks (83%, 5/6), Stamey scores of 0 (50%, 3/6), and ≥ 50% improvement in QOL scores (83%, 5/6 for IIQ-7; 67%, 4/6 for UDI-6).

Conclusions: Intrasphincteric injection of AMDC at doses of 10, 50, 100, and 200 x 106 cells appears safe with no serious treatment-related AEs reported. Preliminary effectiveness data suggest that more patients may be responsive to higher doses of AMDC.

5:30 pm – 7:00 pm: **Keynote Forum**

Bernard Siegel, J.D., Genetics Policy Institute, "The Power of Stem Cell Advocacy"

Mahendra Rao, M.D., Ph.D., Director, Center for Regenerative Medicine, NIH, "NIH CRM-An Update on Efforts in Translational Science"

The NIH CRM is a Common Fund initiative established to accelerate the transition of basic science advances related to stem cells and regenerative medicine to the clinic. We have broadly interpreted this mandate to include screening using stem cells and their derivatives to identify small molecules or biologics that modulate disease as well as identifying opportunities for cell replacement therapy. We will update the audience on the efforts as related to developing uniform procedures, assays and differentiation techniques using a variety of disease models.

Saturday, October 6, 2012

8:00 am – 9:15 am: **Plenary Session II**: Stem Cell Biology I

Craig Atwood, Ph.D., University of Wisconsin Medical Center, "Human Embryonic Stem Cells as a Model System for Understanding Early Human Embryogenesis: Human Chorionic Gonadotropin Induction of the Proliferation and Differentiation of hESC into Neural Precursor Cells"

The physiological signals that direct the division and differentiation of the zygote to form a blastocyst, and subsequent embryonic stem cell division and differentiation during early embryogenesis, are unclear. We have been utilizing human embryonic stem cells (hESC) as a model of inner cell mass differentiation to examine the hormonal requirements for the formation of embryoid bodies (EB's; akin to blastulation) and neuroectodermal rosettes (akin to neurulation). Although a number of growth factors, including the pregnancy-associated hormone human chorionic gonadotropin (hCG) are secreted by trophoblasts that lie adjacent to the embryoblast in the blastocyst, it is not known whether these growth factors directly signal human embryonic stem cells (hESCs). We have found that hCG promotes the division of hESCs and their differentiation into EB's and neuroectodermal rosettes. Inhibition of luteinizing

hormone/chorionic gonadotropin receptor (LHCGR) signaling suppresses hESC proliferation, an effect that is reversed by treatment with hCG. hCG treatment rapidly upregulates steroidogenic acute regulatory protein (StAR)-mediated cholesterol transport and the synthesis of progesterone (P4). hESCs express P4 receptor A, and treatment of hESC colonies with P4 induces neurulation, as demonstrated by the expression of nestin and the formation of columnar neuroectodermal cells that organize into neural tubelike rosettes. Suppression of P4 signaling by withdrawing P4 or treating with the P4-receptor antagonist RU-486 inhibits differentiation of hESC colonies into EB's and rosettes. Our findings indicate that hCG signaling via LHCGR on hESC promotes proliferation and differentiation during blastulation and neurulation. Moreover, these results suggest that trophoblastic hCG secretion and signaling to the adjacent embryoblast is the commencement of trophic support by placental tissues in the growth and development of the human embryo.

Nissim Benvenisty, M.D., Ph.D., Hebrew University, "The Role of Pluripotent Stem Cells in Modeling Human Disorders"

Human pluripotent stem cells hold the promise to change that way we model human disorders. In the past few years we have demonstrated different methodologies to create such models, either by mutating human embryonic stem (ES) cells, by generating human ES cells from pre-implantation genetic diagnosis embryos, or by establishing human induced pluripotent stem (iPS) cells from patients' somatic cells. We have thus generated models for congenital disorders such as Lesch-Nyhan syndrome, Turner syndrome, Down syndrome, and Fragile X syndrome.

Fragile X syndrome is the most common form of inherited mental retardation. The vast majority of Fragile X patients do not express the FMR1 protein as a result of a CGG triplet repeat expansion at the 5' UTR of the gene. Through the generation of a model for Fragile X in human ES cells we were able to show that the silencing of FMR1 is differentiation dependent, and that histone modifications precede DNA methylation during the FMR1 inactivation. We have also generated human iPS cells from fibroblasts carrying the Fragile X mutation, and demonstrated that the Fragile X iPS cells have an epigenetic memory that prevents the recapitulation of the temporal regulation of FMR1 gene silencing, present in the human ES cell model. Nevertheless, the cells are highly suitable in the study of the neural phenotype in Fragile X patients. Using this model in iPS cells, we have established a system to screen for drugs that activate the silent gene, and may serve to treat the molecular pathology of this disease.
Human pluripotent stem cells may also serve as models for developmental disorders. We have used human pluripotent stem cells to study pattern formation and imprinting in early human embryos. Dicephaly is a rare disorder in which the fetus develops two axes, probably as a result of the formation of two gastrula organizers. We have identified the human organizer cells in human embryoid bodies derived from ES cells, and demonstrated their ability to induce a second axis when injected into frog embryos. Parthenogenesis is a condition in which the embryo is composed of only maternal genomes. We have generated parthenogenetic human iPS cells, and utilized these cells to characterize the global expression of parentally imprinted genes, identifying multiple novel imprinted micro RNAs, and suggesting their role in human development.
Our strategies emphasize the usefulness of human ES and iPS cells in studying human genetic diseases, and in modeling developmental disorders that are otherwise inaccessible for research.

Mervin Yoder, M.D., University of Indiana, "Challenges to the Stem Cell Theory of Hematopoiesis"

The stem cell theory of hematopoiesis predicts that all mature blood cell lineages are derived from pools of definable progenitor cell precursors that are all direct progeny of a single hematopoietic stem cell (HSC). Thus, to reconstitute a hematopoietic system in an animal that has been lethally irradiated, one must ultimately provide a HSC from which all the progenitors and mature blood cells emerge. Following this logic, one might anticipate that the first blood cells to emerge during embryogenesis might be the direct progeny of a HSC. However, we will review the data derived from the murine system which indicates that a variety of committed progenitor cells are the first cells to develop. Furthermore, a hemogenic endothelial precursor for the hematopoietic cells has been identified at multiple stages during murine development. Recently, we have identified B and T cell progenitor cells that are descendents of hemogenic endothelial cells resident in both the yolk sac and embryo proper that display the capacity to generate a variety of B and T cell subsets upon transplantation into immunodeficient newborn mice. Of interest, these lymphoid precursors emerge prior to the detection of the first HSC. In sum, the emerging evidence indicates that there is a progressive increase in the number and diversity of hematopoietic lineages that arise prior to the first HSC and only after that time does hematopoiesis follow the HSC theory.

9:30 am – 11:00 am **Focus Session A**: Cancer Stem Cell Biology

Sarah Krueger, Ph.D., Beaumont Health System, "Recruitment and Retention of Bone Marrow–derived Progenitor Cells Following Radiation-induced Lung Damage"

Complications from late-responding tissues such as the lung can become a major health problem after radiation treatment. The lung is considered a dose-limiting organ and the pathogenesis of radiation-induced lung injury involves a complex cascade of events at the cellular and molecular level. Several studies have demonstrated that bone marrow (BM) cells may promote the repair of pulmonary epithelium after various types of injury and it has been shown that bone marrow progenitor cells are capable of incorporating into lung tissue and taking on the phenotype of lung epithelial cells. This project seeks to elucidate how lung-specific irradiation effects the bone marrow population and whether transplanted bone marrow-derived progenitor cells can replace damaged cells in the lungs of C57BL/6 mice after irradiation.

Sarah Conley, Ph.D., University of Michigan, "Cancer Stem Cells: Attacking Cancer at its Roots"

There is increasing evidence supporting the "cancer stem cell" hypothesis in breast cancer, which deems that tumors are driven by a small population of cells exhibiting stem cell properties. These cancer stem cells may also be responsible for mediating tumor metastasis and resistance to cancer treatments. Recently, several new cancer therapies targeting tumor angiogenesis have been developed and validated in clinical trials. However, clinical practice has revealed that these therapies ultimately result in drug resistance and do not prolong breast cancer patient survival by more than a few months. It has been reported that these angiogenesis inhibitors promote tumor invasiveness and metastasis in rodent breast cancer models. We have now shown that breast tumor stem cell populations increase in response to hypoxia in vitro and in tumors from anti-

angiogenic treated mice leading to increased tumor aggressiveness. We are now testing the ability of several agents to block the increase in CSCs seen in mice treated with anti-angiogenic drugs. These studies may reveal that therapies targeting tumor angiogenesis should be combined with treatments targeting hypoxia signaling and/or the cancer stem cell population.

George Wilson, Ph.D., Beaumont Health System, "The Role of CD44-associated Stem Cells in Recovery of Head and Neck Squamous Cell Carcinoma Following Radiation"

Purpose/Objectives: There is growing evidence that cancer stem cells (CSCs) may be an important factor in disease progression and resistance to current treatments. The rationale for this study was to investigate the possible role of CD44-associated CSCs in the recovery of head and neck cancer (HNSCC) xenografts following treatment with radiation.
Material & Methods: Flow cytometry was used to sort five untreated, low passage HNSCC cell lines (UT14, UT16A, UT24A, UT30, UT33) into CSC-enriched and CSC-depleted populations based upon expression of the putative cancer stem cell marker CD44. Gene expression microarray analysis was employed to develop a gene expression profile of the cancer stem cell population. In a separate study, UT14 cells were injected into the flanks of female nu/nu mice and allowed to grow to a size of 400-500mm3; they were then treated with either sham RT or 15 Gy in one fraction. Tumors were harvested at 4, 7, 12, and 21 days following radiation treatment and compared to untreated controls using immunohistochemistry (IHC) and gene expression microarray analysis. Partek Genomics Suite and Ariadne Pathway Studio were used to investigate the changes seen in the in vitro and in vivo results.
Results: Microarray analysis of the in vitro data was used to develop a gene expression profile characteristic of CSCs that included 77 differentially expressed genes between the CSC-enriched and CSC-depleted populations. 15 Gy arrested tumors for the first 21 days after RT and growth resumed at a linear rate thereafter. Gene expression analysis showed that ten of the genes, identified in vitro, were also altered in the xenografts at a minimum of one timepoint following radiation; these included chemokine (C-X-C motif) ligand 11 (CXCL11) and metastasis associated in colon cancer 1 (MCC1). In comparison to the in vitro cell sorting data, the only timepoint that showed commonly altered categories of biological process as well as Ariadne sub-networks of genes regulating cell processes was at Day 7 following radiation treatment. This time point preceded a rapid rise in CD44 staining by IHC. The common biological processes included mitotic cell cycle, cell cycle, and mitosis and cell processes of G2/M transition and spindle assembly.

Conclusions: This study suggests a possible role of cancer stem cells in the recurrence of head and neck squamous cell cancer following radiation treatment. Global gene expression patterns of CD44-positive CSCs demonstrate similarities to those of xenografts following radiation, particularly 7 days following treatment. Interestingly, Day 7 precedes the recovery of the xenograft from the sub-curative dose of radiation. From these studies we hope to gain greater insight into the importance of stem cells in HNSCC as well as the importance of targeting the stem cells to achieve more successful treatment options.

Gerard Madlambayan, Ph.D., Oakland University, "Migration of Hematopoietic Stem and Progenitor Cells (HSPCs) to Tumors Following Radiation: A Role of HSPCs in Tumor Re-growth Following Treatment"

The ability of tumors to maintain their growth *in vivo* is dependent on various factors including new blood vessel formation facilitating the delivery of factors that support tumor cell survival. Recently, the role of bone marrow (BM)-derived cells in tumor growth has become apparent. For example, BM-derived hematopoietic cells of the myelomonocytic lineage have been shown to be important for tumor growth through the paracrine secretion of factors that promote angiogenesis and tumor cell proliferation. It has also been shown that BM-derived endothelial progenitor cells (EPCs) are capable of directly contributing to tumor neovessel formation. We previously demonstrated that hematopoietic stem and progenitor cells (HSPCs) also play a direct role in tumor growth and neovascularization. As radiation therapy (RT) is a standard method of treatment, we utilized our experience in this area to analyze the involvement of HSPCs on tumor re-growth post RT. In these studies, we show that RT directly affects the levels of BM-derived HSPC migration to tumors, and that the levels of migration correlate to tumor re-growth rates. We also show that recruited HSPCs maintain their functionality suggesting a supportive niche within tumors. Furthermore, using a small animal radiation research platform (SARRP) we show that HSPCs home to areas receiving site-directed radiation indicating that RT generates localized tumor microenvironments that specifically promote recruitment of HSPCs. Overall, this data suggests a mechanism wherein RT initiates the directed migration of HSPCs to tumors that may aid in the re-growth of tumors following therapy.

9:30 am – 11:00 am **Focus Session B**: Stem Cell Business and Entrepreneurial Opportunities: Panel Discussion

Michael Gilkey, MBA, MS, National Center for Regenerative Medicine, "Commercialization of Regenerative Medicine Products Through State Funding"

Mr. Gilkey will discuss Ohio's strategic investments in regenerative medicine through the Ohio Third Frontier Program and its newest investment in OH-Alive, an optimized manufacturing platform for translational cell culture. Ohio's funding has provided the essential catalyst for cooperation between academic and commercial entities to assertively grow the biotechnology sector in Ohio. One of its primary investments has been the National Center for Regenerative Medicine (NCRM), which has profoundly enhanced Ohio's biomedical and biotechnology industry by motivating and organizing the immense clinical capabilities of the partner institutions to create a critical mass in the area of stem cell and regenerative medicine research and commercialization. This has led to increased clinical volume, expansion of the research base, new inventions, new companies, new investments, and hundreds of new jobs. NCRM is an expanding enterprise that is producing financially self sufficient spin-outs supported by federal and state funding, institutional support, commercial private equity and investment as well as sponsored research. This dynamic matrix of support has encouraged explosive growth of NCRM both in terms of members, funding, commercial partners and national recognition.

Irene Spanos, Oakland County, "Medical Main Street"

Medical Main Street offers diverse services—from introducing companies that are new to the area to networking opportunities to providing information about available tax abatements and access to resources for such things as FDA consulting and more. We listen to what a company

needs and bring them the right resources, whether federal, state or local. Because of Michigan's strong automotive history and abundant use of advanced technologies, we have a special blend of manufacturing expertise, top doctors and hospitals, and recognized universities and colleges that all come together in the Medical Main Street network. And, our goal is to fortify and grow this health care and life sciences hub for our community.

9:30 am – 11:00 am **Focus Session C**: Stem Cell Differentiation

Dan Rappolee, Ph.D., Wayne State University, "Hypoxia and Other Stresses that Diminish Growth Cause Imbalanced Stem Cell Differentiation, Stress Enzymes and Mitochondria are Critical"

Our lab has discovered that stem cells differentiate when stress exposures diminish stem cell accumulation. We call this "compensatory differentiation" since more differentiated function/cell is induced. Stressed stem cells undergoing compensatory differentiation induce early essential lineages while suppressing later essential lineages. We call this "prioritized differentiation" and it occurs in the first two stem cell lineages; embryonic (ESC) and placental trophoblast stem cells (TSC). Prioritized differentiation is a hallmark of stress exposures dangerous to normal development as stem cell potency is depleted and lineage imbalance occurs. All our previous studies on the stress response were performed at 20% O2 as are most published studies. This is a stressful O2 level and 2% is the least stressful; promoting highest proliferative and potency for TSC. Very high stress is attained at very low O2 levels from 0-0.5% O2. At 0.5% O2 stress is dominant and three nuclear differentiation factors are highest and three potency factors lowest despite the presence of potency-maintaining growth factor FGF4. Although highest preparation for differentiation is at 0.5% O2, when FGF4 is removed for 7 days 0.5% O2 supports the lowest level of five terminal differentiation markers. This surprising finding suggests a deficit due to insufficient stress or mitochondrial function. But hyperosmolar stress levels that activate high stress enzyme activity known to drive differentiation at 20% don't increase differentiation at 0.5% O2. Interestingly stress-activated protein kinase (SAPK) induces highest early lineage nuclear differentiation factor at 20% and 0.5% O2 At these O2 levels SAPK mediates highest suppression of a later lineage nuclear differentiation factor. At 2% O2 SAPK activity is lowest, stemness is highest, and SAPK-mediated affects on early/late differentiated lineages is lowest. Thus SAPK appears to "read" the stem cell state and adjust prioritized differentiation programs as O2 levels depart from the optimum for stemness. A mitochondrial activator increases differentiation of stem cells at 2% O2 but not 0.5%. This is reasonable since mitochondrial charge (and efficient ATP production) doesn't develop when FGF4 is removed at 0.5% although charge develops with FGF4 removal at 2%-20% O2. Two mitochondrial inhibitors decrease differentiation at the highest differentiation-mediating dose at 20% O2. We are currently testing the hypothesis that hypoxia immediately imbalances stem cell differentiation through stress enzyme-dependent mechanisms but that completion of normal or imbalanced differentiation requires levels of O2>0.5% and mitochondrial functions.

Supported by NIH R03HD061431, R01HD40972, and the Office of the Vice President for Research, WSU

Paul Dyce, Ph.D., University of Western Ontario, "Can In Vivo Conditions Improve Oocyte Development from Somatic Stem Cells?"

The skin harbors multiple classes of stem cells with differing differentiation potential. Previous work has shown that stem cells isolated from newborn mouse skin have the ability to differentiate *in vitro* into cells with some characteristics of oocytes, although these oocyte-like cells (OLCs) fail to reach meiotic competence and are therefore unable to develop following fertilization. Here we report that combining early stage OLCs with ovarian somatic cells and using a combined *in vitro* and *in vivo* differentiation protocol improves their differentiation. By transplanting such reaggregated "ovaries" under the kidney capsule, follicles representing all stages of follicular development could be recovered. However, the stem cell-originating follicles are largely restricted to primary and rarely early secondary stage follicles. Following isolation and *in vitro* growth and maturation the OLCs remain unable to mature. This presentation will be an overview on current culture conditions, and the functional status of OLCs derived from somatic stem cells.

This work was funded by the Canadian Institutes of Health Research.

Xianghong Luan, M.D., University of Illinois at Chicago, "SCF/C-kit Promotes Dental Pulp Cell Migration Through Rapid Activation of PI3K and MEK/ERK Pathways - Potential Applications in Pulp Regeneration"

Stem cell factor (SCF) and its receptor C-kit are considered critical regulators involved in a variety of cell functions, such as proliferation, differentiation, survival, and chemotaxis. In the present study, we determined the effects and the molecular mechanisms of SCF/C-kit on dental pulp progenitor cell migration and its applicability for cell homing-based dental pulp regeneration. Multipotentiality of dental pulp progenitor cells was confirmed using odonto-/osteogenic differentiation and neurogenic differentiation assays. Expression of the SCF receptor, C-kit, was detected in dental progenitor cells, including dental pulp cells, periodontal ligament cells, alveolar bone cells and dental follicle cells. To test the effect of SCF on cell proliferation, dental pulp cells were subjected to SCF at a 100nM concentration over a period of 7 days, and cell number was determined in daily intervals during the entire period using an MTT assay. Our data indicated that dental pulp cell number gradually increased in the SCF treated group until a 1.72-fold elevation over the control at day 7. Using a transwell culture system, dental pulp cell number in transwell plates was determined after 24 hours culture and addition of recombinant SCF. A 20nM SCF concentration increased the number of cultured pulp cells to 143.95±52.27%, while a 150 nM SCF concentration caused an increase to 265.22±66.37%, suggesting that SCF increased dental pulp cell proliferation activity and increased number of migratory cells. To explain the stimulatory effect of SCF on dental pulp cells, we hypothesized that SCF might affect the phosphorylated state of extracellular matrix pathway intermediaries. Our western blot assays confirmed that SCF induced phosphorylation of both AKT and ERK1/2. To test the involvement of extracellular matrix pathways in SCF induction, PI3K and MEK/ERK pathways were blocked by LY294002 and UO126 pathway inhibitors in the presence of SCF. There was a reduction in the number of migrated cells as a result of LY294002 block to a level of 80.22±27.05% and a reduction to 69.29±14.23% following UO126 block, while SCF treatment alone caused an increase to 196.23±67.31%. In addition, RhoA expression decreased 2.37 fold after LY294002

treatment and 2.022 fold after UO126 treatment compared to the SCF treated group, illustrating that SCF affects cell migration through both the PI3K/Akt and MEK/ERK pathways. In addition, application of SCF resulted in cytoskeletal rearrangement and actin polymerization of hDPs as visualized by rhodamine-phalloidin staining as well as G-Actin/F-Actin ratio assays. To examine the *in vivo* applicability of SCF as a homing factor for stem cell recruitment into implanted tissue scaffolds, subcutaneous collagen sponge implants were treated either with SCF or seeded with dental pulp stem cells or both. There was a 7.6-fold increase in cell number in SCF-treated implants when compared to untreated controls, suggesting that SCF dramatically improved cell homing properties in collagen scaffolds. Together, these studies indicate that SCF/C-kit promotes hDPs migration through rapid activation of PI3K and MEK/ERK pathways. The chemotaxis effect of SCF on hDPs might have potential applications for dental pulp regeneration by cell homing. Funding by NIDCR grant DE019463 to XL is gratefully acknowledged.

Dean Tantin, Ph.D., University of Utah School of Medicine, "Transcriptional Mechanism of the Reprogramming Factor Oct4"

Building on data identifying the mechanism by which Oct1, a crucial transcriptional regulator, controls transcription, we identify a related mechanism for the related Oct4 protein. Oct4 is a crucial regulator of embryonic stem cell pluripotency and a frequent component of cocktails used to generate induced pluripotent stem cells. Oct1 is known to derepresses transcription through recruitment of Jmjd1a, an H3K9me2-specific histone lysine demethylase. In differentiating embryonic stem cells, Oct4 opposes the accumulation of H3K9me2, and opposes Dnmt3a-mediated deposition of DNA methyl marks. Instead of Jmjd1a, Oct4 recruits the related Jmjd1c protein. We identify a stepwise mechanism for Oct4 transcriptional regulation involving H3K9me2 demethylation, recruitment of the FACT complex, and nucleosome depletion. These findings indicate that Oct1 and Oct4 can block stable gene repression through related mechanisms involving distinct Oct/histone demethylase pairs.

9:30 am – 11:00 am **Focus Session D**: *In Vivo* Image-based Stem Cell Analysis

Ali S. Arbab, M.D., Ph.D., Henry Ford Health System, "Tracking of Stem Cells by In Vivo Magnetic Resonance Imaging"

Hematopoietic, non-hematopoietic and organ specific stem cells are being used routinely not only in the animal models but in clinical trials too. With current widespread interest in cell-based therapies in cardiac, neurological and other disorders, in order to evaluate efficacy and appropriateness, it becomes critically important to track the movement and localization of selected cell populations. Different stem cells are being considered as gene carrier/delivery vehicles for the treatment of different disease processes and it is absolutely necessary to know the migration and homing of these cells at the sites of interest before targeting them. Moreover tracking of administered stem cells is also necessary to determine their engraftment efficiency anunctional capability following transplantation. There have been different imaging modalities used to track the movement and incorporation of administered stem cells by in vivo and ex vivo imaging techniques. Recently published reports showed that magnetically labeled stem cells can be used as cellular magnetic resonance imaging (MRI) probes to show the neovascularization in the tumors. Recent advancement in cell labeling with different MR contrast agents and tracking using MRI will be presented.

Quan Jiang, Ph.D., Henry Ford Health System, "Imaging in Stem Cell Therapy of Brain Injury"

Stem cell and neurorestorative approach become a promising direction in restoring brain function after injury. However, mechanism related cell-tissue interaction and brain tissue structure remodeling remain unclear. This talk introduces advance medical imaging methodologies in monitoring the structural substrates of brain recovery with spontaneous or neurorestorative treatment after injury. The use of MRI and its associated challenges to monitor stem cell migration, distribution, concentration, and to measure vascular and neuronal remodeling in response to spontaneous and therapy induced brain recovery will be described. This talk will demonstrate that MRI methodologies can be used in real-time monitoring of recovery from brain injury.

Branislava Janic, Ph.D., Henry Ford Health System, " Long Term In Vitro Expanded Cord Blood Derived AC133+ Endothelial Progenitor Cells in MCAo Rat Model for Cerebral Ischemia"

Background: Stem cells/progenitors are important for the development of cell therapies for vascular ischemic diseases. The crucial step in rescuing tissues from ischemia is improvement of vascularization that can be achieved by promoting neovascularization or growth of new blood vessels. Endothelial Progenitor Cells (EPCs) are the best candidates for developing such an approach due to their ability to self-renew, circulate and differentiate into mature endothelial cells (ECs). However, the successful clinical application of such therapy is limited by low quantities of EPCs that can be generated from patient and by the lack of adequate non-invasive imaging approach for in vivo monitoring bio-distribution of transplanted cells.
Hypothesis: Long term expanded cord blood derived AC133+EPCs will selectively migrate to the ischemic brain parenchyma and exert their angiogenic effect and this process can be monitored by MRI due to the ability of these cells to create sufficient T2 and T2* shortening (MRI parameters) when magnetically labeled.

Methods and Results: AC133+ cells were collected from CB using MidiMACS system. Cells were maintained in culture for 5 to 30 days at the cell concentration of 1x106/ml. At days 5-15 and 20-30 of the primary in vitro culture, cells were magnetically (FePro) and fluorescently (DiI) labeled and immediately IV injected into the rats with ischemic stroke. Rat stroke model was generated by transiently occluding middle cerebral artery for 2 hours. Twenty four hours later, animals underwent MRI to confirm and characterize stroke lesion and after the MRI scanning animals received IV injection of FePro labeled AC133+ EPCs. Seven and 14 days after injection, animals were again analyzed by MRI. Susceptibility weighted MR imaging (SWI) showed accumulation of FePro labeled cells in stroke affected hemispheres that was also detected by Prussian blue (PB) tissue section staining (detects iron in FePro labeled cells). Injected cells accumulated mainly within the ischemic boundary, within and around large thin blood vessels that are indicative of neo-angiogenesis. Analysis of T2 maps constructed from T2WI images acquired with different echoes revealed that over the course of 15 days, stroke affected areas shrunk at the significantly higher rate in animals that received FePro labeled AC133+ EPCs as compared to the control animals.

Conclusion: Data presented indicate that long term, in vitro expanded CB AC133+EPCsselectively migrated to the ischemic brain parenchyma, where they may have

exerted therapeutic effect on development and extent of tissue damage, inflammation and time course of resolution following stroke onset.

11:05 am – 12:35 pm **Focus Session E**: Adult Stem Cell Development

Vince Tropepe, Ph.D., University of Toronto, "FGF Dependent Zfhx1b Gene Expression Promotes Definitive Neural Stem Cell Development"

FGF signaling has been implicated as a major regulator of neural specification in various vertebrate model organisms, but it remains unclear to what extent this pathway is involved in mammalian neural stem cell (NSC) development. Mouse definitive NSCs are derived from a population of LIF-responsive primitive NSC (pNSC) within the neurectoderm and there has been some debate as to whether FGF signaling affects the induction of pNSCs or the transition from pNSC to NSC. Using an *ex vivo* embryo model, our studies demonstrate that acute activation of FGF signaling in the anterior neurectoderm causes an increase in neurectoderm specific gene expression (e.g. *Sox2, Nestin, Zfhx1b*) and results in an increase in the number of clonal colony forming NSCs subsequently derived from the anterior neural plate, whereas inhibition of FGF signaling significantly reduces the number of NSC colonies. Interestingly, inhibition of FGF signaling causes the persistence of LIF-responsive pNSCs within the anterior neural plate and over-expression of *Zfhx1b* in these cells is sufficient to rescue the transition from a LIF-responsive pNSC to an FGF-responsive NSC. Thus, definitive NSC fate specification in the mouse neurectoderm is facilitated by FGF activation of *Zfhx1b*. We also asked whether *Zfhx1b* is similarly required during neural lineage development of embryonic stem (ES) cells *in vitro*. *Zfhx1b* gene expression is rapidly up regulated in mouse ES cells cultured in a permissive neural inducing environment, compared to ES cells in a standard pluripotency maintenance environment, and is potentiated by FGF signaling. However, over expression of *Zfhx1b* in ES cells in maintenance conditions, containing serum and LIF, is sufficient to induce *Sox1* expression, a marker found in neural precursors, and to promote definitive neural stem cell colony formation. Knockdown of *Zfhx1b* in ES cells using siRNA did not affect the initial induction of a pNSC fate, but did diminish the ability of these neural cells to further transition into definitive NSCs. Our findings using ES cells are congruent with evidence from mouse embryos and support a model whereby intercellular FGF signaling induces *Zfhx1b*, which promotes the development of definitive NSCs subsequent to an initial neural specification event that is independent of this pathway.

Jose Luis Garcia-Perez, Ph.D., Pfizer-University of Granada-Junta de Andalucía Center for Genomics and Oncological Research, "LINE-1 Retrotransposition in Somatic Stem Cells"

Long INterspersed Element class 1 (LINE-1 or L1) retrotransposons comprise a fifth of the human genome and their ongoing activity continues to impact the genome. Heritable LINE-1 retrotransposition events must occur in cell types that ensure their transmission to newborns. Previous reports have detected LINE-1 expression and activity of engineered elements in cultured human cells that mimic an early embryo. These include human embryonic stem cells (hESCs), human embryonic carcinoma cells (hECs) and induced pluripotent stem cells (iPSCs). Additionally, recent reports have revealed the expression and mobilization of LINE-1 elements in selected somatic human cells including Neuronal Progenitor Cells (NPCs). Here, we used a panel of pluripotent and differentiated cell cultures to inspect the expression and

retrotransposition levels of engineered LINE-1 retrotransposons. Remarkably, we observed that LINE-1s are expressed in pluripotent neuronal and embryonic cell types, although expression is higher in embryonic cell types. Additionally, we recapitulated engineered LINE-1 retrotransposition in pluripotent neuronal and embryonic cell types, but observed that retrotransposition rates can vary more than 200-fold among different pluripotent cell types. Indeed, under our experimental conditions, the highest rate of engineered LINE-1 retrotransposition is observed in neuronal cell types. These data suggest that the main load of LINE-1 retrotransposition in humans may occur in selected somatic cells and that most mobilization events will not be transmitted to newborns.

Diana L. Ramírez-Bergeron, Ph.D., Case Western Reserve University School of Medicine, "Hypoxic Responses in the Bone Marrow's Vascular Stem Cell Niche"

Recent studies have shown that endothelial progenitor cells (EPCs) are an important contributor to neovascularization and re-endothelialization after acute vascular injury. Bone marrow (BM) sinusoidal endothelial cells (SEC) are considered to impart an important role as a vascular stem cell niche for hematopoietic stem cells and likely influence BM-derived EPCs. As the BM microenvironment experiences a relatively low gradient of O_2, we conditionally inactivated in mice the transcriptional activity of Hypoxia Inducible Factor (HIF), a key determinant of oxygen-dependent gene regulation, by inducing the deletion of its required heterodimeric subunit ARNT *(Aryl hydrocarbon Receptor Nuclear Translocator, or HIF-1beta*) exclusively in adult endothelial cells ($Arnt^{iEC}$) to examine the requirements of hypoxic signals from the BM vascular niche during neoangiogenic responses.

Feng Lin, Ph.D., Case Western University School of Medicine, "Mesenchymal Stem Cells are Injured by Complement After their Contact with Serum"

Despite the potent immunosuppressive activity that mesenchymal stem cells (MSC) display in vitro, recent clinical trial results are disappointing, suggesting that MSC viability and/or function are greatly reduced after infusion. In this report, we demonstrated that human MSC activated complement of the innate immunity after their contact with serum. Although all three known intrinsic cell surface complement regulators were present on MSC, activated complement overwhelmed the protection of these regulators and resulted in MSC cytotoxicity and dysfunction. In addition, autologous MSC suffered less cellular injury than allogeneic MSC after contacting serum. All three complement activation pathways were involved in generating the membrane attack complex (MAC) to directly injure MSC. Supplementing an exogenous complement inhibitor, or upregulating MSC expression levels of CD55, one of the cell surface complement regulators, helped to reduce the serum-induced MSC cytotoxicity. Finally, adoptively transferred MSC in complement deficient mice or complement-depleted mice showed reduced cellular injury in vivo compared with those in wild type mice. These results indicate that complement is integrally involved in recognizing and injuring MSC after their infusion, suggesting that autologous MSC may have advantages over allogeneic MSC, and that inhibiting complement activation could be a novel strategy to improve existing MSC-based therapies.

11:00 am – 12:30 pm **Focus Session F**: Bio-engineering

Gary Smith, Ph.D., University of Michigan, "Integration of Bioengineering to Improve Stem Cell Culture"

Classically, mammalian preimplantation embryos and embryonic stem cells have been grown under static culture conditions, in relatively large amounts of media, without precise alterations in the chemical environment, and with little appreciation for the microenvironment that supports their development *in situ*. Recent advancements in Biomedical and Chemical Engineering have provided new tools and platforms for altered cell culture. These include, yet are not limited to, microfluidics, nano-engineering, and hydrogel technologies. The translational question is whether these bioengineering tools provide added value in improved cell growth and/or normalcy, novel analytical capabilities, or biological hypothesis testing. Through interdisciplinary collaborations, data have been generated that demonstrate 1) microfluidics can be used to provide a precise dynamic culture environment for improved preimplantation embryo development; 2) that integration of micro- and nano-engineering can be used to integrate automated real-time embryo biochemical analysis with culture in a "laboratory on a chip"; and 3) fully-synthetic and artificial hydrogels can replace embryonic fibroblast requirement for growth and passage of human embryonic stem cells (hESCs). In relation to embryology, these advancements will provide a greater basic understanding of embryo nutrient requirements, usage, and biomolecule secretions. Collectively these advancements in embryo production and analysis will provide more efficient treatment of infertility while reducing unwanted multiple pregnancies. Finally, the replacement of hESC fibroblast co-culture requirements with fully-defined hydrogels and soluble components paves the way for hESC production under good manufacturing practices (GMP), which will facilitate hESC utility in cell-replacement therapies, pharmacological and toxicology screening, and elucidating basic developmental biology queries on stem cell growth and differentiation. Research discussed supported by the National Institutes of Health, United States Department of Agriculture, Michigan Economic Development Corporation, U.S. Army Research Laboratory/U.S. Army Research Office, and Colulter foundation.

Shuichi Takayama, Ph.D., University of Michigan, "Microfluidic Stem Cell Manipulations"

Many biological studies and drug assays require culture and manipulation of living cells outside of their natural environment in the body. The gap between the cellular microenvironment in vivo and in vitro, however, poses challenges for obtaining physiologically relevant responses from cellular drug screens and for drawing out the maximum functional potential from cells used therapeutically. One of the reasons for this gap is because the fluidic environment of mammalian cells in vivo is microscale and dynamic whereas typical in vitro cultures are macroscopic and static. This presentation will give an overview of efforts in our laboratory to develop microfluidic systems that enable spatio-temporal control of both the chemical and fluid mechanical environment of stem cells. The technologies and methods close the physiology gap to provide biological information otherwise unobtainable and to enhance cellular performance in therapeutic applications. We also develop microfluidic technologies to make stem cell handling, such as colony picking, more efficient. Specific biomedical topics that will be discussed include,

microfluidic technologies to enhance stem cell differentiation by cell micropatterning, formation of uniform embryoid bodies, and colony picking.

Ferman Chavez, Ph.D., Oakland University, "Potential Bio-engineering Applications of Self-Assembling Scaffold"

Self-assembling biocompatible and biodegradable nanomaterials have promising applications in tissue engineering and regenerative medicine as well as drug delivery. Ideally suitable and active biological scaffolds will stimulate and promote cell differentiation. Self-assembling scaffolds could help repair tissues which are difficult to regenerate and structures such as spinal cord, tendon and cartilage. Every year in the United States alone, about 15,000 people damage their spines. Few recover fully as it is difficult for damaged nerves to grow across the gap in a severed spinal cord. We have investigated several synthetic nanomaterials (such as polycaprolactone, poly (ethylene oxide), poly(lactic acid), and poly(lactic acid co-glycolic acid) and biomolecules (such as proteins, peptides, and carbohydrates) for use in developing scaffolds that mimic in vivo microenvironments for 3-D tissue engineering. The scaffolds promoted cellular growth of embryonic and cord blood stem cells and their differentiation into osteogenic, chondrogenic, and neural lineages. We are currently developing nanomaterials that self-assemble to produce scaffolds for generating tissues of various organs such as heart and liver. In this study we synthesized thiol-functionalized dextran (Dex-SH, Mn 25K) and investigated it for in situ hydrogel scaffold formation via Michael type addition using poly(ethylene glycol)tetra-acrylate (PEG-4-Acr). Dex-SH was prepared by activation of the hydroxyl groups of dextran with 4-nitrophenyl chloroformate and the subsequent reaction with cysteamine. The Dex-SH is highly air sensitive in aqueous solution and must be handled under nitrogen. We will present our preliminary results for in situ hydrogel formation in the presence of pluripotent stem cells.

Donggang Yao, Ph.D., Georgia Institute of Technology, "Hierarchically functional porous structures for tissue engineering applications"

Porous materials, as extracellular scaffolds, are widely used in tissue engineering. Besides a cocontinuous porous matrix, 'designed' structural hierarchy is desired in such applications. In this talk, some new developments in hierarchically functional porous materials are communicated and their potential applications in tissue engineering are discussed. In particular, gradients in pore size distribution can now be incorporated in the porous matrix by controllable thermomechanical processing. Likewise, pore orientations as well as micropatterns on external surfaces can also be specified in the new scaffold design. Additionally, new biomaterials and biocomposites have been added to the platform, resulting in new scaffolds that can be *in vivo* monitored, promote mineralization, and/or have enhanced load-bearing characteristics. The new spectra particularly include highly elastic scaffolds that can undergo large strains exceeding 200%. Some preliminary but promising results on the use of these new scaffolds in tissue engineering are highlighted.

11:05 am – 12:35 pm **Focus Session G**: Development and Regeneration

Gregory Dressler, Ph.D., University of Michigan Health System, "Stem Cells in Kidney Development and Regeneration"

My laboratory has studied the embryonic development of the urogenital system for more than 20 years. During that time, the lab has made significant contributions to understanding cell signaling and gene regulation in the mammalian kidney. We have discovered multiple genes and pathways that are essential for kidney development and that also function in chronic and acute diseases. We identified GDNF as the ligand for the c-ret tyrosine kinase and demonstrated that activation of PI3K promotes chemotaxis during ureteric bud growth. Also, we identified the first extracellular enhancer of BMP signaling, the KCP protein, which is essential for mediating the responses to renal injury. Genetic models, cell biology, and biochemistry are utilized to address the functions of these newly discovered genes and proteins.

Zhengqing Hu, M.D., Ph.D., Wayne State University, "A Stem Cell-Based Strategy for Inner Ear Regeneration"

Hearing loss is one of the major disabilities affecting millions of patients in the world. The long-term goal of my research is to develop stem cell-based replacement strategies aimed at restoring damaged auditory neural pathways, which may lead to a novel therapeutic approach to deafness. In particular, we identified stem cells in the mammalian inner ear and we induced these stem cells to become sensory hair cells and spiral ganglion neurons. We found that a mesenchymal-to-epithelial transition is involved in sensory hair cell generation. Further, inner ear stem cells were introduced back to the adult mammalian inner ear. Implanted stem cells were found to survive and differentiate into cells expressing neuronal proteins. In conclusion, the results provide insights into reconstructing the auditory neural pathways. The establishment of an animal model may lead to a novel treatment option for patients with hearing loss.

Suresh Palaniyandi, Ph.D., Henry Ford Health System, "Activation of Aldehyde Dehydrogenase in Cardiac Stem/Progenitor Cells: A Novel Approach to Boost Regeneration?"

Oxidative stress damages cardiac stem/progenitor cells in cardiac diseases. Reactive aldehydes generated from oxidative stress can form protein adducts in cardiac progenitor/stem cells (CPCs) and which may form cellular dysfunction and death of CPCs in cardiovascular diseases. Aldehyde dehydrogenases (ALDHs) metabolize reactive aldehydes such as 4-hydroxy-2-nonenal (4HNE) into non-toxic acid. Moreover, increased ALDH activity in CPCs (ALDHhigh) is known to have enhanced regeneration capacity. Purpose: We tested whether activation of ALDH isozymes in CPCs boost their survival, self renewal and stemness. Methods and Results: We evaluated the levels and activity of ALDH isozymes in CPCs. Though ALDH 1, 2 and 3 were present in CPCs, ALDH1 activity was higher in relation to other isozymes. We treated the cells with Alda-1, a small molecule ALDH activator and found that Alda-1 increase the ALDH+ cells. Then, we checked whether Alda-1 treated cells survive longer in mice after injection. CPCs isolated from Alda-1 treated mice show less non-progenitor cell populations compared to vehicle-treated mice. More importantly, Alda-1 treatment increased the self renewal markers expression in CPCs. We sorted CPCs into ALDH+ and ALDH- cells based on ALDH activity. There was increased expression of self renewal markers in ALDH+ cells compared to ALDH-

cells. Conclusion: Finally, activation of ALDH may improve the stemness and regeneration capacity of cardiac stem cells in disease condition like diabetic cardiomyopathy.11:00 am –

11:05 am-12:35 pm **Focus Session H**: Drug Discovery and Therapy

Peter Sartipy, Ph.D., Cellartis AB Sweden, "Derivation and Use of Cardiomyocytes from Human Pluripotent Stem Cells"

Recent developments have resulted in the possibility to generate differentiated cells displaying a cardiac phenotype from human pluripotent stem cells (hPSCs). Detailed interrogations of the molecular processes governing cardiogenesis in hPSCs have furthered our understanding of these intricate series of events allowing the establishment of highly effective differentiation protocols. Extensive characterization of the differentiated cardiomyocytes has provided critical information about the molecular and functional properties of the cells. Taken together, the data have shown that the cells share many similarities with bona fide human cardiomyocytes, while some functional aspects remain fetal-like (e.g., Ca^{2+}-handling and some electrophysiological properties). Even though much research remains, the current state-of-the-art processes of cost-effective derivation of cardiomyocytes from hPSCs have been standardized and implemented in an industrial setting. These cells are now being used for in vitro applications in drug discovery, and especially the use of the cells in safety pharmacological testing have been demonstrated. This presentation will illustrate some of the molecular and functional characteristics of the hPSC-derived cardiomyocytes and highlight recent applications for these cells, with emphasis on the comparison with existing model systems. These results provide support for the on-going improvement of new applications of the cells in drug discovery, ultimately contributing to the development of safer and more effective drugs.

Ralf Huss, M.D., Ph.D., Apceth GmbH in Munich, Germany, "Clinical Development of Pharmaceutical Grade Cellular Therapeutics"

Cell-based therapies and in particular stem cell-derived therapeutics are expected to revolutionize clinical medicine in the same way as monoclonal antibodies did. Although the idea to use cells as pharmaceutical compounds is not new, the clinical application of Cell Therapeutics represent a new challenge for clinical scientists and any pharmaceutical applicant with regard to the current regulatory requirements for manufacturing, quality control and clinical trial approval in many parts of the world. The guidelines and standards are currently harmonized within the EU / FDA area of responsibility.

Within the North American / European regulatory area, S*omatic Cell Therapeutics* must comply with the regulations for advanced therapies (ATMP). The GMP-compliant manufacturing and quality control of cell-based products follow the pharmaceutical requirements for medicinal products starting from cell culturing and cell biology, rigorous GMP/GLP standards to regulatory affairs. The procurement of (stem) cells as well as their origin, the handling of cells/ tissues and the *ex vivo* expansion require highly-qualified and continuously trained personnel. The quality control of the cells and cell products comprises the extensive characterization of somatic cells with regard to identity, purity, potency, genetic stability and sterility. The non-cellular

components such as media or growth factors have to be vigorously tested. All measures contribute to the significant cost of goods (COGS) for a somatic cell product.

The development of a new therapeutic modality like (stem) cell therapeutics as a pharmaceutical product is certainly a feasible challenge, but also requires identifying the demands of the health care market in relation to reimbursement and (premium) pricing. Innovations like cell-based therapeutics have to show more than just incremental improvement compared the current standard of care.

Jason A. Hamilton, Ph.D., Athersys, Inc., "Pre–Clinical Development of MultiStem for Treatment of Multiple Sclerosis"

Stem cell therapies are currently being investigated as potential therapeutic treatments for autoimmune disorders such as multiple sclerosis (MS). However, the mechanistic interaction between the diseased tissue environment and transplanted cells is poorly understood. In the present study, we demonstrate sustained functional benefit in mice with experimental allergic encephalomyelitis (EAE) after intravenous (IV) administration of MultiStem®, an adherent human adult stem cell product. MultiStem administration was tested using three different doses of stem cells, as well as three different times of administration. Behavioral assessment was performed daily for 28 days after cell administration. Each cell dose level resulted in statistically significant improvement compared to vehicle treatment; however, no functional benefit was observed when the cells were administered pre-symptomatically whereas cell administration early or late after symptom onset was efficacious. Luxol fast blue (LFB) staining demonstrated decreased lesion burden within the spinal cord and a shift from complete to partial lesions in MultiStem-treated animals compared to controls. Toluidine blue staining, and electron microscopic analysis, provided evidence of reduced myelin debris and improved remyelination, respectively. To look for specific effects of MultiStem upon remyelination, we tested administration in lysophosphatidylcholine (LPC)-lesioned rats. Increased LFB staining of myelin within the lesions of MultiStem-treated animals was observed, and was confirmed using myelin basic protein (MBP) immunohistochemistry. Immunohistochemical examination of macrophage/microglia status demonstrated significant changes in immune cell infiltration of the lesions, as well as a shift in activation status (M1 to M2) of infiltrating macrophages/microglia in MultiStem-treated animals. The results of these studies suggest that treatment of MS patients with MultiStem may provide clinical benefit through modulation of immune status and promotion of remyelination. This work was funded by a collaboration with Fast Forward LLC and the National MS Society, as part of a translational effort to find meaningful therapies for patients suffering from chronic Multiple Sclerosis.

Ronnda Bartel, Ph.D., Chief Scientific Officer, Aastrom, "Patient Specific Stem Cell Therapies"

Aastrom Biosciences is the leader in developing patient-specific, expanded multicellular therapies for use in the treatment of patients with severe, chronic cardiovascular diseases. The company's proprietary cell-processing technology enables the manufacture of ixmyelocel-T, a patient-specific multicellular therapy expanded from a patient's own bone marrow and delivered directly to damaged tissues. Aastrom has advanced ixmyelocel-T into late-stage clinical

development, including a Phase 3 clinical program to study patients with critical limb ischemia and a planned Phase 2b clinical trial in patients with ischemic dilated cardiomyopathy.

1:30 pm – 3:30 pm **Plenary Session III**: Stem Cell Biology II

Ales Hampl, D.V.M., Ph.D., Masaryk University, "Human Embryonic Stem Cells – Strong or Vulnerable?"

They are two defining properties of stem cells including human embryonic stem cells (hESC), self-renewal and pluripotency, which position them to a forefront of future regenerative medicine. Along with these positive qualities, however, stem cells seem to also possess undesirable properties that may result in their unpredictable behavior. Among them genetic instability of stem cells, particularly of hESC, propagated in culture is of paramount importance. Unfortunately, molecular mechanisms, by which alterations to the genome of hESC develop, as well as the biological outcomes of such genetic changes are not yet understood. We focus our attention on unraveling of which types of stress induce damage to genetic complement in hESC and on determining a functionality in hESC of molecular circuitries that are known to mediate a response to DNA damage in somatic cells. We have shown that generation of gross chromosomal mutations, amplifications and translocations, which are frequently generated in hESC is most likely contributed by alterations in the metabolism of centrosomes. We have also shown that undifferentiated hESC has established at least certain segments of molecular circuitries that are effective in sensing damage to DNA and in executing an appropriate response to it. Still, classical checkpoint pathway involving p21 inhibitor of cyclin dependent kinases is not operative in hESC due to a significant contribution from hESC-specific microRNA family miR-302. Finally, we have shown that cultured hESC, despite expressing cell death receptors on their cell membrane, are resistant to TRAIL-induced apoptosis, most likely due to the high levels of antiapoptotic proteins FLIP and Mcl-1. This resistance can, however, be eliminated by chemically sensitizing hESC.

In summary, we demonstrate that although undifferentiated hESC possess some protective mechanisms to maintain its DNA pristine, they still develop conditions that are favorable to generation and maintenance of genetic abnormalities.

Jose Cibelli D.V.M., Ph.D., Michigan State University, "Egg to Reprogram Cell"

Paul Krebsbach, D.D.S., Ph.D., University of Michigan, "The Role of mTOR Signaling in Balancing Self-renewal and Differentiation in Pluripotent Stem Cells"

Like other stem cells, human pluripotent stem cells (hPSC) have the capacity for self-renewal and differentiation into specialized cell types. However, pluripotent cells are unique in their ability to self-renew indefinitely. They also feature the unique capacity to differentiate into all of the approximately 200 specialized cell types of the body. These two fundamental characteristics make hPSCs a potential source of cells for regenerative medicine, drug discovery, disease modeling and studies aimed to better understand human development. It is well known that the global protein translation level in stem cells is lower than differentiated cells, whereas the activation of protein translation in these stem cells can initiate differentiation. Mammalian target of rapamycin (mTOR) is one signaling pathway that is important for cell growth and

differentiation. mTOR is the catalytic subunit of two distinct signaling complexes, mTOR complex 1 and 2 (mTORC1 and mTORC2). mTORC1 activates ribosomal S6 kinase (S6K) and inactivates eukaryotic initiation factor 4E binding protein 1 (4EBP1) and thus stimulates protein synthesis, cell growth, cell proliferation, and progression through the cell cycle. Promotion of cell survival and cytoskeleton reorganization is also enhanced when mTORC2 activates Akt and PKCα. This presentation will summarize recent data demonstrating the role of mTOR in self-renewal of human embryonic stem cells

Thomas Diekwisch, D.M.D., Ph.D. (sc.), Ph.D. (phil.), University of Illinois at Chicago, "Learning from Development: Cellular, Molecular, and Topographical Clues for Periodontal Tissue Regeneration and Tooth Replantation"

Chromatin dynamics assume key functions in the lineage differentiation and gastrulation of bilaterian embryos. Here we have studied the role of a SRCAP chromatin complex member, the chromatin factor CP27, during mouse development and germ layer differentiation. The yeast homologue of the SRCAP complex, the SWR complex, is required for the exchange of the histone H2A with its variant Htz1 (H2A.Z in mammals). Here we show that loss of CP27 in *cp27* null mice resulted in early lethality and offspring resembled slightly advanced stages of the H2A.Z null phenotype. CP27 also regulated H2A.Z expression in embryoid bodies and cells and interacted with the variant histone H2A.Z on a chromatin level. Moreover, loss of CP27 caused severely disturbed epiblast development and prolonged endoderm survival. Together, these findings suggest a direct link between CP27 and H2A.Z chromatin complex interactions and early mouse development. Studies presented here shed light on the chromatin-level regulation of early mouse development by the chromatin remodeling complex SRCAP and the resulting effect on ES cell lineage specification and gastrulation.

Hillard Lazarus, M.D., FACP, Case Western University, "Novel Applications of Multipotent Mesenchymal Stromal Cells"

Although their major site of residence and true physiologic role remain unclear, multi-potent mesenchymal stromal cells (MSCs) are a unique cell with varied properties. These cells arise from a lineage different from hematopoietic cells and have the ability to produce many cytokines and chemokines that stimulate and support hematopoiesis. Further, these cells exhibit immunosuppressive properties while usually behaving as though they were immunologically privileged. MSCs will home to areas of inflammation and can be collected from a variety of both marrow and non-marrow tissues including fat and placenta. The ability to expand MSCs *ex vivo* many fold makes these cells ideal for study and potential therapeutic applications. The earliest clinical trials, undertaken in hematologic malignancy patients, showed both autologous as well as allogeneic MSCs enhanced hematopoietic engraftment; in several trials, the likelihood and severity of graft-versus-host disease were reduced with infusion of allograft cells. More recently, MSCs have been studied in other immunologic settings such as prevention of renal (solid organ) allograft rejection. In the area of regenerative medicine/tissue repair, one potential target for MSC therapy is multiple sclerosis, a debilitating chronic neurologic disorder characterized by both inflammation and incomplete host repair. We used our pre-clinical murine animal model (experimental autoimmune encephalomyelitis) to show that tail vein infusions of human MSCs (1×10^6/mouse) migrated into the CNS and appeared to ameliorate the disorder "clinically" and

histopathologically. Hence, we designed and activated a currently on-going clinical trial in which we identify and treat multiple sclerosis patients with a single IV infusion of 1 x 10^6/kg culture-expanded autologous MSCs. Twelve subjects median (range) age 44 (39-55) years with secondary progressive and relapse remitting multiple sclerosis have been treated; median (range) for cell passage was 2 (1-3) and 2.9 (1.0-6.4) x 10^6/kg were generated during a median (range) of 24 (16-49) days in culture. Cells were infused without untoward effects and the patients followed. Evaluations included recipient MRI brain and marrow exams as well as studies of visual pathways (Sloan low-contrast letter acuity, visual evoked potentials, optical coherence tomography) and sophisticated immunologic mechanistic studies.

Other applications for MSCs include the therapy of intervertebral disc disease. Based on our porcine model, we have activated a clinical trial in which under radiographic guidance we will infuse 2-4 x 10^6 culture-expanded autologous MSCs as an intra-articular injection into the affected intervertebral disc area. Successor studies will include the addition of a matrix for cellular retention. Other applications of MSCs for which we have clinical trials in development include use in macular degeneration, early rheumatoid arthritis and urinary incontinence. The future of using MSCs in organ transplantation and regenerative medicine remains promising.

3:45 pm – 5:30 pm **Focus Session I**: Programming and Differentiation

Kapil Bharti, Ph.D., NIH, "Generating Authentic RPE from iPS Cells: Lessons from Mouse Eye Development"

Age-related Macular Degeneration (AMD) is a leading cause of vision loss in the US. AMD disease processes are thought to originate in the back of the eye in the photoreceptor-retinal pigment epithelium (RPE)-choroid complex. Recent advances show that disease progression can be slowed in some patients, but currently there is no treatment that reverses or prevents AMD. The recent transplantation of stem cell-derived RPE has provided hope for a therapeutic intervention. The use of stem cell-derived RPE for cell-based therapy requires growing cells using current Good Manufacturing Protocols (cGMP). But, the currently available RPE differentiation protocols are not optimized for this purpose. We have developed a reporter induced pluripotent (iPS) cell line for optimizing RPE differentiation. This line contains a constitutively expressed red fluorescent protein (RFP) and an RPE-specific green fluorescent protein (GFP). When this iPS cell line is differentiated into RPE, the GFP expression marks cells that attain an epithelial morphology, express RPE-specific genes, and become pigmented. The reporter line was used to optimize RPE differentiation from iPS cells. Based on the knowledge of mouse embryonic development, we have modified existing protocols for iPS cell to RPE differentiation. By manipulating FGF, BMP, NODAL, & WNT pathways we can differentiate up to 92% cells in a dish into RPE-like cells. The newly generated RPE cells were authenticated using molecular and physiological assays. Our results show significant differences in differentiation-ability of iPS cells generated from generically identically but epigenetically distinct tissue sources. In conclusion, the use of this GFP reporter iPS cell line has led a RPE-differentiation protocol that is scalable, cGMP-amenable, and represents a critical first step in the creation of transplantable tissue that contains fully-differentiated, functional monolayers of polarized RPE cells. We anticipate that such cells will also be valuable in the analysis of degenerative eye diseases that significantly involve the RPE.

Melvin McInnis, M.D., University of Michigan, "Induced Pluripotent Stem Cell (iPSC) Models to Study Bipolar Disorder"

Bipolar disorder (BP) is a common neuropsychiatric disorder characterized by pathological mood swings. It is highly heritable; typically first diagnosed in late adolescence or early adulthood. Little is established regarding its pathogenesis, etiology, or anatomical substrates, and there is a critical unmet need for informative models and more efficacious treatments. In the last decade, considerable effort was made to identify susceptibility genes, or genomic "hot spots", for BP. These studies have identified susceptibility genes with Odds Ratios of 1.1 – 1.3, but no single gene has emerged with sufficient effect to be a candidate for targeting in animal models; the vast majority of biological risk is undetermined. Although there is a clear need for patient-derived models, there are no reliable cell based models of BP since affected neurons (the presumed target tissue) are not available for study. The aim of this investigation, therefore, is to develop induced pluripotent stem cell (iPSC) lines to study BP. This research builds on the emerging concept that abnormalities of CNS development underlie many complex neurological and neuropsychiatric disorders that are only diagnosed decades later. Developmental approaches are critical to elucidate where in the differentiation of neurons and glial cells development goes awry. In the current investigation, iPSC lines were developed by reprogramming dermal fibroblasts obtained from individuals enrolled in a longitudinal study of BP disorder. We have dichotomized the sample based on dimensional measures of high or low neuroticism (using the NEO-PI). 44 cell lines have been developed for this study: from three bipolar patients (24 iPSC lines) and four control individuals (20 iPSC lines). The iPSC have been phenotyped; they express pluripotency markers Oct4, Sox2, Klf4, Nanog and SSEA4. In addition, with reprogramming the fibroblast restricted marker Te-7 is down-regulated. They have been differentiated into neurons, and their synaptic characteristics are being assessed, using immunohistochemistry and simultaneous voltage and calcium mapping. Gene expression analysis is being performed at sequential stages of differentiation to identify novel pathways and thereby new approaches to BP. The iPSC will form an important resource for model building and comparative studies of other neuroaffective disorders, and will identify new approaches to etiological study and identification of novel therapeutic approaches to BP.

Supported by the Hans C Prechter Fund, the A. Alfred Taubman Medical Research Institute and the Steven Swartzberg fund for Bipolar Research.

Jan Jensen, Ph.D., Cleveland Clinic, "A New Take on Notch in the Directed Differentiation of Insulin-producing Cells"

In the US alone, 25.8 million people suffer from diabetes and an associated wide array of cardiovascular, neurologic, renal and retinal complications. These complications result in substantial morbidity and mortality, resulting in app. $116 billion per year in direct medical costs. Islet cell replacement therapy promises a future restoration of normoglycaemic control in type I diabetic patients. Although cadaveric islet cell transplantation is currently possible, the scarcity of human donors has highlighted the need of an unlimited islet cell source. Directing the differentiation of pluripotent embryonic stem (ES) cells to islet cells has been demonstrated, though such cells typically show an immature character, and the efficiency of differentiation remains poor. Current methodology generally relies on our understanding of the formation and patterning of the pancreas during embryogenesis. We here present evidence for, and discuss the

relevance of in context of directed differentation, the induction of the TrPC state from pluripotent cells. This transient state, which arises from multipotent pancreatic progenitors is the normal ancestral state of beta cell precursors expressing the pro-endocrine factor Ngn3. The pancreatic organ establishes the TrPC state through a process that we refer to as "organ domain patterning". Of note, these developmental underpinnings provide an entirely new approach to modulating the Notch pathway during a directed differentiation process.

Stacey A. Sakowski, Ph.D., University of Michigan, "Outcomes of the First Completed FDA Phase 1 Intraspinal Stem Cell Transplantation Trial for ALS"

The FDA-approved trial, "A Phase 1, Open-label, First-in-human, Feasibility and Safety Study of Human Spinal Cord-derived Neural Stem Cell Transplantation for the Treatment of Amyotrophic Lateral Sclerosis, Protocol Number: NS2008-1," has been completed in 18 patients with amyotrophic lateral sclerosis (ALS). Patient cohorts, consisting of 3 ALS patients each, followed a "risk escalation" paradigm progressing from non-ambulatory to ambulatory patients receiving unilateral (n=5) or bilateral (n=10 total) lumbar or cervical injections. The final cohort of patients that received cervical injections included the same patients that received bilateral lumbar injections. All injections delivered 100,000 cells in a 10 µl volume, for a dosing range between 500,000 to 1.5 million cells in the various cohorts. The injection procedure utilized a novel stabilization and injection device that mounts to the patients vertebrae and includes a floating cannula to prevent shearing of the spinal cord during the surgical procedure. The procedure was well-tolerated by all patients with minimal perioperative or postoperative complications. Cervical kyphosis developed in one patient following the multi-level laminectomy. Some patients experienced gastrointestinal distress due to the immunosuppressive paradigm, which included a combination of tacrolimus and mycophenolate. Although this was a safety trial, clinical progression was monitored and disease progression continued in all patients, with the exception of one patient who exhibited remarkable clinical and electrophysiological improvements. Presently, 4 patient deaths have occurred and postmortem analyses are underway. Results of this trial demonstrate that intraspinal transplantation of neural progenitor cells in patients with ALS is feasible and well-tolerated. The established safety of this approach supports future trial phases examining therapeutic efficacy of neural stem cell transplantation for this yet untreatable, devastating neurodegenerative disorder.

Saba Valadkhan, Ph.D., Case Western Reserve University, "Long Non-coding RNA-mediated Trans-differentiation of Adult Cells into Neurons"

A large fraction of the higher eukaryotic genomes are transcribed into long RNAs that lack protein-coding potential and perform their cellular function as RNA molecules. It is thought that these RNAs might form a hitherto unknown layer of regulatory networks, however, their role in reprogramming and cell fate determination remains largely unstudied. Here we show that a long intergenic non-protein-coding RNA, which is physiologically expressed almost exclusively in neurons, can reprogram a variety of cells including myoblasts and fibroblasts to a neuronal fate with high efficiency. The reprogrammed cells show neuronal morphology, express neuron-specific markers, have a reprogrammed gene expression pattern and synaptic function. Further, the expression of this RNA is strongly upregulated during neuronal differentiation in both mouse and human stem cells and neuronal progenitor cell lines and is required for neuronal differentiation. In contrast, the level of the RNA is downregulated during the differentiation of

pluripotent cells into oligodendrocytes. Raising the expression level of the RNA in immature neuronal cells leads to enhanced neuronal differentiation, resulting in the development of longer neurites, a higher number of dendritic spines and synaptic densities. Together, these findings indicate that a long non-coding RNAs is a critical factor in neuronal differentiation program. Further, our findings prove that long non-coding RNAs can indeed play critical roles as master regulatory switches in differentiation and cell fate specification and provide the first instance of cellular reprogramming mediated by a long non-protein-coding RNA.

3:45 pm – 5:30 pm **Focus Session J**: Epigenetic Regulation

Linheng Li, Ph.D., Stowers Institute for Medical Research, "Niche, Signaling, and Epigenetic Regulation of Stem Cells"

Mono-allelic methylation, prenatal or maternal, at the imprinting gene loci remaining unchanged in postnatal somatic cells has been a dogma. Earlier studies from our laboratory have revealed expression of a cluster of imprinting genes, such as H19 and Gtl2, predominantly in the 'reserved' (or quiescent) compared to 'primed' (or active) hematopoietic stem cell (HSC) population, suggesting a role for these genes in regulation of HSC state and function. Since imprinting genes are regulated by differential methylated domains (DMD) and are mono-allelic in expression, we carried out experiments in animals with a conditional deletion of the DMD of the H19 imprinting gene in an allele specific manner and analyzed the corresponding phenotypic changes in hematopoiesis. Unlike inheritance of the deletion from the paternal allele ($H19^{\Delta DMD}$), inheritance of the deletion from the maternal allele resulted in sequential reduction in phenotypic quiescent long-term-HSCs (LSK $CD34^{-}Flk2^{-}$), then active short-term HSCs (LSK $CD34^{+}Flk2^{-}$), and eventual exhaustion of the absolute number of bone marrow cells with the aging of the mutant mice. Changes in phenotype were accompanied by compromised function as assessed by long-term engraftment assays. Mechanistically, downregulation of H19 due to removing the DMD region in the promoter led to reciprocal upregulation of IGF2 and an increase in its downstream phospho-FoxO, resulting in promoting the switching of quiescent $CD34^{-}Flk2^{-}$ LSK (LT-HSC) into active LSK $CD34^{+}Flk2^{-}$ LSK (ST-HSC) and further into $CD34^{+}Flk2^{+}$ LSK (MPP). At the epigenetic level, there was also a concomitant increase in hydroxyl-methylation in long-term stem cells. In conclusion, our data from a combination of genetic and functional approaches clearly demonstrate that genetic deletion of the H19-DMD region influences HSC fate and function.

Gokul Gopinathan, Ph.D., University of Illinois at Chicago, "High Throughput Histone Modification Profiling of Multipotent Odontogenic Stem Cells Reveals Distinct Epigenetic Signatures for Individual Neural Crest Derived Subpopulations"

The developing tooth is a complex organ comprised of a number of closely related, but seemingly different progenitor populations, all of them derived from the neural crest. While originally derived from the neural crest, these tissues nevertheless belong to different migratory subpopulations and are subjected to different transcriptional and environmental cues to ultimately develop into different target tissues. In previous studies we have demonstrated that the unique individual tissues of the developing tooth are characterized by corresponding marker genes which in turn are subjected to transcriptional regulators. In addition to the transcriptional machinery regulating individual levels of gene expression, dental progenitor genes are subjected

to epigenetic modes of regulation through DNA methylation and histone modification. Here we have asked the question how key genes involved in dental progenitor fate determination and tissue-specific gene expression are affected by active and inactive histone modifications. Using ChIP on chip promoter studies, we have generated genome-wide H3K4me3, H3K9me3 and K3K27me3 histone modification maps for human dental follicle (DF), pulp (DP), periodontal ligament (PDL), alveolar bone (AB) and cementum (CEM) progenitor cells. Our analysis demonstrated that many of the key genes involved in extracellular matrix secretion, cell adhesion, and osteogenesis were enriched for the active histone mark, H3K4me3. These included matrix molecules such as collagen I, III, V; growth factors such as TGFb2,3 and the SMAD2 intermediary, FGF9, as well as transcription factors such as DLX1,2 and Runx2. Other genes including CTGF and periostin were only selectively enriched in individual cell populations or repressed throughout, such as collagen II. In addition to static enrichment data, we have used chromatin immunoprecipitation assays and DNA methylation analyses to analyze epigenetic dynamics of select gene promoters upon induction. Together, our study is the first epigenetic state comparison of key odontogenic regulatory and structural genes between the major odontogenic progenitor lineages. Data from this analysis hold valuable insights both for developmental analysis and future craniofacial tissue engineering applications. Funding by NIDCR grant DE019463 is gratefully acknowledged.

Dean Betts, Ph.D., University of Western Ontario, "Alternative Splicing of Telomerase Reverse Transcriptase (Tert) in Human Embryonic Stem Cells"

Telomerase reverse transcriptase (TERT) is the catalytic component of telomerase and is necessary and sufficient to extend telomeres *in vitro*. The human TERT gene has at least 10 splice sites, giving as many as 1024 possible combinations. Alternative splicing of TERT has been observed to be widespread in various tissues, and particularly in many cancers. Stem cells possess many similarities to cancer cells, particularly in its up-regulation of telomerase. We present new data elucidating the behaviour of TERT splicing in human embryonic stem cells under varying culture conditions. Our results indicate microenvironments (2% oxygen) promoting pluripotency increases total TERT levels. High (21%) oxygen conditions decrease the levels of both total TERT and full-length (fl) TERT (flTERT) concomitantly with a decrease in pluripotency marker expression. Likewise spontaneous differentiation initiated by the addition of serum causes massive down-regulation of total and flTERT. However, down-regulation of total and flTERT occurs with a massive up-regulation of alternative splice forms including known alpha-, beta- and newly discovered splice variants of TERT. This alteration in TERT splicing is not random, and we present data that demonstrates that TERT isoforms play a significant extra-telomeric role in the process of pluripotency maintenance and differentiation. In addition, we present evidence for this using a newly generated antibody targeting beta-variant deletions and allowing measurement of the native expression of these splice forms. The authors acknowledge the financial support of CIHR and MITACS.

Ivan Maillard, M.D., Ph.D., University of Michigan Medical School, "Cooperative Effects of Trithorax Group Histone Methyltransferases in the Regulation of Hematopoietic Stem Cell Homeostasis"

Adult hematopoietic stem cells are maintained in a quiescent state protecting them from metabolic and genetic insults. This state of cell cycle arrest is acquired shortly after birth when fetal liver hematopoietic stem cells (HSCs) migrate to the bone marrow niche. While several bone marrow stromal factors have been implicated in promoting this cell cycle exit, factors contributing to the HSC-intrinsic molecular regulation of this phenomenon remain undefined.

Trithorax group genes were first identified in *Drosophila* as epigenetic regulators of *Homeobox* (*Hox*) gene expression. We have discovered that the mammalian Trithorax group gene *absent, small, or homeotic 1-like* (*ash1l*) is required for the maintenance of adult, but not fetal HSCs. Mice homozygous for a gene trap insertion into the first intron of *ash1l* (*GT/GT*) had a ca. 90% reduction in *ash1l* transcripts. These animals had normal numbers of phenotypic fetal liver HSCs, but a 5-10-fold reduction in bone marrow HSCs already by 6 weeks after birth. Both fetal liver and adult bone marrow were incapable of providing long-term reconstitution in lethally irradiated recipients, indicating that neither compartment could maintain detectable HSC activity in host BM. *GT/GT* bone marrow HSC depletion began in the first three weeks of life, the period during which HSCs enter quiescence. Cell cycle analysis revealed that *GT/GT* HSCs had an increased cycling fraction with a profound reduction in quiescent HSCs in the G0 phase of the cell cycle. Gene expression analysis showed decreased expression of the cyclin-dependent kinase inhibitors *p27Kip1* and *p57Kip2* in Ash1L-deficient HSCs. This suggested that *ash1l* is essential for establishing bone marrow HSC quiescence at the time of initial cell cycle exit. In addition, *GT/GT* hematopoietic progenitors showed decreased expression of multiple *Hox* genes, including *Hoxa7*, *Hoxa9*, *Hoxa10* and *Hoxb4*. *Hox* genes are also regulated by the mammalian *trithorax* homolog *Mixed Lineage Leukemia* (*MLL)*. Studies in *Drosophila* indicate that *ash1* works cooperatively with *trithorax*, a H3K4 methyltransferase, to facilitate *homeobox* gene expression. Thus, we evaluated a similar collaboration in mice deficient for *ash1l* and Menin, a factor required for proper MLL targeting to *Hox* loci. Strikingly, these animals rapidly progressed to hematopoietic failure with a complete obliteration of the HSC compartment, a phenotype not observed in either genetic background independently. These data suggest that Ash1l and MLL work cooperatively in hematopoiesis. *In vitro* data indicate that Ash1l is a histone 3 lysine 36 (H3K36) methyltransferase, a function associated with transcriptional activation. Together, our data are the first to indicate an essential function of *ash1l* in maintenance of adult HSCs and suggest that Ash1l functions as an H3K36 methyltransferase in cooperation with MLL's H3K4 methyltransferase activity.

Q. Tian Wang, Ph.D., University of Illinois at Chicago, "Epigenetic Regulation of Cardiac Development and Regeneration"

Cardiomyocytes proliferate extensively during fetal stages but permanently withdraw from cell cycle soon after birth. In the event of disease or injury, the adult heart has very limited capacity to repair itself. This is in contrast to other organs such as the liver, where hepatocytes retained regenerative capacity by their ability to re-enter the cell cycle. Regeneration could also be achieved by the proliferation and differentiation of adult stem/progenitor cells. This mechanism is used in the hematopoietic system, in which stem cells in the bone marrow constantly replenish

the differentiated blood cell types. Recent studies suggest that the adult epicardium harbors dormant progenitors that may be re-activated to produce new cardiomyocytes, albeit with low efficiency. Asxl2, a regulator of histone methylation and deubiquitination, is expressed in both the developing and adult heart. *Asxl2*$^{-/-}$ hearts undergo highly unusual postnatal growth that cannot be explained by cardiac hypertrophy. Interestingly, *Asxl2*$^{-/-}$ hearts exhibited up-regulation of proliferation markers and elevated proliferation index. Furthermore, Asxl2 plays a role in regulating the development and activity of epicardium. A better understanding of Asxl2 and its downstream molecular pathways has significant implications for cardiac repair and regeneration.

3:45 pm – 5:30 pm **Focus Session K**: Tissue Engineering

Mervin Yoder, M.D., University of Indiana, "Engineering Blood Vessel Formation and Repair"

While the vast majority of circulating endothelial cells in human peripheral blood represent dead or dying cells, reports over 4 decades have suggested that some viable cells with proliferative potential also circulate. We have developed methods to isolate, expand, and test the in vitro and in vivo properties of these viable clonogenic endothelial cells, we have termed endothelial colony forming cells (ECFC). We will review the fundamental properties of these cells and discuss the assays required to test for in vivo vessel forming ability. We will further examine potential methods to modulate the vessel forming potential of the ECFC in vivo and conclude with a review of recent published preclinical evidence that circulating ECFC play roles in vascular repair and regeneration. B1 and T cell lineages emerge from hemogenic endothelium prior to a stem cell precursor in the developing murine embryo; exceptions or contradictions to the stem cell theory of hematopoiesisThe stem cell theory of hematopoiesis predicts that all mature blood cell lineages are derived from pools of definable progenitor cell precursors that are all direct progeny of a single hematopoietic stem cell (HSC). Thus, to reconstitute a hematopoietic system in an animal that has been lethally irradiated, one must ultimately provide a HSC from which all the progenitors and mature blood cells emerge. Following this logic, one might anticipate that the first blood cells to emerge during embryogenesis might be the direct progeny of a HSC. However, we will review the data derived from the murine system which indicates that a variety of committed progenitor cells are the first cells to develop. Furthermore, a hemogenic endothelial precursor for the hematopoietic cells has been identified at multiple stages during murine development. Recently, we have identified B and T cell progenitor cells that are descendents of hemogenic endothelial cells resident in both the yolk sac and embryo proper that display the capacity to generate a variety of B and T cell subsets upon transplantation into immunodeficient newborn mice. Of interest, these lymphoid precursors emerge prior to the detection of the first HSC. In sum, the emerging evidence indicates that there is a progressive increase in the number and diversity of hematopoietic lineages that arise prior to the first HSC and only after that time does hematopoiesis follow the HSC theory.

Judith Fulton, Ph.D., Akron General Medical Center, "Wound Healing Using Progenitors, Natural Matrices and Cold Plasma"

Chronic wounds affect 6.5 million Americans with an annual price tag of $25 billion. During normal wound healing, resident progenitor cells facilitate regeneration of the epidermis; however, when skin cells are cultured and used for tissue engineering, normal skin is not generated. One advanced treatment option currently on the market is a tissue engineered skin

equivalent that serves as a temporary growth factor factory, but does not replace lost skin tissue. Factors affecting tissue repair include cells, matrix and environment. Cell populations are normally diverse and cross-talk between cell types is important. The extra cellular matrix provides the scaffold within which the cells function and communicate reciprocally. In addition, the extra cellular environment includes a wide variety of cytokines, small molecules and redox states that are also critical to tissue health. Non-thermal plasma is a new healing enhancing technology currently under investigation, which may target a variety of the factors involved in tissue repair.

Qi Li, Ph.D., University of Illinois at Chicago, "Lyophilization of PRF as a Strategy to Improve Cell Proliferation, Osteogenic Differentiation, and Tissue Integration for Craniofacial Tissue Engineering"

Platelet-rich fibrin (PRF) is a second generation platelet concentrate prepared from centrifuged blood without addition of thrombin and considered an improvement over its predecessor platelet-rich plasma (PRP). In recent years, there has been increased interest in the use of autologous PRF as a scaffold material for tissue engineering. So far, clinical applications of PRF have focused on the use of fresh PRF, requiring immediate or same-day transfer of plasma preparations into the patient. To address the issue of PRF storage and delayed clinical application, we have now focused on the use of lyophilized PRF. Freeze drying (lyophilization) is a commonly used process to improve the stability and long-term storage of proteins used for tissue regeneration. Freeze-dried protein-based materials not only have the advantage of better stability and storage, but also may have other biological benefits as scaffold materials for tissue engineering. In the present study we have examined the use of lyophilized PRF as a scaffold material for periodontal tissue regeneration. Here we have compared fresh and lyophilized PRF using microscopy as well as biological assays for migration, proliferation, mineralization, and gene expression. We also tested PRF scaffold properties in subcutaneous implants in nude mice. Our scanning microscopy studies demonstrated 10-fold larger pore size in lyophilized versus fresh PRF. While fresh PRF revealed a fiber-like appearance with 1µm pores, lyophilized PRF resembled a sponge containing 10µm diameter pores. In cell proliferation assays using PDL fibroblasts, dental follicle progenitors, and alveolar bone osteoblasts, both fresh and lyophilized PRF caused a gradual increase in cell density over a culture period of 7 days. Both fresh and lyophilized PRF resulted in higher proliferation rates than DMEM medium alone or platelet-poor plasma (PPP). However, after 6 and 7 days of culture, the lyophilized PRF induced increase in proliferation surpassed the fresh-PRF proliferation rate by 30-40% in all cell cultures examined. Migration assays revealed that both lyophilized and fresh PRF caused a highly significant ($P>0.0001$) approximately 15-fold increase in the number of migrated cells when compared to DMEM medium, while platelet-poor plasma (PPP) only caused a moderate 5-10 fold increase. Both fresh and lyophilized PRF demonstrated osteoconductive properties, exceeding those of PPP and DMEM in mineralization assays. Comparing the effects of fresh and lyophilized PRF on odontogenic periodontal progenitors, lyophilized PRF caused a dramatic increase in the osteogenic transcription factor Runx2, while PPP induced matrix gla protein (MGP) expression. In subcutaneous implants, fresh PRF largely remained intact and separated from proximal tissues while lyophilized PRF was penetrated by surrounding cells, resulting in improved tissue integration. Together, this study demonstrates the suitability of lyophilized PRF as a scaffold for

tissue engineering. Our data suggest that lyophilized surpasses fresh PRF as a scaffold material in terms of proliferation induction, osteogenic differentiation, and tissue integration.

3:45 pm – 5:30 pm **Focus Session L**: Biomaterials and Stem Cell Maintenance

Luis G. Villa-Diaz, Ph.D., University of Michigan, "Derivation of Transgene Integration-free Human Induced Pluripotent Stem Cells in Xeno-free and Synthetic Conditions"

Introduction. Advances in cell reprogramming have allowed the derivation of induced pluripotent stem cells (iPSCs) from somatic cells, which like embryonic stem cells (ESCs) have the potential to differentiate into all cell types. Human iPSCs have important implications for use in regenerative medicine. However, for their effective use in clinical applications, these cells must be derived using non-integrating transgenes vectors and cultured in xeno-free conditions.

Objective. To develop methods to derive human iPSCs in a transgene integration-free, xeno-free and synthetic environment.

Methods. Human fibroblast cell lines derived from gingival and foreskin tissue were reprogrammed into iPSCs by over-expression of Oct4, Sox2, c-Myc and Klf4 genes encoded in Sendai Virus (SeV) constructs. Five days post-infection, fibroblasts were subcultured in human cell conditioned medium (hCCM) and seeded onto a synthetic polymer (PMEDSAH)- or Matrigel-coated plates. Resulting human iPSC colonies were quantified and clonally expanded for further characterization.

Results. Nine days post-infection, the first iPSC colonies were observed and were positive for alkaline phosphatase (ALP) and Nanog expression, suggesting effective reprogramming. The overall reprogramming efficiency was less that 0.0001% and not different between parental cells lines and substrates (PMEDSAH and Matrigel). For each parental cell line, 2 colonies were selected for further expansion and characterization; one to grow on PMEDSAH while the other on Matrigel for over a period of 3 months. This resulted in 6 stable human iPSC lines that expressed human ESCs markers (Oct4, Sox2, TRA-1-60, TRA-1-81, SSEA3, SSEA4, Nanog and ALP activity). Cell lines derived/cultured on PMEDSAH were further expanded and characterized, and exhibited an un-methylated status of Oct4 and Nanog promoters. Furthermore, their genomic stability was demonstrated by karyotype analysis by a G-banding assay and aCGH analysis after 9 months in culture. In vitro and in vivo three germ layer differentiation validated their pluripotent status.

Discussion and conclusion. SeV is a negative sense single-stranded RNA virus that does not integrated in the host genome. PMEDSAH is a synthetic polymer coating that we previously demonstrated to support self-renewal of human ESCs. The results here demonstrate that PMEDSAH also supports derivation of human iPSCs. The combination of PMEDSAH with hCCM is an ideal xeno-free microenvironment, while culture on Matrigel or iMEF denotes animal contaminated conditions. The successful derivation and expansion of 3 transgene integration-free human iPSC lines from independent parental somatic cells in xeno-free conditions using SeV, hCCM and PMEDSAH, shows the strength that the combination of factors offer to derive clinical-grade human iPSCs.

Chenran Wang, Ph.D., University of Michigan, "FIP200 is Required for Maintenance and Differentiation of Postnatal Neural Stem Cells Through Regulation of Oxidative State"

Despite recent studies showing depletion of hematopoietic stem cells (HSCs) pool accompanied by increased intracellular ROS upon autophagy inhibition, it remains unknown whether autophagy is essential in the maintenance of other stem cells. Moreover, it is unclear whether and how the aberrant ROS increase causes depletion of stem cells, as they were not examined in previous studies on HSCs and a recent study indicates that a high level of ROS is required for self-renewal of neural stem cells (NSCs). Here, we report that ablation of *FIP200*, an essential gene for autophagy induction in mammalian cells, results in a progressive loss of NSC pool and impairment in neuronal differentiation specifically in the postnatal brain, but not the embryonic brain. The defect in maintaining the postnatal NSC pool was caused by p53-dependent cell cycle arrest and apoptotic responses in SVZ and SGZ of mutant mice. However, the impaired neuronal differentiation was rescued by anti-oxidant NAC treatment, but not by p53 inactivation *in vivo*. These data reveal a role of FIP200-mediated autophagy in the maintenance and functions of NSCs through regulation of oxidative state.

Xu Qian, Doctoral Candidate, University of Michigan, "Effects of Surface Thickness on the Ability of Synthetic Polymer Coatings to Support Human Embryonic Stem Cell Self-renewal"

Background- Poly [2-(methacryloyloxy) ethyl dimethyl-(3-sulfopropyl) ammonium hydroxide] (PMEDSAH), a fully defined synthetic polymer coating supports human embryonic stem (hES) cell expansion and self-renewal within completely defined culture conditions that are free from xenogeneic contamination. This synthetic coating offers multiple advantages compared to the commonly used conditions that include the use of mouse embryonic feeder cells (MEFs) and Matrigel ^{TM}. Hence, understanding the molecular mechanisms that maintain hES cell self-renewal on PMEDSAH is important and may further advance our knowledge of self-renewal of pluripotent stem cells and pave the way for clinical use of these cells. Recent evidence indicates that the physical properties of PMEDSAH can be impacted substantially by modifying the film surface thickness. Therefore, we hypothesize that physico-chemical properties such as surface thickness influence self-renewal of hES cells cultured on PMEDSAH.
Methods- PMEDSAH was modified by atom transfer radical polymerization (ATRP), a controlled radical polymerization method. In this method, increasing the reaction time of ATRP, results in greater PMEDSAH thickness. Single hES cells and hES cell clusters were cultured on both PMEDSAH and three types of modified PMEDSAH plates (thin, medium and thick). Cell adhesion, proliferation and self-renewal were assayed by determining the number and area of undifferentiated colonies among the different cell culture conditions.

Results- This study indicated that 1) single hES cells cultured on modified PMEDSAH with a medium surface thickness lead to a higher number of undifferentiated colonies compared to the other experimental groups; 2) hES cell clusters cultured on modified PMEDSAH with medium thickness have a higher number and larger area of undifferentiated colonies than the other experimental groups.
Conclusions- Surface thickness plays a crucial role in the ability of PMEDSAH to support hES cell self-renewal. Modifying the thickness of PMEDSAH surface coating may advance our current techniques of hES cell expansion and maintenance. (Supported by NIH 2R01DE016530-06 to PHK)

Katrina Fox, M.S., Kansas State University, College of Veterinary Medicine, "Comparing Methods for Cryopreservation of Rat Sperm with Intrauterine Insemination"

Artificial insemination and cryopreservation of sperm allows continuation of lines of animals while reducing the amount of animals housed in research facilities. It permits long term storage of these lines, as well as eases the transportation of the lines to other research facilities. This is vital to supporting stem cell research that utilizes some of the less common rat strains. Thus far, only one other group has been successful in creating live pups via sperm cryopreservation and surgical intrauterine insemination. There have been other advances in cryopreservation media that improves sperm motility post-thawing, but no live pups resulted from this work. In this study, two cryopreservation media were utilized to perform intrauterine inseminations with both fresh samples of sperm as well as samples that were cryopreserved in liquid nitrogen. Utilizing fresh epidiymal spermatozoa in Sprague-Dawley rats, the Nakatsukasa media produced 13 pups in 3 litters from 4 inseminations. Yamashiro media without dbcAMP added produced 20 pups in 3 litters from 4 inseminations. When dbcAMP was added to the Yamashiro media, 4 pups were produced in 2 litters from 4 inseminations (fourth insemination is pending ultrasound confirmation on August 6 with pups expected August 15). Fresh sperm inseminations were also performed utilizing Nakatsukasa media in Fischer 344 rats and Beta-galactose transgenic rats (pups expected August 15 and August 1 respectively). Epidiymal sperm was then collected into the various media and frozen in liquid nitrogen. At this point, we have been unable to maintain motility following thawing, but are continuing to optimize the process and will perform inseminations when motile samples are obtained. Sperm parameters are compared prior to freezing as well as post-thawing using CASA software as well as live/dead sperm staining. We also explored pharmacoejaculation as a means to obtain spermatozoa without euthanizing the male to collect the epididymis, but were unable to obtain a sample large enough or consistently enough to utilize it in intrauterine inseminations. Further development of these techniques will allow for advances to be made in stem cell research.

Bradly Alicea, Doctoral Candidate, Michigan State University, "Simulating the Dynamic Regulation of a Cell: Relevance to Cell Reprogramming"

The field of cellular reprogramming (converting one cell type into another) involves many changes to the input cell. Some of these involve changes in translation, cell cycle, and physiological state. How do we simulate these changes in an entire cell population? To accomplish this, we have developed a technique that combines drug treatment, looking at different RNA fractions, and mathematical modeling. Using three drug treatments (Mitomycin C, Actinomycin D, and Saporin), we were able to knock-down cell cycle, protein synthesis, and ribosomal function, respectively. After drug treatment, time-series measurements of RNA were assayed. We isolated and quantified two fractions of RNA: transcription-associated RNA (transcriptome) and translation-associated RNA (translatome) for each time point. We then constructed a control systems model based on the RNA quantifications, which were used to characterize the dynamic aspects of regulatory changes associated with the environmental stimulus for selected genes (see Figure 1).

We found that over the course of 72-96 hours post-treatment, the RNA profiles for each gene respond in a stimulus- and function-specific manner. Differences were observed between the transcriptome and translatome, with decay being accelerated in the translatome. However, in some cases, aggregation in the translatome occurs. Our analysis also explores the differences between genes specific to various phenotypes and functions (e.g. cell-specific genes vs. non-specific genes). To do this, we calculated decay rate using curve-fitting techniques and conducted a bivariate analysis of decay. The control systems model was then used to infer the course-grained dynamics of RNA regulation in the cell due to mechanism alteration. Future directions involve applying this experimental approach and model to cells during the course of direct cellular reprogramming to observe the consequences of active phenotypic remodeling during conversion of fibroblasts to iPS (induced pluripotent stem) and iN (induced neural) cells.

Ying Nie, Ph.D., Lonza Walkersville, Inc., "A Novel cGMP-compliant Method for Passaging of Human Pluripotent Stem Cells"

Advancing pluripotent stem cell research to clinical applications requires adapting laboratory-scale cultivation methods to large-scale manufacturing platforms. As a first step, we looked to improve upon existing methods for passaging adherent human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs). Current practices are labor intensive and highly dependent on the proficiency of skilled technical personnel. In addition, these methods result in substantial loss of cells due to post-detachment cell death. Several alternative methods have been proposed and include the use of enzymes to dissociate hESCs and hiPSCs to single cells. However, continuous cultivation using single cell passaging methods often promotes chromosomal aneuploidy and aberrant gene expression.

To improve upon these existing methods, we developed a chemically-defined, non-enzymatic cell detachment formulation that permits non-mechanical harvesting of multicellular colony fragments. This reagent gently dislodges adherent hESCs and hiPSCs from their substrate and promotes high post-detachment viability (97% +1%) as well as plating efficiency (47% +5%). We have further demonstrated that cells can be cultured for over 25 passages while maintaining pluripotency. Moreover, no morphological or genetic abnormalities were observed. In conclusion, continuous cultivation of hESCs and iPSCs using this method permits streamlining of cell culture processes for both small- and large-scale applications.

6:30 pm – 7:10 pm: **Dinner Lecture**

Mahendra Rao, M.D., Ph.D., Director, Center for Regenerative Medicine, NIH, "Regenerative Medicine – An International Perspective"

Activity in the Regenerative Medicine field is not simply occurring in the United States or Europe but rather seems to be evolving along distinct paths in different countries.
I will discuss examples of how regulations in different countries have altered the field. I will use examples from the cosmeceutical industry, clinical trials organizations, the cord blood banking industry and the regulatory processes for cells, devices and combination products.

Sunday, October 7, 2012

8:00 am – 10:00 am **Plenary Session IV**: Special Topics in Translational and Stem Cell Therapy II

Gary Hammer, M.D., Ph.D., University of Michigan Medical School, "Translation of Adrenal Stem Cells"

Our laboratory focuses on the underpinnings of adrenocortical growth in development and disease. Molecular approaches to signaling and transcriptional activation are combined with whole animal biology to characterize the mechanisms by which adrenocortical stem/progenitor cell populations in the adrenal capsule/cortical unit are established and maintained. We aim to understand how altered regulation of these cells contributes to adrenocortical hypoplasias, dysplasias and cancer. Ongoing molecular studies detail the mechanisms by which a variety of these signals mediate SF1 transcription and activation, thereby providing a layer of regulatory control over organ homeostasis. Studies have provided a paradigm by which self-renewal pathways (WNT, NOTCH, SHH and IGF2) regulate the stem/progenitor pools of the adrenal cortex. With collaborators, we are investigating how these and other pathways contribute to adrenal failure and adrenal tumorigenesis and aim to use new targeted biological‐based therapies designed against these stem/progenitor signatures to treat disease.

Mark Weiss, Ph.D., Kansas State University, "PiggyBac Transposon Mutagenesis in Rat Embryonic Stem Cells"

Using a piggyBac transposon vector (PB) for insertation mutagenesis, we created gene trap rat embryonic stem cells (ESCs). A single transfection protocol introduced both PB and transposase via lipofection into ESCs. ESCs with the transposon insertions express TdTomato and were selected by antibiotic resistance gene introduced by the transposon. Twenty ESC clones out of approximately two hundred produced were expanded and cryopreserved. Two ESC clones were randomly selected for karyotyping and blastocyst injection. Both the first clone and the second clone produced chimeric rats and may transmit via the germline since TdTomato-positive sperm were observed and since PCR for genomic DNA collected from sperm revealed the presence of PB. Germline transmission was shown by the second clone; however, PCR confirmation of PB in genomic DNA from the heterozygote is pending. By adjusting the PB and transposase concentrations it is possible to modify the number of PB insertions. In the present experiment, 36 PB insertions were found in clone 1 (with 3-4 gene traps) and 15 insertions in clone 2 (and 1-2 gene traps). In clone 2, the gene Nrg3 (a neural specific gene) was trapped, but further testing revealed that PB is in the incorrect orientation. Since about 200 clones were produced by a single transfection, and since Splinkerette PCR can rapidly screen insertion sites, this method lends itself to producing a bank of ESCs with known traps, similar to the strategy in the knockout mouse project (KOMP). Following checking ESCs out of the bank, the ESCs can be expanded and rapidly produce gene trap knockout rats for phenotyping and functional genomics. In the present project, the time from PB transfection to the production of the F1 containing the PB vector was 5-6 months. Therefore, this method has the potential to rapidly deliver KO rats for functional genomic screening.

Dan Kaufman, M.D., Ph.D., University of Minnesota, "Human Pluripotent Stem Cell-derived Natural Killer Cells to Treat Cancer and HIV/AIDS"

Previous studies by our group have demonstrated derivation of natural killer (NK) cells from human embryonic stem cells (hESCs) and induced pluripotent stem cells (iPSCs). These hESC and iPSC-derived NK cells have potent ability to kill diverse tumor cell types and HIV-infected cells both in vitro and in vivo (using xenograft models). We now aim to produce "off-the-shelf" product for anti-tumor immunotherapy, rather than needing to obtain NK cells from donors on a patient-specific basis. To reach this goal, we have now used a new completely defined culture system suitable for clinical scale-up to produce large numbers of hESC and iPSC-derived NK cells. Using a combination of embryoid body formation in defined media and IL21 expressing artificial antigen presenting cells, one plate of undifferentiated hESCs or iPSCs (typically with 5-10 x 10^6 undifferentiated cells) can serve as the starting point to treat several patients. These studies demonstrate clinical translation of hESC and/or iPSC-derived NK cells for treatment of refractory malignancies and chronic infections is now very feasible.

Rasul Chaudhry, Ph.D., OU-WB ISCRM, Oakland University, "Retinal Regeneration"

Late onset macular degeneration, which causes a loss of retinal tissue function, is one of the most common causes of blindness in the United States affecting over 6 million Americans. There are two types of late onset macular degeneration: 1) Dry, which is a slow sloughing off of retinal tissue and 2) Wet, an abnormal growth of blood vessels into other layers causing rupture of the vessels. There is no effective treatment or a cure for this debilitating disease. The goal of our research is to investigate the potential of embryonic stem cells (ESCs) and adult stem cells (ASCs) to rescue macular degeneration. Our hypothesis is that stem cell-derived neural progenitors can differentiate and replace or regenerate damaged tissue directed by the retinal microenvironment. In our earlier studies, we tested our hypothesis using murine ESCs tagged with transgenic expression of yellow fluorescent protein (YFP) as a reporter in a mouse model homozygous for the Rpe65/rd12 mutation that expresses itself as a time progressive degenerative retinal disease. The YFP-tagged murine ESCs were induced to differentiate into neural lineage in vitro. Both ESC and the neural derivatives were injected into 5-weeks old mice vitreous. At pre-determined intervals, mice were euthanized by following the IACUC guidelines and the eyes were removed for examination by fluorescent microscopy of whole mount or cryostat sections of the retina and molecular analysis of retinal tissue. The results from microscopic observations of the whole mounts and cryostat sections of the retinal tissue indicated that both mouse ESCs and differentiated cells of neural lineage attached to the retinal surface, survived and proliferated in the vitreous environment. In addition, the injected cells further differentiated into specific neural cells including neuron, oligodendrocytes and astrocytes as well as integrated into retinal tissue as evident from the immunohistochemical analysis. Analysis of the retinal tissue using reverse transcriptase-polymerase chain reaction (RT-PCR) showed expression of neural lineage-specific markers such as nestin, and Mbp but not oct-4 suggesting that injected ESCs differentiated in the vitreous environment. More recent studies are focused on differentiating cord blood stem cells (CBSCs) into neuroprogenitors and testing them into the animal model. Preliminary results of these studies and a review of application of ESCs will be presented.

Vilma Yuzbasiyan-Gurkan, Ph.D., Michigan State University, "Evaluation of OCT4 expression as a cancer stem cell marker in canine and human osteosarcoma: Insights and challenges"

Osteosarcoma (OS) is a challenging tumor that causes morbidity and mortality in humans and dogs. It is the most common primary bone tumor in both species. Canine OS closely resembles human OS in terms of clinical and molecular features, histopathological appearance, and response to therapies. Thus, canine OS is an excellent spontaneous tumor model for translational studies on biology of OS as well as for therapeutic targeting. The tumors are highly resistant to conventional chemo-and radiotherapies in both species, and are composed of a varying proportion of undifferentiated and differentiated cell types of mesenchymal lineages. These attributes make OS as a good candidate for being a cancer driven by stem cells. Cancer stem cells (CSCs), cells comprising the tumor-initiating fraction of a tumor, have been proposed to express the pluripotency-associated transcription factor, OCT4, the product of POU5F1, POU class 5 homeobox 1 gene. We have used various approaches to test this hypothesis in canine and human OS cell lines and in xenotransplantation studies. Our findings indicate that the OCT4 positive cells are present in both canine and human OS cell lines. While OCT4 positive and negative subpopulations of cells have discrete biological behaviors, our studies point to interactions between these populations. Therefore, designing a therapy against a particular subpopulation of tumor cells may not translate into successful clinical outcome, and all subpopulations of tumor initiating cells need to be identified and targeted for successful treatment. Spontaneously occurring canine malignancies are useful model systems to probe the biology of such complex interactions and for establishing novel approaches to treatment of these diseases.

10:15 am – 12:00 noon Focus **Session M**: Disease Models

Jack Mosher, Ph.D., University of Michigan Center for Stem Cell Biology, "Modeling Ewing's Sarcoma with Neural Crest Stem Cells"

Ewing's sarcoma (ES) is a highly malignant bone and soft tissue tumor that primarily affects children and young adults. These tumors are characterized by chromosomal translocations, most commonly t(11;22)(q24;q12), which generates the EWS-FLI1 fusion oncogene. Although the presence of this translocation is well established, the origin of the cell from which ES arises is not. One candidate is neural crest stem cells (NCSCs). Although ES tumors arise primarily in bone and soft tissue they have features consistent with a neuroectodermal origin such as the expression of early neural markers, neurosecretory granules and the upregulation of many neural crest genes. Additionally, lineage-tracing experiments have identified NCSCs in the bone marrow of mice. To assess the potential of NCSCs as the cell or origin for ES we are testing whether fetal and adult mouse NCSCs can tolerate EWS-FLI1 and to what extent its expression leads to ES-like changes. This assay will provide insight into the origins of ES and allow for the further genetic dissection of events important for ES tumorigenesis.

Graham Parker, Ph.D., Wayne State University School of Medicine, "Advancing Spinal Muscular Atrophy Interventions Using Stem Cell Research"

Stem cell research offers the ability both to study development and the nascent potential to develop therapeutics. By their very intractability, few areas of potential stem cell therapy have engendered more excitement and investment as neurological disorders. This presentation will review our recent findings that relate to spinal muscular atrophy, an autosomal recessive motor

neuron disease caused by a genetic defect carried by as many as one in 75 people. Using in vitro and in vivo models of neuromuscular disorders to identify gene and pharmacologic therapeutic targets to treat or cure Spinal Muscular Atrophy.

Craig Atwood, Ph.D., University of Wisconsin Medical Center, "Human Embryonic Stem Cells as a Model System for Understanding Alzheimer's Disease: The Role of the Amyloid-beta Precursor Protein in the Differentiation of Neurons"

The amyloid-β precursor protein (AβPP) is a ubiquitously expressed transmembrane protein whose cleavage product, the amyloid-β (Aβ) protein, deposits in amyloid plaques in neurodegenerative conditions such as Alzheimer's disease (AD), Down syndrome (DS) and head injury. We have found that this protein, and all the known secretase enzymes that cleave AβPP, are expressed by human embryonic stem cells (hESC). The differential processing of AβPP via secretase enzymes regulates the proliferation and differentiation of hESC. hESCs endogenously produce A β, which when added exogenously in soluble and fibrillar forms but not oligomeric forms, markedly increases hESC proliferation. The inhibition of AβPP cleavage by β -secretase inhibitors significantly suppresses hESC proliferation and promotes nestin expression, an early marker of neural precursor cell (NPC) formation. The induction of NPC differentiation via the non-amyloidogenic pathway was confirmed by the addition of secreted AβPPβ, which suppresses hESC proliferation and promotes the formation of NPC. Together, these data suggest that the differential processing of AβPP is normally required for embryonic neurogenesis.

Sumi Dinda Ph.D., Oakland University, "Differentiation and proliferation of embryonic stem cells by hormonal regulation."

Estrogen (E_2) and progesterone are major steroids known to play an important role in the normal growth and differentiation of breast and uterine cells in women. E_2 is a proliferative hormone and progesterone is a differentiating hormone in the uterus, while estradiol and progesterone both have proliferative effects on breast epithelium cells. Testosterone (dihydrotestosterone) is known to influence many reproductive functions, protein metabolism, muscle building and other functions. These steroids influence physiological processes by initially interacting via cognate receptors which act as transcription factors influencing the hormone-responsive genes. The use of estrogen and progesterone replacement therapy for postmenopausal symptoms has been implicated in increasing the risks of breast and uterine cancers. Testosterone may have a role in breast or uterine cancers which is not clearly understood. However, the precise roles of sex hormones during embryonic development are not completely elucidated. In order to understand the developmental effects and molecular regulation of sex steroids, we have used embryonic stem cells (ESCs) as a model system, which mimic early embryonic development. We have examined the effects of E_2, progesterone, dihydrotestosterone, anti-estrogen (ICI 182,780) and anti-progesterone (Ru-486) on the proliferation and differentiation of ESCs. Our results demonstrated a higher rate of differentiation of ESCs when treated with a combination of hormones, estrogen and progesterone, and individually, progesterone and dihydrotestosterone, in a concentration dependent manner (1 nm to 1uM) as compared with the untreated controls. These proliferative and differentiative properties were inhibited by treatment with anti-hormones. A rapid rate of differentiation and proliferation (2 to 3 fold) of retinoic acid (RA) treated embryoid bodies (EBs) derived from ESCs were observed in the presence of estrogen, progesterone, or

dihydrotestosterone. Our observation also suggests an increased expression of estrogen receptors in the EBs treated with progesterone.

Andrew M. Tidball, Doctoral Candidate, Vanderbilt University, "Selective Metal Sensitivity in hiPSC–derived Neural Progenitors from a Preclinical Parkinson's Disease Patient"

A constellation of environmental and genetic risk factors for Parkinson's disease (PD) are thought to modify disease onset and progression in a patient-specific manner. We sought to assess interactions between these factors in a human subject with preclinical PD by measuring toxicological sensitivities to PD-relevant environmental toxicants in neural cultures derived from that subject.

Human induced pluripotent stem cells (hiPSCs) were generated from patient SM and healthy control subjects to allow differentiation of patient-specific neural progenitor cells (NPCs). The patient (SM) has biallelic mutations to *PARK2* yet lacks parkinsonian motor symptoms by neurological exam, while the healthy controls (CA and CB) have no known PD genetic risk factors. We assessed the sensitivity of these NPCs cultures to heavy metal cytotoxicity and mitochondrial-related phenotypes. DaTscan imaging of the patient (SM) revealed preclinical PD consistent with biallelic *PARK2* mutations. SM NPCs but not the patient's primary fibroblasts were significantly more sensitive to copper and cadmium cytotoxicity than those derived from controls. No differences in cellular copper accumulation were observed. However, SM NPCs exhibit increased cellular ROS accumulation and enhanced mitochondrial fragmentation and depolarization following copper exposure versus controls.

Given the role of *PARK2* in mitochondrial integrity, we hypothesized that heightened sensitivity of SM NPCs to copper was due to enhanced mitochondrial-related abnormalities after exposure. Our results suggest that PD genetic risk factors may increase sensitivity to a subset of environmental risk factors. Furthermore, we demonstrate that hiPSC technology can detect subject-specific differences in vulnerability to PD-environmental risk factors.

10:15 am – 12:00 pm **Focus Session N**: Biobanking

Erik Forsberg, Ph.D., WiCell Research Institute and the University of Wisconsin-Madison, "Challenges of Making, Banking and Distributing Pluripotent Stem Cells"

The number of pluripotent stem cell lines is expected to grow rapidly, primarily due to increasing public and private funding for the creation of iPS cells for use as disease models. However, the usefulness of the thousands of iPS cell lines that will likely be generated will depend on many factors including the method and thoroughness of reprogramming, the extent of pre- and post-reprogramming characterization, their ease of culture, their genetic stability, their ability to differentiate into cell types of interest, and their availability and cost. To achieve a reasonable level of quality and consistency, standardization of protocols, tests, and documentation will be important. Another challenge will be how to make iPS cell lines available for wide distribution to academic, non-profit and commercial organizations. Who pays for banking and testing the cells, how much the cells cost, and how material and intellectual property rights will be protected are examples of questions that need to be addressed by funding agencies and organizations that

generate the cell lines. Banking and distribution models for pluripotent stem cells exists (for example the WISC Bank at WiCell) but will need to be modified to accommodate the much larger number of iPS cell lines that will be generated.

George Wilson, Ph.D., Beaumont BioBank, "Multidisciplinary Translational Research Facility"

The Beaumont BioBank was established in October 2008 and was developed to create a research resource that promotes and facilitates Translational Research without all the traditional barriers and silo mentality that can exist in large Academic Institutions with their inevitable bureaucratic organization. The cornerstone was to develop a system which was easy for clinical investigators to appreciate and to use such that they could undertake Translational Research in a quick, efficient and productive way and exploit the huge repository of patients within the Beaumont Health System. Therefore, the BioBank developed an alternative approach that combined high quality, well annotated biobanking across multiple clinical specialties with state-of-the-art technologies to undertake research all under a single entity. The integration of the biobanking function with the associated clinician-driven translational research provides a seamless process to accelerate the overall goal of advancing personalized medicine. Stem cell banking represents a challenge for a multidisciplinary biobank due to the constraint that specimens are usually required to be utilized by the investigator as quickly as possible. The BioBank at Beaumont is set up to use a generic consent form that can be applied to any patient in which they are consenting to donate their specimen to future unspecified research. The vast majority of specimens are collected, processed and stored. Once stored the samples are considered as retrospective and this facilitates the research/analysis phase which can carried out with an expedited IRB application. We have established a system where investigators from OU, interested in stem cell research, could access specimens at Beaumont. The procedure involves partnering with a Beaumont clinician through a contract, establishing IRBs at both Institutions, A data use agreement is signed by senior members of research administration at both Institutions and an approved waiver of authorization is in place. Once this is established specimens are collected, deidentified and entered into the BioBank informatics system, a "pick" list is immediately generated and specimens are signed out through a Material Transfer Agreement, placed in the appropriate transfer receptacle and transported to Oakland University. Currently, there are two approved collections for stem cells, one from bone marrow aspirates of patients with acute lymphoblastic leukemia and the other for umbilical cord at delivery.

Dan O'Donnell, Fisher Biosciences, "Logistical Considerations for Biologic Product Storage and Transport"

An overview of how product and clinical trial design impact the distribution and logistical requirements for phase II and phase III clinical trials. Decisions made in the early stages of product development can have a profound effect on the cost and efficiency of delivering cell based products to investigative sites and ultimately commercial distribution. The primary focus of the discussion is to identify those key decision points, weigh options and understand the implications of the choices available.

10:15 am – 12:00 pm **Focus Session O**: Political, Ethical, and Regulatory: Panel Discussion

Bernard Siegel, J.D., Genetics Policy Institute

Ernest F. Krug, III, M.Div., M.D., FAAP, OUWB School of Medicine "Stem cell research: what does our humanity require of us"

Stem cell research and regenerative medicine are a constantly changing landscape as new discoveries and therapeutic advances impact our thinking about this endeavor as a moral enterprise. Accepting the premise that we are all moral agents with choices to make, relevant moral values needing our consideration will be outlined. The Beaumont Health System's policy on human embryonic stem cell research will be described, and some persistent ethical concerns will be noted. Finally, I will suggest that issues of social justice are the most compelling to insure that the choices made in stem cell research and its clinical application are the desired reflection of our humanity.

10:15 am – 12:00 pm **Focus Session P**: Applications of Stem Cell Therapy

Chunying Li, Ph.D., Wayne State University School of Medicine, "A Critical Role of CXCR2 PDZ–mediated Interactions in Endothelial Progenitor Cell Neovascularization"

Bone marrow (BM)-derived endothelial progenitor cells (EPCs), circulating in peripheral blood, migrate toward target tissues, differentiate, and contribute to the formation of new vessels in response to a variety of growth factors and cytokines. Transplantation studies have revealed that EPCs incorporate into active neovasculature in ischemic tissues and growing tumors. Therefore, EPCs have been exploited for establishing new intervention strategies for therapeutic neovascularization (as in ischemia) and angiogenesis-dependent diseases (such as cancer). It has been reported that the chemokine receptor CXCR2 and its cognate ligands mediate EPC recruitment and angiogenesis in injured endothelium, ischemic myocardium, and allergic airway. CXCR2 possesses a consensus PDZ (**P**SD-95/**D**lgA/**Z**O-1) motif at their carboxyl termini, and the PDZ motif has been reported to modulate post-endocytic sorting and cellular chemotaxis. In a recent study, we demonstrated that the PDZ motif of CXCR2 plays an important role in regulating neutrophil functions as disrupting PDZ motif-dependent interactions significantly inhibited CXCR2-mediated neutrophil functions (Wu et al., 2012).

Here, using the isolated BM-derived EPCs, we first examined the effects of CXCR2 blockade on EPC *in vitro* migratory and angiogenic activities. We observed that CXCR2 blockade by anti-CXCR2 antiserum or CXCR2 antagonist (SB225002) significantly inhibited EPC migration, adhesion, invasion, and EPC *in vitro* incorporation into endothelial tubule network in response to CXCR2 ligands, but not to CXCR4 ligand CXCL12 or VEGF. To elucidate the potential role of the PDZ motif in CXCR2-mediated EPC motility and angiogenesis, we delivered an exogenous CXCR2 C-tail peptide or DNA construct (encoding the CXCR2 PDZ motif -TTL) into EPCs and monitored EPC functions. We observed that the synthetic CXCR2 C-tail peptide or DNA construct exhibited significant inhibitory effects on EPC *in vitro* migratory responses and angiogenic activities, CXCR2-mediated cell signaling (i.e., intracellular calcium mobilization), as well as EPC *in vivo* incorporation and angiogenesis in a Matrigel plug mouse model. However, the CXCR2 C-tail that lacks the PDZ motif (ΔTTL) did not cause any significant changes in EPC *in vitro* and *in vivo* functions. In addition, using pull-down and co-immunoprecipitation, we demonstrated that the PDZ scaffold protein NHERF specifically interacts with CXCR2 and its downstream effector, PLC-β, in EPCs. This suggests that NHERF

might cluster CXCR2 and its relevant signaling molecules (such as PLC-β) into a PDZ motif-dependent macromolecular complex, which could form the basis for CXCR2-mediated EPC homing and angiogenesis. Taken together, our data revealed a critial role of a CXCR2 macromolecular complex mediated by PDZ-based interations in EPC homing and angiogenesis, suggesting that targeting the PDZ-based CXCR2 complex might be a novel and effective strategy to treat angiogenesis-dependent diseases (such as tumors).

Chien-Wen Chen, M.D., Ph.D., University of Pittsburgh, "Human Pericytes: The Anti–fibrotic, Anti–inflammatory, and Angiogenic Roles for the Treatment of Myocardial Infarction"

Introduction: Microvascular pericytes purified from multiple human organs possess multipotency and repair/regenerate defective tissues, notably skeletal muscle. However, pericytes' ability to repair the ischemic heart remains unknown. This study aims to examine the therapeutic potential of human skeletal muscle derived microvascular pericytes and associated mechanisms of action in a murine myocardial infarction (MI) model.

Methods and Results: Cultured human $CD146^{+}/34^{-}/45^{-}/56^{-}$ pericytes were injected into acutely infarcted myocardium of immunodeficient mice (3.0×10^{5} cells). Echocardiographic analysis of pericyte-treated hearts revealed reduced left ventricular dilatation and significant improvement in cardiac contractility for up to 8 weeks when compared to PBS-injected controls. Moreover, pericyte-treated hearts exhibited significantly better cardiac function when compared to hearts treated with CD56+ myogenic progenitor cells purified from the same adult muscle biopsy. Host angiogenesis was significantly increased by 42.8% and 33.2% around and within the infarct area respectively. Vascular support by pericytes was illustrated by their perivascular homing in vivo and the formation of capillary networks with/without endothelial cells in two- and 3-dimensional co-cultures. Under hypoxia, human pericytes dramatically increased expression of VEGF-A, PDGF-β, TGF-β1 and corresponding receptors while expression of bFGF, HGF, EGF, and Ang-1 was repressed. Nearly no Ang-2 secretion was detected. High expression of MMP-2, but not MMP-9, by pericytes was observed in hypoxic cultures. Pericyte treatment substantially reduced myocardial fibrosis by 45.3% and significantly diminished focal infiltration of host inflammatory cells at the infarct site. Furthermore, hypoxic pericyte-conditioned medium suppressed fibroblast proliferation and inhibited monocyte/macrophage proliferation in vitro. High expression of immunoregulatory molecules by pericytes, including IL-6, LIF, COX-2 and HMOX-1, was sustained under hypoxia, except MCP-1. Little expression of IL-1α as well as no expression of IL-4, IL-10, iNOS, 2,3-IDO, TNFα, and IFNγ by pericytes were detected under both normoxic and hypoxic conditions. Finally, GFP-based cell tracking revealed that pericytes differentiate into and/or fuse with cardiomyocytes, endothelial and smooth muscle cells, though to a very minor extent.

Conclusion: Intramyocardial transplantation of pericytes promotes functional and structural recovery after acute MI, presumably attributable to multiple restorative mechanisms involving indirect paracrine effects and direct cellular interactions.

Financial Disclosure: Commonwealth of Pennsylvania (B.P.), R01AR49684 (J.H.), R21HL083057 (B.P.), and AHA predoctoral fellowship (C.W.C.). J.H. received remuneration from Cook MyoSite, Inc. for consulting services and for royalties received from technology

licensing during the period that the above research was performed. All other authors have no conflict of interest to disclose.

Anna Sonstegard B.S., University of Minnesota, "Intra–arterial Infusion of Human UCSCs in Rats 48 Hours after Middle Cerebral Artery Stroke"

Previously, we have demonstrated a beneficial therapeutic effect of human umbilical cord stem cells (UCSCs) delivered intravenously (IV) for the treatment of brain ischemia. In control groups significant neurological deficits are observed after temporary occlusion (1 hour) of the right middle cerebral artery (MCAO). Animals treated 48 hours after occlusion, however, with human UCSCs administered intravenously demonstrate significant improvement in the neurological severity score (NSS) and smaller infarct volume by 4 weeks. Interestingly, most of the infused cells are sequestered in the peripheral organs such as lungs and spleen, with few cells reaching the penumbra region of ischemia. Presuming that treatment effect is either reflected by the number of infused cells reaching the brain or circulating in the cerebral arterial system we hypothesis that intra-arterial (IA) delivery directly into the carotid artery will result in better therapeutic effects.
In the following study we performed a dose escalation study in which we will first determine the equivalent IA dosage via a catheter injection, then, compared three doses to our previous IV dosage. We then monitor for improved neurological deficits and decreased infarct size. Intra-arterial (IA) administration has the potential of circumventing problems associated with intravenous injection. We believe that lower cell concentrations with an IA injection still promote behavioral recovery and decrease infarct size and may have more beneficial effects.

Tristan Maerz, M.S., Beaumont Health System, "Tissue Engineering of the Intervertebral Disc: In Vitro and In Vivo Studies of Combinations of a Natural Hydrogel, Morphogenic Growth Factors, a Proteinase Inhibitor, and Allogenic Mesenchymal Stem Cells"

Introduction – Considerable research is underway to devise a biologic strategy aimed at regenerating the intervertebral disc. Many of these strategies address the anabolic needs of disc regeneration with a single growth factor, and do not address the considerable inflammatory and degenerative environment with an injured or diseased disc. The aim of this study was to investigate the *in vitro* and *in vivo* efficacy of a combination of anabolic growth factors (TGF-b_3 and BMP-4) and a proteinase inhibitor (TIMP-2) to induce de novo disc tissue formation when delivered directly to cells *in vitro* or via a Chitosan hydrogel following acute nucleotomy in a rabbit. In addition, the effect of rabbit allogenic bone-marrow (BM) derived stem cells in combination with this therapy is also explored.

Materials & Methods – In the *in vitro* portion of this study, normal human articular chondrocytes(nHAC), a model cell type for intervertebral disc-like cells, were treated with the following combinations of transforming growth factor-β3 (TGF- β3), bone morphogenetic protein-4 (BMP-4) and tissue inhibitor of matrix metalloproteinase-2 (TIMP-2): 1) TGF- β3 2) BMP-4 3) TIMP-2 4) TGF- β3 + BMP-4 5) TGF- β3 + TIMP-2 6) BMP-4 + TIMP-2 7) TGF- β3 + BMP-4 + TIMP-2. Gene expression of Collagen1a1, Collagen2a1, Collagen10a1, and Aggrecan, and glycosaminoglycan (GAG) concentrations were assessed at 24 hrs, 72 hrs, and 7 days. Immunocytochemistry staining was performed at 72 hrs. Rabbit bone marrow-derived stem cells were obtained by aspirating 3-4 mL of bone marrow from the femur and tibiae of three

rabbits, performing two consecutive red blood cell lyses, and plating them in tissue culture flasks in DMEM containing 10% FBS, 1% Pen/Strp. Non-adherent cells were removed after 24 hrs and remaining cells were a heterogeneous cell population previously shown to include many multipotent stem cells. The multipotency of these cells were assessed with bi-lineage differentiation assays and structural stains to quantify mineralization (osteoblastic) and proteoglycan production (chondroblastic). Staining was assessed and quantified at 14 and 21 days.

In the *in vivo* investigation, 30 New Zealand White rabbits underwent a percutaneous nucleotomy of L3-L4 and L1-L2 under fluoroscopy using an 18G spinal needle. The nucleotomized levels were randomized to serve either as the defect-only control, or to receive an percutaneous injection of a Chitosan hydrogel containing either TGF- β_3 + BMP-4, or TGF- β_3 +BMP-4 + TIMP-2, or no growth factors into the disc space. Half the rabbits also received 5 x 10^5 BM cells via direct injection into the nucleus. Lumbar spines were harvested *en bloc* after six weeks and subjected to magnetic resonance imaging with a 3T clinical scanner. T2 FSE and quantitative T2 mapping was obtained. Safranin-O/Fast Green staining and IHC of Collagen II, Aggrecan, and Collagen III of decalcified histologic sections will be used to compare proteoglycan content in discs. All discs were compared to endogenous controls of the "defect only" disc, as well as intact discs.

Results – qPCR experimentation indicates that TGF-β3 (1), TGF-β3 + BMP-4 (4), TGF-β3 + TIMP-2 (5) and TGF-β3 + BMP-4 + TIMP-2 (7) significantly upregulated Collagen1a1, Collagen2a1, and Collagen10a1. BMP-4 (2) and BMP-4 + TIMP-2 (6) upregulated Aggrecan expression. Treatment with TGF-β3 + BMP-4 (4) and TGF-β3 + BMP-4 + TIMP-2 (7) showed markedly high GAG content compared to the control. BM cells treated with chondrogenic and osteogenic medium expressed significantly more GAGs and mineralizations, respectively, compared to control cells, indicating differentiation of BM cells into both lineages (Figure 1).

No evidence of hydrogel leakage was observed at the time of explantation of the rabbit spines, nor did any animal display symptoms of neuritis that would be expected with hydrogel expulsion from the disc space. Qualitative and quantitative MRI analysis of the explanted spines shows obliteration of the disc space at the "defect only" level, with significant loss of disc height and bony changes. At the levels treated with Chitosan hydrogel, disc spaces maintained original height. Discs that received Chitosan loaded with TGF- β_3, BMP-4 and TIMP-2 displayed signal intensities nearly identical to the intact, control discs, as shown in Figure 1. MRI analysis and histology is ongoing.

Discussion - The growth factors and proteinase inhibitor studied show efficacy in upregulating important ECM genes *in vitro* and show efficacy in restoring disc morphology, appearance, and quantitative parameters on MRI. In the acute setting, the percutaneous injection of Chitosan loaded with anabolic growth factors and a proteinase inhibitor into the disc space mitigates disc space obliteration and stimulates de novo disc tissue formation. Ongoing studies will further elucidate the effect of this tissue engineering-based approach on histology and continued MRI analysis.

Christina McKee, M.S., Doctoral Candidate, Oakland University, "Self-assembling Scaffold Supports Pluripotent Growth of Embryonic Stem Cells"

Embryonic stem cells (ESCs) have unlimited self-renewal and differentiation potential. *In vitro* culturing of ESCs is laborious, technically challenging, and often leads to the loss of cell lines due to differentiation. To address these problems, considerable attention has been focused on devising culture conditions that mimic *in vivo* stem cell microenvironments. We have developed a self-assembling scaffold supportive of ESC growth by mixing thiol-functionalized dextran (Dex-SH) and poly (ethylene glycol) tetra-acrylate (PEG-4-Acr) via Michael addition reaction. We optimized culture conditions using Dex-SH/PEG-4-Acr scaffolds to maintain the self-renewal and pluripotency potential of ESCs for an extended period of time. The cell growth and proliferation were determined by microscopic studies and cell viability assays. Stem cell renewal and differentiation was further investigated by analyzing the cell specific markers using quantitative reverse transcriptase-polymerase chain reaction (qPCR). The scaffold grown cells exhibited ESC morphology, expressed pluripotent markers and were capable of differentiation into various cell lineages. Overall, our findings provide a reliable, reproducible, cost effective, and robust culturing system that should lead to increased applications of ESCs for understanding basic development and differentiation mechanisms, tissue engineering and cell therapy.

Naimisha Reddy Beeravolu, Doctoral Candidate, Oakland University, "The Effect of Arsenite on Cord Blood Stem Cells"

Environmental arsenic exposure has known correlations with cancer as well as other severe afflictions including neurological and cardiovascular diseases, presenting an important public health issue. Populations are mainly exposed to arsenic via food and drinking water contamination. Some countries have reported excessive arsenic concentrations in their groundwater supply, exposure to which has been linked to specific and proportional adverse effects.Therefore it is important to establish the impact of arsenic on human cells and damage induced by exposure to acute and chronic exposure of arsenic. The use of human cord blood stem cells (CBSCs) is a good platform to investigate these effects as CBSCs have already been used for therapeutic treatments against many haematopoietic and other blood disorders via regenerative medicine therapy. Human CBSCs also have a high level of stemness and culture tolerance but reduced research implications compared to human embryonic stem cells and thus are the best alternative. Arsenic exposure has been investigated with a plethora of cell types in a variety of environments, yet none with CBSCs. However, bone marrow mesenchymal stem cells (MSCs) are the closest in association to the CBSCs used in our investigation. In this study, CBSCs were exposed to varying concentrations of inorganic arsenite (iAs^{III}) 10 nM – 50 µM for 24 -72 hr. There was a clear dual effect on the growth of CBSCs. At lower concentrations up to 100 nM, arsenite stimulated growth but at higher concentrations it progressively inhibited the cell proliferation. Concentrations higher than 20 µM caused increased apoptosis. There was a significant increase in the cell size correlated with increasing dose of arsenic suggesting that cells exposed to arsenic could be arrested in G2/M phase with concomitant decrease in cell proliferation. These results showed that CBSCs, similar to embryonic stem cells, are more resistant to arsenite as compared to bone marrow mesenchymal stem cells, adult stem cells and other primary cells like fibroblasts. These findings have implications in the cancer developing and devising remedial strategies for treating patients exposed to arsenic.

Poster Session Abstracts

Poster Session Abstracts

POSTER #1

Neural Progenitor Cell-Mediated Magnetic Hyperthermia of Preclinical Melanoma Tumors

Sivasai Balivada†, Rajashekhar Rachakatla†, Hongwang Wang‡, Gwi Moon Seo†, Raj Dani‡, Marla Pyle†, Viktor Chikan‡, Stefan H. Bossmann‡, Deryl L. Troyer†.
†-Department of Anatomy & Physiology ‡- Department of Chemistry, Kansas State University, Manhattan, KS

Magnetic hyperthermia using magnetic nanoparticles (MNPs) to absorb alternating magnetic field (AMF) energy as a method of generating localized hyperthermia has been shown to be a potential cancer treatment. Many attempts have been made to increase the tumor localization of MNPs, for example by attaching antibodies recognizing tumor-specific epitopes or peptides binding receptors on tumor cells or neovasculature. Several research groups have shown reliable results using tumor-homing cells as delivery cells for different therapeutics. Here we hypothesized that tumor-homing cells can carry MNPs specifically to the tumor site, and that tumor burden will decrease after AMF exposure. To test this hypothesis, first we loaded Fe/Fe3O4 bi-magnetic NPs into neural progenitor cells (NPCs), which were previously shown to migrate towards melanoma tumors. We observed that NPCs loaded with MNPs travel to subcutaneous melanoma tumors. After AMF exposure, the targeted delivery of MNPs by the NPCs resulted in a significant decrease in tumor size. Based on these observations, we concluded that development of localized hyperthermia using tumor tropic cells can be a potential therapy for cancer.

POSTER #2

A Focused Microarray for Screening Rat Embryonic Stem Cell Lines.

J. Hong[1], Hong He[1], P. Bui[1], B. Ryba[1], M.A.K. Rumi[3], M.J. Soares[3], D. Dutta[3], S. Paul[3], M. Kawamata[4], T. Ochiya[4], Q. Ying[5], P. Rajanahalli[1], and Mark Weiss [1,2]
[1]Department of Anatomy and Physiology, Kansas State University College of Veterinary Medicine, Manhattan, KS; [2]The Midwest Institute of Comparative Stem Cell Biology, Kansas State University, Manhattan, KS; [3]Department of Pathology and Laboratory Medicine, University of Kansas Medical Center, Kansas City, KS, [4]Division of Molecular and Cellular Medicine, National Cancer Center Research Institute, 5-1-1, Tsukiji, Chuo-ku, Tokyo, Japan, [5]Department of Cell & Neurobiology, Keck School of Medicine, University of Southern California, Los Angeles, CA

We developed a focused DNA microarray to use as a simple one step characterization method of gene expression of rat embryonic stem cells (ESCs). Here, we validated the comparison of undifferentiated germline-competent ESCs, chimera-competent ESCs, ESC differentiated for 5 days and 10 days to embryoid bodies (EBs), and rat trophoblast stem cells (TS), extraembryonic endoderm cells (XEN), mouse embryonic fibroblast feeder cells (MEFs). Using this tool, genuine rat ESC lines which have been expanded in a conventional rat ESC medium containing

two inhibitors (2i), e.g., GSK3 and MEK inhibitors, and leukemia inhibitory factor, and genuine rat ESCs which have been expanded in rat ESC medium containing four inhibitors (4i), e.g., GSK3, MEK, Alk5, and Rho-associated kinase inhibitors, were compared, as were genuine rat ESCs from four different strains of rats. Expression of Cdx2, a gene associated with trophoblast determination, was observed in genuine, undifferentiated rat ESCs from four stains and from both 2i and 4i ESC derivation medium. This finding is in contrast to undifferentiated mouse ESCs which do not express Cdx2. The rat ESC focused microarray described in this report has utility for rapid screening of rat ESCs. This tool will enable optimization of culture conditions in the future.

POSTER #3

Differentiation of Cord Blood Stem Cells into Chondrogenic Derivatives.

Naimisha Reddy Beeravolu[1,4], Christina McKee[1,4], A. Mitchell[2,4], M. Perez-Cruet[4,5], Sumi Dinda[3,4], G. Rasul Chaudhry[1,4]
[1]Department of Biological Sciences, [2]School of Nursing, [3]School of Health Sciences, [4] OU-WB Institute for Stem Cell and Regenerative Medicine, Oakland University, Rochester, MI
And [5]Beaumont Health System, Royal Oak, MI

Stem cell based regenerative therapies have gained fast growing attention recently. Umbilical cord blood has more primitive and promising populations of multipotent stem cells compared to bone marrow derived cells. Human cord blood stem cells differentiation potentials is not fully elucidated yet. This study is focused on understanding their potential to differentiate into chondro- progenitors capable of yielding cells that produce extracellular matrix, glycosaminoglycans (GAGs). Chondrogenic differentiation of cord blood stem cells (CBSCs) were performed by pellet/ spheroid culture technique. For the formation of spheroids, CBSCs grown to 60% confluency were dissociated by Tryple into single cell suspension. They were then suspended at $1X10^5$ cells/ml in eppendorfs and centrifuged at 3K rpm for 10 mins in chondrogenic differentiation medium consisting of high glucose DMEM, 10% fetal bovine serum, 10ng/ml recombinant human TGF-β1, 10µg/ml insulin like growth factor, 50µg/ml ascorbic acid and 100nM dexamethasone. Eppendorfs were incubated at 37ºC and 5% CO_2, undisturbed, for five days of the induction period. Spheroids were then harvested, transferred onto culture plates, cultured in differentiation medium allowing the CBSCs to migrate and differentiate into chondro-progenitors for additional 30 days. The medium was changed every two days. The potentiality of chondrogenic differentiation was evaluated by Alcian Blue staining and RT-PCR analysis of expression of the chondrogenic markers. Non-induced CBSCs were used as negative control. The spheroids, cultured in the eppendorfs, allowed the majority of CBSCs to induce differentiation towards the chondro-progenitor like cells. Spheroids transferred onto culture plates allowed the CBSCs to migrate from the spheroids onto the culture plates allowed for the comparison of the uniformity of cell migration, cell morphology and the amount of extracellular matrix, GAG, accumulated, based on the results obtained from light microscopy and Alcian Blue staining. It was also observed that CBSCs require a longer time to differentiate into chondro-progenitors than the 21 days usually necessary for other stem cell sources. The differentiated cell expressed chondrogenic markers as judged by the RT-PCR and immunocytochemical analysis. This study demonstrates that CBSCs have reliable migration and differentiation capabilities, particularly into chondroprogenitors. Therefore, CBSCs can be used

as a gold standard cell source for autologous or allogenic skeletal and neuroregenerative therapies. However, further *in vivo* studies will be required to substantiate our *in vitro* findings.

POSTER #4

The Consortium for Stem Cell Therapies Core Laboratory in the A. Alfred Taubman Medical Research Institute

C.J. DeLong, S. Mojica, M. Mhaskar, A. Montero da Rocha, H. Chen, C. Pacut, G.D. Smith, K.S. O'Shea

The CSCT is a tissue culture Core facility established to maintain and derive new human Embryonic Stem (hESC) cell lines and induced pluripotent stem cell (iPSC) lines, provide quality control, and share expertise, protocols and reagents within the U of M scientific community. We provide hands on training in the culture of hESC and iPSC for U of M faculty, staff and students. Education of the general public regarding the facts and potential benefits of stem cell research is also part of our goal. The Center participates in community outreach programs and educational opportunities in the form of tours, forums, discussion groups, etc.The Michigan Center for human Embryonic Stem Cell Research was established in 2002 with funds from the Medical School's Endowment for Basic Sciences. In 2003, the Center was awarded an Exploratory Center Grant for Human Embryonic Stem Cell Research from the National Institutes of Health (1 P20 GM069985-01) to expand and further support hESC research at the University. In 2009, the Consortium for Stem Cell Therapies (CSCT) was established in the A. Alfred Taubman Medical Research Institute.

POSTER #5

Induction of Steroid Receptors by Sex Hormones in Embryonic Stem Cells

Sumi Dinda[1,2], Sarah Chaudhry[1], Christina McKee[2], Amy Siebert[1,2], Donald Taylor[3], Faisal Chaudhry[1], Mick Perze-Cruet[3], & G. Rasul Chaudhry[2]
School of Health Sciences[1], Department of Biological Sciences[2], Oakland University, Rochester, MI, USA, William Beaumont Hospital[3], Royal Oak, MI

Normal cellular growth and proliferation are highly regulated processes. It is known that estrogen (E_2) and progesterone (P) as the major sex steroids play an important role in the normal development. For example, E_2 and P have both proliferative and differentiating effects on uterine and breast cells and testosterone (dihydrotestosterone) is known to influence many reproductive functions, protein metabolism, muscle building and other functions. These steroids influence physiological processes by initially interacting via cognate receptors which act as transcription factors influencing the hormone-responsive genes. The use of estrogen and progesterone replacement therapy for postmenopausal symptoms has been implicated in increasing the risks of breast and uterine cancers. Testosterone may have a role in breast or uterine cancers which is not clearly understood. However, the precise roles of sex hormones during embryonic development are not completely elucidated. In order to understand the developmental effects of sex steroids, we have used embryonic stem cells (ESCs) as a model system, which mimic early embryonic development. We have examined the effects of E_2, progesterone, dihydrotestosterone, anti-estrogen (ICI 182,780) and anti-progesterone (Ru-486) on the proliferation and differentiation of

ESCs. Our results demonstrated a higher rate of differentiation of ESCs when treated with a combination of hormones, estrogen and progesterone, and individually, progesterone and dihydrotestosterone, in a concentration dependent manner (1 nm to 1uM) as compared with the controls. The proliferative and differentiative properties of hormones were inhibited by treatment with anti-hormones. Retinoic acid (RA) treated embryoid bodies (EBs) derived from ESCs differentiated at a higher rate (2 to 3 fold) in the presence of estrogen, progesterone, or dihydrotestosterone. Immunocytochemical analysis revealed an increased expression of estrogen receptors in the nucleus of the cells, derived from the RA-treated EBs in the medium containing estrogen and dihydrotestosterone. Our observation also suggests an increased expression of estrogen receptors in the EBs treated with progesterone. Preliminary results of quantitative polymerase chain reaction also indicated increased expression of estrogen receptor in ESCs treated with E_2 and progesterone.

POSTER #6

Transplantation of Adenovirus-generated Induced Pluripotent Stem Cells Protects Against Motor Deficits in a Rat Model of Huntington's Disease.

Kyle D. Fink, [1, 2, 3] Andrew T. Crane, [1] Julien Rossignol, [1, 4, 5] Robert D. Wyse, [1] Lucas Huffman, [1] Allison Moore, [1] Ming Lu, [1, 3] Laurent Lescaudron,[2, 7] and Gary L. Dunbar ,[1, 4, 5]
Field Neurosciences Institute Laboratory for Restorative Neuroscience, Department of Psychology, Central Michigan University, [2] Univ. de Nantes, Faculté des Sci. et des Techniques, Nantes, [3] INSERM UMR 1043, ITERT, CHU Hotel Dieu, Nantes, France 44093, [4] College of Medicine, Central Michigan University Field Neuroscience Institute

Huntington's disease (HD) is a devastating neurodegenerative disorder caused by an expanded tri-nucleotide repeat CAG on chromosome 4 leading to cognitive and motor dysfunction in mid-life and death 15-20 years after the clinical onset. The use of induced pluripotent stem cells (iPSCs) has gained recent attention as a viable strategy for treating HD. Unfortunately, the original method of producing iPSCs involves pro-oncogenes, such as c-Myc and Klf4, which become permanently integrated into the genome during reprogramming with retroviruses or lentiviruses. Recent work in our lab has shown that using adult stem cells, derived from tail-tip fibroblasts and reprogrammed with two adenoviruses to become iPSCs, could survive and differentiate into neuronal lineages in the absence of tumor formation when transplanted into the striata of healthy adult rats. However, because the ability of these iPSCs to survive, differentiate, and provide functional recovery in a rodent model of HD had not been investigated, it became the focus of the current study.

Adult rats received a regimen of 3-nitropropionic acid (3-NP) to induce Huntington's disease-like behavioral deficits and cell loss within the striatum. Three treatment groups of 3-NP rats were bilaterally transplanted with 400,000 iPSCs into the striatum at 7- and 21-days following 3-NP administration. To distinguish variance in motor deficits, the rats were assessed for 6 weeks on an accelerod that increased from 4RPM to 16RPM during a 2-minute testing session and in an open field task to examine exploratory behaviors. A significant interaction between weeks and genotype was observed [$F(18,228)=3.494, p<0.01$] on the accelerod. *Post hoc* analysis reevealed that the 3-NP rats that did not receive iPSC transplants showed significant motor impairments when compared to the sham animals and that the 3-NP rats that received iPSC transplants

showed behavioral sparing when compared to untreated 3-NP rats. A significant interaction between weeks and genotype was observed [$F(18,210)=2.837, p<0.01$] for the time rearing in the open field task. *Post hoc* analysis revealed that the 3-NP rats that did not receive iPSC transplants spent significantly less time rearing when compared to the sham animals and that the 3-NP rats that received iPSC transplants showed behavioral sparing when compared to untreated 3-NP rats.Following behavioral analysis, the animals were sacrificed and the brains were analyzed for graft survival, inflammatory response, neuronal differentiation and lesion size. Results from this study indicate that iPSCs may be a viable treatment for Huntington's disease.

Support for this project was provided by a PUF grant (to KDF) and funding from the John G. Kulhavi Professorship and Field Neurosciences Institute (to GLD).

POSTER #7

Making P53 Gene Conditional Knockout Rat by Homologous Recombination

Hong He, James Hong and Mark Weiss, Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University

Tp53 gene conditional knockout animals are a new kind of cancer research animal model which can be used to probe, search, find and elucidate the reasons of cancers in animals and humans. For this reason, we generated the conditional cells (Tp53 gene conditional knockout rat cells) by homologous recombination and checked the cells by PCR, Southern Blotting. We subcloned the rat space (F344) Tp53 gene and its arms (5'arm +3'arm) of about 12 kb into the TOPO plasmid. We inserted the Neomycin resistenc gene (Neo) into Intron 8 and Frt sites on each side of Neo gene. We also inserted two LoxP sites, one at 3' of the Neo gene just outside Frt site in intron 8 and another LoxP site inside Intron 4. After Flpe plasmid (pCAG-Flpe) transfection of the conditional knockout cells, the Neo gene will be removed, reverting them to Neomycin sensitive cells. After Cre plasmid (pCAG-Cre) transfection of the conditional knockout cells, Neo gene and exons 5, 6, 7 and 8 will be removed, converting them into Tp53 gene knockout cells.

POSTER #8

Identification of a Subpopulation of Marrow MSC-derived Medullary Adipocytes that Express Osteoclast-regulating Molecules

Vance Holt, B.S.[1], Arnold I. Caplan, PhD.[1], Stephen E. Haynesworth, PhD.[1]
[1]Skeletal Research Center, Department of Biology, College of Arts and Sciences, Case Western Reserve University, Cleveland, Ohio.

The Medullary adipocyte (fat cells in the bone marrow cavity) number increases as a function of age. This increase in marrow fat has been shown to correlate with age-associated bone loss that can progress into senile osteoporosis. In this study we investigated whether cells of the medullary adipocyte lineage have the potential to directly support the formation of osteoclasts, whose activity in bone leads to bone degradation. Our lab previously reported on an in vitro model of medullary adipogenesis from human Mesenchymal Stem Cells (MSC). The MSC-derived medullary adipocytes that are generated using this culture system exhibit a phenotypic expression profile of transcription factors, adipocyte-specific metabolic proteins, and adipokines that is very similar to in vivo derived medullary adipocytes. In this study we used this in vitro

MSC-derived medullary adipocyte lineage culture model to study the expression of the important osteoclast mediators RANKL, M-CSF, SDF-1, and OPG by cells at several stages of differentiation along the medullary adipocyte lineage, in order to determine whether these genes are expressed in a developmentally regulated manner. mRNA expression for these genes was quantified using qPCR. M-CSF mRNA expression was significantly increased over day 0 MSC controls during early stages of medullary adipocyte differentiation (days 3 and 12) and significantly decreased in mature MSC-derived adipocyte lineage cells (days 21 and 25) . Levels of SDF-1 mRNA expression showed no increase at all lineage stages of MSC-derived adipocytes when compared to undifferentiated MSCs but decreased in during the late (days 21 and 25) adipogenic stage cultures that contained predominantly mature adipogenic cells. RANKL mRNA expression was found to be significantly induced in early lineage-stage adipocyte cultures compared to MSC controls. During the adipogenic (induction) timecourse, RANKL expression increased up to day 12, and then dramatically declined during the late culture timepoints (days 21 and 25). Conversely, OPG mRNA expression was low during the earlier timepoints and dramatically increased after day 12. These results indicate that important osteoclastogenic mediators have distinct temporal expression patterns that correlate with MSC-derived adipocyte lineage stage. Further characterization of the MSC-derived medullary adipogenic lineage cells along the time course showed that RANKL expression was predominantly expressed by a previously uncharacterized early lineage-stage medullary adipogenic progenitor that also expressed CEBP-alpha, but not PPAR-gamma. These RANKL-positive early lineage medullary adipogenic progenitors (we term ‘adipofibroblasts’) were capable of supporting osteoclast-like cell formation in co-cultures with peripheral blood mononuclear cells. These results suggest a connection between medullary adipocytes and osteoclast development in vivo and may have major significance in regards to the mechanisms of decreased bone density with age in senile osteoporosis.

POSTER #9

Nestin-mCherry Transgenic F344 Rat Embryonic Stem Cells Driven by the Nestin Intronic Enhancer Shows mCherry Upregulation during Differentiation to NSC and Downregulation during Terminal Differentiation to Neurons

James S. Hong, Hong He and Mark Weiss
Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University

Rat neural progenitor cells are difficult to maintain in culture in vitro long term. We have created F344 rat embryonic stem cells (ESCs) possessing a transgene driven by a rat neural stem cell (NSC) specific promoter to serve as a model to discover molecules to inhibit the propensity of neural progenitors in vitro to differentiate. The rat Nestin gene is expressed in NSCs. We simultaneously subcloned an intronic enhancer, the Nestin minimal promoter and the coding sequence for mCherry into a modified pN1-EGFP plasmid. This plasmid was electroporated into rat ESCs. The electroporated ESCs were selected using geneticin (G418) and the G418 resistant ESCs were again selected by mCherry fluorescence. Five to ten (10) clones were selected and grown together. The final round of selection resulted in clones with homogeneous mCherry expression. The selected clones were differentiated to neural progenitors using fibroblast growth factor 2 (FGF2), cyclic AMP and ascorbic acid in laminin coated microplates. Semi-quantitative

polymerase chain reaction (PCR) analysis showed changes in Nestin and mCherry expression during differentiation. A correlation between Nestin and mCherry downregulation was also supported by the semi-quantitative PCR. Immunoreactivity for beta tubulin 3 (Tubb3) was also shown after terminal differentiation to neurons with BDNF and GDNF treatment of the Nestin-mCherry transgenic F344 ESCs.

POSTER #10

Differentiation of Induced-pluripotent Stem Cells into Dopaminergic Neurons for Transplantation in a Rodent Model of Parkinson 's Disease.

X. Leveque [1,2]., R . Welchko [1,2]., K. Fink [1,2,3]., J . Rossignol [1,2,5]., L. Lescaudron [3,4]., G. Dunbar [1,2,5]

[1]Field Neurosciences Institute Laboratory for Restorative Neuroscience, Department of Psychology, Central Michigan University, Mount Pleasant, Michigan, 48859 USA, [2] Field Neuroscience Institute, 4677 Towne Centre Rd. Suite 101 Saginaw, Michigan 48604 USA, [3] Université de Nantes, Faculté des Sciences et Techniques, Nantes, France 44322, [4] INSERM U791, Laboratoire d'Ingénierie Ostéo-Articulaire et Dentaire (LIOAD), Groupe STEP "skeletal tissue engineering and physiopathology", UFR d'Odontologie, Univ. Nantes, Nantes FRANCE
[5] College of Medicine, Central Michigan University, Mount Pleasant, Michigan

Parkinson's disease (PD) is a neurodegenerative disease characterized by a loss of dopaminergic neurons within the substantia nigra that innervate the neostriatum. Loss of this pathway leads to important motor impairments. Although an effective long-term therapy has not been developed, there have been promising results using transplantation of human fetal neuroblasts in the neostriatum of PD patients. However, issues of tissue availability and ethical concerns limit this approach. As an alternative to transplanting human fetal neuroblasts, the use of induced pluripotent stem cells (iPSCs) is very promising. The goal of this study is to test the efficacy of transplanted iPSCs at various stages of differentiation into the striatum of rats injected with a dopaminergic toxin, the 6-hydroxydopamine (6-OHDA), within the nigrostriatal pathway. The iPSCs were generated from somatic stem cells derived from rat tail-tip fibroblasts (TTF), using a combination of adenoviruses (AD; Oct4, Sox2, Klf4 and c-Myc). The pluripotency of these cells were confirmed using flow cytometry and immunocytochemistry for the pluripotent markers SSEA3, SSEA4, Tra-1-60, Nanog, and Oct4. Differentiation of TTF-AD iPSCs into mature dopaminergic neurons was induced *in vitro* and the different stages of differentiation were determined using immunocytochemistry, flow cytometry and molecular analysis to identify various dopaminergic phenotypically-expressed markers, such as tyrosine hydroxylase (TH), FoxA2, and Nurr1. The initial findings from this study suggest that iPSCs may provide a viable source of dopaminergic cells for potential therapies, but further research is needed to definitively distinguish which stage of differentiation provides the most efficacious results in the 6-OHDA rat model of PD.

This work was supported by the John G. Kulhavi Endowed Professorship in Neuroscience, Central Michigan University Neuroscience Program, and the Field Neurosciences Institute.

POSTER #11

A Critical Role of CXCR2 PDZ–mediated Interactions in Endothelial Progenitor Cell Neovascularization

Chunying Li, Ph.D., Wayne State University School of Medicine

Bone marrow (BM)-derived endothelial progenitor cells (EPCs), circulating in peripheral blood, migrate toward target tissues, differentiate, and contribute to the formation of new vessels in response to a variety of growth factors and cytokines. Transplantation studies have revealed that EPCs incorporate into active neovasculature in ischemic tissues and growing tumors. Therefore, EPCs have been exploited for establishing new intervention strategies for therapeutic neovascularization (as in ischemia) and angiogenesis-dependent diseases (such as cancer). It has been reported that the chemokine receptor CXCR2 and its cognate ligands mediate EPC recruitment and angiogenesis in injured endothelium, ischemic myocardium, and allergic airway. CXCR2 possesses a consensus PDZ (**P**SD-95/**D**lgA/**Z**O-1) motif at their carboxyl termini, and the PDZ motif has been reported to modulate post-endocytic sorting and cellular chemotaxis. In a recent study, we demonstrated that the PDZ motif of CXCR2 plays an important role in regulating neutrophil functions as disrupting PDZ motif-dependent interactions significantly inhibited CXCR2-mediated neutrophil functions (Wu et al., 2012).

Here, using the isolated BM-derived EPCs, we first examined the effects of CXCR2 blockade on EPC *in vitro* migratory and angiogenic activities. We observed that CXCR2 blockade by anti-CXCR2 antiserum or CXCR2 antagonist (SB225002) significantly inhibited EPC migration, adhesion, invasion, and EPC *in vitro* incorporation into endothelial tubule network in response to CXCR2 ligands, but not to CXCR4 ligand CXCL12 or VEGF. To elucidate the potential role of the PDZ motif in CXCR2-mediated EPC motility and angiogenesis, we delivered an exogenous CXCR2 C-tail peptide or DNA construct (encoding the CXCR2 PDZ motif -TTL) into EPCs and monitored EPC functions. We observed that the synthetic CXCR2 C-tail peptide or DNA construct exhibited significant inhibitory effects on EPC *in vitro* migratory responses and angiogenic activities, CXCR2-mediated cell signaling (i.e., intracellular calcium mobilization), as well as EPC *in vivo* incorporation and angiogenesis in a Matrigel plug mouse model. However, the CXCR2 C-tail that lacks the PDZ motif (ΔTTL) did not cause any significant changes in EPC *in vitro* and *in vivo* functions. In addition, using pull-down and co-immunoprecipitation, we demonstrated that the PDZ scaffold protein NHERF specifically interacts with CXCR2 and its downstream effector, PLC-β, in EPCs. This suggests that NHERF might cluster CXCR2 and its relevant signaling molecules (such as PLC-β) into a PDZ motif-dependent macromolecular complex, which could form the basis for CXCR2-mediated EPC homing and angiogenesis. Taken together, our data revealed a critial role of a CXCR2 macromolecular complex mediated by PDZ-based interations in EPC homing and angiogenesis, suggesting that targeting the PDZ-based CXCR2 complex might be a novel and effective strategy to treat angiogenesis-dependent diseases (such as tumors).

POSTER #12

Novel Cardiac Precursor-like Cells from Rat Wharton's Jelly Cells

Yelica López, John Hirt, Mark Weiss
Kansas State University, Department of Anatomy and Physiology, Manhattan, KS 66502.

Wharton's jelly is a mucous connective tissue rich in hyaluronic acid and stromal cells, which provides a cushion support for the umbilical cord (UC) vein and arteries. In mice, the umbilical cord develops early along with hematopoietic stem cells (HSCs) in the aorta gonadal region (AGM) and yolk sac. It has been reported transdifferentiation of mesenchymal stem cells (MSCs) derived from bone marrow (BM-MSCs) and Wharton's jelly (WJ-MSCs) into cardiomyocyte-like cells can be achieved by using inhibitors of DNA methylation, such as 5-azacytidine. These studies support the notion that both BM-MSCs, as well as WJ-MSCs, retain myocardiogenic potential. Since cell fate differentiation, determination, and commitment are decided by an amalgamation of factors such as: morphogenic determinants, intercellular contacts, and extracellular matrix --- we developed WJ-MSC and BM-MSC co-culture methods to evaluate cardiomyogenic potential of both MSC cell sources in two-dimensional (2D) and three-dimensional (3D) environments. We hypothesize that co-culture conditions might generate signals and cell-to-cell contacts which enhance the expression of cardiogenic phenotype in WJ-MSCs. Primary isolations of the rat umbilical cord (UCs) and fetal bone marrow were obtained from 6 pregnant rats. Euthanasia was performed at 19 days post-coitus (dpc). Posterior legs and UCs were collected from fetus. Explants from UCs were plated in individual wells of six-well plates; once the explants were attached, isolated BM-MSCs were placed over the explant at a density of 15,000 cells/cm^2. Cells were fed by using a growth medium containing 20% fetal bovine serum (FBS), 1% glutamine, 1% penicillin-streptomycin in low glucose DMEM. This medium was changed every 48 hours. As early as day 5, multinucleated myotubes growing from UC explants with rhythmic contraction can be observed. Here, co-culture provided cell interaction and signaling to induce cardiomyocyte-like phenotype.

POSTER #13

Endothelial Lineage Cells in Human Umbilical Cord Blood

Christopher Lucier[1,4], Naimisha Reddy-Beeravolu[1,4], Christina McKee[1,4], Sumi Dinda[3,4,], G. Rasul Chaudhry[1,4]
[1]Department of Biological Sciences, [2]Department of Chemistry, [3]School of Health Sciences, and [4]OU-WB Institute for Stem Cell and Regenerative Medicine, Oakland University, Rochester, MI

Although endothelial progenitor cells (EPCs) in human umbilical cord blood have been implicated in vasculogenesis and angiogenesis, the exact source and process of differentiation remains unclear. EPCs undergo many population doublings and prolonging this process will enable these cells to be used, therapeutically, for vascular diseases. The goal of this study is to investigate EPCs in cord blood and determine their potential for prolonged survival. Two selective culture systems were used to explore the most efficient and direct way of isolating EPCs from cord blood. After the isolation of EPCs, several mediums were used to examine proliferation, differentiation and migration capabilities *in vitro*. Heterogeneity of EPCs was examined based on the differences in their morphology and growth using light microscopy. The

spindle type cells were identified by cell migration assays. These studies lead us to readily isolate EPCs from mononuclear cells and amplify them towards the endothelial lineage with the use of endothelial growth medium plus growth factor supplements. After six days in the culture medium the EPCs underwent rapid amplification until day 18. Three cell types qualitatively identified had characteristics of EPCs. The first type were small round and second were spindle shaped, both types adhered to the plate. The third type of cells were large round, but were loosely adherent or floating in the medium. The first two cell types were adhering and migrating when cultured on FN coated plates as compared to the gel coated plates. Further studies are required to confirm these results and quantify the various types of EPCs derived from cord blood.

POSTER #14

Investigating Cbx2 to Better Understand Polycomb Repressive Complex 1 Roles in Epigenetic Regulation

Anna C. Maurer, University of Michigan CMB Undergraduate Honors Thesis

Polycomb Group (PcG) proteins are evolutionarily conserved transcriptional regulators that play roles in both pluripotency maintenance and lineage commitment in the developing embryo. PcG proteins are categorized into two main complex-forming classes, PRC1 and PRC2. The mechanisms by which these proteins are recruited to repress their target genes are largely unknown, but evidence suggests that combinatorial diversity in these complexes plays a role in recruitment to different loci. Members of the mammalian Cbx family of proteins impart an H3K27me3 binding function to PRC1 and have been suggested to contribute to the binding specificity of the complex to different subsets of target chromatin, particularly during the progression from pluripotency to differentiation, during which Cbx inclusion in PRC1 has a dynamic role. The Cbx2 subunit of PRC1 is not well studied, but is of particular interest in that it has a larger repertoire of binding partners than the other Cbx family proteins. Here, I describe the generation, purification, and application of several rabbit polyclonal antisera specific to Cbx2. I present evidence that Cbx2 does not localize to regions of highly condensed chromatin in ES cells. ChIP analysis reveals that Cbx2 binds a subset of PRC1target genes, including endogenous retroviruses. Cbx2 inclusion in PRC1 varies as differentiation progresses, as demonstrated by Cbx2 co-precipitation by other PRC1 subunits from ES cell and 2, 4, and 8-day EB lysates. Future uses of these antisera will help elucidate Cbx2's role in PRC1 and its functions during development, which can advance the field of regenerative medicine by helping understand the complexities of cell fate decisions and how they can be controlled for use in clinical applications.

POSTER #15

Self-assembling Scaffold Supports Pluripotent Growth of Embryonic Stem Cells

Christina McKee[1], Ferman Chavez [2,3], Mick Perez-Cruet [3,4], Rasul Chaudhry [1,3]
[1]Department of Biology, [2]Department of Chemistry, [3]OU-WB Institute for Stem Cell and Regenerative Medicine, Oakland University, Rochester, MI and [4]Beaumont Health System, Royal Oak, MI

Embryonic stem cells (ESCs) have unlimited self-renewal and differentiation potential. *In vitro*

culturing of ESCs is laborious, technically challenging, and often leads to the loss of cell lines due to differentiation. To address these problems, considerable attention has been focused on devising culture conditions that mimic *in vivo* stem cell microenvironments. We have developed a self-assembling scaffold supportive of ESC growth by mixing thiol-functionalized dextran (Dex-SH) and poly (ethylene glycol) tetra-acrylate (PEG-4-Acr) via Michael addition reaction. We optimized culture conditions using Dex-SH/PEG-4-Acr scaffolds to maintain the self-renewal and pluripotency potential of ESCs for an extended period of time. The cell growth and proliferation were determined by microscopic studies and cell viability assays. Stem cell renewal and differentiation was further investigated by analyzing the cell specific markers using quantitative reverse transcriptase-polymerase chain reaction (qPCR). The scaffold grown cells exhibited ESC morphology, expressed pluripotent markers and were capable of differentiation into various cell lineages. Overall, our findings provide a reliable, reproducible, cost effective, and robust culturing system that should lead to increased applications of ESCs for understanding basic development and differentiation mechanisms, tissue engineering and cell therapy.

POSTER #16

Progress Toward Production Of Xeno-Free, Disease-Specific Human Embryonic Stem Cells

S. Mojica, A. Monteiro da Rocha, CJ. DeLong, M. Mhaskar, C. Pacut, M. Hughes, K.S. O'Shea, G.D. Smith.

Objective: Human embryonic stem cells (hESCs) provide potential to understand early development, evaluate pathophysiology of specific genetic diseases, screen therapeutics, and further cell replacement therapies. We aimed to implement stepwise procedures toward derivation of xeno-free, disease-specific hESCs.
Study design**:** Laboratory study
Materials and methods**:** Couples undergoing IVF / PGD for single-gene defects signed informed consent to participate in this IRB-approved study. Embryos with genetic defects responsible for hemophilia-B (H-B) and Charcot Marie Tooth disease (CMT), Hydroxisteroid Dehydrogenase Deficient, Huntington's Disease, Aniridia, Hypertrophic Cardiomyophathy and Multiple Endocrin Neoplasia 2a that would otherwise be discarded, were used to attempt hESC derivation. Toward xeno-free derivation, blastocysts were laser-dissected to remove the inner cell mass (ICM); ICMs were plated on neonatal human foreskin fibroblast (Global Stem); and culture was performed in DMEM with human recombinant / derived proteins at 6%CO_2, 5%O_2 in air and 37°C.
Results: Cryopreserved blastocysts were used to derive most the lines. Two non-cryopreserved blastocysts were used to obtain the CMT-hESC line. All lines displayed normal passage rates, normal hESC morphology, normal karyotype, expressed pluripotency markers (Oct3/4, Nanog, Sox2, SSEA-4, Tra1-60), and formed embryoid bodies. In vivo tri-lineage potential is currently being assessed in teratomas formed in NOS mice. All lines have been cryopreserved by vitrification at early passages.
Conclusions: Collectively, implementation of inner cell mass laser biopsy, co-culture with human fibroblast, and use of human protein additives are extremely efficient means of deriving hESCs. Such procedures pave the way for xeno-free hESC production. Continued efforts are required to produce xeno-free, fully-defined culture systems for hESCs, with a final goal of hESC production with Good Manufacturing Practice. Embryonic Stem Cell lines with the

defects responsible for hemophilia-B, Charcot Marie Tooth disease, Aniridia, Hydroxisteroid Dehydrogenase Deficient, Huntington's Disease and Hypertrophic Cardiomyophaty were approved to the NIH hESC registry and they available for studies funded by Federal grants.

POSTER #17

Differentiation of Human Adipose Tissue Derived Stem Cells in to Pancreatic Islet-like Cells using Non Integrated Lentiviral Vectors Harboring PDX1

Zahra Niki[1], Ahmad Aleyasin[1]
National Institute of Genetic Engineering and Biotechnology, Tehran, Iran.

Type1 diabetes is caused by insulin deficiency because of auto immune destruction of islet beta cells. The pancreatic transplantation is a promising approach for cure of type1 diabetes. However, lack of suitable donor tissues limits the application. Therefore, differentiated mesenchymal stem cells (MSCs) can be a viable therapeutic source for the treatment of type 1 diabetes. The goal of present experiment is derivation of insulin producing cells from human adipose tissue derived mesenchymal stem cells (ADSCs) in vitro by overexpression of PDX1 transcription factor using non integrated lentiviral vectors. In this study human ADSCs were isolated and identified by flow cytometric analysis. ADSCs were differentiated into adipocyte and osteocyte by differentiating medium to confirm of their multipotency. PDX1-harboring lentiviruses were constructed using specific plasmids and HEK 293 cells. Then, ADSCs were infecced by PDX1-lentiviruses. After infection, ADSCs were cultured in high glucose medium supplement by B27, nicotinamid and BFGF for 3 weeks. The appropriate expression of exogenous PDX1 and insulin were confirmed in the level of protein using immunofluorescent analysis. Differentiated cells were secreted insulin (2.32µU/ml) into culture medium in glucose challenge. Also expression of Ngn3, Glut2, insulin, glucagon, Pax4, PDX1 and somatostatin as specific marker genes of pancreatic cells was investigated by quantitative RT-PCR. In conclusion, our results demonstrated that ADSCs are able to differentiate into insulin-producing cells by and differentiated ADSCs have the potential to be used as a viable resource in cell-based gene therapy of type 1 diabetes.

POSTER #18

A Novel cGMP-compliant Method for Passaging of Human Pluripotent Stem Cells

Ying Nie, Lonza Walkersville, Inc.,

Advancing pluripotent stem cell research to clinical applications requires adapting laboratory-scale cultivation methods to large-scale manufacturing platforms. As a first step, we looked to improve upon existing methods for passaging adherent human embryonic stem cells (hESCs) and induced pluripotent stem cells (hiPSCs). Current practices are labor intensive and highly dependent on the proficiency of skilled technical personnel. In addition, these methods result in substantial loss of cells due to post-detachment cell death. Several alternative methods have been proposed and include the use of enzymes to dissociate hESCs and hiPSCs to single cells. However, continuous cultivation using single cell passaging methods often promotes chromosomal aneuploidy and aberrant gene expression.

To improve upon these existing methods, we developed a chemically-defined, non-enzymatic cell detachment formulation that permits non-mechanical harvesting of multicellular colony fragments. This reagent gently dislodges adherent hESCs and hiPSCs from their substrate and promotes high post-detachment viability (97% +1%) as well as plating efficiency (47% +5%). We have further demonstrated that cells can be cultured for over 25 passages while maintaining pluripotency. Moreover, no morphological or genetic abnormalities were observed. In conclusion, continuous cultivation of hESCs and iPSCs using this method permits streamlining of cell culture processes for both small- and large-scale applications.

POSTER #19

Porcine Wharton's Jelly Cells Engraft in the Intestine and Other Organs after Oral and Intraperitoneal Administration to Allogeneic Recipients.

Kreeson Packthongsuk[1], Theresa Rathbun[1], Deryl Troyer[2], and Duane L. Davis[1]
[1]Department of Animal Sciences and Industry and [2]Anatomy and Physiology, Kansas State University, Manhattan, KS, USA.

Pigs are important biomedical models and Wharton's jelly of the umbilical cord is a rich source of mesenchymal stem cells. The purpose of this research is to determine the engraftment and migration of these perinatal mesenchymal stem cells, known as porcine umbilical cord matrix stem (PUCs) to intestines and various organs of healthy neonatal pigs after administration by intraperitoneal (i.p.) or oral routes. Materials and methods: Umbilical cords were collected at farrowing and PUCs were derived by explant cultures. PUCs were grown in vitro to passage 2 or 3 and administered (1 x 107 viable cells) by intraperitoneal injection within 6 h of birth or given orally before nursing. PUCs were labeled with PKH-26, a red fluorescent cell membrane dye.
At 6 hours, 1 day, and 1 week post treatment pigs were sacrificed (3 pigs/group). Blood, internal organs, mesenteric lymph nodes, peritoneal membrane and omentum were collected. Flow cytometry of blood and confocal microscopy of tissues were performed to identify the existence of labeled-PUCs. Male PUCs were transplanted to female recipients and PCR performed to verify the identity of engrafted cells. Re-culture of enzymatically isolated cells from recipient ileum was performed to verify viable donor PUCs.
Results: No adverse effects were observed after i.p. and oral administration of labeled PUCs. With confocal microscopy, the PKH-26-labeled PUCs were found in the intestine of all recipients. In the small intestine, most of donor cells were located in the intestinal mucosa around the base of intestinal villi and crypts of Lieberkuhn. Labeled-donor cells in recipient blood (collected before sacrifice) were not found by flow cytometry. The porcine Y chromosome specific gene, SRY, was detected in the intestine and various organs of female pigs receiving male PUCs by i.p. injection. Re-culture of PUCs isolated from recipient intestines were detected using confocal microscopy and PCR.
Conclusion: Allogeneic PUCs administered by oral and i.p. routes implant in neonatal pigs and persist for at least 1 week in the intestine. PUCs injected intraperitoneally migrate via the omentum and peritoneum and integrate into various organs. The transplanted PUCs might provide for delivery of vaccines and other therapeutics.

POSTER #20

Isolation of Canine Neural Progenitor Cells for Translational Studies

Maciej Parys[1, 2], Matti Kiupel[1, 2, 3], and Vilma Yuzbasiyan-Gurkan[1,2],
Comparative Medicine and Integrative Biology, 2) Small Animal Clinical Sciences, 3) Pathobiology and Diagnostic Investigation, Michigan State University.

Dogs are ideal candidates for translational research of diseases of the central nervous system (CNS). Dogs spontaneously develop disease complexes similar to challenging human diseases such as amyotropic lateral sclerosis and multiple sclerosis and suffer from acute brain or spinal cord injuries. In addition, they live in the same environmental conditions as their human counterparts. Stem-cell-based therapies can be effectively initiated in dogs in clinical trials before they are adopted for human use in a variety of CNS disorders. Isolation of neural progenitor cells (NPC) in dogs has been documented from the olfactory bulb, but has not yet been described from the cerebrum or the cerebellum. Here we describe successful isolation of NPCs from five adult dogs, immediately after euthanasia for reasons unrelated to this study. Brain tissue was removed from the skull, and pieces of cerebrum, including the periventricular area and cerebellum, were excised. Mechanically dissociated tissues were plated on poly-d-lysine plates in DMEM high-glucose medium with 15% FBS. Cells were subcultured and utilized for further growth, RNA isolation, and immunocytochemistry (IHC). The RT-PCR results confirmed that the isolated cells were positive for the stem cell markers SOX2, Nanog, and Nestin. Additionally, the cells successfully formed neurospheres under appropriate culture conditions, further confirming their neural stem/progenitor phenotype. In conclusion we demonstrated that NPCs can be isolated from canine brain. This study paves the way for future studies of cell-based therapies in dogs as a translational model of human CNS diseases.

POSTER #21

Endothelial Cell Activation Modulates Leukemia Cell Proliferation and Resistance to Chemotherapy via a Positive Feedback Loop Mechanism

Bahareh Pezeshkian[1], Christopher Donnelly[1], Kelley Tamburo[1], Timothy Geddes[2] and Gerard J Madlambayan[1]
[1]Department of Biological Sciences, Oakland University, Rochester, MI; [2]Beaumont Hospital BioBank, Royal Oak, MI

Annually, greater than 12,000 new cases of acute myeloid leukemia (AML) are reported with <10% of these achieving disease-free survival and the majority of patients (~80%) relapsing despite initial remission.[1] To overcome these bleak outcomes, a better understanding of how leukemia cells grow and survive therapy must be developed. Studies have demonstrated a supportive role of vascular endothelial cells (ECs) in normal hematopoiesis both *in vitro* and *in vivo*. A similar intercellular relationship may exist in leukemia. Our studies indicate that leukemia cells modulate EC activity, and through this altered activity, ECs produce microenvironments responsible for leukemia growth, survival and, ultimately, relapse. We observed the ability of leukemia cells to change the behavior of resting ECs by inducing the biological process of EC activation. We demonstrate that in this activated state ECs participate in leukemogenesis through two seemingly opposing effects that act in a concerted fashion to orchestrate necessary steps in

the progression and relapse of the disease. First, activated ECs promote the enhanced proliferation of leukemia cells through paracrine mechanisms. Second, activation also promotes the adhesion of a sub-set of leukemia cells in a process resembling leukostasis. In this attached state, leukemia cells become quiescent and are protected from standard chemotherapy. These attached leukemia cells have the ability to later detach and become proliferative suggesting a role of this process in relapse. Interestingly, because we observed the ability of leukemia cells themselves to induce EC activation, we postulate that a positive feedback loop exists between these cell populations that acts to drive the symptoms seen during disease physiology. Overall, our data implicates EC activation as a new mechanism in leukemia, demonstrates that processes involved in the inflammatory response are active in leukemia, and highlights the potential of using anti-inflammatory drugs during standard treatment of the disease.

POSTER #22

MiR-302 cluster completes iPS cell reprogramming through suppression of MBD2

Nutan Prasain[2,3], Man Ryul Lee[1,2], Hee-Don Chae[1,2], Young-June Kim[1,2], Charlie Mantel[1,2], Hal E. Broxmeyer[1,2] and Mervin C. Yoder[2,3]. Departments of [1]Microbiology and Immunology, and [2]Pediatrics, [3]Herman B Wells
Center for Pediatric Research, Indiana University School of Medicine, Indianapolis, Indiana.

Precise regulation in gene expression is critical for complete reprogramming of somatic cells to induced pluripotent stem cells (iPSCs). Increasing evidence suggests that in addition to a few completely (or fully) reprogrammed iPSCs generated during somatic cells reprogramming with the Yamanaka transcription factors, many incompletely (or partially) reprogrammed cells emerge. Partially reprogrammed cells represent cells trapped in a stable intermediate reprogramming state and currently, there are no methods to reliably convert a large pool of partially reprogrammed cells into fully reprogrammed iPSCs. MicroRNAs (miRNAs) post-transcriptionally regulate expression of many genes involved in diverse cellular processes, including expression of pluripotent gens involved in somatic cell reprogramming. However, the individual miRNAs and their molecular targets and functional roles in inducing complete iPSC reprogramming are not understood. To test this idea, we performed miRNA PCR-array analysis of partially and fully reprogrammed cells. Our miRNA PCR-array analysis revealed that partially reprogrammed cells expressed lower levels of human embroynic stem (hES) cell-specific miRNAs, and maintained higher levels of differentiated somatic cell-specific miRNAs compared to fully reprogrammed cells. We found that inability of partially reprogrammed cells to up-regulate hES cell-specific miR-302 cluster expression locked them in an incompletely reprogrammed state and prevented them from becoming fully reprogrammed iPSCs. We also identified that epigenetic regulator methyl-DNA binding domain protein 2 (MBD2) is a bona-fide target gene of miRNA-302 cluster in inducing complete iPSC reprogramming. We found that MBD2 directly binds to Nanog DNA methylated regions and suppresses Nanog expression in partially reprogrammed cells. However, over-expression of the miR-302 cluster caused repression of MBD2 expression relieving its suppression on Nanog expression, resulting in transitioning of partially reprogramed cells to completely reprogramed iPSCs. Thus, enhanced expression of exogenous miR-302 cluster is an efficient tool to promote complete somatic cell reprogramming to iPSCs by relieving MBD2-mediated inhibition of Nanog expression

POSTER #23

A Non-Enzymatic Method for Isolating Human Adipose-Derived Stromal Stem Cells

Forum S. Shah Research Associate, Xiying Wu, Marilyn Dietrich, Jennifer Rood, Jeffrey M. Gimble
Pennington Biomedical Research Center

The isolation of human adipose stem cells (hASCs) currently relies on the use of the enzyme, collagenase, which digests the triple helix region of peptide bonds in the collagen of adipose tissue. Collagenase is an expensive reagent derived from a bacterial source and its use in isolating ASCs is a time consuming procedure. The quality and consistency of collagenase products between lots and vendors has been a recurring variable in the literature. Additionally, adipose tissue exposure to collagenase has been considered to be more than "minimally manipulated" as defined by Food and Drug Administration guidance documents.

To reduce complexity, investigators have been interested in developing non-enzymatic means of isolating ASCs from human lipoaspirates. This experiment evaluated the extraction of ASCs without an enzymatic digest from 10 donors with similar ages, BMI, and serum profiles. We used a simple method of washing adipose tissue from lipoaspirate with PBS to isolate and characterize the cells, in comparison to the enzymatic procedure, based on processing time, stem cell yield, adipogenic and osteogenic differentiation potential, and immunophenotype. We concluded that while using collagenase substantially increases cell yield, the two methods yield a similar cell product in terms of ability to differentiate. However, the ASCs isolated with the washing method displayed a distinct and potentially favorable immunophenotype, based on flow cytometric analysis. This difference may reflect the absence of chemical alteration of the cells by collagenase exposure.

POSTER #24

Stem Cell-Mediated Imaging of Metastatic Melanoma in Mice

Tej B. Shrestha[a], Sivasai Balivada[a] Matthew T. Basel[a], Marla Pyle[a], Stefan H. Bossmann[b], Deryl L. Troyer[a]
[a]Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, Manhattan, KS;
[b]Department of Chemistry, Kansas State University, Manhattan, KS

Tumors share several traits with wounds. For example, they behave like wounds in that they recruit cells from surrounding tissue as well as from bone marrow to provide support and nutrition. Bone marrow mesenchymal stem cells (MSCs) migrate toward wounds and other areas of pathology. Due to tumor tropic behavior of stem cells, stem cell technology for diagnostic and therapeutic purposes is an emerging field in cancer biology. Mouse neural stem cells (NSC) are very similar to bone marrow mesenchymal stem cells and tend to migrate toward cancer sites. Bioluminescence imaging of tumors is a noninvasive tumor imaging modality. *Gaussia luciferase* (Gluc) emits blue light when in the presence of its substrate, coelenterazine. Both Gluc and coelenterazine are non toxic, and the blue light generated by this system can be used for diagnostic and therapeutic purposes using tumor tropic stem cells. We engineered NSC with secretory Gluc (NSC-Gluc). These Gluc-engineered cells were injected systemically into

C57BL/C mice bearing metastatic B16F10 lung melanoma. After IV injection of coelenterazine, these mice were imaged for Gluc on a Caliper IVIS Lumina II bioluminescent imager, the Caliper IVIS Lumina II. The imaging process revealed disseminated bioluminescent regions throughout the body. Necropsy revealed black metastatic tumors in the regions showing bioluminescence signaling. Taken together, these data imply that the NSC-Gluc migrated to the tumor sites and secreted Gluc. Thus, these cells are good candidates for delivery of chemotherapeutic drugs, genes of interest, and imaging contrast agents.

POSTER #25

Developing Enhanced Stem Cells for Therapeutic Application in Alzheimer's Disease
Erika Sims and Eva Feldman

Alzheimer's disease (AD), the most prevalent neurodegenerative disease, is characterized by the loss of neurons and synaptic contacts in the cortex and hippocampus. Current therapies for AD target the neurotransmitter systems, such as the cholinergic system. Enhancing cholinergic function improves both cognitive and behavioral defects associated with AD. Stem cells have the potential to replace neurons and/or provide trophic support to the existing cell population. Thus, stem cells may offer a new approach in the treatment of AD. We hypothesize that enhancing trophic support by combining cortical stem cells (designated HK532 cells) with increased insulin growth factor I (IGF-I) production will delay AD progression by increasing neurogenesis and neuroprotection. IGF-I is a neuroprotective factor known to promote neurogenesis and neurite outgrowth. Our aim in this study is to understand the role of IGF-I in stem cell biology and its potential to enhance the neuroprotective effects of stem cells. Here, we characterize the differentiation phenotypes of HK532 and demonstrate that HK532:IGF-I have an increased neural differentiation and migration. IGF-I production does not affect proliferation. Our findings indicate that enhanced IGF-I production in HK stem cells result in increased integration and neuroprotective properties. Our future studies will further characterize the therapeutic potential of HK532:IGF-I cells for the treatment of AD.

POSTER #26

Gsk3 Beta Activity Dictates the Tumor-like Growth of Mouse Embryonic Stem Cells
Tetsuya S. Tanaka Department of Animal Sciences, Institute for Genomic Biology, University of Illinois at Urbana-Champaign, IL

Replacement tissues derived from induced pluripotent stem cells (iPSCs) and embryonic stem cells (ESCs) possess a risk of developing teratomas. Surprisingly, the genetic mechanism responsible for their tumor-like growth remains poorly investigated. Our recent study has demonstrated that mouse ESCs failed to grow as teratomas but retained pluripotency when cultured under unique chemically-defined serum-free conditions (Li *et al*., *PLoS ONE* 6, e21355, 2011). Also, we have shown in the same study that mouse ESCs cultured under serum-free conditions supplemented with a pharmacological inhibitor of glycogen synthase kinase 3 (Gsk3) beta efficiently developed into teratomas. Therefore, we hypothesize that constitutive activation of Gsk3 beta is sufficient to suppress the tumor-like growth of mouse ESCs even though they are maintained under standard conditions with animal serum. We have tested this hypothesis by

introducing a cDNA encoding the constitutively active form of Gsk3 beta, namely S9A, into mouse ESCs using a novel expression vector. Data show that the growth rate of mouse ESCs that stably express S9A was decreased compared to that of mouse ESCs expressing wild-type Gsk3 beta. When subcutaneously injected into immunocompromised mice, mouse ESCs that harbor S9A developed into significantly smaller teratomas than the same ESCs treated with the Gsk3 beta inhibitor. It is strongly suggested with these results that the downstream of Gsk3 beta is responsible for the tumor-like growth of mouse ESCs, which can be suppressed even under standard culture conditions when the correct target is identified.

POSTER #27

Selective Metal Sensitivity in hiPSC-derived Neural Progenitors from a Preclinical Parkinson's Disease Patient

Andrew M. Tidball1,3*, Asad A. Aboud1*, Kevin K. Kumar1,3, Bingying Han1, Gary G. Li1, Peter Hedera1,2,3, M. Diana Neely1,2,4, Kevin C. Ess1,2,3,5, and Aaron B. Bowman1,2,3,4,5
Vanderbilt University Medical Center, 1Dept. of Neurology, 2Vanderbilt Kennedy Center, 3Vanderbilt Brain Institute, 4Vanderbilt Center in Molecular Toxicology, 5Vanderbilt Center for Stem Cell Biology, Nashville TN 37232-8552

A constellation of environmental and genetic risk factors for Parkinson's disease (PD) are thought to modify disease onset and progression in a patient-specific manner. We sought to assess interactions between these factors in a human subject with preclinical PD by measuring toxicological sensitivities to PD-relevant environmental toxicants in neural cultures derived from that subject. Human induced pluripotent stem cells (hiPSCs) were generated from patient SM and healthy control subjects to allow differentiation of patient-specific neural progenitor cells (NPCs). The patient (SM) has biallelic mutations to PARK2 yet lacks parkinsonian motor symptoms by neurological exam, while the healthy controls (CA and CB) have no known PD genetic risk factors. We assessed the sensitivity of these NPCs cultures to heavy metal cytotoxicity and mitochondrial-related phenotypes. DaTscan imaging of the patient (SM) revealed preclinical PD consistent with biallelic PARK2 mutations. SM NPCs but not the patient's primary fibroblasts were significantly more sensitive to copper and cadmium cytotoxicity than those derived from controls. No differences in cellular copper accumulation were observed. However, SM NPCs exhibit increased cellular ROS accumulation and enhanced mitochondrial fragmentation and depolarization following copper exposure versus controls. Given the role of PARK2 in mitochondrial integrity, we hypothesized that heightened sensitivity of SM NPCs to copper was due to enhanced mitochondrial-related abnormalities after exposure. Our results suggest that PD genetic risk factors may increase sensitivity to a subset of environmental risk factors. Furthermore, we demonstrate that hiPSC technology can detect subject-specific differences in vulnerability to PD-environmental risk factors.

POSTER #28

Targeting CD44 in Head and Neck Cancer for Treatment and Imaging

Ranjeeta Thapa[1, 2], Sandra Galoforo[2], Mohammad El-Dakdouki[3]
Xuefei Huang[3], George D. Wilson[1, 2]
[1]Department of Physics, Oakland University, Rochester, MI

[2]Department of Radiation Oncology, William Beaumont Hospital, Royal Oak, MI
[3]Department of Chemistry, Michigan State University, East Lansing, MI

Stem cells are characterized by their ability to produce varieties of cell types with specialized functions and their self-renewal to produce a number of stem cells. We are focusing here on Head and Neck Squamous cell cancer (HNSCC) stem cells. In HNSCC, it has been suggested that the cancer stem cells (CSC) population is contained within the cell fraction that expresses high levels of the surface glycoprotein CD44. This Transmembrane protein serves as receptor for Hyaluronan (HA) and certain Matrix Metalloproteinases (MMP). HA binding to CD44 promotes its association with epidermal growth factor receptor (EGFR) as well as EGFR phosphorylation. Phosphorylated EGFR signals the phosphorylation of extracellular signal-regulated kinases (ERK) 1 and 2 to promote tumor cell growth, migration, and chemotherapy resistance resulting in head and neck cancer progression. Super paramagnetic iron oxide nanoparticles can be used in medicine for drug delivery, diagnostic imaging, and targeted therapy to different types of cancers. In this study, we used Hyaluronic acid attached dextran coated super paramagnetic iron oxide nanoparticles (HA-DESPIONs) to target CD44.

POSTER #29

The Effects of Arsenite on Human Cord Blood Stem Cells.

Naimisha Reddy Beeravolu[1,2], Afton Turner[3,2], G. Rasul Chaudhry[1,2]
[1]Department of Biological Sciences, [2]OU-WB Institute for Stem Cell and Regenerative Medicine, Oakland University, Rochester, MI and [3]School of Pharmacy and Biomedical Sciences, University of Central Lancashire, UK

Environmental arsenic exposure has known correlations with cancer as well as other severe afflictions including neurological and cardiovascular diseases, presenting an important public health issue. Populations are mainly exposed to a form of arsenic via food and drinking water contamination. Some countries have reported excessive arsenic concentrations in their groundwater supply, exposure to which has been linked to specific and proportional adverse effects (Tokar et al., 2011). Therefore it is important to establish the influence of arsenic on human cells and damage induced at certain concentrations. The use of human cord blood stem cells (CBSCs) is a good platform to investigate this effect as they have already been used for therapeutic treatments against many haematopoietic and genetic diseases via regenerative medicine therapy (Harris, 2008). Human CBSCs also have a high level of stemness and culture tolerance but reduced research implications compared to human embryonic stem cells and thus are the best alternative. Arsenic exposure has been investigated with a plethora of cell types in a variety of environments, yet none with CBSCs. However bone marrow mesenchymal stem cells (MSCs) are the closest in association to the CBSCs used in this investigation (Yadav et al., 2010). Thus for this study, CBSCs have been exposed to varying concentrations of inorganic arsenite (iAsIII) 10 nM – 50 µM for 24 -72 hr. There is an apparent growth trend with the most growth at 100 nM and decreasing at higher concentration with the least growth seen at 50 µM. Growth also depicts trends on both confluency and cell morphology.

POSTER #30

FIP200 is required for maintenance and differentiation of postnatal neural stem cells through regulation of oxidative state

Chenran Wang[1], Chun-Chi Liang[1], Z. Christine Bian[1], Yuan Zhu[1,2] and Jun-Lin Guan[1,2]
[1]Division of Molecular Medicine and Genetics, Department of Internal Medicine, [2]Department of Cell and Developmental Biology, University of Michigan Medical School, Ann Arbor, MI 48109, USA

Despite recent studies showing depletion of hematopoietic stem cells (HSCs) pool accompanied by increased intracellular ROS upon autophagy inhibition, it remains unknown whether autophagy is essential in the maintenance of other stem cells. Moreover, it is unclear whether and how the aberrant ROS increase causes depletion of stem cells, as they were not examined in previous studies on HSCs and a recent study indicates that a high level of ROS is required for self-renewal of neural stem cells (NSCs). Here, we report that ablation of *FIP200*, an essential gene for autophagy induction in mammalian cells, results in a progressive loss of NSC pool and impairment in neuronal differentiation specifically in the postnatal brain, but not the embryonic brain. The defect in maintaining the postnatal NSC pool was caused by p53-dependent cell cycle arrest and apoptotic responses in SVZ and SGZ of mutant mice. However, the impaired neuronal differentiation was rescued by anti-oxidant NAC treatment, but not by p53 inactivation *in vivo*. These data reveal a role of FIP200-mediated autophagy in the maintenance and functions of NSCs through regulation of oxidative state.

POSTER #31

Reprogramming of Hepatic Progenitor Cells Towards a Beta Cell Character Using Pdx1, Ngn3 and MafA

Ying Yang, Ersin Akinci, Anannya Banga, James R. Dutton, Jonathan M.W. Slack
Stem Cell Institute, University of Minnesota

The pancreas and liver arises from adjacent areas in the anterior endoderm of the developing embryo. This close relatedness underlies the possibility of direct reprogramming of the liver or hepatocytes towards pancreatic beta cells. In the present study we showed that E14-16 dissociated hepatoblasts, which are considered as hepatic progenitor cells could be reprogrammed towards a beta like cell fate along with ectopic expression of the pancreatic transcription genes (Pdx1, Ngn3, and MafA) using a polycistronic adenovirus. This was associated with approximately 7% of hepatoblasts expressing insulin as well as C-peptide along with a significant increase in endocrine gene profiles and downregulation of liver markers. Moreover the reprogrammed cells were seen to become green when hepatoblasts were isolated from Pdx1-GFP CreER mice, indicating turning on of the endogenous Pdx1, a hallmark for genuine reprogramming. This allowed us to sort the green cells which upon stimulating with low (2.8mM) and high (20mM) glucose in the medium showed a modest amount of glucose-sensitive insulin release, thus providing evidence that these reprogrammed hepatoblasts were glucose responsive. In undissociated organ culture from E10-12 liver buds, the Ad-PNM could also efficiently transform hepatoblasts into insulin-positive cells, as well as changing the gene expression profiles towards an endocrine lineage. We suppose the mesenchymal cells in organ

culture may support the progenitor state of hepatoblasts, which contributes to their susceptibility to be reprogrammed. In summary, the hepatic progenitor cells, which may possess a similar epigentic pattern to pancreatic progenitor cells, are highly prone to be reprogrammed by overexpressing pancreatic transcription factors. This can be a promising resource of cell therapy for diabetes.

POSTER #32

Guided Axonal Growth of Chicken Embryonic Spinal Motor Neurons on Structured Textile Fibers

Stefan Weigel[1, 2], Li Yao[3, 4], Marcel Halbeisen[1], Abhay Pandit[4], Arie Bruinink[1],
1.Materials Science & Technology (Empa), Lerchenfeldstrasse 5, CH-9014 St. Gallen, Switzerland; 2. Department of Zoology, Technische Universität München, Freising, Germany; 3. Department of Biological Science, Wichita State University, KS; 4. NFB, National University of Galway, Galway, Ireland

Introduction: In the current century, one of the most challenging issues of neuroscience is the regeneration of injured nerves. Today, critical nerve defects are bridged using hollow conduits with or without supporting cells or materials. Approaches using structured textile materials are promising for enhancing their functionality. Usually the success of neurite regeneration is evaluated at one or a few time points. The dynamic processes of growth cone translocation (outgrowth and retraction) can hardly be elucidated in that way. By real time observation additional decisive information can be obtained to optimize neuroregeneration supportive materials.
Materials and Methods Cell culture: Chicken embryonic motoneurons were isolated at stage 28. Reaggregates were formed by shaking and placed near the fibres. On-line CLSM monitoring was started after an equilibrium period of 16 hours.
Plasmid: Cells were transfected with a modified RFP-plasmid vector either in ovo after breeding the eggs for 70 hours at 37 ºC or using the Amaxa Nucleofector II after dissociating the cells.
Textile fibres: To correlate fibre characteristics (chemistry, structure, diameter) with neurite outgrowth different fibres were evaluated: fibres of a diameter of 18-22µm Polyethylenterephthalat (PET), Polylactid (PL), and the Polyamides (PA) 6 and 6.6, PET fibres with a diameter of 50µm and Triacetate and Viscose fibres, which have a natural longitudinal structure and PET fibres with laser-induced artificial groove.
Data collection and analysis: Growth cone behaviour was analysed by comparing subsequent pictures taken every 5 min. Growth cones that could be tracked for at least 3 hours were manually marked in each picture in analogy to Adams and co-workers. Migration (velocity and direction) was quantified using Visiometrics software as previously described.
Results and Discussion The dynamics of axonal growth like outgrowth and retraction can be monitored using fluorescent protein labelled motoneurons. Comparing growth cone behaviour on various textile fibres and plane surfaces we observed that fibres were not seen by the neurite as equivalent substratum to grow on. Migration velocity on the plane surface and the various fibres was not significantly different. However, the movement along the fibre axis differed depending on fibre characteristics. It was especially evident that the application of a groove to the fibre was able to align neurite outgrowth.

Conclusions By observation RFP labelled neurons using a CLSM we can monitor the dynamics of neuronal growth like outgrowth and retraction. In addition to classical end-point observation we demonstrated that neurite outgrowth is usually not straight but can be influenced by fibre surface structure.

POSTER #33

Expression of Stemness Markers and Sarcosphere Formation in Human and Canine Osteosarcoma

Ya-Ting Yang[1], and Vilma Yuzbasiyan-Gurkan[1,2]
[1]Comparative Medicine and Integrative Biology Program, [2,] Small Animal Clinical Sciences, College of Veterinary Medicine, Michigan State University

Osteosarcoma (OS) is the most common primary bone tumor of both humans and dogs. The high recurrence rate, resistance to chemotherapy and radiotherapy requires novel approaches. In various cancers, a small population of cells with self-renewing capacity and responsible for tumor growth and metastasis have been identified and designated cancer stem cells, CSCs. Identification and effective targeting of CSCs are necessary for successful treatment of these cancers. The heterogeneous cell types of OS suggests the involvement of CSCs in OS. In some studies, the ability to form spheres in semi-solid media has been proposed as a characteristic of CSCs and in others, the expression of the general stemness markers such as OCT4 has been proposed as a major phenotype of the CSCs. In this study, we wanted to evaluate the sarcosphere forming fraction of two OS cell lines, D17 and SAOS2, canine and human OS cell lines, respectively. Both D17 and SAOS2 cells were transfected with an OCT4-YFP (yellow florescent protein) reporter construct. The YFP positive and negative cell fractions were isolated from both cell lines by flow cytometry and evaluated for sarcosphere forming ability. In addition, expression of OCT4 and other stemness markers, NANOG and SOX2 were evaluated. All cells were characterized for their tumorigenic potential *in vitro*, including invasion ability, as well as formation of sarcospheres. Our data show that OCT4 positive cells were more invasive than negative subsets in both D17 and SAOS2 cell lines. In addition, both OCT4 positive and negative subsets of both cell lines were able to form sarcopheres. However, OCT4 positive cells formed larger spheres than negative cells. These findings suggest that neither sarcosphere formation nor OCT4 expression are sufficient to define the CSCs in canine and human OS. Further studies are needed to identify CSCs in OS. The similarity of the observations in the canine and human cell lines adds further support to the use of the canine disease as a useful model for human OS.

POSTER #34

The Use of Mesenchymal Stem Cell Therapy for Intervertebral Disc Regeneration

G. Zachary White B.S., Michigan Head and Spine Institute, Medical Student
Fadumo S. Adbi B.S., Michigan Head and Spine Institute, Medical Student
Mick J. Perez-Cruet, M.D., M.S., Michigan Head and Spine Institute, Primary Investigator

The intervertebral disc is an avascular two part structure composed of a highly organized collagen rich lamella outer annulus fibrosis (AF) and a central nucleus pulposus (NP). As age

increases, both the NP and the AF grow less gelatinous, inflammatory processes increase, and the availability of nutrients become limited. This process often results in degenerative disc disease (DDD), which is associated with lower back pain and is a significant source of morbidity and mortality worldwide. DDD is caused by such factors as physical stress, occupational stress, or genetic predispositions to differences in disc protein production which leads to permanent changes of the NP and AF. The treatments for DDD expand from conservative means of physical therapy and epidural injects to minimally invasive surgeries. Given the growing body of scientific research, the treatment option of mesenchymal stem cells (MSCs) treated is becoming a viable option. MSCs with chondrogenic growth factors and transplanted with hydrogel scaffolds intended to aid in optimum restoration of the disc and retardation of degeneration. However, the experimental models have predominantly employed small animals, with very little availability of human models. The goal of this report is to discuss the pathophysiology of DDD and the progress of MSC implantation to slow disc degeneration, while bringing to attention the potential focus areas for clinical application. Determining the patient for whom this is intended for, the appropriate source of stem cells and scaffold, the appropriate dose, and determining if other methods of treatment should accompany implantation are all important focus areas.

POSTER #35

Characterization Of The Cellular Origins Of Autologous Bone Marrow-Derived Mesenchymal Stromal Cells In Ixmyelocel-T

Presenting: Frank Zeigler, Sr. Director of Research, Aastrom Biosciences, Inc.,
F. Zeigler, L. Wolterink, J. Osborne, C. Parrish, A. Wong, H. Evens, E. Murphy, and R. Bartel
Aastrom Biosciences, Inc. Ann Arbor, MI USA

Mesenchymal stromal cells (MSCs) have been shown to regenerate ischemic tissue through induction or stabilization of new blood vessel formation. During embryonic development it is well established that a common progenitor to both the vascular and hematopoietic systems exists, the hemangioblast. In adults however the precise nature of the source of both autologous MSCs and allogeneic MSCs remains uncertain, despite controversial reports that MSC-like, putative endothelial progenitors can be identified in bone marrow mononuclear cells (BMMNC) and peripheral blood, which maintain some capacity for differentiation into de novo endothelial cells. The ixmyelocel-T process, which contains only animal serum and no other exogenous factors, has previously been shown to lead to a reduction of both CD34+Lin- HSC phenotype (approximately 5-fold) and this is mirrored by a concomitant reduction in clonal hematopoietic colony-forming activity, and expansion of adherent stromal cells which are phenotypically, MSCs. We have characterized this culture process which generates patient-specific MSCs from expanded bone marrow in ixmyelocel-T using a number of approaches, including univariate and multivariate statistical analyses, which addressed the hypothesis that a single cell type in adult BMMNCs could be associated with the expanded MSCs (CD90+, CD105+, CD146+, CD45-, CD34-). These results showed that only the hematopoietic stem/progenitor phenotype CD34+Lin- (HSC) number in BMMNCs was significantly associated with the number of CD90+ MSCs (p value 0.0038), and interestingly, that the number of CD90+ cells in BMMNCs did not correlate with the input amount of this same MSC marker (p value 0.8285). These results appeared to indicate an association of the CD34+Lin- HSCs with the MSC phenotype after

expansion, and we therefore attempted to identify a subset of HSCs that expressed MSC markers. We show here that the CD34+Lin- HSC population, which is known to be a mixture of self-renewing stem cells and lineage-committed hematopoietic progenitors, does express a number of well-characterized MSC markers (CD73, CD90, CD105, and CD146) on a discreet subpopulation, but that only CD90 was also expressed on the more primitive HSC, defined by CD133 co-expression. Furthermore, using FACS-sorting we have depleted the BMMNCs of both the CD34 and CD90+ phenotypes in BMMNCs, and show that removing either of these phenotypes also reduces or eliminates the expansion of cells with an MSC phenotype. Since low-level expression of CD90 has also been reported on the definitive, long-term repopulating HSC, we preliminarily conclude that a very rare, putative HSC in adult BMMNCs is the likely source of the MSCs in ixmyelocel-T, and that this cell may in fact be derived from the pool of hematopoietic progenitors.

POSTER #36

A Novel Reporter System to Identify Osteogenic Progenitor Cells Derived from hESCs

Li Zou, Ross Kopher, Aarathi Shanmugam, Dan Kaufman
Stem Cell Institute, University of Minnesota

Purpose: in order to identify osteogenic progenitor cells derived from human embryonic stem (hES) cells and to evaluate the osteogenic effect of various reagents in vitro, the RUNX2-YFP reporter system was developed and integrated into H9-hESCs. The reliability of the reporter system in osteogenic differentiated hESCs was evaluated in vitro.

Methods: The RUNX2-YFP reporter system, a plasmid encoded with promoter for RUNX2 driving YFP expression and with promoter for constitutive luciferase expression, was introduced into the H9-hESCs by nucleoinfection. By selecting luciferase positive cells, the RUNX2-YFP tagged hESCs were purified and subcultured on MEF feeder cells. To induce osteogenic progenitor cells, H9-ESCs were cultured on different extracellular matrix in various differentiation media. The YFP expression level in the RUNX2-YFP hESCs was monitored under fluorescent microscope qualitatively and evaluated by flow cytometry. And RUNX2 expression level in the cells was further assessed by quantitative rt-PCR. The mineralization of the differentiated cells was visualized by von Kossa staining in vitro.
Results: First, we confirmed that in our reporter system, the expression profile of YFP in the H9-YFP-RUNX2 hESCs is consistent to that of RUNX2 expression level, when cells were cultured in the osteogenic differentiation media. Von Kossa staining showed obvious mineralization of the osteogenic progenitor cells in the differentiation media. After seeded on different extracellular matrix, the H9-RUNX2-YFP hESCs demonstrated higher YFP expression level on gelatin or matrigel, but not on fibronectin or on the regular cell culture surface. Compared to the serum free media, the presence of serum, even at 2% of FBS, in the differentiation media is required for the osteogenic differentiation of these cells.
Conclusion and future works: Our preliminary data shows gelatin and Matrigel are two important extracellular matrix to promote osteogenic differentiation in the proper differentiation media. And our RUNX2-YFP reporter system tagged with luciferase provides an easy and efficient way to monitor the osteogenic potential of differentiated cells, although further study is needed to test the osteogenic capability of these YFP positive cells in vitro and in vivo.

Conference Participants

Bradly Alicea (doctoral candidate)
Michigan State University
Anthony hall
474 S Shaw Ln Rm B270A
East Lansing, MI 48824
Michigan State University
freejumper@yahoo.com

Ali S. Arbab, M.D., Ph.D.
Henry Ford Health System
Senior Scientist and Director
CMIL, Radiology, HFH, Detroit, MI 48202
Tel: 313-874-4435
Fax: 313-874-4494
saali@rad.hfh.edu

Craig S. Atwood, Ph.D.
University of Wisconsin Medical Center
William S. Middleton Memorial Veterans Hospital
GRECC 11G
2500 Overlook Terrace
Madison, WI 53705
Tel: 608-256-1901 Ext. 11664
Fax: 608-280-7291
csa@medicine.wisc.edu

Frank Baaijens, Ph.D.
Eindhoven University of Technology
Biomedical Engineering | Eindhoven University of Technology, P.O. Box 513, 5600 MB Eindhoven, Netherlands
Tel: +31-40-2474888
F.P.T.Baaijens@tue.nl

Naimisha Reddy Beeravolu M.S.
Oakland University
2200 N Squirrel Road
Rochester, MI 48309
Tel: (248) 370-3350
Fax: (248) 370-3586
nbeeravo@oakland.edu

Ronnda L. Bartel, Ph.D.
Aastrom Biosciences, Inc.
Dominos Farms, Lobby K
24 Frankloy Wright Dr.
Ann Arbor, MI 48105
Tel: 734-418-4400
rbartel@aastrom.com

Nissim Benvenisty, M.D., Ph.D.
The Hebrew University of Jerusalem,
Givat-Ram, Jerusalem 91904, Israel.
Tel: 972-2-6586774
Fax: 972-2-6584972
nissimb@cc.huji.ac.il

Dean H. Betts, Ph.D.
University of Western Ontario
Schulich School of Medicine & Dentistry
Dental Sciences Building, Room DSB 2022
Western University
London, Ontario, Canada
N6A 5C1
Tel: 519-661-3786
Fax: 519-661-3827
dean.betts@schulich.uwo.ca

Kapil Bharti, Ph.D.
NIH: Ophthalmic Genetics and Visual Function Branch
Building 10, Room 10N226
10 Center Drive, MSC 1860
Bethesda, Maryland 20892-1860
Tel: 301-496-3577
Fax: 301-402-1214
kapilbharti@ninds.nih.gov

G. Rasul Chaudhry, Ph.D.
Oakland University
2200 N Squirrel Road
327 Science and Engineering Building
Rochester, MI 48309
Tel: 248-370-3350
Fax: 248-370-3586
chaudhry@oakland.edu

Ferman Chavez, Ph.D.
Oakland University
2200 N Squirrel Road
260 Science and Engineering Building
Rochester, MI 48309-4477

Tel: 248-370-4092
Fax: 248-370-2321
chavez@oakland.edu

Chien-Wen Chen, M.D., Ph.D.
University of Pittsburgh
Stem Cell Research Center
Bridgeside Point II Bldg, Suite 206
450 Technology Drive,
Pittsburgh, PA 15219
williamcwchen@gmail.com

Jose Cibelli, Ph.D.
Michigan State University
Anthony hall
474 S Shaw Ln Rm B270A
East Lansing, MI 48824
Tel: 517-432-9206
cibelli@anr.msu.edu

Sarah Conley, Ph.D.
University of Michigan
2800 Plymouth Rd
NCRC Bldg 26 Rm 333S
Ann Arbor MI 48109-2800
Tel: 734-763-3748
sarsanto@med.umich.edu

Thomas Diekwisch, D.M.D., Ph.D. (sc.), Ph.D. (phil.)
University of Illinois, UIC College of Dentistry
801 South Paulina Street, MC 690
Chicago, Illinois 60612
Tel: 312-413-9683
Fax: 312-996-6044
tomdkw@uic.edu

Sumi Dinda, Ph.D.
3164 HHB, School of Health Sciences
2200 N Squirrel Road
Oakland University
Rochester, MI 48309.
Tel: 248-364-8676
Fax: 248-364-8657
sdinda@oakland.edu

Greg Dressler, Ph.D.
University of Michigan
BSRB 2049
109 Zina Pitcher Dr.
Ann Arbor, MI 48109-2200
Tel: 734-764-6490
dressler@med.umich.edu

Paul Dyce, Ph.D.
University of Western Ontario School of Medicine
1151 Richmond St.
London, ON N6A 3K7, CA
Tel: 519-661-2111 ext. 86925
Paul.Dyce@schulich.uwo.ca

James Eliason, Ph.D.
Wayne State University
Great Lakes Stem Cell Innovation Center
440 Burroughs, Suite 520
Detroit, MI 48202
Tel: +1 (313) 405-7705
aa3574@wayne.edu

Richard Fessler, M.D., Ph.D.
Northwestern University
676 N. St. Clair St., Suite 2210
Chicago, IL 60611
Tel: 312-695-0087
Fax: 312-695-0025
RFessler@nmff.org

Erik J. Forsberg, Ph.D.
WiCell Research Institute and the University of Wisconsin-Madison 614 Walnut Street, 13th Floor
Madison, WI 53726
Tel:608-334-7876
eforsberg@wicell.org

Katrina Fox, M.S.
Kansas State University, College of Veterinary Medicine
3901 Rainbow Blvd
Kansas City, KS 66160
kfox@vet.k-state.edu

Judith Fulton, Ph.D.
Akron General Medical Center
400 Wabash Ave
Akron, OH 44307
Tel: 330-344-6394
judy.fulton@akrongeneral.org

Jose L. Garcia-Perez, Ph. D.
Pfizer-University of Granada-Junta de Andalucía Center for Genomics and Oncological Research Parque Tecnológico de Ciencias de la Salud
Avenida de la Ilustración 114 18007
Granada, Spain
Tel: 958-637-082
Fax: +34-958-637-071
jlgp@genyo.es

Michael Gilkey, MBA, M.S.
National Center for Regenerative Medicine
2103 Cornell Rd, Wolstein Research Building 2-501
Cleveland, OH 44106
Tel: 216-368-2079
Fax: 216-368-6020
meg14@case.edu

Gokul Gopinathan, Ph.D.
University of Illinois, UIC College of Dentistry
801 South Paulina Street, MC 690
Chicago, Illinois 60612
Tel: 312-413-9683
Fax: 312-996-6044
ggokul@uic.edu

Jason A. Hamilton, Ph.D.
Athersys, Inc.
3201 Carnegie Ave.
Cleveland, Ohio 44115
Tel: 216-431-9900
Fax: 216-361-9495
jhamilton@athersys.com

Gary Hammer, M.D., Ph.D.
University of Michigan Medical School
109 Zina Pitcher Place, 1502 BSRB,
Ann Arbor, Michigan 48109-2200
Tel: 734-936-5033
ghammer@med.umich.edu

Ales Hampl, D.V.M., Ph.D.
Masaryk University
Žerotínovo náměstí 617/9, 601 77
Brno Czech Republic
ahampl@med.muni.cz

Zhengqing Hu, M.D., Ph.D.
Wayne State University School of Medicine
550 E. Canfield St. 258 Lande
Detroit, MI 48201
Tel: 313-577-0594
zh@med.wayne.edu

Ralf Huss, M.D., Ph.D.
Apceth GmbH in Munich, Germany
Max-Lebsche-Platz 30
D-81377 Munich
r.huss@apceth.com

Branislava Janic, Ph.D.
Henry Ford Health System,
1 Ford Place, 2F
Detroit, MI 48202
Phone: 313-874-1681
bjanic@rad.hfh.edu

Jan Jensen, Ph.D.
Cleveland Clinic
Department of Stem Cell Biology and Regenerative Medicine
9500 Euclib Ave
Cleveland, OH 44195
jensenj2@ccf.org

Quan Jiang, Ph.D.
Henry Ford Health System
Department of Neurology
Henry Ford Health System
Tel: 313-916-8735
Fax: 313-916-1324
qjiang1@hfhs.org

Dan Kaufman, M.D., Ph.D.
University of Minnesota
2221 Southeast University
Avenue Minneapolis, MN 55414
Tel: 612-624-092
kaufm020@umn.edu

Paul H. Krebsbach, DDS, Ph.D.
University of Michigan
School of Dentistry
1011 North University
Ann Arbor, MI 48109
Tel: 734-936-2600
paulk@umich.edu

Sarah Krueger, Ph.D.
William Beaumont Hospital
Research Institute
3811 W. Thirteen Mile Rd.
Royal Oak, MI 48073
Office: 248-551-4182
Fax: 248-551-0670
Sarah.Krueger@beaumont.edu

Ernest F. Krug, III, M.Div., M.D., FAAP
OUWB School of Medicine
Oakland University
2200 N. Squirrel Road
122 O'Dowd Hall
Rochester, Michigan 48309
Tel: 248-370-3664
krug@oakland.edu

Hillard Lazarus, M.D.
Case Western University
11100 Euclid
Cleveland, OH 44106
Tel: 216-844-3629
Fax: 216-844-5979
hml@case.edu

Chunying Li, Ph.D.
Wayne State University School of Medicine
540 E. Canfield Avenue, 5312 Scott Hall
Detroit, MI 48201
cl@med.wayne.edu

Linheng Li, Ph.D.
Stowers Institute for Medical Research
1000 East 50th Street
Kansas City, MO 64110
lil@stowers.org

Qi Li, Ph.D.
UIC College of Dentistry
801 South Paulina Street, MC 690
Chicago, Illinois 60612
Tel: 312-413 9683
Fax: 312-996-6044

Feng Lin, Ph.D.
Case Western Reserve University
2085 Adelbert Road, R 306
Cleveland, OH 44106
Tel: 216-368-2118
Feng.Lin@case.edu

Xianghong Luan, M.D.
UIC College of Dentistry
801 South Paulina Street, MC 690
Chicago, Illinois 60612
Tel: 312-413-9683
Fax: 312-996-6044
luan@uic.edu

Domenico Luongo, M.S., C.H.M.M.
Oakland University
2200 N Squirrel Rd
Rochester, MI 48309-4401
Tel: 248-370-4314
Fax: 248-370-4376
luongo@oakland.edu

Gerard Madlambayan, Ph.D.
Oakland University
Engineering Biology Program
325 DHE, Oakland University
Rochester, MI 48309
(248) 370-3585
madlamba@oakland.edu

Tristan Maerz, M.S.
Beaumont Health System-Research Institute

3811 W. 13 Mile Rd., Ste 404
Tel: 248-551-6281
Fax: 248-551-0191
Tristan.Maerz@beaumont.edu

Ivan Maillard, M.D., Ph.D.
University of Michigan
210 Washtenaw Ave
Ann Arbor, MI 48109-2216
Tel. 734-763-3599
imaillar@umich.edu

Martin Marsala, M.D.
University of California -San Diego
Sanford Consortium for Regenerative Medicine
2880 Torrey Pines Scenic Drive
La Jolla, CA 92037
Tel: 858-822-3805
Fax: 858-822-3249
mmarsala@ucsd.edu

Melvin McInnis, M.D.
University of Michigan
Department of Cell and Developmental Biology
109 Zina Pitcher Place 3061 BSBR
Ann Arbor, MI 48109
mmcinnis@med.umich.edu

Christina McKee, M.S.,
Oakland University
2200 N Squirrel Rd
Rochester, MI 48309
Tel: 248-370-3350
Fax: 248-370-3586
cmmckee@oakland.edu

Anne Mitchell, Ph.D., R.N., C.R.N.
Oakland University
School of Nursing
418 O'Dowd
Rochester Michigan 48309-4401
Tel: 248-370-4089
mitchell@oakland.edu

Jack T. Mosher, Ph.D.
University of Michigan Center for Stem Cell Biology
Life Sciences Institute, Medical School
Ann Arbor, MI 48109
Tel: 734-615-3588
mosherjt@umich.edu

Ying Nie, Ph.D.
Lonza Walkersville, Inc.
8830 Biggs Ford Road
Walkersville, MD 21793
Tel: 301-898-7025
ying.nie@lonza.com

Dan O'Donnell
Fisher BioServices
14665 Rothgeb Drive
Rockville, MD 20850
Tel: 240-401-4524
Dan.h.Odonnell@thermofisher.com

Jon Odorico, M.D.
University of Wisconsin Hospital
H4/756 CSC
600 Highland Ave.
Madison, WI 53792
Tel: 608-263-4768
Fax: 608-262-6280
jon@surgery.wisc.edu

Suresh Selvaraj Palaniyandi, Ph.D.
Henry Ford Health System
2799 W. Grand Blvd, Education and Research Building Room 7044
Detroit, MI 48202
Tel: 313 916-7055
Fax: 313 916-8759
spalani2@hfhs.org;

Graham Parker, Ph.D.
Wayne State University School of Medicine
3901 Beaubien
Detroit MI 42801
Tel: 313-993-3843
gparker@med.wayne.edu

Mick Perez-Cruet, M.D., M.S.
William Beaumont Hospital
Michigan Head and Spine Institute
3577 West 13 Mile Road Ste 206
Royal Oak MI, 48073
perezcruet@yahoo.com

Kenneth Peters, M.D.
Beaumont Hospital
Comprehensive Urology
31157 Woodward Ave
Royal Oak, MI, 48073
Tel: 248-551-0387
Fax: 248-551-8107
kmpeters@beaumont.edu

Xu Qian, Doctoral Candidate
University of Michigan School of Dentistry
1011 N. University Ave.
Ann Arbor, Michigan 48109-1078
Tel: 734-223-8940
xuqian@umich.edu

Diana L. Ramírez-Bergeron, Ph.D.
Case Western Reserve University School of Medicine
Iris S. & Bert Wolstein Research Building
10900 Euclid Avenue
Cleveland, OH 44106
2103 Cornell Road, WRB 4-532
Tel: 216-368-5269
Fax: 216-368-0556
dlr36@case.edu

Daniel Rappolee, Ph.D,
Wayne State University School of Medicine
CS Mott Center for Human Growth and Development
275 East Hancock St
Detroit, MI 48201
Tel: 313-577-1228
Fax: 313-577-8554
drappole@med.wayne.edu

Stacey A. Sakowski, Ph.D.
University of Michigan
109 Zina Pitcher Place
4021 AAT-BSRB
Ann Arbor, MI 48109
Tel: 734-763-8284
staceysa@med.umich.edu

Peter Sartipy, Ph.D.
Cellartis AB Sweden
8RUE De La Croix Jarry
75013Paris
Tel: 46-31-7580930
peter.sartipy@cellectis.com

Bernard Siegel, J.D.
Genetics Policy Institute
2875 South Ocean Blvd
Palm Beach, Fl. 33480
Tel: 888-238-1423
bernard@genpol.org

Gary Smith, Ph.D.
University of Michigan
2828 Med Sci Rm 1137
East Catherine St.
Ann Arbor, MI 48109-5622
Tel: 734-764-4134
smithgd@med.umich.edu

Anna Sonstegard
University of Minnesota
210 Delaware Street
Southeast Minneapolis, MN 55455
anna.m.sonstegard@gmail.com

Irene Spanos
Oakland County
1200 N Telegraph Courthouse Tower
Pontiac MI, 48341
spanose@oakgov.com

David M. Svinarich, Ph.D., M.S.
St. John's Health System
16001 West Nine Mile Rd.
Southfield, MI 48075

Tel: 248-849-3997
david.svinarich@providence-stjohnhealth.org

Shuichi Takayama, Ph.D.
University of Michigan
A183, Bldg 10, Biointerfaces Institute,
2800 Plymouth Rd.
Ann Arbor, MI 48109-2800
Tel: 1-734-615-5539
takayama@umich.edu

Dean Tantin, Ph.D.
University of Utah School of Medicine
JMRB, Room 5700B
15 No. Medical Dr. East
Salt Lake City, UT 84112
Tel: 801-587-3035
Fax: 801-585-2417
dean.tantin@path.utah.edu

Andrew M. Tidball, Doctoral Candidate,
Vanderbilt University
2201 West End Avenue
Nashville, TN 37212
Bowman Lab
jreqan@gmail.com

Vince Tropepe, Ph.D.,
University of Toronto
25 Harbord Street
Toronto, ON, M5S 3G5
Tel: 416-946-0338
v.tropepe@utoronto.ca

Luis G. Villa-Diaz, Ph.D.,
University of Michigan
1011 N. University Av,
Ann Arbor, MI 48109
Tel: 734-615-2411
Fax: 734-647-2110
luisv@umich.edu

Chenran Wang, Ph.D.,
University of Michigan Medical School
3368 BSRB, 109 Zina Pitcher place
Ann Arbor, MI 48109
Tel: 734-6154635
chenran@umich.edu

Q. Tian Wang, Ph.D.,
University of Illinois at Chicago
840 S Wood St #440CSM
Chicago, Il 60612
Tel: 312-413-2408
qtwang@uic.edu

Mark Weiss, Ph.D.
Kansas State University
Medical Center
3901 Rainbow Blvd
Kansas City, KS 66160
Tel: 913-588-5000
weiss@vet.k-state.edu

George Wilson, Ph.D.
Beaumont BioBank
William Beaumont Hospital
Research Institute
3811 W. Thirteen Mile Rd.
Royal Oak, MI 48073
Tel: 248-551-0214
george.wilson@beaumont.edu

Donggang Yao, Ph.D.
Georgia Institute of Technology
School of Materials Science & Engineering
801 Ferst Drive, NW
Atlanta, GA 30332-0295
Tel: 404-894-9076
Fax: 404-894-8780
yao@gatech.edu

Mervin Yoder, M.D.
University of Indiana
Herman B Wells Center for Pediatric Research
1044 W. Walnut Street, R4-W125
Indianapolis, IN 46202
Tel: 317-274-4738
Fax: 317-274-8679
myoder@iupui.edu