

## Schedule of Events

- 7:45 am–8:30 am **REGISTRATION & CONTINENTAL BREAKFAST**
- 8:30 am–8:40 am **Welcome**  
Robert N. Golden M.D., Carl E. Gulbrandsen, Ph.D., J.D., William A. Linton
- 8:40 am–9:20 am **Nuclear Reprogramming by Eggs and Oocytes**  
John Gurdon, Kt., DPhil., DSc., FRS
- 9:20 am–10:00 am **Epigenetic State and Genetic Stability of Human iPSC Cells**  
James A. Thomson, Ph.D.
- 10:00 am–10:20 am **BREAK AND POSTER VIEWING**
- 10:20 am–11:00 am **Gene Networks in Stem Cells and Cancer**  
Stuart H. Orkin, M.D.
- 11:00 am–11:40 am **Recapitulation of Human Premature Aging by Using iPSCs from Hutchinson-Gilford Progeria Syndrome**  
Juan Carlos Izpisua Belmonte, Ph.D.
- 11:40 am–1:00 pm **LUNCH AND POSTER VIEWING**
- 1:00 pm–1:40 pm **Of Newts and Niches: Regenerating Tissues by Mimicking Natural Processes**  
Helen M. Blau, Ph.D.
- 1:40 pm–2:20 pm **Dynamically Tunable Hydrogels as 3D Culture Platforms**  
Kristi S. Anseth, Ph.D.
- 2:20 pm–2:40 pm **BREAK AND POSTER VIEWING**
- 2:40 pm–3:20 pm **A Chemical Approach to Cellular Reprogramming**  
Sheng Ding, Ph.D.
- 3:20 pm–4:00 pm **Tailored Synthetic Surfaces to Control Cell Propagation and Differentiation**  
Laura Kiessling, Ph.D.
- 4:00 pm–4:15 pm **CONCLUDING REMARKS**
- 4:15 pm–5:30 pm **RECEPTION**  
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## Speakers

- Kristi S. Anseth, Ph.D.** (Tisone Professor, Associate Professor of Surgery, HHMI Investigator, Chemical and Biological Engineering, University of Colorado-Boulder, Boulder, CO)
- Helen M. Blau, Ph.D.** (Donald E. and Delia B. Baxter Professor & Director, Baxter Laboratory for Stem Cell Biology, Stanford University School of Medicine, Stanford, CA)
- Sheng Ding, Ph.D.** (Professor, Chemistry Department, The Scripps Research Institute, La Jolla, CA)
- Robert N. Golden, M.D.** (Dean, University of Wisconsin School of Medicine and Public Health, Madison, WI)
- Carl E. Gulbrandsen, Ph.D., J.D.** (Managing Director, Wisconsin Alumni Research Foundation, Madison, WI)
- John Gurdon, Kt., DPhil., DSc., FRS** (Emeritus Professor & Distinguished Group Leader, The Wellcome Trust/ Cancer Research UK Gurdon Institute, University of Cambridge, UK)
- Juan Carlos Izpisua Belmonte, Ph.D.** (Professor, Gene Expression Center, Salk Institute for Biological Studies, La Jolla, CA)
- Laura Kiessling, Ph.D.** (Professor, Department of Chemistry and Department of Biochemistry & Director, Keck Center for Chemical Genomics, University of Wisconsin-Madison, Madison, WI)
- William A. Linton** (Chairman and CEO, Promega Corporation, Madison, WI)
- Stuart H. Orkin, M.D.** (Professor, Department of Pediatric Oncology, DFCI; Children's Hospital and Dana Farber Cancer Institute; Howard Hughes Medical Institute; Harvard Stem Cell Institute, Boston, MA)
- James A. Thomson, Ph.D.** (Director, Regenerative Biology, Morgridge Institute for Research, University of Wisconsin-Madison, Madison, WI)
- Moderators**
- Emery H. Bresnick, Ph.D.** (Professor, Wisconsin Institutes of Medical Research Department of Cell and Regenerative Biology, Paul Carbone Cancer Center, Madison, WI)
- William L. Murphy, Ph.D.** (Associate Professor, Biomedical Engineering, School of Engineering, University of Wisconsin-Madison, Madison, WI)

## 6<sup>th</sup> Annual Wisconsin Stem Cell Symposium

# REPROGRAMMING AND CONTROLLING STEM CELL Phenotype

April 27, 2011

BioPharmaceutical Technology Center  
Madison, WI

## Key Topics

Coordinated by the University of Wisconsin Stem Cell & Regenerative Medicine Center and the BTC Institute, this symposium brings together world leaders in the area of cellular reprogramming. The focus is on using intracellular or extracellular cues to manipulate gene regulation and control stem cell pluripotency and lineage-specific differentiation.

How can we understand and manipulate gene regulation to control stem cell self-renewal and lineage-specific differentiation?

What are the signaling mechanisms that are shared among multiple stem cell types?

What are the key mechanisms by which natural stem cell niches influence phenotype?

Can components of natural stem cell niches be effectively mimicked to control stem cell phenotype?

How can somatic cells be reprogrammed to pluripotent phenotype using intracellular or extracellular cues?

For more information & to register,  
please visit: [www.btc.org](http://www.btc.org)

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## Abstracts in order of presentation

### Nuclear Reprogramming by Eggs and Oocytes

John Gurdon

Oocytes and eggs of mammals and amphibia have a remarkable capacity to reprogram the nucleus of adult differentiated cells towards embryonic gene expression. The efficiency with which they achieve this is considerably greater than by transcription factor overexpression (iPS) or by cell fusion (heterokaryons). The efficiency with which reprogramming is achieved by all methods declines dramatically as the nuclei of increasingly differentiated cells are used. Current work aims to (1) identify the reprogramming components of eggs and oocytes, and (2) to identify the components of differentiated cells that restrict the responsiveness of their nuclei to reprogramming components. A major component of the reprogramming activity of oocytes and eggs is a massive decondensation of chromatin accompanied by exchange and modification of histones. This seems to result in a global activation of transcription of many genes not normally associated with germ cells or early embryos. Progress in identifying reprogramming factors as well as components of chromatin that resist reprogramming will be reviewed.

### Epigenetic State and Genetic Stability of Human iPS Cells

James A. Thomson

Human Embryonic Stem (ES) cells and Human induced Pluripotent Stem (iPS) cells can both proliferate without limit, and yet they retain the ability to differentiate to advanced derivatives of all three embryonic germ layers. In spite of these basic similarities, recent evidence suggests that the two cell types are not identical. This talk will review recent results from my laboratory, and from the San Diego Epigenome Center, on the epigenetic state and genetic stability of human ES and iPS cells.

### Gene Networks in Stem Cells and Cancer

Stuart H. Orkin

We have combined proteomic and genomic approaches to elucidate gene networks responsible for maintaining the pluripotent state. Remarkable combinatorial action of the core pluripotency factors has been observed. Through assessment of common gene targets, we have defined submodules within the ES cell transcriptome that center on core pluripotency, Polycomb, and myc targets. These submodules are useful as analytical tools to probe various relationships, including the relatedness of cancer and ES cells. Prominent expression of Polycomb components is shared between ES cells, many stem

cells, and cancer cells. Polycomb group proteins constitute epigenetic repressors of cell fates and differentiation. We have focused on the composition and function of Polycomb Repressive Complex-2 (PRC2) in ES cells, the hematopoietic system, and oncogenesis. Findings will be reviewed regarding the composition of PRC2 in ES cells, the identification of Jarid 2 (Jmj) as a critical component, and the PRC2 transcriptional network. In our studies we have used knockout and conditional gene targeting to examine the roles of PRC2 by formal genetics. Recent findings regarding the requirements for PRC2 components in hematopoietic stem cells (HSCs), hematopoietic differentiation, and leukemogenesis will be presented. The overexpression of PRC2 in various cancers has suggested that PRC2 is oncogenic, and might represent a therapeutic target. Efforts to determine the contribution of PRC2 to both hematopoietic and solid tumor malignancies will be discussed. Overall, our findings provide insights into the complex roles of Polycomb proteins in stem cell biology and cancer.

### Recapitulation of Human Premature Aging by Using iPSCs from Hutchinson-Gilford Progeria Syndrome

Juan Carlos Izpisua Belmonte

Hutchinson-Gilford progeria syndrome (HGPS) is a rare and fatal human premature aging disease, characterized by premature arteriosclerosis and degeneration of vascular smooth muscle cells (SMCs). HGPS is caused by a single-point mutation in the LMNA gene, resulting in the generation of progerin, a truncated splicing mutant of lamin A. Accumulation of progerin leads to various aging-associated nuclear defects including disorganization of nuclear lamina and loss of heterochromatin. Induced pluripotent stem cells (iPSCs) are generated from fibroblasts obtained from patients with HGPS. HGPS-iPSCs show absence of progerin, and more importantly, lack the nuclear envelope and epigenetic alterations normally associated with premature aging. Upon differentiation of HGPS-iPSCs, progerin and its aging-associated phenotypic consequences are restored. Specifically, directed differentiation of HGPS-iPSCs to SMCs leads to the appearance of premature senescence phenotypes associated with vascular aging. These phenotypes were rescued by inhibiting progerin expression in HGPS-iPSC-derived SMCs, and were recapitulated in human primary vascular SMCs when progerin was overexpressed. Additionally, our studies identify DNA-dependent protein kinase catalytic subunit (DNAPKs)

as a downstream target of progerin. The absence of nuclear DNAPK holoenzyme correlates with premature as well as physiological aging. Since progerin also accumulates during physiological aging, our results provide an in vitro iPSC-based model to study the pathogenesis of human premature and physiological vascular aging.

### Of Newts and Niches: Regenerating Tissues by Mimicking Natural Processes

Helen M. Blau

We are exploiting natural mechanisms to derive mammalian cell sources for regenerative medicine: (1) by recapitulating pathways used by newts and zebrafish, (2) by mimicking biophysical cues to which adult stem cells are exposed in the body, (3) by gaining insights into the mechanisms such as DNA demethylation by which adult cells are reprogrammed to pluripotency (iPS) by cell fusion in heterokaryons and (4) by studying stem-cell based diseases. These approaches provide fundamental mechanistic insights into stem cell fate determination and should enable clinical applications.

### Dynamically Tunable Hydrogels as 3D Culture Platforms

Kristi S. Anseth

A better understanding of the dynamic physical and biomolecular cues in the stem cell niche has led to a growing interest in the development of material systems for improved 3D culture environments, as well as delivery vehicles to promote cell survival and differentiation. As a result, hydrogels based on both protein components (e.g., collagen and Matrigel) and highly-tunable synthetic chemistries (e.g., PEG) have evolved to address many of these needs. However, as advances in real-time tracking of dynamic cellular functions have emerged, complementary approaches to alter the surrounding extracellular environment in a user-defined and highly-controlled fashion are extremely limited. Such material systems would have the potential to significantly improve our understanding of how stem cells receive information from their microenvironment and the role that these dynamic processes may play in biological questions related to their differentiation. Towards the goal of developing a dynamically tunable scaffold, we recently reported approaches for in situ hydrogel property manipulation with light, allowing intimate control of a cell's microenvironment in both time and space.

These photoresponsive hydrogels afford unique user-defined manipulation of the biochemical and biomechanical nature of the extracellular microenvironment. This talk will present several examples where user-triggered changes in the material environment can be used to both better understand and direct the function of bone marrow derived mesenchymal stem cells.

### A Chemical Approach to Cellular Reprogramming

Sheng Ding

Recent advances in stem cell biology may make possible new approaches for the treatment of a number of diseases. A better understanding of molecular mechanisms that control stem cell fate, as well as an improved ability to manipulate them, are required. Toward these goals, we have developed and implemented high throughput cell-based phenotypic screens of arrayed chemical and gene libraries to identify and further characterize small molecules and genes that can control stem cell fate in various systems. This talk will provide latest examples of discovery efforts in my lab that have advanced our ability and understanding toward controlling stem cell fate, including self-renewal, survival, differentiation and reprogramming of pluripotent stem cells.

### Tailored Synthetic Surfaces to Control Cell Propagation and Differentiation

Laura Kiessling

In vivo, cell fate decisions result from cues present in the extracellular microenvironment or the niche. To exploit the full potential of human pluripotent stem cells for regenerative medicine, developmental biology, and drug discovery, defined culture conditions are needed for propagation and directed differentiation. Cell fate decisions are directed not only by soluble signals of the niche but also by insoluble components such as the substratum. To identify substrata capable of promoting cell propagation or differentiation, we have developed surface arrays. These arrays provide the means to screen multiple substrates that engage different cell surface receptors. The arrays give rise to surfaces that promote the long-term propagation of human pluripotent stem cells. We also have devised tailored synthetic surfaces that exert precise spatial control over signaling and therefore cell fate decisions. We anticipate that these findings will yield advances in culturing human pluripotent cells and insight into the signaling mechanisms underlying pluripotency and differentiation.

Coordinated by the University of Wisconsin Stem Cell & Regenerative Medicine Center and the BioPharmaceutical Technology Center Institute. For more information & to register, please visit [www.btc.org](http://www.btc.org).