Cambridge Healthtech Institute’s Second Annual

STEM CELLS
in Drug Discovery and Development

November 2-3, 2011 • THE US GRANT • San Diego, CA

Coverage Includes:

- Stem Cells for Drug Screening
- Stem Cells for Toxicity Profiling
- Stem Cell Models for Functional Analysis and Target Discovery
- Targeting Cancer Stem Cells
- Induced Pluripotent Stem Cells as Tools in Drug Discovery
- New Company Spotlights

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The human stem cell line, TERA2.cl.SP12. Neurons derived from these cells offer an opportunity to develop functional models amenable to high-throughput, low compound usage assays. Our work has focused on cardiomyocytes, specifically developing a pro-arrhythmia assay to screen for pro-arrhythmic potential early in development.

Combining HTS and HCS with Pluripotent Stem Cells in the Search for Treatments of Monogenic Diseases
Marc Peschanski, M.D., Ph.D., Head, Stem Cell Research and Therapy, I-Stem

Pluripotent stem cell lines derived from donors who carry a mutant gene at the origin of a monogenic disease can be used to screen libraries of compounds in a search for new treatments. Robust read-outs relevant to the pathological mechanisms should first be identified. On this basis, a screening platform either in high-throughput or in high content can be implemented, as derivatives of pluripotent stem cells can be obtained at near homogeneity and are amenable to miniaturization and standardization of cell processes. In parallel, functional genomics can also be implemented on large-scale platforms, in a search for yet unknown mechanisms and proteins involved in pathological signaling pathways.

Using iPS Cells to Study Cellular and Molecular Phenotypes Associated with Human Brain Disorders
Alex Shcheglovitov, Ph.D., Postdoctoral Fellow, Department of Neurobiology, Stanford University

The outstanding question of contemporary neuroscience is to understand the molecular and cellular basis of the human brain disorders. This knowledge would allow us to develop effective strategies to intervene and correct pathological changes. Induced pluripotent stem cells (iPSCs) are a new tool in our arsenal to study neurobiology in humans. These cells have the ability to generate any cell type from the human body including neurons. As iPS-derived neurons share the precise genetic background of a patient, they offer unique opportunities to probe the cellular and molecular properties of the human brain, to generate in vitro models of human diseases, and to develop high-throughput screens to identify potential therapeutics. In my presentation I will discuss the progress we have been making in the generation of a specific population of functional iPS-derived neurons and our attempts to find and rescue the cellular phenotypes associated with Phelan-MacDermid syndrome (a rare autism-related neurodevelopmental disorder).

Physiologically Functional Cellular Models for Modern Drug Discovery
Marsha Roach, Ph.D., Executive Vice President, Research & Development, GigaCyte

Early identification of safety and efficacy issues for drugs in humans is often difficult with lead discovery and screening occurring in animal cells or tumor cells expressing targets of interest. This can be overcome by early evaluation in normal human cells displaying physiologically relevant expression, metabolism and responses. To assist in the generation of these contextual safety and efficacy models we have focused our efforts on developing physiologically-relevant functional cell types from renewable stem/progenitor cells to produce predictive cellular assay systems. Here data will be presented that demonstrates how liver biomatrix is the key to producing functional human hepatocytes on a scale needed for safety and efficacy evaluation early in the drug discovery process; how media formulation directs the differentiation of human neural stem cells into very mature excitatory and inhibitory neurons for high-throughput screening; and how process optimization impacts purity and quality of human islets for drug testing.
TARGETING CANCER STEM CELLS

8:25-8:30 Chairperson’s Opening Remarks

8:30-9:00 Targeting Cancer Stem Cells
Markus H. Frank, M.D., Assistant Professor of Pediatrics and Dermatology, Harvard Medical School; Associate Physician, Brigham & Women’s Hospital Transplantation Research Center, Brigham & Women’s Hospital and Children’s Hospital Boston

Cancer stem cells represent subpopulations of cancer cells that drive tumor initiation and metastatic progression based on selective prolonged self-renewal capacity. Cancer stem cells have been identified in diverse human malignancies, and specific roles of these virulent subpopulations have been documented in tumorigenic growth, metastatic dissemination, therapeutic resistance, and malignant recurrence. Recent findings have provided preclinical proof-of-concept for the potential therapeutic utility of the cancer stem cell concept. Therefore, cancer stem cell-directed therapeutic approaches represent promising novel strategies to improve clinical cancer therapy.

9:00-9:30 Targeting Telomerase in Cancer Stem Cells and Cancer Progenitor Cells
Ning Go, Ph.D., Associate Director, Translational Oncology, Geron Corp.

Telomerase expression is upregulated in cancer cells and particularly in the progenitor cell subcompartment of tumors. Inhibition of telomerase with a 13mer oligonucleotide (imetistat, GRN163L) can numerically reduce the stem cell compartment of tumors and inhibit clonogenic growth in vivo and in vitro. Phase I studies have been completed and Phase II studies are underway in NSCLC, breast cancer, myeloma and myeloproliferative diseases.

9:30-10:00 Development of New Anti-Cancer Therapeutics that Reduce Tumor-Initiating Cell Frequency
Tim Hoey, Ph.D., Senior Vice President, Cancer Biology, OncoMed

Colon cancer stem cells (or tumor-initiating cells) mediate tumor progression, metastasis and recurrence after therapy. We have developed new agents that block key CSC pathways including Notch and Wnt. Currently, we have three therapeutic antibodies which are in clinical testing, anti-DLL4, anti-Notch2/3, and anti-FZD, and others in pre-clinical development. These treatments inhibit tumor growth through multiple mechanisms and reduce CSC frequency.

10:00-10:45 Networking Coffee Break in the Exhibit Hall with Poster Viewing

10:45-11:15 Targeting Cancer Stem Cells with Therapeutic Antibodies
Robert Hollingsworth, Ph.D., Director, Cancer Biology, MedImmune, Inc.

Cancer stem cells (CSCs) are drivers for many cancer types, and may be responsible for resistance to current therapies and relapse. As such, they represent a promising new target for anticancer drug development. At MedImmune, we have developed several new models and methods to study CSCs, and are using these to discover new therapeutic antibodies. For instance, we have established a novel assay for tracking CSCs within cell populations that obviates the need to isolate them. These approaches, as well as several additional challenges that must be addressed in targeting CSCs, will be described.

11:15-11:45 Identification of Novel Antibody Targets on Cancer Stem Cells in Hematological Malignancies
Robert Tressler, Ph.D., Vice President, Research & Development, Cellerant Therapeutics

Key obstacles to the treatment of cancer are disease recurrence that is resistant to treatment. These aspects are driven by a subset of cells present in cancers called cancer stem cells (CSCs). CSCs have tumor-initiating and metastatic potential and divide asymmetrically, with one daughter cell having high proliferative capacity and typically is sensitive to antiproliferative agents, while the other daughter cell is quiescent and resistant to standard debulking agents. Agents that can eradicate the quiescent CSC are needed to better target CSCs. An antibody-based approach to select antigen targets expressed on both proliferating and quiescent CSCs is a potentially promising approach to accomplish this. The isolation of CSCs from solid tumor malignancies for target discovery has been difficult, while the presence of CSCs of true stem cell origin is better characterized in hematological cancers. We have enriched CSCs from hematological malignancies for target discovery and have identified targets that are specific and selective in their expression on CSCs versus normal stem cells. Monoclonal antibodies selective for AML patient CSCs with cell-killing potential in vivo have been characterized and have shown efficacy in vivo in AML tumor models.

11:45-12:15 pm Characterization of the Tumor Cell Populations Responsible for Chemoresistance and Relapse in Non-Small Cell Lung Cancer
Erica Jackson, Ph.D., Scientist, Cancer Targets, Genentech

12:15-12:45 Therapeutic Antibodies Targeting Colon Cancer Stem Cells
Peter Chu, Ph.D., CEO, Eclipse Therapeutics

Eclipse Therapeutics is dedicated to the discovery and development of therapeutics that target cancer stem cells (CSCs). Eclipse has a therapeutic antibody program that targets a high value cancer stem cell target overexpressed in multiple solid tumors. Eclipse is also developing a CSC screening strategy to discover additional functional therapeutic antibodies that inhibit CSCs. This cancer stem cell screen is effective because it combines key aspects of CSC biology and therapeutic antibody drug development in a unique manner. This presentation will discuss Eclipse’s cancer stem cell therapeutic antibody program and provide insights on the development of effective, functional antibodies targeting cancer stem cells.

12:45 Close of Conference
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