McGill

Centre universitaire de santé McGill
McGill University Health Centre

DDTP Symposium

Tissue Engineering and Drug Discovery

Friday, November 29, 2013

8:00 AM to 12:30 PM

Jeanne Timmins Amphitheatre

Montreal Neurological Hospital and Institute

presented by

McGill-CIHR

Drug Development

Training Program

CIHR IRSC

Canadian Institutes of Health Research | Instituts de recherche en santé du Canada

Schedule

8:30 - 9:15 **Breakfast/Registration**

9:15 – 9:30 **Dr. Phil Oldfield**

Introductory Comments

9:30 - 10:15 **Dr. Julie Fradette**

Human Tissue-engineered Substitutes: Tools for *in vitro* Testing and Discovery

10:15 -10:30 **Health Break**

10:30 -11:15 **Dr. Daniel LaBarbera**

Drug Discovery and Preclinical Development of Novel Anticancer Agents

11:15 –12:00 **Dr. Shuichi Takayama**

Microfluidics for Cancer Therapeutics & Diagnostics Development

12:00 –12:30 **Table Discussion and Wrap Up**

Chair: **Dr. Phil Oldfield**

Dr. Julie Fradette, PhD

Centre LOEX de l'Université Laval, Axe médecine régénératrice, CR du CHU de Québec, et Département de Chirurgie, Faculté de Médecine, Université Laval
Ste-Foy, QC

Human Tissue-engineered Substitutes: Tools for *in vitro* Testing and Discovery

Regenerative medicine and tissue engineering applications have greatly expanded with the discovery of postnatal mesenchymal stem cells featuring great plasticity. Such stem cells can be harvested from adipose tissue which represents an almost ideal cell source. My team is using these adipose-derived stem/stromal cells (ASCs) as building blocks for the production of various human tissues, including adipose tissue itself and connective tissues serving as stromal compartments for skin and bladder reconstruction. These unique tissues feature a rich extracellular matrix produced by the mesenchymal cells, recreating a very physiological 3D environment without exogenous biomaterials (self-assembly approach). These engineered tissues are not only structurally relevant but also recapitulate important biological responses when tested for functionality. Additional cell types such as endothelial cells can be added during tissue production, which results in the development of a preformed capillary network. This presentation will discuss how tissue-engineered adipose tissues can be used in vitro to study the impact of different molecules/products on adipocyte's metabolism and secretory activity. The pro/anti-angiogenic properties of inflammation-related molecules such as TNFa and IL-1b has also been tested on the reconstructed adipose tissues featuring a capillary network. Tools allowing detailed characterization of 3D tissue samples such as confocal imaging and software analysis is of prime importance in this context. Finally, other examples of how tissue engineering can contribute to the field of pharmaceutical testing will be presented. Supported by CIHR, NSERC and CFI.

Daniel V. LaBarbera, PhD

The Skaggs School of Pharmacy and Pharmaceutical Sciences; The University of Colorado Anschutz Medical campus
Aurora, CO

Drug Discovery and Preclinical Development of Novel Anticancer Agents: Applications of novel 3D multicellular tumor spheroid models

Aberrant regulation of epithelial-mesenchymal transition (EMT) is a driving force in the most prominent human diseases, including: cancer, organ fibrosis, and diabetes. In particular, EMT driven tumor progression promotes the expansion of cancer stem cells, drug resistance, and the mesenchymal phenotype, which is invasive with a high metastatic potential. Therefore, one therapeutic strategy to prevent metastatic dissemination is to develop small molecule drugs that can revert the mesenchymal phenotype to the more benign epithelial state. Using novel 3D multicellular tumor spheroid (MCTS) models of EMT, suitable for high-throughput and high-content screening (HTS/HCS), we have identified topoisomerase IIα (TopoIIα) as a key regulator of the mesenchymal phenotype in colorectal cancer and breast cancer. Specifically, we show that TopoIIα is required for TCF/Lef/β-catenin (TCF) transcription, which is primarily activated through Wnt signaling. This pathway regulates / activates normal adult stem cells, but aberrant regulation of TCF transcription promotes a tumor-initiating cell (TIC) phenotype. Importantly aberrant TCF-activity is linked to 80% of sporadic colorectal carcinomas, and familial adenomatous polyposis (FAP) tumors and metastasis. Using HTS/HCS we identified neoamphimedine (neo), a marine alkaloid and ATP-competitive inhibitor of TopoIIα that blocks TCF-activity in CRC cells. Finally, in this presentation we will describe our current research and medicinal chemistry toward the development of neo derivatives as antineoplastic agents for the treatment of cancer.

Dr. Shuichi Takayama

University of Michigan
Ann Arbor, MI

Microfluidics for Cancer Therapeutics & Diagnostics Development

Many biological studies and pharmacological 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, 3D, and dynamic whereas typical in vitro cultures are macroscopic, 2D, and static. This presentation will give an overview of efforts in our laboratory to develop microfluidic systems that enable spatiotemporal control of chemical, cellular and fluid mechanical environment of cells. The technologies and methods close the physiology gap to provide biological information otherwise unobtainable and to enhance cellular performance in therapeutic applications. The seminar will also present technologies to perform biochemical analysis of protein biomarkers from small volume samples of microfluidic models of the body as well as real patients and disease. Specific biomedical topics that will be discussed include, in vitro fertilization on a chip, microfluidic analysis of EGFR signaling, microfluidic testing of CXCL12 inhibitors, engineered 3D microtissues for anti-cancer and anti-fibrosis drug testing, and diagnosis of bone marrow transplant rejection.

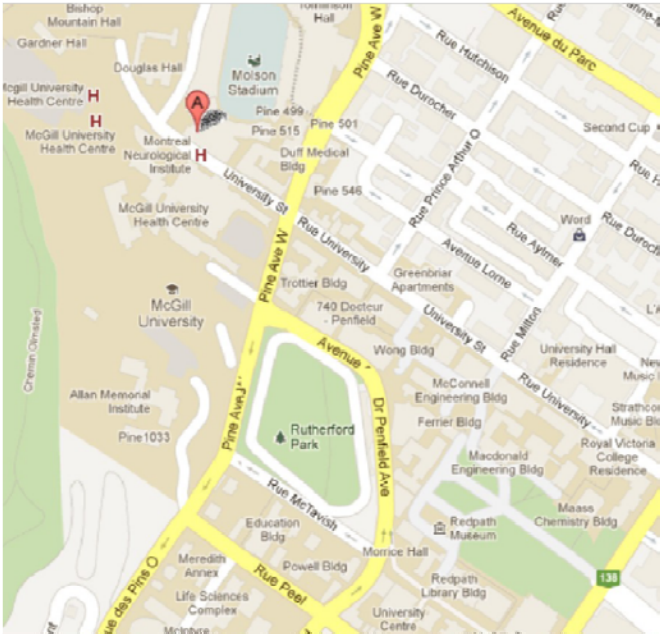
Directions

Montreal Neurological Hospital and Institute
Jeanne Timmins Amphitheatre

3801 University Street

Montreal, Quebec H3A 2B4

Tel: 514.398.6644



Drug Development Training Program

514-934-1934 ext. 34460
trainingindrugdev@mcgill.ca
contact: Aube Mamias