Targeting Mitochondrial Dysfunction & Toxicity
Treating Disease and Improving Drug Safety

Featuring Cutting-Edge Research Presentations from:

- Center for Mitochondrial and Epigenomic Medicine, Children’s Hospital of Philadelphia and University of Pennsylvania
- Neuropsychopharmacology Laboratory, Mayo Clinic
- Mitochondrial Research, Nestlé Institute of Health Sciences, Switzerland Astellas Research Institute of America LLC
- Muscle Diseases Group, Novartis Institutes for Biomedical Research
- GALLY International Biomedical Research Consulting LLC
- Based Assays and Mitochondrial Biology, Pfizer R & D
- Pioneer Valley Life Sciences Institute
- Institute of Translational Medicine, The University of Liverpool
- Lilly Research Laboratories
- Elliott-Barnett-Head Breast Cancer Research and Treatment
- Biochemistry and Molecular Biology, Dalhousie University
- University of Arizona
- Metabolic Solutions Development Company

March 19-20, 2014
Omni Parker House, Boston, MA

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Short Course:
Imaging of Mitochondria: Seeing the Action Up Close and Live
March 19, 2014 9:00 am - 12:00 pm

Healthtech.com/Mitochondrial-Targeting

Organized by Cambridge Healthtech Institute
Mitochondrial dysfunction has been identified as an important factor in diseases ranging from neurodegenerative conditions (ALS, Alzheimer’s, Parkinson’s Disease), epilepsy, psychiatric illness and autism, to cardiovascular disease, liver/kidney disease, diabetes and cancer. The wide-ranging impact of mitochondria in so many diseases makes them prime targets for therapeutics.

Additionally, medications for many diseases cause unwanted toxicity to the mitochondria. Mitochondrial toxicity is one of the leading causes of attrition in the drug development process, as well as in post-market drug withdrawals. This conference (the first of its kind in the US) will present the latest research in new targeting pathways, novel therapeutics, and methods to decrease or eliminate mitochondrial toxicity when developing therapeutics for many indications.

If you have questions, please contact:

Elizabeth J. Lamb  
Senior Conference Director  
Cambridge Healthtech Institute  
Ph: 781-247-6259  
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Our International Panel of Speakers:

Yvonne Will, Ph.D.  
Robert L. Elliott, M.D.  
Martin Picard, Ph.D.  
Pilar M. Corena-McLeod, Ph.D.  
Zhidan Wu, Ph.D.  
Gjumrakch Aliev, Ph.D.  
Noah M. Walton, Ph.D.  
Paola Marignani, Ph.D.  
Jana Jandova, Ph.D.  
Andreas Wiederkehr, Ph.D.  
Nagendra Nadava, Ph.D.  
Amy Chadwick, M.Chem, Ph.D  
Sashi Nadanaciva, Ph.D.  
Jerry R. Colca, Ph.D.

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implications of these findings will contribute to novel insights regarding clinical function, mitochondrial movement and the direction of this movement. Our latest results show that mood stabilizers have an effect on mitochondrial signaling and neuroplasticity in relationship with mood disorders is scarce. Movement direction is regulated by serotonin and dopamine levels. However, mitochondrial movement range is regulated by phosphorylation of cytoskeletal nuclear gene expression.

1:30 Chairperson’s Welcoming Comments

NEW DATA WITH WIDE IMPLICATIONS

1:40 Mitochondrial Allostatic Load and Therapeutic Windows
Martin Picard, Ph.D., Post-Doctoral Researcher, Center for Mitochondrial and Epigenomic Medicine, Children’s Hospital of Philadelphia and University of Pennsylvania

With the aim of preventing dysfunction and offsetting toxicity without destroying basic adaptive mitochondrial functions, Mitochondrial Allostatic Load identifies stressors to which mitochondria exhibit particular sensitivity, defines key elements of mitochondrial dysfunction, and describes molecular mechanisms by which mitochondrial damage accumulate and disrupt normal cellular physiology. As an example, we report a non-linear pattern of communication between mitochondria and nucleus, whereby increasing levels of a pathogenic mitochondrial DNA mutation cause bi-phasic reprogramming of nuclear gene expression.

MUSCLE, NEURODEGENERATIVE AND PSYCHIATRIC

2:10 Mitochondrial Movement and Mood Stabilizer Treatment
Pilar M. Corena-McLeod, Ph.D., Neuropsychopharmacology Laboratory, Mayo Clinic

Mitochondrial movement range is regulated by phosphorylation of cytoskeletal and motor proteins in addition to changes in mitochondrial membrane potential. Movement direction is regulated by serotonin and dopamine levels. However, data on mitochondrial movement defects and their involvement in defective signaling and neuroplasticity in relationship with mood disorders is scarce. Our latest results show that mood stabilizers have an effect on mitochondrial function, mitochondrial movement and the direction of this movement. The implications of these findings will contribute to novel insights regarding clinical treatment and the mode of action of these drugs.

2:40 Adult Neurogenesis Transiently Generates Oxidative Stress
Noah M. Walton, Ph.D., Astellas Research Institute of America LLC

We hypothesized that the energetic demands of highly proliferative progenitors generates localized oxidative stress that contributes to ROS-mediated damage within the neuropaenotic microenvironment. To confirm these findings in vivo, we identified a set of oxidation-responsive genes, which respond to antioxidant administration and are significantly elevated in genetic- and exercise-induced models of hyperactive hippocampal neurogenesis. While no direct evidence exists coupling neurogenesis-associated stress to CNS disease, our data suggest that oxidative stress is produced as a result of routine adult neurogenesis.

3:10 Refreshment Break in the Exhibit Hall with Poster Viewing

3:45 Genomic and Proteomic Profiling Reveals Reduced Mitochondrial Function and Disruption of the Neuromuscular Junction Driving Rat Sarcopenia
Zhidan Wu, Ph.D., Muscle Diseases Group, Novartis Institutes for Biomedical Research

Molecular mechanisms underlying sarcopenia, the age-related loss of skeletal muscle mass and function, remain unclear. To identify molecular changes that correlated best with sarcopenia and might contribute to its pathogenesis, we determined global gene expression profiles in muscles of rats aged 6, 12, 18, 21, 24, and 27 months. Specifically, mitochondrial energy metabolism (e.g., tricarboxylic acid cycle and oxidative phosphorylation) pathway genes were the most downregulated and most significantly correlated with sarcopenia. Our findings suggest that therapeutic approaches that simultaneously stimulate mitochrondrogenesis and reduce muscle proteolysis and inflammation have potential for treating sarcopenia.

4:15 Link between Cancer and Alzheimer’s Disease via Oxidative Stress Induced by Nitric Oxide-Dependent Mitochondrial DNA Over-Proliferation and Deletion
Gumrakch Aliev, Ph.D., GALLY International Biomedical Research Consulting LLC

Nitric oxide-(NO)- dependent oxidative stress results in mitochondrial ultrastructural alterations and DNA damage in cases of Alzheimer’s disease (AD). We speculate that mitochondrial involvement may play a significant role in the etiopathogenesis of cancer. Recent advances in the cell-cycle reentry of the terminally differentiated neuronal cells indicate that NO-dependent mitochondrial abnormal activities and mitotic cell division are not the only important pathogenic factors in pathogenesis of cancer and AD, but open a new window for the development of novel treatment strategies for these devastating diseases.

4:45 Sponsored Presentation (Opportunity Available)

5:00-6:00 Welcome Reception in the Exhibit Hall with Poster Viewing

6:00 Close of Day 1

Present a Poster

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To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by February 14, 2014.
THURSDAY, MARCH 20

7:45-8:20 am Morning Coffee

8:25 Chairperson’s Comments

CANCER

8:30 Isolated Normal Mitochondrial Organelle Transplantation to Cancer Cells
Robert L. Elliott, M.D., Elliott-Barnett-Head Breast Cancer Research and Treatment

In the 1930s, Otto Warburg demonstrated mitochondrial dysfunction and defective respiration in cancer cells. Cancer cells have a glycolytic phenotype with increased glucose uptake. Isolated normal mitochondria rapidly enter cancer cells. This uptake inhibits proliferation, glycolysis, and increases drug sensitivity. We believe that isolated normal mitochondria could be utilized as a biological nanoparticle for cancer therapy. Our mitochondrial organelle transplantation of normal isolated mitochondria to cancer cells supports Warburg's theory that cancer is a metabolic disease caused by defective mitochondria.

9:00 Targeting Mitochondrial Function for the Treatment of Breast Cancer
Paola Marignani, Ph.D., Associate Professor, Biochemistry and Molecular Biology, Dalhousie University

Numerous studies have shown a correlation between mitochrondria dysfunction and aberrant signaling pathways that give rise to disease. As such, we have re-engineered a mouse to develop breast cancer that is hyperactive for mTOR and metabolically active. With this new tool, we are conducting preclinical trials to test combinations of drugs that target hyperactive mTOR and cancer cell metabolism in our model of breast cancer.

9:30 The Role of mtDNA Mutations in Keratinocyte Neoplasia
Jana Jandova, Ph.D., Research Instructor, University of Arizona

This presentation will show the importance of mtDNA alterations in finding novel, more effective agents for skin photo protection and identifying new potential targets for skin cancer chemoprevention since there is an increasing evidence of skin cancers in the U.S. and solar UV-radiation is a major environmental carcinogen.

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

DIABETES AND METABOLIC DISORDERS

10:30 Mitochondria Are at the Center of Islet Beta-Cell Signaling and Metabolism-Secretion Coupling
Andreas Wiederkehr, Ph.D., Head, Mitochondrial Research, Nestlé Institute of Health Sciences, Switzerland

β-Cell nutrient sensing depends on mitochondrial function. The sustained, amplifying pathway of insulin release also depends on mitochondrial Ca(2+) signals, which likely influence the generation of glucose-derived metabolites serving as coupling factors. Therefore, mitochondria are both recipients and generators of signals essential for metabolism-secretion coupling. Activation of these signaling pathways would be an attractive target for the improvement of β-cell function and the treatment of type 2 diabetes.

11:00 New Drug Discovery: Induction of Protective Genes Against Unwanted Toxicity to the Mitochondria
Grace Wong, Ph.D., CEO, ActoKine Therapeutics

ActoKine Therapeutics has discovered that ActoKine 1 (AK-1) can induce the expression of manganese superoxide dismutase (MnSOD). MnSOD, identified as one of the protective enzymes, is a mitochondrial enzyme that scavenges superoxide radicals (O2-). Overexpression of MnSOD but not CuZnSOD or EC-SOD enhances cellular resistance to radiation & chemotherapeutic drugs. Conversely, silencing MnSOD RNA diminishes cellular protection. Transfection of cells with MnSOD lacking the mitochondrial matrix signal does not provide protection against radiation or cancer drugs. However, insertion of the mitochondrial signal sequence into CuZnSOD or EC-SOD results in significant protection. AK-1 does not induce MnSOD in tumor cells; nor does AK-1 protect the tumor cells against radiation or cancer drugs. Actually, AK-1 pretreatment can sensitize tumor cells to killing by radiation or chemotherapeutic drugs.

11:30 Targeting Mitochondrial Dysfunction with Bendavia: A Novel First-in-Class Therapeutic
Mark Bamberger, Ph.D., CSO, Stealth Peptides, Inc.

Bendavia is a first-in-class mitochondrial therapeutic that has demonstrated efficacy in a number of disease models, including acute coronary syndrome, acute and chronic kidney disease, heart failure and neurodegeneration. By selectively interacting with the inner mitochondrial membrane, Bendavia normalizes electron flux and ATP levels, while reducing the production of reactive oxygen species in dysfunctional mitochondria, without affecting healthy mitochondria. The clinical potential of Bendavia is currently being assessed in several Phase 2 trials in the U.S. and Europe.

12:00 pm Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

AVOIDING MITOCHONDRIAL TOXICITY

1:55 Chairperson’s Comments
Yvonne Will, Ph.D., Compound Safety Prediction- WWMC, Cell Based Assays and Mitochondrial Biology, Pfizer R&D

2:00 In vitro Approaches to Assess Mitochondrial Toxicity and Mitochondria-Mediated Drug Toxicity: A Decade of Learning
Yvonne Will, Ph.D., Compound Safety Prediction- WWMC, Cell Based Assays and Mitochondrial Biology, Pfizer R&D

2:30 Novel Tools to Assess Mitochondrial Toxicity Under Physiological Conditions
Nagendra Nadava, Ph.D., Principal Investigator, Pioneer Valley Life Sciences Institute

Mitochondrial toxicity is the major cause for the failure of drugs. Therefore, early screening of drugs for mitochondrial safety under physiological conditions is essential. In this talk, I plan to discuss: 1) a novel technology to assess mitochondrial function in cell cultures that eliminates the need for isolated mitochondria following permeabilization with perfringolysin-O (a pore forming cytolsin); and 2) a novel Ndufa1S55A allele knock- in mouse model with systemic respiratory chain Complex I insufficiency to assess drugs sensitivity in vivo.

3:00 Metabolically-Modified Liver Models to Examine the Role of Mitochondrial Dysfunction in Drug-Induced Liver Injury
Amy Chadwick, MChem, Ph.D., Tenure Track Fellow, Institute of Translational Medicine, The University of Liverpool

This presentation will showcase data from the MIP-DILI consortium of 26 participants from the pharmaceutical industry, SMEs and academic institutions. This objective of this unique consortium is to develop and evaluate innovative preclinical test systems to improve the current test-systems which are poorly predictive of DILI, which is a major health problem (global incidence of 13.9 per 100 000 inhabitants/year). Drug-induced mitochondrial dysfunction has been hypothesized to be a determining link in the onset of such idiosyncratic DILI and 50% of drugs with Black Box Warnings for DILI contain mitochondrial liabilities. We will provide an overview of the MIP-DILI project goals and objectives and will show how our mechanistic mitochondrial toxicity data form part of a larger effort to better predict DILI.

3:30 Assessment of Drug-Induced Mitochondrial Dysfunction via Altered Cellular Respiration and Acidification Measured in a 96-Well Platform.
Sashi Nadanaciva, Ph.D., Compound Safety Prediction, Worldwide Medicinal Chemistry, Pfizer, Inc.

High-throughput applicable screens for identifying drug-induced mitochondrial impairment are necessary in the pharmaceutical industry. Hence, we evaluated the XF96 Extracellular Flux Analyzer, a 96-well platform that measures changes in the oxygen consumption rate (OCR) and extracellular acidification rate (ECAR) of cells. The sensitivity of the platform was benchmarked with known modulators of oxidative phosphorylation and glycolysis. We show that the XF96 platform is a robust, sensitive system for analyzing drug-induced mitochondrial impairment in whole cells. We identified changes in cellular respiration and acidification upon addition of therapeutic agents reported to have a mitochondrial effect.

4:00 Closing Comments

4:15 End of Conference
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