Treating Disease & Improving Drug Safety

Targeting Mitochondrial Dysfunction & Toxicity

Coverage Includes:
• Advancing the Science of Mitochondria
• Targeting Mitochondrial-Related Disease & Injury
• Mitochondrial Targeting & Toxicity

KEYNOTE PRESENTATION:
 Genetic Approaches to Identify Mitochondria-to-Nucleus Retrograde Targets Involved in Drug Toxicity
Keshav K. Singh, Ph.D., Departments of Genetics, Pathology, and Environmental Health; Center for Free Radical Biology, Center for Aging and UAB Comprehensive Cancer Center, University of Alabama at Birmingham

EVENT SHORT COURSE:
 Drug-Induced Mitochondrial Toxicity
Yvonne Will, Ph.D., Senior Director & Head, Science and Technology Strategy, Drug Safety Research and Development, Pfizer R&D
Kendall B. Wallace, Ph.D., Professor, Biochemistry & Molecular Biology, University of Minnesota-Duluth
Rick G. Schnellmann, Ph.D., Professor, College of Pharmacy, Medical University of South Carolina

March 19-20, 2015
Hyatt Regency Cambridge | Cambridge, MA

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Mitochondrial failure and/or dysfunction has been identified as an important factor in diseases ranging from neurodegenerative conditions (ALS, Alzheimer’s, Parkinson’s Disease), epilepsy and autism, to diseases of the cardiovascular system, liver, and kidney, as well as cancer and diabetes. The broad impact of mitochondria in so many diseases makes them prime targets for therapeutics.

Since medications for many diseases cause unwanted toxicity to the mitochondria, it is extremely critical for drug discovery and development researchers to be able to predict and prevent this serious side effect for their compounds. This conference will present the latest research in new targeting pathways, novel therapeutics, and new breakthroughs in the understanding of mitochondrial function, as well as methods to decrease or eliminate mitochondrial toxicity when developing therapeutics.

If you have questions, please contact:

Elizabeth J. Lamb
Senior Conference Director
Cambridge Healthtech Institute
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Mitochondria produce almost all the energy in cells, but also chronically expose the cell to cytotoxic free radicals. Mitochondrial disease and toxicity is a rapidly advancing field and the consequences of mitochondrial impairment should be appreciated by scientists in all disciplines. Numerous widely prescribed therapeutics can undermine mitochondrial function by interfering with DNA replication or expression, and more acutely, by uncoupling or inhibiting oxidative phosphorylation, leading to organ dysfunction and damage. This course will review fundamental concepts of mitochondrial biology and the many different mechanisms by which xenobiotics interfere with mitochondrial function. Both common and novel in vitro screening approaches will be described as well as lectures on mitochondrial dysfunction in the kidney, liver and heart.

* Separate registration required
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### Agenda

#### THURSDAY, MARCH 19

8:00 am – 12:00 pm SC1: Drug-Induced Mitochondrial Toxicity*

Chair: Yvonne Will, Ph.D., Senior Director & Head, Science and Technology Strategy, Drug Safety Research and Development, Pfizer R&D
Kendall B. Wallace, Ph.D., Professor, Biochemistry & Molecular Biology, University of Minnesota-Duluth
Rick G. Schnellmann, Ph.D., Professor, College of Pharmacy, Medical University of South Carolina

Mitochondria contain multiple copies of mtDNA, varying from 100-1000 copies per cell among different tissues. mtDNA content is reduced by a variety of drugs resulting in toxicity. We have developed genetic approaches to identify nuclear targets involved in retrograde signaling involved in communicating the mitochondrial state to the nucleus, resulting in altered nuclear gene expression, cell physiology, and metabolism mediating drug toxicity.

1:00 Registration for Main Conference

2:00 Chairperson’s Opening Remarks
Elizabeth Lamb, Senior Conference Director, CHI

#### ADVANCING THE SCIENCE OF MITOCHONDRIA

2:50 Next-Generation Mitochondrial Medicine Platform: Integrated Bioenergetic Phenotyping in Oncology as a Case Study
Anne Diers, Ph.D., Program Leader, Cancer Biology, Berg

A next-generation mitochondrial medicine platform was developed that allows for identification of unique bioenergetic facets that predict cellular responses to stress (e.g., therapeutics, microenvironmental conditions). Using whole-cell integrated energy metabolism parameters coupled with mitochondrial substrate-level oxidation measurements, predictive phenotypic signatures for anti-cancer responses can be identified and molecular adaptive therapy strategies devised. Here, we report the use of this approach to identify the phenotypic signature for sensitivity to BPM 31510, a ubiquinone-containing formulation that alters mitochondrial metabolism currently in clinical trials for treatment of solid tumors, and highlight the clinical correlates from patients treated with this compound.

3:20 AIF Mediates Cell Survival, but Not Death, in Lymphocytes by Regulating Complex I Integrity
Sandra Melasta, Ph.D., Professor, Immunology, St. Jude Children’s Research Hospital

Apoptosis inducing factor (AIF) is a mitochondrial inter-membrane space protein initially described to mediate cell death that proceeds in the absence of caspase activity. More recent studies revealed that AIF is required for the efficient assembly of complex I of the respiratory chain and thus plays a role in maintaining normal oxidative phosphorylation (OXPHOS). Thymocytes and B cells lacking AIF displayed normal caspase-dependent and -independent cell death. These studies suggest that the primary role of AIF in lymphocytes relates to complex I function and not to mediating cell death. Therefore, a cell’s dependence on AIF is dictated by its reliance on OXPHOS to generate ATP.

3:50 Refreshment Break in the Exhibit Hall with Poster Viewing

4:30 A New Answer to an Old Problem: The Energization of Brain Mitochondria is Regulated by Cytosolic Calcium via the “Mitochondrial Gas Pedal” and Does Not Require the Mitochondrial Ca Uptake via the Ca Unipporter
Frank Gellerich, Ph.D., Head, Bioenergetic Laboratory, Neurological University Hospital, Otto-von Guericke-University Magdeburg

In contrast to the classic opinion that the mitochondrial activity is regulated by Ca2+ after its uptake via the Ca2+ unipporter, we found that the energization of mitochondria is realized by the “mitochondrial gas pedal” and is strongly regulated by cytosolic Ca2+ but not by matrix Ca2+. The "mitochondrial gas pedal" realizes the mitochondrial pyruvate supply via oxidizing reactions of pyruvate formation as LDH and GAPDH both generating NADH together with the malate/aspartate shuttle (G3PS) both oxidizing NADH. Our model predicts that at sufficiently low Ca2+cyt mitochondria (e.g. in neurons and red muscle) switch into a substrate-limited state preventing dangerous large ROS.
Mitochondrial dysfunction has long been recognized as a hallmark of cancer, and many neurodegenerative conditions are associated with excessive mitochondrial fission and inhibition of mitophagy. However, it is not clear whether these abnormalities in mitochondrial dynamics and removal are the cause of or the result of the pathology. Using a variety of pharmacological tools that we developed rationally, we find that inhibition of mitochondrial fission inhibits neurodegeneration in several models of Parkinson’s and Huntington’s. A critical role from mitophagy was also identified. The molecular basis for protection from neurodegeneration and the potential utility of our novel pharmacological tools as leads for drug development will be the topic of our presentation.

Mitochondrial Immobilization Mediated by Syntaphilin Facilitates Survival of Demyelinated Axons
Bruce D. Trapp, Ph.D., Department Head, Department of Neurosciences, Lerner Research Institute, Cleveland Clinic
The purpose of this study was to define the roles of mitochondrial volume and distribution in axonal degeneration following acute CNS demyelination. We show that the axonal mitochondrial volume increase following acute demyelination of WT CNS axons does not occur in demyelinated axons deficient in syntaphilin, an axonal molecule that immobilizes stationary mitochondria to microtubules. These findings were supported by time-lapse imaging of WT and syntaphilin-deficient axons in vitro. These results support the concept that syntaphilin-mediated immobilization of mitochondria to microtubules is required for the volume increase of axonal mitochondria following acute demyelination and protects against axonal degeneration in the CNS.

Welcome Reception in the Exhibit Hall with Poster Viewing
6:30 End of Day 1

FRIDAY, MARCH 20
8:00 Morning Coffee

TARGETING MITOCHONDRIAL-RELATED DISEASE & INJURY

8:25 Chairperson’s Remarks
Johannes Ehinger, M.D., Mitochondrial Pathophysiology Unit, Lund University

8:30 Adaptive Metabolic Targeting of BPM 31510 for the Treatment of Cancer
Michael Kiebish, Ph.D., Director, Integrative Systems Medicine, Diagnostics, Berg Research Institute, Cleveland Clinic
The purpose of this study was to determine the roles of mitochondrial volume and distribution in axonal degeneration following acute CNS demyelination. We show that the axonal mitochondrial volume increase following acute demyelination of WT CNS axons does not occur in demyelinated axons deficient in syntaphilin, an axonal molecule that immobilizes stationary mitochondria to microtubules. These findings were supported by time-lapse imaging of WT and syntaphilin-deficient axons in vitro. These results support the concept that syntaphilin-mediated immobilization of mitochondria to microtubules is required for the volume increase of axonal mitochondria following acute demyelination and protects against axonal degeneration in the CNS.

9:30 Targeting Mitochondrial Dysfunction in Burn Injury
A. Aria Tzika, Ph.D., Director, NMR Surgical Laboratory, Department of Surgery, Massachusetts General Hospital and Shriners Burns Institute
Burn injury represents a significant public health problem in roughly 500,000 people per year in the USA. We probe mitochondrial skeletal muscle dysfunction that occurs in response to burn injury in a preclinical mouse burn model using novel methods. Our studies have the potential for strong clinical relevance with respect to the recovery and management of individuals with burn trauma.

10:00 Coffee Break with Exhibit & Poster Viewing

10:30 Supporting Mitochondrial Function in Cells with Complex I Dysfunction using Cell-Permeable Complex II Substrates: A Potential Novel Therapy for Complex I-Linked Mitochondrial Disease
Johannes Ehinger, M.D., Mitochondrial Pathophysiology Unit, Lund University
Chemically modified mitochondrial complex II substrates with increased cell membrane permeability can support mitochondrial respiration, increase ATP production and uphold mitochondrial membrane potential in cells with deficiencies in complex I-linked mitochondrial metabolism. This new compound class introduces the possibility to pharmacologically support patients with metabolic decompensation due to mitochondrial complex I deficiency, such as children with inborn errors of metabolism.

11:00 The Mitigation of Cytotoxic and Genotoxic Effects of Drugs on Mitochondrial DNA
Adam E. Osborne, Ph.D., Biology Department, Brandeis University
Millions of TB and HIV patients are treated with drugs that have toxic side effects. AZT, an inexpensive nucleotide reverse transcriptase inhibitor used in highly active anti-retroviral therapy, is associated with mitochondrial oxidative stress and DNA damage. Isoniazid (INH), a first line antibiotic used to treat or prevent tuberculosis, alters liver function in ~20% of patients and is fatal in 1%-2%. Toxic intermediates of INH in the liver deplete glutathione and oxygen radical scavenging enzymes. The resulting increase in free radicals can irreversibly damage mitochondria and mitochondrial DNA (mtDNA). We are investigating AZT and INH dependent mtDNA damage in cultured human liver cells, as well as whether palm fruit juice (PFJ), an extract rich in polyphenols from the fruit of the oil palm (Elaeis guineensis),...
mitochondrial health in cells and provides a powerful tool to predict whether novel mutations without sequencing is broadly applicable and could be used for early drug development or monitoring.

11:30 Sponsored Presentation (Opportunity Available)
12:00 Luncheon Presentation (Sponsorship Opportunity Available) or Lunch on Your Own

MITOCHONDRIAL TARGETING & TOXICITY

1:50 Chairperson’s Remarks
Padma K. Narayanan, Ph.D., Director, Pre-Clinical, Toxicology, Amgen

2:00 A Systematic Assessment of Mitochondrial Function Identified Novel Signatures for Drug-Induced Mitochondrial Disruption in Cells
Padma K. Narayanan, Ph.D., Director, Pre-Clinical, Toxicology, Amgen

Mitochondrial perturbation has been recognized as a contributing factor to various drug-induced organ toxicities. To address this issue, we developed a high-throughput flow cytometry-based mitochondrial signaling assay to systematically investigate mitochondrial/cellular parameters known to be directly impacted by mitochondrial dysfunction: mitochondrial membrane potential (MMP), mitochondrial reactive oxygen species (ROS), intracellular reduced glutathione (GSH) level, and cell viability. Disruptors of mitochondrial function depolarized MMP at concentrations lower than those that caused loss of cell viability, especially in cells cultured in GSM; cellular GSH levels correlated more closely to loss of viability in vitro. Subsequent classification of compounds based on ratios of IC50s of cell viability; MMP determined that this parameter is the most critical indicator of mitochondrial health in cells and provides a powerful tool to predict whether novel small molecule entities possess this liability.

2:30 Screening Small Molecules for Mitofunctional Effects: Implications for Mitochondrial Therapeutics and Mitotoxins
Gino Cortopassi, Ph.D., Professor, Molecular Biosciences, University of California, Davis; CEO, Ixchel PharmA

Mitochondrial disease is a rare/ orphan indication, with no approved or effective therapy. Thus screening known FDA-approved drugs for effects on mitochondrial function is a rational approach to shorten the usual time for clinical therapeutic development. Using 4 high-throughput assays we have identified a subset of FDA-approved drugs that target mitochondria. In addition, we have used these assays to screen potential toxicants, and identify known and novel toxicants.

3:00 Targeting Disease-Causing Defects of the Mitochondrial Genome with Engineered Mitochondrial Nucleases
Carlos T. Moraes, Ph.D., Professor, Neurology and Cell Biology, University of Miami

3:30 Inhibitors of Mitochondrial Fission as a Therapeutic Strategy for Diseases with Oxidative Stress and Mitochondrial Dysfunction
P. Hemachandra Reddy, Ph.D., Executive Director and Chief Scientific Officer, Garrison Institute on Aging; Professor of Cell Biology & Biochemistry, Neuroscience & Pharmacology and Neurology Departments, Texas Tech University Health Science Center

Research into mitochondria and cell function has revealed that mitochondrial dynamics is impaired in a large number of aging and neurodegenerative diseases, and in several inherited mitochondrial diseases, and that this impairment involves excessive mitochondrial fission, resulting in mitochondrial structural changes and dysfunction, and cell damage. Attempts have been made to develop molecules to reduce mitochondrial fission while maintaining normal mitochondrial fusion and function in those diseases that involve excessive mitochondrial fission.

4:00 Use of Multiparametric Assays on Isolated Liver Mitochondria and HepaRG Cells to predict DILI
Annie Borgne-Sanchez, Ph.D., CEO/CSO, Mitologics

We combined mitochondrial and cellular assays to predict drug-induced mitochondrial dysfunction in liver. Extensive screening of reference compounds on isolated liver mitochondria revealed a highly significant relationship between acute mitochondrial toxicity detected by this system and DILI occurrence in human. We next showed that human HepaRG differentiated cells is a pertinent and complementary model allowing detection of long-term and/or metabolites mitochondrial toxicity.

4:15 Close of Conference
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Targeting Mitochondrial Dysfunction & Toxicity

March 19-20, 2015
Hyatt Regency Cambridge | Cambridge, MA

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* CHI reserves the right to publish your poster title and abstract in various marketing materials and products.

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