Targeting Mitochondrial Dysfunction & Toxicity
Treating Disease & Improving Drug Safety

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

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

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Healthtech.com/Mitochondrial-Targeting

Organized by
Cambridge Healthtech Institute
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
Phone: 781-247-6259
Email: elamb@healthtech.com

Should you be on this list? 2014 Participating Institutions Included:

- Achillion Pharmaceuticals Inc.
- ActoKine Therapeutics
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- Astellas Research Institute of American LLC
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- Vertex Pharmaceuticals Inc.
patients treated with this compound. In the clinical trials for treatment of solid tumors, and highlight the clinical correlates from the formulation that alters mitochondrial metabolism currently in clinical use. The phenotypic signature for sensitivity to BPM 31510, an ubidecarenone-substrate-level oxidation measurements, predictive phenotypic signatures for anti-cancer responses can be identified and molecular adaptive therapy (e.g., therapeutics, microenvironmental conditions). Using whole-cell integrated energy metabolism parameters coupled with mitochondrial dysfunction in the kidney, liver and heart. Numerous widely prescribed therapeutics can undermine mitochondrial function by interferring 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

1:00 Registration for Main Conference

2:00 Chairperson’s Opening Remarks
Richard Chapleau, Ph.D., Biochemist, Applied Technology & Genomics Center, US Air Force School of Aerospace Medicine

2:10 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

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.

Richard Chapleau, Ph.D., Biochemist, Applied Technology & Genomics Center, US Air Force School of Aerospace Medicine

As the powerhouse of the cell, the mitochondria are critically involved in ensuring optimal cellular function and ultimately in cognitive and physical performance. Due to the unique demands placed upon Air Force personnel in theater, the Airman is constantly in a state of high alert and physical exertion. Therefore, it is of critical importance that we have a solid foundational knowledge of the effects of materials and deployment requirements on the mitochondria. Here I provide an overview of the mitochondrial research program within the 711th Human Performance Wing and present recent data and observations investigating the effects of operational stressors on mitochondrial performance.

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 Uniporter
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+ uniporter, 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 (MAS) or glycerophosphate shuttle (GP3S) 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.

5:00 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.

5:30 Welcome Reception in the Exhibit Hall with Poster Viewing

6:30 End of Day 1
signal. Targeting mitochondria as a cancer therapeutic strategy has attracted
metabolic reprogramming in a cancer cell is mechanistically linked to oncogenic
an increase in reactive oxygen species generation. These metabolic changes
of energy metabolism from oxidative phosphorylation to active glycolysis and
In many cancer cells, mitochondria seem dysfunctional, manifested by a shift
of the pathology. Using a variety of pharmacological tools that we developed
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.

9:00 Correcting Abnormal Mitochondrial Dynamics and Mitophagy
in Neurodegenerative Diseases
Daria Mochny-Rosen, Ph.D., Professor, Chemical and Systems Biology, Stanford
University School of Medicine
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.

9:30 Targeting Mitochondrial Dysfunction in Burn Injury
A. Ari Taka, 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 Targeting Mitochondria of Cancer Cells: Mitochondria as a Therapeutic Approach
Peng Huang, Ph.D., MD Anderson Cancer Center
In many cancer cells, mitochondria seem dysfunctional, manifested by a shift
of energy metabolism from oxidative phosphorylation to active glycolysis and
an increase in reactive oxygen species generation. These metabolic changes
are often associated with up-regulation of NAD(P)H oxidase. Importantly, the
metabolic reprogramming in a cancer cell is mechanistically linked to oncogenic
signals. Targeting mitochondria as a cancer therapeutic strategy has attracted
much attention in the recent years and multiple review articles in this area have
been published. This article attempts to provide an update on recent progress
in identification of mitochondria-associated molecules as potential anticancer
targets and the respective targeting compounds.

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 PharmaA
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
Conference Hotel:

Hyatt Regency Cambridge
575 Memorial Dr
Cambridge, MA 02139
T: 1-888-421-1442

Discounted Room Rate: $209 s/d
Discounted Room Cut-off Date: February 16, 2015

Please call the hotel directly to reserve your sleeping accommodations. You will need to identify yourself as a Cambridge Healthtech Institute conference attendee to receive the discounted room rate with the host hotel. Reservations made after the cut-off date or after the group room block has been filled (whichever comes first) will be accepted on a space-and-rate-availability basis. Rooms are limited, so please book early.

Top Reasons to Stay at The Hyatt Regency Cambridge
• Complimentary internet in guestrooms
• Hotel will provide shuttle to/from Kendall and Harvard Square each evening from 6-10pm
• Approximately 15 minutes from Boston Logan International Airport
• Sundeck overlooks the beautiful Boston skyline along the Charles River

Flight Discounts:

Special discounts have been established with American Airlines for this conference.
• Call American Airlines 1-800-433-1790 and use Conference code 000000.
• Go to www.aa.com/group and enter Conference code 6134AF in promotion discount box.
• Contact our designated travel agent, Rona Meizler, at 617-859-3735 or rona.meizler@protravelinc.com

Sponsorship, Exhibit & Lead Generation Information

CHI offers comprehensive sponsorship packages which include presentation opportunities, exhibit space and branding, as well as the use of the delegate lists. Sponsorship allows you to achieve your objectives before, during, and long after the event. Any sponsorship can be customized to meet your company’s needs and budget. Signing on early will allow you to maximize exposure to qualified decision-makers.

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Showcase your solutions to a guaranteed, targeted audience. Package includes a 15- or 30-minute podium presentation within the scientific agenda, exhibit space, on-site branding and access to cooperative marketing efforts by CHI.

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Opportunity includes a 30-minute podium presentation. Boxed lunches are delivered into the main session room, which guarantees audience attendance and participation. A limited number of presentations are available for sponsorship and they will sell out quickly. Sign on early to secure your talk!

Invitation-Only VIP Dinner/Hospitality Suite
Sponsors will select their top prospects from the conference pre-registration list for an evening of networking at the hotel or at a choice local venue. CHI will extend invitations and deliver prospects. Evening will be customized according to sponsor’s objectives i.e.:
• Purely social
• Focus group
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• Plated dinner with specific conversation focus

Exhibit
Exhibitors will enjoy facilitated networking opportunities with qualified delegates. Speak face-to-face with prospective clients and showcase your latest product, service, or solution.

Inquire about additional branding and sponsorship opportunities!

To secure your participation, please contact:
Carolyn Benton
Business Development Manager
Phone: 781-972-5412
Email: cbenton@healthtech.com
### Pricing and Registration Information

#### SHORT COURSE PRICING

(Primarily includes access to short course only)

<table>
<thead>
<tr>
<th>Category</th>
<th>Commercial</th>
<th>Government, Hospital-affiliated</th>
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<td>Drug-Induced Mitochondrial Toxicity</td>
<td>$699</td>
<td>$399</td>
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#### CONFERENCE PRICING

(Includes access to 1.5-day conference, excludes short course)

<table>
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<tr>
<th>Category</th>
<th>Early Registration Pricing Until December 19</th>
<th>Advance Registration Pricing Until February 13</th>
<th>Late Registration Pricing Until March 19</th>
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<td>Commercial</td>
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<td>Government, Hospital-affiliated</td>
<td>$679</td>
<td>$759</td>
<td>$829</td>
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#### CONFERENCE DISCOUNTS

Register 3 - 4th is Free! Individuals must register for the same conference or conference combination and submit completed registration forms together for discount to apply. Please reproduce this registration form as needed.

- **ALUMNI DISCOUNT:** Alumni Discount - SAVE 20%: CHI appreciates your past participation at Targeting Mitochondrial Dysfunction & Toxicity. As a result of the great loyalty you have shown us, we are pleased to extend to you the exclusive opportunity to save an additional 20% off the registration rate.

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#### POSTER DISCOUNT

$50

Poster abstracts are due by February 13, 2015. Once your registration has been fully processed, we will send an email containing a unique link allowing you to submit your poster abstract. If you do not receive your link within 5 business days, please contact jring@healthtech.com.

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

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I cannot attend but would like to purchase the Targeting Mitochondrial Dysfunction & Toxicity CD for $350 (plus shipping), please visit healthtech.com/mitochondrial-targeting. Massachusetts delivery will include sales tax.

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