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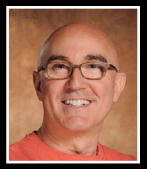
Cambridge Healthtech Institute's Inaugural

Chemical Biology for Target Validation

Minimizing Molecular & Biological Attrition by Interrogating Target-Phenotype Relationships

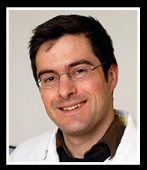
May 22-23, 2014
Westin Boston Waterfront
Boston, MA

» KEYNOTE SPEAKERS:

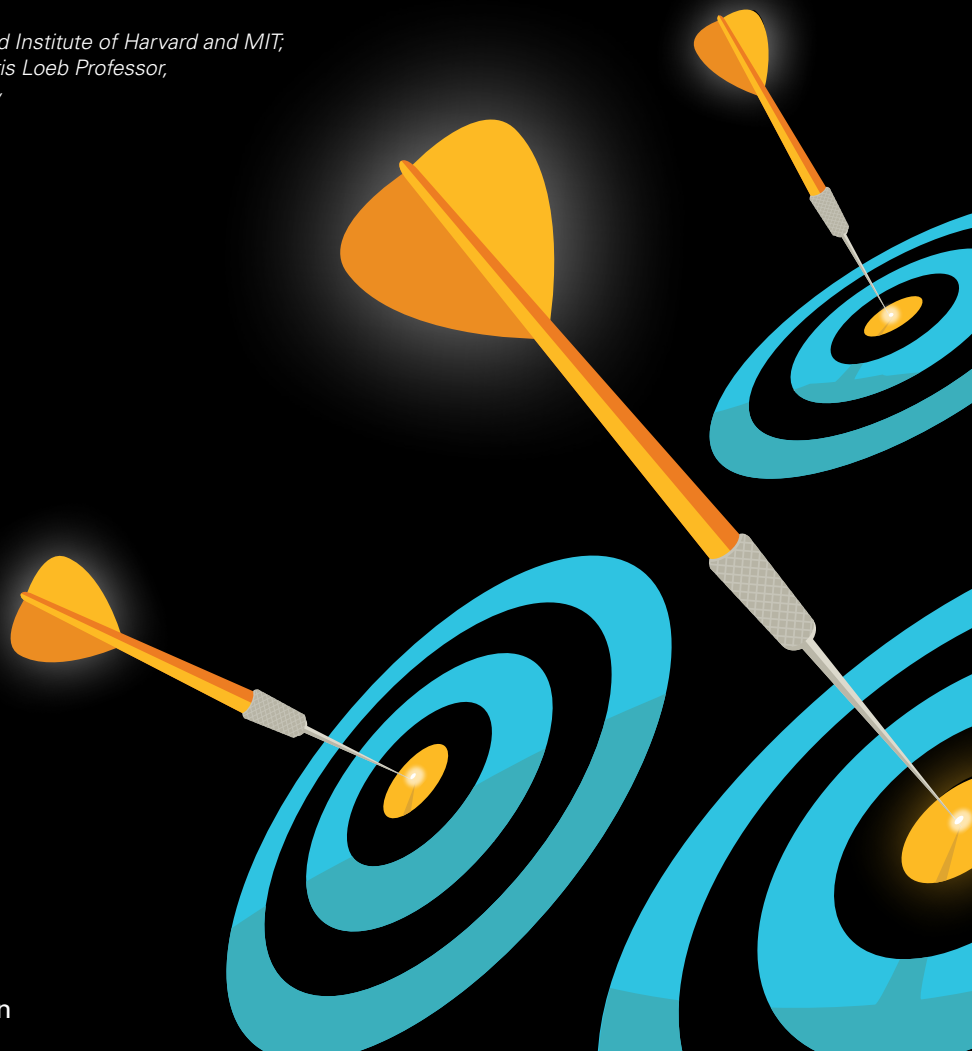


Stuart L. Schreiber, Ph.D.
Director, Chemical Biology, Founding Member, Broad Institute of Harvard and MIT; Howard Hughes Medical Institute Investigator; Morris Loeb Professor, Chemistry and Chemical Biology, Harvard University

Chas Bountra, Ph.D.
Professor, Translational Medicine; Head, Structural Genomics Consortium, University of Oxford



Nathanael Gray, Ph.D.
Professor, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School; Professor, Cancer Biology, Dana-Farber Cancer Institute



» TOPICS INCLUDE:

- Academic-Industry Strategies to De-Risk Discovery Initiatives
- Utilization of Human Genetics and Chemical Biology for Target Validation
- Case Studies in Epigenetics, Protein-Protein Interactions and Novel Biology
- Phenotypic Screening, Target Identification and MOA of Novel Compounds
- Chemical Tools and Strategies to Modulate Biological Processes
- Technological Advances Enabling Target Validation

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About the Conference

Small molecule drug discovery has approached a critical junction where the rigorous preclinical validation and prioritizing of novel targets is of utmost importance. Challenged with thinning development pipelines and significant losses in revenue, greater emphasis is being placed on the stringent selection and validation of targets and candidate molecules to increase success and reduce attrition rates in phase II trials. In response to this challenge, a synergy between drug discovery and chemical biology is emerging as a vital component to providing adequate confidence before launching full discovery programs. The development and utilization of high-quality chemical probes in combination with disease-relevant phenotypic systems provides a powerful approach to obtain a deeper interrogation of target-phenotype relationships - ultimately enriching target validation.

Cambridge Healthtech Institute is proud to announce the Inaugural **Chemical Biology for Target Validation** conference, established to convene an interdisciplinary collection of leaders in chemical/structural biology, chemical proteomics, medicinal chemistry, synthetic chemistry and chemogenomics to discuss strategies to de-risk novel discovery initiatives.

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Mastering Medicinal Chemistry

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Final Agenda

THURSDAY, MAY 22, 2014

11:15 am KEYNOTE PRESENTATION: Structures, Chemical Probes, New Biology, New Targets for Drug Discovery: Is This the Right Sequence?

Chas Bountra, Ph.D., Professor, Translational Medicine; Head, Structural Genomics Consortium, University of Oxford

In my presentation, I will discuss our partnership with nine large pharmaceutical companies to generate structure enabled, freely available, chemical probes; our collaborations with a network of academic labs to use these probes to dissect biological and disease networks; our plans to further improve target validation by using patient derived primary cells, and a new initiative to advance new clinical candidates into Phase IIa studies, pre-competitively.

12:00 pm Enjoy Lunch on Your Own

PHENOTYPIC SCREENING, TARGET IDENTIFICATION AND MECHANISM OF ACTION OF NOVEL BIOACTIVE SMALL MOLECULES

12:55 Chairperson's Opening Remarks
Iván Cornella-Taracido, Ph.D., Head, Chemical Biology, AstraZeneca

1:00 Systematic Assembly of Chemical Probe Libraries to Explore and Validate Novel Biology
Iván Cornella-Taracido, Ph.D., Head, Chemical Biology; Associate Director, Discovery Sciences Chemistry Innovation Centre, AstraZeneca

Chemical probes, drug-like or not, have been used for years to identify new therapeutic targets as well as to perform validation studies directed to assess their efficacious engagement and pharmacological modulation. Herein I will elaborate on the physicochemical and biological features of a good tool compound, review historical work to assemble a comprehensive, properly annotated, collection of optimal chemical probes and discuss its use towards exploratory phenotype-driven biology (target discovery) and target validation.

1:30 Systematic Chemical Biology: Building the Novartis MOA Box
Jeremy L. Jenkins, Ph.D., Senior Investigator I, Developmental & Molecular Pathways, High-Throughput Biology, Novartis Institutes for BioMedical Research

Integrating chemical bioactivity knowledge from large-scale assay data is only the first step to carrying out chemical biology robustly. To use our integrated chemogenomics data effectively, we created an automated rule-based system to score tool compounds for targets based on common-sense assertions such as potency, selectivity, and fame. Consequently, the Mechanism-of-Action Box was created, a set of important tool compounds used widely for opportunistic discovery of targets that modulate phenotypic assays. Further, the chemogenomics data is used to create thousands of probabilistic models capable of predicting targets for new compounds.

2:00 Chemogenomic Profiling: A Systems-Level View of the Cellular Response to Small Molecules
Guri Nina Giaever, Ph.D., Associate Professor, Faculty of Pharmaceutical Sciences, The University of British Columbia

Genome-wide characterization of the cellular response to small molecules is fundamental to understanding the cell as a system and the mechanisms of drug action in a cellular context. We profiled 3,250 diverse small molecules genome-wide in a systematic and unbiased manner, identifying 317 compounds that specifically perturb 121 unique genes. Global analysis of the dataset revealed that the majority of the cellular response to small molecules can be described by a network of chemical moiety-associated biological signatures that provide a unique resource for the discovery of functional interactions between genes, chemicals and biological processes.

2:30 Sponsored Presentations *(Opportunities Available)*

3:00 Refreshment Break in the Exhibit Hall with Poster Viewing

CASE STUDIES IN EPIGENETICS, PROTEIN-PROTEIN INTERACTIONS AND NOVEL BIOLOGY

3:45 CREB Binding Protein Inhibition and Target Engagement
Lyn Jones, Ph.D., Head, Rare Diseases Chemistry; Head, Chemical Biology, Pfizer

This presentation will discuss the structure-based drug design and novel computational techniques applied to the creation of selective inhibitors of the CREBBP bromodomain. Synthetic library enablement and fragment replacement unearthed new bromodomain inhibitors, and a new technology was developed to assess bromodomain target engagement. These methods will facilitate target validation and drug discovery efforts in the epigenetic arena.

4:15 Targeting Protein-Protein Interactions as an Anticancer Strategy
Haian Fu, Ph.D., Professor, Pharmacology, Hematology & Medical Oncology; Director, Emory Chemical Biology Discovery Center; Director, Discovery & Developmental Therapeutics Program of Winship Cancer Institute, Emory University

4:45 Chemical Probing Protein Interactions of the Urokinase Receptor in Cancer
Samy Meroueh, Ph.D., Associate Professor, Biochemistry and Molecular Biology, Indiana University School of Medicine

We have developed small molecules that target protein-protein interactions of the urokinase receptor, a target in tumor invasion and metastasis. We have used innovative structure-based computational methods to identify small molecules that inhibit protein-protein interactions of the urokinase receptor. The presentation will discuss the design, synthesis, biochemical, cellular and *in vivo* characterization of small molecules that inhibit protein-protein interactions that are critical in tumor invasion and metastasis.

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5:15 KEYNOTE PRESENTATION: Selecting and Modulating Therapeutic Targets Using Human Biology and Chemical Biology

Stuart L. Schreiber, Ph.D., Director, Chemical Biology & Founding Member, Broad Institute of Harvard and MIT; Howard Hughes Medical Institute Investigator; Morris Loeb Professor, Chemistry and Chemical Biology, Harvard University

Human genetics can reveal 'experiments of Nature', even providing information related to a 'dose/response' through the analysis of allelic series of genetic variants that suggest the impact of caring about the activity of a target in terms of both efficacy and toxicity. Chemical biology can provide small-molecule modulators of the implicated targets, providing an independent means of target validation. This lecture will provide illustrations of an integrated approach to target validation using human genetics and chemical biology.

6:00 Close of Day and Workshop Registration

6:30 Dinner Workshop: Emerging Methods for Measuring Target Engagement *in vivo

The increase in usage of small molecule probes for the validation of novel therapeutic targets requires effective means of assaying target engagement in living systems. Importantly, measuring the extent to which a target is engaged (or not) provides critical information regarding probe selectivity and attributed efficacy modulating a biological process, while informing of any off-target interactions and potential toxicity. The workshop is designed to discuss emerging techniques and technologies for measuring target engagement *in vivo*.

Instructors: Erik Hett, Ph.D., Senior Scientist, Chemical Biology, Medicinal Chemistry, Pfizer

Additional Instructors to be Announced

**Separate Registration Required*

FRIDAY, MAY 23, 2014

7:30 am Continental Breakfast and Breakout Discussions

Enjoy breakfast while joining a discussion group. These are moderated discussions with brainstorming and interactive problem solving, allowing conference participants from diverse backgrounds to exchange ideas, experiences, and develop future collaborations around a focused topic.

CHEMICAL TOOLS AND STRATEGIES TO EXPAND PHARMACOLOGICAL MODULATION OF BIOLOGICAL PROCESSES

8:35 Chairperson's Remarks

Lyn Jones, Ph.D., Head, Rare Diseases Chemistry; Head, Chemical Biology, Pfizer

8:45 KEYNOTE PRESENTATION: Covalent Inhibitors of Oncogenic Signaling Pathways

Nathanael Gray, Ph.D., Professor, Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School; Professor, Cancer Biology, Dana-Farber Cancer Institute

There has recently been a resurgence of interest in covalent inhibitors. This lecture will discuss our efforts to develop efficient chemical approaches to generate and characterize covalent inhibitors of oncogenic kinases and of KRAS.

9:30 Chemical Proteomic Strategies to Investigate Reactive Cysteines

Eranthie Weerapana, Ph.D., Assistant Professor, Chemistry, Boston College

We have applied chemical proteomics to identify and characterize functional cysteines in the human proteome. By combining small-molecule probe synthesis with mass spectrometry-based proteomics, we have identified reactive and functional cysteines that can be targeted for covalent inhibitor development. Our small-molecule probes act as pharmacological modulators of diverse protein activities.

10:00 Sponsored Presentation *(Opportunity Available)*

10:15 Coffee Break in the Exhibit Hall with Poster Viewing

11:00 Diversity-Oriented Synthesis for Oncology Drug Discovery

Lisa Marcaurelle, Ph.D., Vice President, Discovery Chemistry, H3 Biomedicine

H3 Biomedicine's approach to oncology drug discovery leverages the vast amount of available cancer genomics data to identify novel molecular targets. This genomics-based approach is coupled with the creation of a unique compound collection with the potential to modulate a broad range of oncology targets. Libraries of sp3-rich small molecules containing one or more stereogenic centers have been assembled using the most recent developments in synthetic organic chemistry facilitated by parallel synthesis techniques. Library design is inspired by the molecular architecture of natural products and enabled by cheminformatics to yield compounds with maximal diversity and optimal physicochemical properties. To date over 15,000 compounds have been produced representing >100 distinct synthetic pathways. An overview of this work will be presented.

11:30 Natural Product-Based Strategies in Diversity-Oriented Synthesis

Derek Tan, Ph.D., Member and Laboratory Head, Molecular Pharmacology & Chemistry Program, Sloan–Kettering Institute for Cancer Research, Memorial Sloan–Kettering Cancer Center

Advances in genomic technologies and molecular cell biology have revealed myriad new biological targets that are implicated in human diseases. However, our ability to translate these discoveries into new therapeutics is severely limited by the fact that existing small-molecule drugs address only a very small subset of ≈200 protein targets encoded in the human genome (≈1%). To address this critical problem, our laboratory is developing discovery libraries based on privileged structural motifs from natural products, which have a demonstrated ability to bind diverse biological targets. We develop new chemical methodologies to provide efficient and flexible access to these molecules, with current targets including spiroketals, macrocycles, and medium rings.

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

TECHNOLOGICAL ADVANCES ENABLING TARGET VALIDATION

12:55 Chairperson's Remarks *(Sponsorship Opportunity Available)*

1:00 Paradigm Shift in Hit Identification and Lead Optimization
Litao Zhang, Ph.D., Executive Director, Applied Biotechnology, Lead Evaluation and Mechanistic Biochemistry, Bristol-Myers Squibb
This presentation will outline critical roles of hit identification and lead optimization for target validation. Technology innovation has been and will continuously guide our ways to select right targets and deliver right therapeutic agents. Future trends in hit ID and lead optimization will center around complex biology, systematic approaches and chemical biology.

1:30 Multiplexed, Proteome-Wide Protein Expression Profiling to Explore Biological Function and Response
Steven P. Gygi, Ph.D., Professor, Cell Biology, Harvard Medical School
Mass spectrometry (MS) is a powerful measurement tool in biology. Using MS-based Proteomics, up to 10 samples can be simultaneously profiled for protein expression or posttranslational modification differences. This lecture will highlight i) the rationale for proteome-wide measurements, ii) the current status of multiplexing, and iii) future needs in the field. Examples of global expression profiling in colorectal cancer cell lines will be described.

2:00 Superbright Fluorophore-Tetrazine Turn On Probes for Bioorthogonal Imaging
Jonathan Carlson, M.D., Ph.D., Instructor, Medicine, MGH Cancer Center; Center for Systems Biology, Massachusetts General Hospital
In recent work we have developed fluorescent turn-on probes that exploit through-bond energy transfer (TBET) to achieve >1500-fold signal amplification upon bioorthogonal activation. These tetrazine-fluorophore derivatives are exceptionally quenched (non-fluorescent) until their characteristically fast, catalyst-free reaction with transcyclooctenol (TCO). This presentation will describe our progress in developing "clickdyes" that display excellent performance in real time, no-rinse imaging of TCO-labeled targets *in vitro* and *in vivo*.

2:30 Clickable Probes for Target ID, Mechanism of Action Studies, and Imaging: Case Study using Clickable g-Secretase Photoaffinity Probes
Doug Johnson, Ph.D., Associate Research Fellow, Neuroscience, Medicinal Chemistry, Pfizer
This presentation will describe how we have used clickable photoaffinity probes to investigate the mechanism of action studies of g-secretase inhibitors (GSIs) and modulators (GSMs), potential therapeutic agents for Alzheimer's Disease (AD). Presenilin-1 N-terminal fragment (PS1-NTF) was identified as the protein target for GSMs and GSIs, however our data demonstrates that they bind to distinct sites. Furthermore, these clickable photoprobes enabled target engagement to be determined in live cortical neurons. Lastly, we developed a platform to image Cu-free clickable probes using the HaloTag protein as a model system in different subcellular compartments. This technology will be applied to image active g-secretase using Cu-free clickable GSI photoprobes.

3:00 End of Conference

PRESENT A POSTER AND SAVE $50!

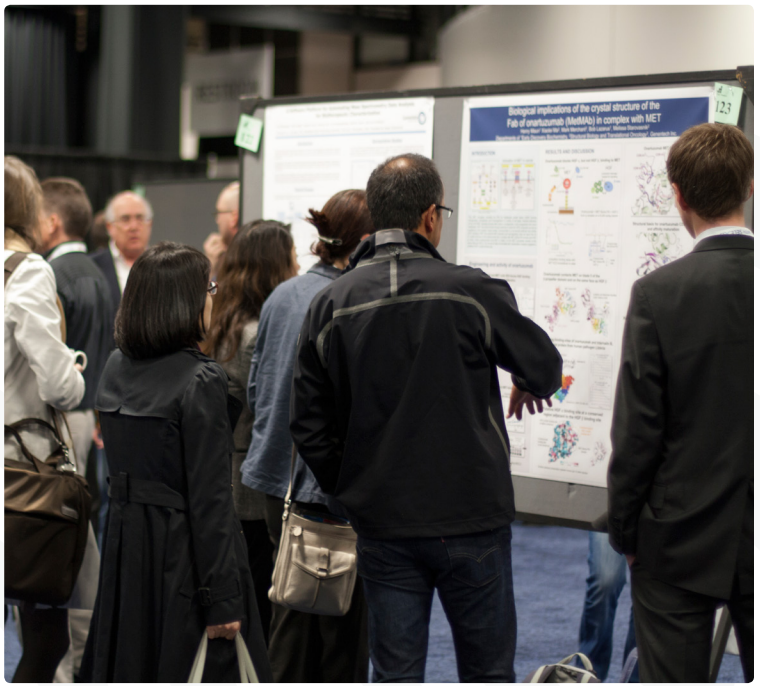
Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. To secure a poster board and inclusion in the conference materials, your abstract must be submitted, approved and your registration paid in full by April 4, 2014.

Register online, or by phone, fax or mail. Please indicate that you would like to present a poster. Once your registration has been fully processed, we will send an email with a unique link and instructions for submitting your abstract using our online abstract submission tool. Please see below for more information.

Reasons you should present your research poster at this conference:

- Your poster will be exposed to our international delegation
- Receive $50 off your registration
- Your poster abstract will be published in our conference materials
- Your research will be seen by leaders from top pharmaceutical, biotech, academic and government institutes

Note: Posters should be portrait orientation, with maximum dimensions of 36 inches wide (3 feet) x 48 inches high (4 feet).



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CHI offers comprehensive packages that can be customized to your budget and objectives. Sponsorship allows you to achieve your goals before, during, and long after the event. Packages may include presentations, exhibit space and branding, as well as the use of delegate lists. Signing on early will maximize your exposure to qualified decision-makers and drive traffic to your website in the coming months.

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Showcase your solutions to a guaranteed, targeted audience through a 15- or 30-minute presentation during a specific program, breakfast, lunch, or a pre-conference workshop. Package includes exhibit space, on-site branding, and access to cooperative marketing efforts by CHI. For the luncheon option, lunches are delivered to attendees who are already seated in the main session room. Presentations will sell out quickly! Sign on early to secure your talk.

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For more information, please contact:

Joseph Vacca
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781-972-5431 | jvacca@healthtech.com

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425 Summer St.
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T: 617-532-4600
Hotel Website

Discounted Room Rate: $269 s/d
Discounted Room Rate Cutoff Date: April 23, 2014

Please visit our conference website to make your reservations online or 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.

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American Airlines

Special discounts have been established with American Airlines for this conference. Please use one of the following methods:

- Call 1-800-433-1790 and use Conference code 7654AA
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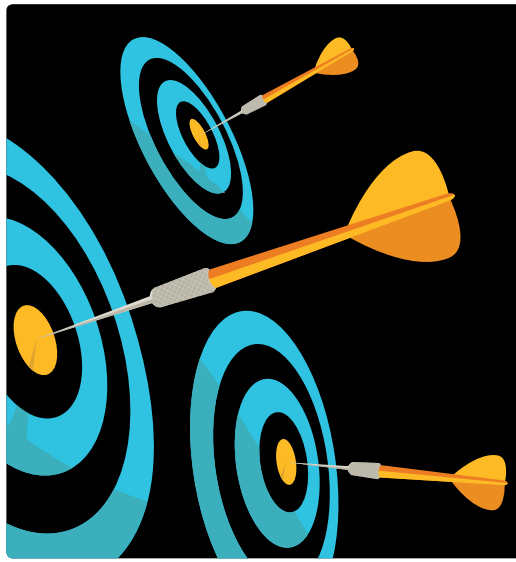

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Advance Registration Discount until April 18, 2014	$1599	$729
Late Registration After April 18, 2014	$1799	$799

If you are unable to attend but would like to purchase the Chemical Biology for Target Validation CD for $350 (plus shipping), please visit http://chidb.com/register/2014/tvd/reg.asp. Massachusetts delivery will include sales tax.

CONFERENCE DISCOUNTS

Poster Submission - Discount ($50 Off): Poster abstracts are due by April 4, 2014. 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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Group Discounts: Discounts are available for multiple attendees from the same organization. For more information on group rates contact David Cunningham at +1-781-972-5472

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