



Cambridge Healthtech Institute's Inaugural

# Linking Phenotype to Genotype

The Identification of Disease Pathways and Models of Disease

April 24-25, 2003 • Hilton Munich Park • Munich, Germany

Held concurrently with Second Annual Proteins to Profits conference

## Sponsoring Publications:



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**Scientific Advisors:** Dr. Monica J. Justice, Baylor College of Medicine, and Dr. Laura Shawver, Phenomix Corp.

Phenotypes are generally difficult to recognize and validate, especially at the cellular level. Providing an association between phenotype and genotype is critical to being able to understand and create models of disease. This association is also key to targeting critical pathways in disease and identifying the genes and proteins that regulate biological processes, thus identifying better drug targets. The use of chemical genomics will be a powerful technique for phenotype screening. Case studies and the latest approaches will be highlighted that give clear examples of linking genotype with clinical conditions and the reverse process of using small molecules to probe genotype. The promise of isolating specific disease mechanisms on the basis of both forward and reverse genetics is that it will enable both disease prevention and early intervention. The ability to correlate clinical phenotype with genotype will give highly validated targets for drug discovery, improve the models that are used for drug testing, and provide rationale for improved clinical trial designs. This will result in a greater success rate for drug development.

### Keynote Presentations

Searching for Therapeutic Strategies from Genetic Analysis and Primary Disease Mechanisms

*Prof. John Todd, Professor of Medical Genetics and Director of JDRF/WT Diabetes & Inflammation Laboratory, University of Cambridge*

The Proteome: How Do We Find Any More Pharmacologically Active Proteins?

*Dr. Timothy Wells, Head of Discovery, Serono Pharmaceutical Research Institute*

*Dr. Jan-Anders Karlsson, Executive Vice President, Pharma Research, Bayer AG Leverkusen*

### Additional Speakers

*Dr. S. Lee Adamson, University of Toronto*

*Dr. Reuven Agami, Netherlands Cancer Institute*

*Prof. Steve D.M. Brown, MRC Mammalian Genetics Unit and UK Mouse Genome Centre*

*Dr. Hans Clevers, UMC Utrecht*

*Dr. Martin Hrabe de Angelis, GSF-Institute of Experimental Genetics*

*Dr. Paz Einat, Quark Biotech, Inc. (USA) & QBI Enterprises (Israel)*

*Dr. José Luis Pérez Gracia, Eli Lilly & Co., Inc.*

*Dr. Jonathan Hall, Novartis Pharmaceutical Corporation*

*Dr. Christoph Hüls, Protagen AG*

*Dr. Curtis T. Keith, CombinatoRx, Inc.*

*Dr. Hans Lehrach, Max-Planck-Institut für Molekulare Genetik*

*Dr. Michael C. Nehls, Ingenium AG*

*Dr. Smita Patel, Merck Sharp & Dohme*

*Dr. Ketty Schwartz, INSERM*

*Dr. Gill Smith, AstraZeneca R&D Charnwood*

*Dr. Giulio Superti-Furga, Cellzome AG*

*Dr. Hans-Peter Vornlocher, Ribopharma AG*

*Dr. Claes Wahlestedt, Karolinska Institute*

*Dr. Lutz Weber, Morphochem AG*

### Models of Disease

Large-Scale Isolation and Rapid Mapping of Recessive Mouse Mutations

Phenotype-Driven Mouse Mutagenesis

From Functional Genomics to Systems Biology

Characterization of Novel Genes

### Forward Genetics in Mammalian Systems

Forward Genetics on Drug Discovery and Development

Systematic Analysis of Mammalian Gene Function

Industrializing Discovery Biology and Target Validation

Mouse Models of Cardiovascular Disease Using Random Mutagenesis

Genomic and Genetic Strategies in Cardiac Hypertrophy

### Functional Validation of Targets for Disease:

#### RNA Interference and HT Genomic Screens

Inhibition in Colorectal Cancer Cells by siRNA Expression Vector

Developing RNAi Tools for Cancer Applications

RNA-Interference as a Platform for the Development of Therapeutics

Using Oligonucleotides in Functional Genomics

From Phenotype to Drug Targets

Inhibiting the Ras-Raf Interaction: From Phenotypes to Genotypes

Multicomponent Chemical Genetics Using cHTS

### Drug Discovery Applications

Identification of Drug Targets for CNS Disorders

Lead Compounds via Integrated Proteomics Approaches

Exploiting Tractable Drug and Target Space

Finding Drug Targets Using Functional Genomics

Phenotype Selection Studies in Cancer Research

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## Wednesday, April 23

16.00- Early Registration

18.00

## Thursday, April 24

7.00 Registration, Poster and Exhibit Set-up, and Light Continental Breakfast

8.30 Chairperson's Remarks

*Dr. Mathias Uhlén, Department of Biotechnology, Division of Molecular Biotechnology, Royal Institute of Technology (KTH)*

### KEYNOTE PRESENTATIONS

(combined session with **Proteins to Profits**)

**8.40 Searching for Therapeutic Strategies from Genetic Analysis and Primary Disease Mechanisms**

*Prof. John Todd, Professor of Medical Genetics and Director of JDRF/WT Diabetes & Inflammation Laboratory, University of Cambridge*

The interrogation of the allelic variation of the genome responsible for common human disease and for experimental models of these disorders is in its infancy. The search for disease risk causing variants is now aided by advances in genome sequence determination, genotyping methods, and the acquisition of appropriately large study sample sizes. Identification of candidate causal variants directs functional studies that lead to insights into the causal mechanisms of disease, thereby avoiding research effort into pathways that are an effect of the disease process rather than a primary etiological factor.

**9.15 The Proteome: How Do We Find Any More Pharmacologically Active Proteins?**

*Dr. Timothy Wells, Head of Discovery, Serono Pharmaceutical Research Institute*

One of the key hopes of the genome age is that the deeper understanding of the human genome would lead to a wave of new therapeutics. As one of the world's leading biotechnology companies, Serono is searching for the next generation of protein products in its disease areas, be they cytokines, growth factors and hormones, or engineered proteins that can block the action of such cytokines. Our project to understand the secreted protein universe will be discussed—from novel bioinformatics that is still identifying the sequence of proteins, through to disease-based technologies for understanding the therapeutic applications of proteins.

9.50 Opening of Poster and Exhibit Hall, Refreshment Break

### MODELS OF DISEASE

10.30 Chairperson's Remarks

*Dr. Laura Shawver, President and Chief Executive Officer, Phenomix Corp.*

**10.35 Large-Scale Isolation and Rapid Mapping of Recessive Mouse Mutations**

*Dr. Monica J. Justice, Assistant Professor, Department of Molecular and Human Genetics, Baylor College of Medicine*

The post-sequencing challenge is to define the function of genes, and large-scale high-throughput mouse mutagenesis is one of the best avenues for determining mammalian gene function. A powerful approach for mutagenesis combines gene-based targeting in embryonic stem cells with phenotype-driven ethylnitrosourea (ENU) mutagenesis. The ability to engineer whole chromosome regions using Cre/*loxP* technologies allows for the creation of genetic reagents such as deletions and balancer chromosomes to isolate, map, and manage the large number of mutations that can be obtained after ENU mutagenesis.

**11.05 Phenotype-Driven Mouse Mutagenesis**

*Dr. Martin Hrabe de Angelis, Director, GSF-Institute of Experimental Genetics*

The large-scale mouse-mutagenesis efforts in Germany have been complemented by the German Mouse Clinic (GMC) to characterize mouse models for a wide variety of phenotypes. The projects discovered many genotype-phenotype correlations involved in inherited diseases. The next step will be the dissection of genetic pathways and understanding of genetic networks by sensitized screens and proteomics and bioinformatic tools.

**11.35 From Functional Genomics to Systems Biology**

*Dr. Hans Lehrach, Director, Max-Planck-Institut für Molekulare Genetik*  
Biological research is moving rapidly from the focused analysis of single genes and gene products to the systematic analysis of the entire network of biological processes in structural and functional genomics. The deluge of complex, interrelated data will require the development of databases able to link across different types of data and different organisms, as well as the development of quantitative modeling tools able to reproduce the complexity of biological processes in the computer.

## 12.05 Characterization of Novel Genes

*Dr. Claes Wahlestedt, Professor and Chairman, Center for Genomics and Bioinformatics, Karolinska Institute*

Over the past several years we have studied the transcriptome, including a large set of well-known drug target family genes as well as novel genes that show orthologs in several species. A number of techniques and approaches have been employed, and these will be described briefly. In the course of this work, we have, e.g., had reason to assess similarities and differences between antisense and RNAi strategies for efficient gene knockdown *in vitro* and *in vivo*. Like with antisense oligonucleotides, key issues surrounding optimal *in vitro* and/or *in vivo* use of (chemically synthesized) siRNA are/will be (1) delivery, (2) chemistry, and (3) mRNA target site selection.

## 12.35 Lunch (on your own)

## FORWARD GENETICS IN MAMMALIAN SYSTEMS

### 14.00 Chairperson's Remarks

*Dr. Monica J. Justice*

### 14.05 The Impact of Forward Genetics on Drug Discovery and Development

*Dr. Laura Shawver*

Genetic manipulations that lead to loss or gain of function for a specific protein are a very powerful method of assessing the impact that protein plays in a particular pathophysiological process. This is exemplified by the numerous mouse models of disease created by targeted disruption and transgenic lines. However, there still remains a considerable gap between the number of genes identified and the amount of phenotype information for these genes. Using a "forward genetics" approach to examine gene function will impact drug discovery and development at several key points. The approach identifies gene alterations causative in disease and, in addition, allows for pathway determination, the ability to generate clusters of disease models, and the application of drug testing in an appropriate pharmacological model. It is also informative about patient selection for clinical trials.

### 14.35 Mutagenesis and Genomics in the Mouse: Towards a Systematic Analysis of Mammalian Gene Function

*Prof. Steve D.M. Brown, Director, MRC Mammalian Genetics Unit and UK Mouse Genome Centre*

Systematic approaches to mouse mutagenesis are vital for future studies of gene function. We have undertaken a major ENU mutagenesis program incorporating a large genomewide screen for dominant mutations (Nolan et al., *Nature Genetics* 25: 440-443). Nearly 30,000 mice have been produced, and around 500 mutants have been recovered from the screening program. We have mapped over 70 mutants to date and confirmed that many of the novel phenotypes represent mutations at previously unidentified loci in the mouse genome. We have also begun to develop gene-driven mutagenesis approaches using ENU (Coghill et al., *Nature Genetics* 30: 255-256). The approach promises a rapid methodology to recovering an allelic series of point mutations for any gene in the mouse genome enabling a more profound analysis of gene function. The use of both phenotype-driven and gene-driven ENU mutageneses for the generation of a new mutant map of the mouse represents a powerful combination of approaches for gene function studies.

## 15.05 Deductive Genomics: Industrializing Discovery Biology and Target Validation in the Post-genome Era

*Dr. Michael C. Nehls, Chief Executive Officer, Ingenium AG*

Until recently, the use of the mouse as a model organism in drug discovery was dominated by reverse genetic approaches. With the advent of ENU mutagenesis in mice, genomewide forward genetics approaches have become feasible. Ingenium Pharmaceuticals has established a screen for recessive mutants relevant for the therapeutic areas of neurobiology, immunology/hematology, metabolic diseases, and cancer biology. An overview of the results of the program, including early-stage drug targets and target validation approaches, will be presented.

## 15.35 Poster and Exhibit Viewing, Refreshment Break

### 16.15 Creating New Mouse Models of Cardiovascular Disease Using Random Mutagenesis

*Dr. S. Lee Adamson, Director, CMHD Mouse Physiology Lab, Senior Scientist, Samuel Lunenfeld Research Institute, and Professor, Obstetrics & Gynecology, University of Toronto*

Toronto's Centre for Modelling Human Disease is creating new mouse models of human disease using random mutagenesis. C57BL/6J male mice are injected with ethylnitrosourea (ENU) to generate mutations in sperm, then bred with normal C3H/HeJ females. G1 offspring are screened for cardiovascular and other physiologic abnormalities. "Outliers" are bred to establish heritability. Dominant mutations responsible for traits are localized using a genome scan. We are screening mice for blood pressure and heart rate abnormalities using a tail cuff system, ascending aortic blood velocity abnormalities using pulsed Doppler while under isoflurane anesthesia, for hematologic abnormalities (hematology analyzer and blood smear) and for abnormal ECGs. The program is always seeking new collaborators and new screening protocols. See [www.cmhd.ca](http://www.cmhd.ca) for details and a list of the heritable models available.

### 16.45 Genomic and Genetic Strategies in Cardiac Hypertrophy

*Dr. Ketty Schwartz, Director of Research, New Technologies, INSERM*

Genetic and genomic studies in hereditary forms of cardiac hypertrophy and of cardiomyopathies showed that at least 20 to 30 different genes are involved in the development of these diseases. The talk will focus on two genes, cardiac myosin-binding protein C and lamin A/C. In both cases, the results of family analysis, of *ex vivo* cellular models, and of mouse knock-in models will be presented.

### 17.15 High Throughput Gene Expression in Mammalian Cells: Applications in Target Discovery

*Dr. Ulrich Brinkman, Chief Scientific Officer, Xantos Biomedicine AG*

We have set up a high-throughput expression screen where single cDNA clones are prepared on a robotics platform. Subsequently, an automated transfection and readout system completes the four robot cascade. This enables genome wide, unbiased screens with 150,000 complete functional assays per month including further analysis. We will discuss the application in the search for targets from phenotypic screens as well as results of a first screen for novel apoptosis inducing genes with new disease associations.

## 17.45 Networking Reception

## 19.00 Close of Day One

**Friday, April 25**

**8.00 Poster and Exhibit Viewing, Light Continental Breakfast**

**FUNCTIONAL VALIDATION OF TARGETS FOR DISEASE: RNA INTERFERENCE AND HT GENOMIC SCREENS**

**8.30 Chairperson's Remarks**

*Dr. Claes Wahlestedt*

**8.35 Inhibition of  $\beta$ Catenin Expression in Colorectal Cancer Cells by a Stable, Integrated, Inducible siRNA Expression Vector**

*Dr. Hans Clevers, Professor and Chairman, Department of Immunology, Faculty of Medicine, UMC Utrecht*

TCF target gene expression is induced by Wnt pathway mutations and constitutes the primary transforming event in colorectal cancer (CRC). We have previously shown that disruption of  $\beta$ catenin/TCF4 activity in CRC cells by overexpression of dominant-negative TCF induces a rapid G1 arrest and differentiation. To extend these observations by a loss-of-function strategy, we have designed a doxycyclin-inducible version of the polymerase III H1 promoter driving siRNA expression. Stable integration of this plasmid vector in CRC cells carrying the tetracyclin repressor allowed the rapid downregulation of  $\beta$ catenin by doxycyclin induction. This resulted in inhibition of TCF reporter gene expression, G1 arrest, and differentiation of the CRC cells. Our vector system is widely applicable for inducible knock-down of gene expression.

**9.05 Developing RNAi Tools for Cancer Applications**

*Dr. Reuven Agami, Group Leader, Division of Tumor Biology, Netherlands Cancer Institute*

For a long period, the lack of tools to efficiently generate stable loss-of-function phenotypes hindered mammalian genetic approaches to study gene function. Recently, we have developed a novel vector system, named pSUPER, that directs persistent and specific inhibition of gene expression through RNA interference (RNAi). With it we targeted the dominant-mutant oncogene K-RASV12 without affecting its wild-type counterpart and showed that the tumorigenicity of cell lines that harbor this exact type of genetic alteration is abrogated. In a complementary approach, we make use of this system to target putative tumor-suppressor genes in order to comprehend their tumorigenic function and identify and define combinations of genetic events that promote cancer. The identified cancer relevant targets can be further used to discover drugs for cancer therapy.

**9.35 RNA-Interference as a Platform for the Development of Therapeutics**

*Dr. Hans-Peter Vornlocher, Head, Research & Development, Ribopharma AG*

Inhibition of gene expression by siRNAs has proven to be a powerful tool for the analysis of protein function *in vitro*. In order to determine the potential of these molecules as therapeutics, Ribopharma targeted a number of tumor-relevant genes with siRNAs. Analysis of these molecules in various mammalian tissue culture systems reveals a substantial reduction of the corresponding mRNA/protein levels as well as an effective interference with cellular processes like, e.g., apoptosis. In a mouse model system we demonstrate that siRNA is capable of mediating RNA interference in living adult mammals. Presently, the effectiveness of siRNA tar-

geting different tumor-related mRNAs is analyzed in different human cancer SCID mouse xenotransplantation models.

**10.05 Poster and Exhibit Viewing, Refreshment Break**

**10.30 Using Oligonucleotides in Functional Genomics**

*Dr. Jonathan Hall, Head of Nucleic Acid Sciences, Functional Genomics, Novartis Pharmaceutical Corporation*

Oligonucleotide reagents are powerful tools for the discovery and validation of novel pharmaceutical targets. Examples of the use of these reagents in both throughput screening applications, and selected animal models will be described.

**11.00 From Phenotype to Drug Targets: High-Throughput Genetic Screens for the Identification of Genes Modulating Specific Disease Phenotypes**

*Dr. Paz Einat, Chief Scientist, Quark Biotech, Inc. (USA) & QBI Enterprises (Israel)*

Current functional genomics technologies are not suited for direct identification of genes modulating specific phenotypes and are thus deficient in their ability to identify drug targets. Our technology platform, termed BiFAR™, is a unique high-throughput approach for the direct identification of genes modulating specific disease-related cellular phenotypes. The technology uses a random gene inactivation process in mammalian cells and employs DNA microarrays to identify genes whose inhibition leads to a change in specific cellular phenotypes. The applicability of the platform to a wide variety of diseases will be presented.

**11.30 Inhibiting the Ras-Raf Interaction: From Phenotypes to Genotypes**

*Dr. Lutz Weber, Chief Executive Officer, Morphochem AG*

Morphochem has identified proprietary compounds capable of inhibiting Ras-induced Raf-1 activation in multiple cell lines, as well as the activities of other cancer-related enzymes such as MEK and MMP-9. A chemical genomics approach was used to identify compounds that reverse several cancer-related morphological changes, including loss of stress fiber formation and *in vitro* invasiveness. Morphochem's RPM compounds also inhibit proliferation and anchorage independent growth in clinically relevant cell lines including those derived from human pancreatic, colon, and breast cancers.

**12.00 Multicomponent Chemical Genetics Using cHTS**

*Dr. Curtis T. Keith, Vice President, Research, CombinatoRx, Inc.*

Forward chemical genetic screens have traditionally been used to identify individual compounds that effect phenotypic changes via single molecular targets. One limitation of the phenotypic approach is that a compound may act on a disease-relevant cellular process, yet be silent when used in isolation. We have developed cHTS, a chemical genetic method that identifies synergistic combinations of compounds that act simultaneously at multiple points in cellular networks. These combinations can reveal previously unknown interactions between signaling pathways or genes that would be missed in the single compound paradigm. We are using cHTS to discover multicomponent drugs that act synergistically on disease systems with mechanisms that cannot be achieved by individual compounds.

**12.30 Lunch (on your own)**

## **DRUG DISCOVERY APPLICATIONS** **(combined session with Proteins to Profits)**

### **13.45 Chairperson's Remarks**

*Dr. Giulio Superti-Furga, Vice President, Biology, Cellzome AG*

### **13.50 Keynote Address**

*Dr. Jan-Anders Karlsson, Executive Vice President, Pharma Research, Bayer AG Leverkusen*

### **14.30 Use of Microarray Technology in the Identification of Drug Targets for CNS Disorders**

*Dr. Smita Patel, Senior Research Fellow, Department Biochemistry and Molecular Biology, Merck Sharp & Dohme*

The beauty of microarray technology is the ability to monitor expression levels of thousands of genes simultaneously in response to different treatments. We are using CNS-focused microarrays to identify key genes and biological pathways of potential importance in neuropsychiatric disorders. Microarray analysis of brain regions from mouse models of schizophrenia revealed significant gene expression variances. Analysis of this data for clusters of functionally related genes and independent confirmation of key gene expression changes by RT-PCR and *in situ* hybridization may provide insights into the molecular basis of schizophrenia and point to potentially novel therapeutic targets.

### **15.00 New Lead Compounds via Smart Integrated Proteomics Approaches**

*Dr. Christoph Hüls, President and Chief Executive Officer, Protagen AG*

The post-genomic era left pharmaceutical R&D with a huge number of possible disease-related targets, their respective validation in accepted pharmaceutical *in vitro* and *in vivo* models, and the task to design and to develop lead candidates and new chemical entities (NCEs). Until today, proteomics technologies proved to be decisive for target discovery and validation only. Protagen shows that the strategic application of its proprietary integrated proteomics technology (IPT™) platform allows the straightforward design of small molecule lead compounds with significant biological activity. The Protagen strategy is based on the identification of regulatory networks of cellular proteins affected by already marketed drugs in diseased and normal states. The extraction of knowledge from these proteomics studies and its correlation with the basics in cell biology, biochemistry, and pharmacology can be applied to the design of small molecule drugs. In this study, an anti-proliferative and anti-inflammatory drug was used to identify a set of proteins all belonging to the major cellular energy generating machinery. The comparison of drug structures and natural substrates as well as effectors of these proteins gave guidance for the synthesis of P@G1011. The new lead candidate has been tested *in vitro* and in animal models and showed efficacy in different cell lines and in a rat cancer model. These data strongly demonstrate the potential of smart designed proteomic studies in delivering superior quality of targets and lead compounds and in speeding up the pharmaceutical R&D process.

### **15.30 Poster and Exhibit Viewing, Refreshment Break**

### **16.00 Drug Proteomics: Exploiting Tractable Drug and Target Space**

*Dr. Giulio Superti-Furga*

Cellzome AG is an emerging biopharmaceutical company using known drug and target space to exploit the proteome in an efficient and focused approach. Previously unrecognized connections between proteins and

protein complexes, drugs, and biological processes are identified with proprietary proteomics technologies. Using this unique perspective, Cellzome has the ability to select druggable targets, choose lead molecules with key features, and reject targets with safety concerns. This can be accomplished very early in the drug discovery process, circumventing future safety concerns and streamlining the process to focus only on the most promising compounds.

### **16.30 Trying to Find the Best Drug Targets Using Modern Functional Genomics**

*Dr. Gill Smith, Director of Molecular Biology and Global Head of Molecular and Cell Biology, AstraZeneca R&D Charnwood*

The challenges of the post-genomic era for the drug discovery industry is trying to select the best drug targets from the vast array of potential candidates. Genetics and genomics approaches to target discovery often generate a wide range of potential drug targets which need further investigation. I will describe how in AstraZeneca we try to bring a range of functional genomics and target validation techniques together to select the best targets from genetics and genomics target discovery programmes.

### **17.00 Extreme Phenotype Selection Studies in the Identification of Relevant Genotypes in Cancer Research**

*Dr. José Luis Pérez Gracia, Clinical Research Physician, European Medical Department, Eli Lilly & Co., Inc.*

The investigation of genetic alterations that are potentially related to the prognosis of cancer patients has become a frequently used strategy in recent years, but many times it has led to conflicting results. In contrast, the identification and the study of subjects or families with very characteristic phenotypes have yielded outstanding results in the identification of the genetic characteristics underlying such phenotypes. While on most occasions the individuals selected for these types of studies were characterized by a negative phenotype-for example, an increased risk to develop a determined disease-a few studies have been directed towards individuals with phenotypes of unusual good prognosis-i.e., those presenting a decreased risk of developing determined diseases despite an important exposure to well-known risk factors. Therefore, it seems logical to further develop this strategy as a valid methodology for the study of other diseases such as cancer. The study of individuals with phenotypes of extremely good prognosis, such as long-term survivors of theoretically incurable tumors or of subjects that seem to be protected against certain neoplastic disorders despite possessing a markedly increased risk to develop them, could unveil the genetic alterations that explain such characteristic phenotypes and could provide potentially useful therapeutic targets against this disease.

### **17.30 Close of Conference**

#### **CALL FOR POSTERS**

Cambridge Healthtech Institute encourages attendees to gain further exposure by presenting their work in the poster sessions. Please fill out the registration form, with the poster title and primary author. To ensure inclusion in the conference binder, a one-page summary must be submitted and registration must be paid in full by March 21, 2003.

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## Call for Sponsors and Exhibitors

Linking Phenotype to Genotype and Proteins to Profits concurrent conferences will provide an excellent venue for companies wishing to network with scientists from the biotechnology and pharmaceutical industries involved in the correlation of phenotype to genotype and/or scientists involved in the technical developments or applications in the fields of Protein and Peptide Arrays and Proteomics. Cambridge Healthtech Institute offers an array of sponsorship packages for you to most successfully reach this select audience. Make a lasting impression as a leader in these areas by taking advantage of these marketing tools. All packages can include an exhibit space or an exhibit space can be purchased alone.

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Please call the hotel directly to make your room reservation. Identify yourself as a Cambridge Healthtech Institute conference attendee to receive the reduced room rate. 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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\$1,145  
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#### Academic, Government, Hospital-Affiliated

\$685  
 \$775  
 \$835

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**Linking Phenotype to Genotype**  **Proteins to Profits**

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Enclosed is a check or money order payable to Cambridge Healthtech Institute, drawn on a U.S. bank, in U.S. currency.

Invoice me, but reserve my space with credit card information listed below. **Invoices unpaid one week prior to conference will be billed to credit card at full registration rate. Invoices must be paid in full and checks received by the deadline date to retain registration discount.** If you plan to register on site, please check with CHI beforehand for space availability.

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### CALL FOR POSTERS

- I am interested in presenting a poster at  **Linking Phenotype to Genotype** or  **Proteins to Profits** and will submit a completed one-page abstract by March 21, 2003. (Please Note: Registration must be paid in full to present poster.)

Title

### REPORTS

CHI offers a complete line of reports on all aspects of genomics and related technologies. For information about CHI's Life Science Reports, visit [www.chireports.com](http://www.chireports.com), or call Cindy Ohlman at 617-630-1334.

### ADDITIONAL REGISTRATION DETAILS

Each registration includes all conference sessions, posters and exhibits, one reception, continental breakfasts, refreshment breaks, and a copy of the document binder.

### GROUP DISCOUNTS

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### SUBSTITUTION/CANCELLATION POLICY

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NOTE: Cancellations will only be accepted up to one week prior to the conference.

Program and speakers are subject to change.

