

siRNA

Prospects for New Therapeutics & Commercial Opportunities for Pharma & Biotech

MARCH 24-25, 2003
Hilton La Jolla Torrey Pines
La Jolla, CA

SECTIONS:

**siRNA IN TARGET VALIDATION & THERAPEUTICS
RELATED ANTISENSE TECHNOLOGIES
PROTEIN PROFILING & NUCLEIC ACID DRUG DELIVERY
INTELLECTUAL PROPERTY
PARTNERING OPPORTUNITIES**

KEYNOTE ADDRESSES:

RNAi: Revolutionized Functional Genomics; Therapeutics Next?

Martin C. Woodle, Ph.D., President
INTRADIGM CORPORATION

Novel Antisense Mechanisms for Drug Discovery and Therapeutics

Frank Bennett, Ph.D., Vice President of Antisense Research
ISIS PHARMACEUTICALS

Sponsor:



To Register Call 1-888-666-8514 or 646-336-7030 or online at www.srinstitute.com/cs248

Dear Colleague:

Small interfering RNAs (siRNAs) have gained much attention in drug discovery and development due to their powerful ability in selective gene silencing. The revolutionary discovery is simple and elegant. The road to realize commercial promise of this simple and elegant idea will, however, more likely be anything but straightforward, as we have learned from antibody and antisense drug development.

What are the challenges and hurdles in the siRNA industry? How will big pharmaceutical companies integrate and utilize the technology in accelerating drug development? How will smaller biotech companies specialized in siRNAs make creative deals and partnerships? What are the bottlenecks in realizing commercial value? What are intellectual property landscapes? What prospects of siRNAs are new therapeutics, in addition to a powerful tool in target identification and validation? When will an siRNA drug be on market? What are the market prospects and trends for siRNA industry in one year, five years or twenty years from now?

Prior to the emerging of siRNAs, tremendous efforts have been made in developing various oligonucleotide-based therapeutics and technologies for decades. The most prominent one, antisense-based drug. What impact will they have on the siRNA industry? What can be learned from these related technologies? When will oligonucleotide-based therapeutics emerge as a significant player in the pharmaceutical market?

Come to Strategic Research Institute's 1st International siRNA in Drug Discovery and Development to hear the opinions of siRNA and related companies, large and small, regarding business development, deal making, market trends and prospects of siRNA industries, as well as the latest technology development. Prepare for the opportunity!

Sincerely,



Jing Xu, Ph.D., President
BIOMINERVA GROUP



David Palella, President
BIOSCIENCE VENTURES, INC.

siRNA

Prospects for New Therapeutics & Commercial Opportunities for BIG PHARMA

MARCH 24-25, 2003 • Hilton La Jolla Torrey Pines • La Jolla, CA

5 easy ways to register

PHONE 888-666-8514

646-336-7030

8:30 - 5:30, Eastern Time

Monday - Friday

FAX 646-336-5891

(24 Hours a Day)

MAIL Return Registration Form to:
Strategic Research Institute
236 West 27th Avenue, 8th Floor
New York, NY 10001

E-MAIL info@srinstitute.com

WEB www.srinstitute.com

PAYMENTS: The conference registration fee is \$1195 until February 3, 2003 and \$1395 thereafter. The registration fee includes all breakfasts, lunches, breaks and reception. Payments may be made by company check, American Express, Visa, MasterCard, Discover Card or Diner's Club. Please make all checks payable to Strategic Research Institute, L.P. and include registrant's name on face of check along with conference code CS248 to ensure proper credit. **PAYMENTS MUST BE RECEIVED FIFTEEN (15) DAYS PRIOR TO THE CONFERENCE.**

SUGGESTED DRESS: Business Casual

SPONSORSHIP & EXHIBITION: Contact Mark Alexay at malexay@srinstitute.com or 212.967.0095 x251 to determine what level of participation works for you.

Discounts

Conference attendees may register at \$1195 until February 3, 2003 and \$1395 thereafter.

Register 3 or more individuals from your organization and each registration fee at \$1395 will be discounted 25%. Please register all at the same time to ensure proper credit.

Academic Rate is \$695.

VENUE: Hilton La Jolla Torrey Pines
10950 North Torrey Pines Road
La Jolla, Ca, 92037
Tel: 1-858-558-1500
Fax: 1-858-450-4584
March 24-25, 2003

CANCELLATIONS: All cancellations will be subject to a \$227 administration fee. In order to receive a prompt refund, your notice of cancellation must be received in writing (by letter or fax) fifteen (15) days prior to the conference. Thereafter, no refunds will be issued. The registration fee may be transferred to another member of your organization or applied towards another Strategic Research Institute conference during the ensuing 18 months. In the event of conference cancellation, Strategic Research Institute assumes no liability for transportation costs, hotel costs, or other costs incurred by registrant.

HOTEL ACCOMMODATIONS: We have reserved a limited number of rooms for speakers and attendees at a discounted rate. To secure this rate, please contact the hotel at least four weeks prior to the conference and stipulate that you will be attending the conference.

To Register Call 1-888-666-8514 or 646-336-7030 or online at www.srinstitute.com/cs248

MONDAY, MARCH 24, 2003

7:15 - 8:00

Registration, Breakfast & Exposition

8:00 - 8:05

Chairpersons' Opening Remarks

Jing Xu, Ph.D., President
BIOMINERVA GROUP

David Palella, MBA, President
BIOSCIENCE VENTURES, INC.

8:05 - 8:50

RNAi: Revolutionized Functional Genomics; Therapeutics Next?



RNAi has revolutionized studies of gene function by sequence specific inhibition of protein expression in wide variety of organisms. Now RNAi therapeutic development is emerging as a potentially powerful and efficient means to convert validated targets into drug leads. Therapeutic application will require addressing many pharmacological aspects including pharmacokinetics, pharmacodynamics, immune response and target tissue bio-availability - most of which can be greatly enhanced by effective drug delivery.

We have established highly effective, proprietary nucleic acid delivery of both siRNA and dsRNA into human xenograft tumors. The Efficacy-First target discovery method combines 1) perturbation of animal disease resulting in induction of processes involved in efficacy with 2) pathway analysis of genes and proteins associated with the induced processes. This method selectively and rapidly identifies the novel targets, operating in complex biological processes, which are activated as disease pathology expands or contracts. The Disease-Control Validation method rapidly determines the functional efficacy of candidate targets directly in animal disease models. These two methods have been enabled by adapting proprietary nucleic acid delivery technologies to express and inhibit specific proteins directly in the pathological tissues active in animal disease models. We will present 1) successful cancer protein drug target discovery based on perturbed tumor growth and 2) successful demonstration of RNAi inhibition of endogenous genes including genes in the VEGF pathway in human tumor xenografts in mice and results validating novel endogenous human genes discovered.

Martin C. Woodle, Ph.D., President
INTRADIGM CORPORATION

siRNA IN TARGET VALIDATION I

8:50 - 9:15

High Throughput Target Identification and Validation In Vitro and In Vivo

RNA interference (RNAi) holds promise as a general approach to ablating or downregulating gene expression in mammalian cells. We present work based on intracellular transcription of double-stranded RNA (dsRNA) from DNA templates, an approach that adds powerful functionality to RNAi. For *in vitro* reduction of targeted gene activity, DNA-based delivery affords one-step cloning strategies that can be used to prepare libraries of silencing constructs. But perhaps the most important application of DNA-based delivery is for *in vivo* target identification and validation. DNA-based silencing constructs can be integrated into the zygote genome using standard techniques for transgenesis. Transcription of dsRNA is controlled by a promoter that can impose temporal, spatial or stimulus specificity, providing conditional downregulation of targets for simulation of both diseases and drug effects. Importantly, this is not dependent on ES cells so is not restricted to mice: for the first time, *in vivo* target validation can be applied to rats, the standard therapeutic model. In brief, DNA-based induction of RNAi offers speed and certainty throughout the drug development pipeline.

Ken C. Reed, Ph.D., Director, Research and Technology
BENITEC AUSTRALIA LTD

9:15 - 9:40

Development of High-Throughput siRNA Technology for Applications in Functional Genomics

The effectiveness of RNA-mediated interference (RNAi) in sequence-specific gene silencing has proved it to be a valuable and robust method for gene knockdown in a variety of fields of study. The success of RNAi is dependent on the quality of oligonucleotide synthesis and design of the siRNA duplexes. The 2'-ACE[®] RNA technology provides fast, dependable, scalable synthesis of any sequence, with a stable, well-behaved intermediate that is readily deprotected in aqueous buffer. The speed and versatility of 2'-ACE chemistry, along with its adaptability to a broad range of modifications that address issues of siRNA stability and delivery, opens new frontiers for development of siRNA-based applications in functional genomics and target validation.

Stephen Scaringe, Ph.D., CEO & CSO
DHARMACON RESEARCH INC

9:40 - 10:05

Target Validation by RNA interference in Zebrafish

The zebrafish embryo has become a widely used model organism for the study of vertebrate development. As a free-living, rapidly developing and transparent embryo, it is also uniquely suitable for drug screening and target validation. Using RNA interference, we have examined the function of several genes involved in angiogenesis and showed that the same genes regulate angiogenesis in mammals and zebrafish. In addition, we have been able to correlate gene knock-down phenotypes with anti-angiogenic drug activity. We have compared the efficacy of morpholino oligos with small interfering RNA (siRNA) for accomplishing RNA interference. Currently, we are investigating the loss of function phenotypes of several key disease genes in zebrafish.

Chaoyong Ma, Business Development Manager
PHYLONIX PHARMACEUTICALS, INC.

10:05 - 10:50

Refreshments, Networking & Exposition

siRNA IN TARGET VALIDATION II

10:50 - 11:15

RNAi and Antisense Technologies: Applications for Drug Target Discovery and Validation

RNAi and antisense technologies enable systematic gene function analysis and drug target validation. We will present data that demonstrate and compare the intracellular delivery, specificity and activity of siRNAs and antisense cleavers and blockers. We will give examples of gene knock-downs with siRNA and antisense compounds, as well as phenotypic results in a variety of disease model systems, including the validation of the Alzheimer's beta-secretase. The data obtained with siRNA will also include: role of nucleotide modifications for siRNA activity, improved methods for monitoring of siRNA intracellular delivery, and increasing siRNA efficiency and specificity. We will also discuss the OmniScreen program, which combines siRNA and antisense compounds with high throughput phenotypic assays, and allows for one-step target discovery and validation.

Tod Woolf, Ph.D., President
SEQUITUR, INC.

11:15 - 11:40

Potent and Specific Inhibition of Human Immunodeficiency Virus Type 1 Replication by RNA Interference

RNA interference (RNAi) represents a powerful technique to silence individual genes in human cells. Because RNAi probably evolved as an antiviral defense, and is clearly important in this regard in plants, it seems possible that RNAi could be used as an antiviral treatment in humans. As an initial test of this hypothesis, we have assessed the ability of RNAi to block HIV-1 replication. I will present data obtained using siRNAs introduced by direct transfection, or transcribed from plasmids or retroviral vectors, that show efficient inhibition of HIV-1 replication in human cells after targeting either HIV-1 mRNAs directly or CCR5, a human receptor that is critical for HIV-1 infection but dispensable for host cell viability.

Bryan R. Cullen, Ph.D., James B. Duke Professor of Genetics, Director, Duke University Center for Virology; Department of Molecular Genetics and Microbiology, Investigator, Howard Hughes Medical Institute
DUKE UNIVERSITY MEDICAL CENTER

To Register Call 1-888-666-8514 or 646-336-7030 or online at www.srinstitute.com/cs248

KEYNOTE ADDRESS

11:40 - 12:05

The Prospects and Challenges of siRNA as a Therapeutic

The RNAi pathway is a powerful naturally occurring cellular process that can be harnessed to down-regulate the expression of virtually any endogenous or exogenous RNA target. This process is mediated by small interfering RNA molecules (siRNA) that may be synthesized chemically and added exogenously to cells. The majority of the work in the field has been carried out in cell culture systems with unmodified siRNA that do not reflect the *in vivo* setting that siRNA will be required to work in as a therapeutic. As has been the case in the development of other RNA-based therapeutics, principally ribozymes and aptamers, chemical modification of the parent RNA molecules is an absolute requirement for *in vivo* stability and efficacy. We have designed and synthesized chemically modified siRNAs that are highly resistant to nuclease degradation in serum and tissue while retaining biological activity *in vitro* and *in vivo*. The *ex vivo* human serum half-life of these molecules is >30 days compared to seconds for unmodified siRNA. Most significantly, the modifications required for enhanced stability do not negatively impact biological activity.

Nassim Usman, Ph.D., CSO, Vice President, R&D
RIBOZYME PHARMACEUTICALS, INC.

12:05 - 1:25

Luncheon Sponsored By: Ribozyme Pharmaceuticals, Inc.

RPI is focused on leveraging its expertise in nucleic acid technology to develop and commercialize products for the treatment and diagnosis of human diseases. In addition to considerable experience in nucleic acid stabilization chemistry, process development, cGMP manufacturing and clinical development, the Company owns or has exclusive license to more than 180 issued or allowed patents relating to nucleic acid technology and nucleic acid-based products. To complement its RNA-based therapeutics pipeline, RPI has established an RNA interference program aimed at developing effective therapeutics for diseases such as hepatitis C. RPI has ongoing strategic corporate relationships with Chiron Corporation, Elan Corporation, Fujirebio, and Geron Corporation.



siRNA IN TARGET VALIDATION III

1:25 - 1:50

Developing a Complete siRNA Product Line

siRNA is revolutionizing the field of drug target validation, target identification, and pathway elucidation, which presents significant commercial opportunities. In this talk, we will present using statistical design of experiments to optimize transfection conditions and transfection reagents for different cell lines. The goal of this type of research effort is to maximize the use of siRNAs by the end user to increase the siRNA market size.

David Dorris, Ph.D., Manager, Custom RNA Services
AMBION, INC.

1:50 - 2:15

Ribozymes, siRNA and Inverse Genomics

We have developed a technology platform called Inverse Genomics to identify and functionally validate therapeutic drug target genes in different disease areas. Inverse Genomics uses a combinatorial library of over 10 million unique hairpin ribozymes with randomized substrate binding sequences. Once introduced into a disease-based cell system, a ribozyme will recognize and cleave unique RNA transcripts, thereby decreasing translation of various proteins. Ribozymes that confer a desired phenotype to a cell can be selected for, based on differential growth or expression of reporter genes. From the ribozyme's substrate binding sequence, a biologically relevant target gene, which is linked to the therapeutic effect, can be identified. Genes of potential interest are further validated using ribozymes designed against other regions of the same mRNA. Using this technology, we have identified functional genes involved in regulation of tumor suppressor genes, HCV and HIV infection and neuronal cell apoptosis. Recently, we have used siRNA as an alternate or adjunctive tool for the validation phase of Inverse Genomics. Furthermore, we are developing randomized siRNA vector libraries for the discovery phase of Inverse Genomics.

Flossie Y. Wong-Staal, Ph.D., CSO
IMMUSOL, INC.

2:15 - 2:40

Effective Strategies for Delivery of siRNAs to Mammalian Cells In Vitro and In Vivo

Utilization of RNAi in the drug discovery process has the potential to lead to both the identification of novel drug targets (target identification) and elimination of targets that are not disease-relevant (target validation). In order to exploit RNAi in the drug discovery process, we have developed reagents and techniques that allow for efficient delivery of siRNA to mammalian cells *in vitro* and to adult mice *in vivo*.

The *in vitro* siRNA delivery reagent, TransIT-TKO®, is a proprietary cationic polymer/lipid mixture optimized for siRNA delivery to mammalian cells. This reagent enables highly efficient siRNA transfection in a wide variety of mammalian cell lines. We have used TransIT-TKO® to deliver siRNAs targeted against several endogenous genes in multiple cell lines. In most cases, we have observed greater than 90% knock-down of target gene expression. In adult mice, we are able to efficiently deliver naked siRNAs to multiple tissues using a "high-pressure" intravascular injection method. Using this method we are able to demonstrate at least 80% knock-down of target gene expression in all organs examined. The ability to deliver siRNA and utilize RNAi in mammalian model systems *in vitro* and *in vivo* will lead to a better understanding of gene function and more robust target validation in drug discovery.

David L. Lewis, Ph.D., Senior Scientist
MIRUS CORPORATION

2:40 - 3:00

Refreshments and Networking

3:00 - 3:25

Transcriptome-Wide siRNA Platform

We will present Compugen's recent collaboration with Novartis on the development of a transcriptome-wide siRNA collection. The siRNA platform is used for large scale gene function analysis and target validation. The collaboration leverages Compugen's expertise in transcriptome analysis and the modeling of phenomena such as alternative splicing and antisense genes, and Novartis' extensive functional genomics capabilities. The jointly developed siRNA platform will subsequently be applied for both internal research as well as further commercialization as a powerful functional genomics solution.

Alon Amit, Ph.D., Executive Director, Technical Marketing
COMPUGEN INC.

3:25 - 3:50

siRNA-Mediated Gene Silencing In Vitro and In Vivo

RNA interference is now established as an important biological strategy for gene silencing, but its application to mammalian cells has been limited by nonspecific inhibitory effects of long double-stranded RNA on translation. Here, we describe a viral mediated delivery mechanism that results in specific silencing of targeted genes through expression of small interfering RNA (siRNA). We establish proof of principle by markedly diminishing expression of exogenous and endogenous genes *in vitro* and *in vivo* in brain and liver, and further apply this novel strategy to a model system of a major class of neurodegenerative disorders, the polyglutamine diseases, to show reduced polyglutamine aggregation in cells. This viral mediated strategy should prove generally useful in reducing expression of target genes in order to model biological processes or to provide therapy for dominant human diseases.

Beverly L. Davidson, Ph.D., Roy J. Carver Professor in Internal Medicine Professor in Neurology, and Physiology & Biophysics Director, Gene Transfer Vector Core Associate Director, The Iowa Center for Gene Therapy Co-Director, Iowa Biosciences Initiative
UNIVERSITY OF IOWA COLLEGE OF MEDICINE

3:50 - 4:15

Viral Vector Delivery and Expression of RNAi Inducing Hairpins

Abstract Unavailable at time of print.

Jay Morgenstern, Ph.D., Senior Scientist
MILLENNIUM PHARMACEUTICALS, INC.

4:15 - 4:35

Refreshments, Networking & Exposition

siRNA IN TARGET VALIDATION IV

4:35 - 5:00

siRNA: Target Validation & Beyond

This presentation will address the current understanding of the mechanism of RNAi, its applications as a technology for drug discovery, and its potential as a therapeutic modality. We will also discuss

- ▶ an approach for picking functional siRNA triggers for gene targets
- ▶ a brief comparison between antisense and RNAi technologies
- ▶ potency, specificity and duration of siRNA mediated gene silencing

Sumedha Jayasena, Ph.D., Research Scientist
AMGEN

5:00 - 5:25

LineSilence, the Best Platform for RNAi

In order to apply the powerful RNAi technology to drug target discovery and validation, a number of criteria have to be achieved: high efficiency, low cost, ease for automation and HTS, as well as broad application in all mammalian cells. This presentation will discuss how linear siRNA expression cassettes are generated and illustrate simple PCR reactions that give ready-to-transfect products. The cost is only a fraction of synthetic siRNA or other DNA-based RNAi vectors that would require lengthy cloning steps. Linear DNA cassettes can be easily conjugated with markers to monitor transfection, or tags to facilitate delivery into hard-to-transfect cells.

Jiwu Wang, Ph.D., President and co-CEO
ALLELE BIOTECHNOLOGY & PHARMACEUTICALS

5:25 - 5:50

RNAi-Based Validation Platform for Rapid Characterization of Functional Role of Brain Damage Related Genes

The complexity of CNS system poses a great need and challenge to rapidly and efficiently identify key genes responsible for acute and chronic brain disorders, such as Stroke and Alzheimer's Disease. A high throughput validation platform, based on systematic and rapid modulation of gene expression levels through RNAi-mediated knockdown and functional assays mimicking the disease conditions in primary neurons, brain tissue slices and relevant animal models will be highlighted. As part of the imAGYne™ platform, the functional role of potential targets in neurological disorders will be characterized. In parallel, we apply an automated fluorescence imaging-based cell analysis instrument to examine the effect of RNAi-mediated target silencing in disease relevant functional assays. Together, the RNAi-based imAGYne™ validation platform allows for faster systematic identification and characterization of key genes and their products responsible for CNS diseases *in vivo* and *in vitro*. The validated drug targets constitute the basis for further and ongoing drug discovery and development efforts that will yield novel therapeutics for brain disorders.

Karoly Nikolich, Ph.D., CEO
AGY THERAPEUTICS INC.

5:50 - 6:00

Chairpersons' Day One Closing Remarks

6:00 - 8:00

Cocktail Reception



TUESDAY MARCH 25, 2003

7:15 - 8:00

Registration, Breakfast & Exposition

8:00 - 8:05

Co-Chairs' Recap of Day One

KEYNOTE

8:05 - 8:50

Novel Antisense Mechanisms for Drug Discovery and Therapeutics

Frank Bennett, Ph.D., Vice President of Antisense Research
ISIS PHARMACEUTICALS



siRNA, ANTISENSE AND OTHER RNA THERAPEUTICS I

8:50 - 9:15

Towards the Development of Novel Therapeutics on the Basis of Small Synthetic Double-Stranded RNAs (SIRPLEX)

Small chemically synthesized RNA duplexes ("SIRPLEX") have been used to specifically inhibit the expression of the green fluorescent protein (GFP) in living, adult GFP-transgenic mice. Repetitive intravenous injection of chemically unmodified siRNAs without any particular delivery system or conjugate gave rise to distinct reduction of the GFP expression level in several organs. Moreover, in xenograft mouse models of human tumors (malignant melanoma, pancreatic carcinoma), a significant decrease in the tumor growth rate upon application of specific siRNAs was observed. The potential of the siRNA approach for the development of drugs is further demonstrated by means of *in vitro* models with relevance to different severe diseases, as, e.g., hepatitis C or acute myeloid leukemia.

Stefan Limmer, Ph.D., CSO
RIBOPHARMA AG, GERMANY

9:40 - 10:05

Can siRNAs Be Drugs?

It is increasingly clear that the mechanism of RNAi can be harnessed to reduce the expression of most genes in most cell types *in vitro*. Thus the opportunity to create drugs based upon siRNA technology appears vast, and Alnylam Pharmaceuticals is creating an intellectual property base from which this promise may be realized. Nevertheless, it remains to be understood what the pharmaceutical attributes of siRNA truly are *in vivo* - the very attributes that must be understood in order to turn what is at present solely a drug discovery tool into a bona fide class of drugs. In this talk we will identify therapeutic opportunities through the examination of both enabling and targeted pharmacological studies.

Nagesh K. Mahanthappa, Ph.D., Director of Corporate Development
ALNYLAM PHARMACEUTICALS, INC.

10:05 - 10:45

Refreshments, Networking & Exposition

siRNA, ANTISENSE AND OTHER RNA THERAPEUTICS II

10:45 - 11:10

The Application of siRNA Molecules as a Novel Approach to HIV Therapeutics Development

The application of the new siRNA approach to HIV-1 inhibition has been independently validated *in vitro* by a number of groups utilizing a variety of siRNA constructs and varying methods of delivery. International Therapeutics, Inc. (ITI) is studying siRNA constructs targeting the Rev exons in HIV-1. These siRNA constructs were initially described by Dr. John Rossi of the Beckman Research Institute at City of Hope as effective inhibitors of HIV-1 replication. The Rev-specific siRNA constructs are being tested at ITI using *in vitro* systems of HIV infection that include peripheral blood mononuclear cells (PBMC), monocytes-derived macrophages, and lymph tissue-derived primary lymphocytes. Infections are achieved in these cell systems using a panel of primary and clinical virus isolates. The siRNA constructs are delivered into the cells by either direct transfection of plasmid DNA or by transduction with retroviral vectors carrying the appropriate DNA. These modes of delivery allow de novo expression of the siRNA inside the target cell which results in higher levels of inhibitor concentration.

Omar K. Haffar, Ph.D., CSO, Vice President R&D
INTERNATIONAL THERAPEUTICS, INC.

10:45 - 11:10

Clinical Development of Specifically Configured Double-Stranded RNA Therapeutic (Ampligen)

Hemispherx Biopharma is a biopharmaceutical company focusing on the development of nucleic acids to enhance anti-viral defense systems. Its lead compound, a specifically configured double-stranded RNA (Ampligen®), is in Phase II-III clinical development for immune-based therapies primarily addressing the diseases of HIV/AIDS and Chronic Fatigue Syndrome. Preclinical studies have shown that Ampligen® has anti-viral activities

against a broad spectrum of viruses. Other drug candidates in our anti-viral pipeline include small molecular weight RNAs denoted Oragens. The Oragens also offer the potential of a broad anti-viral spectrum by activation of an intracellular antiviral enzyme cascade.

William Carter, M.D., CEO & Chairman
HEMISPHERX BIOPHARMA, INC.

11:10 - 12:15

Strategies for Protecting siRNA Related Intellectual Property

Protecting your intellectual capital requires attention to the value of Intellectual Property (IP) assets. With the advent of the human genome project, followed by the rush of proteomics and bioinformatics, many companies and other entities have built up solid patent portfolios around their intellectual property. This panel of experts in the life sciences industry and IP, will discuss effective IP asset management, effective procurement, enforcement and leverage of IP assets with respect to siRNA and related technologies. Join us to discuss this important topic and subjects including:

- ▶ What are the considerations to take into account when developing a patent strategy for siRNA technology?
- ▶ Are siRNA molecules patentable, given the number of sequences in the public databases and the public domain generally?
- ▶ How do the most recent utility guidelines from the USPTO affect patentability of siRNA? What criteria must be met for siRNA to have a "substantial, specific and credible" utility as compared with other nucleic acid molecules?
- ▶ How does a company increase its "investment appeal" by putting the intellectual property portfolio into perspective, relative to the competition and the industry?
- ▶ Does an extensive patent portfolio assure freedom to operate in this specific technology area? What other technology areas may include dominating or blocking patents for siRNA technologies?

MODERATOR:

Lisa A. Haile, Ph.D., J.D., Partner and Co-Chair, Life Sciences Group
GRAY CARY WARE & FREIDENRICH LLP

PANELISTS

Cathryn A. Campbell, Ph.D., J.D., Founding Partner
CAMPBELL & FLORES LLP

Dale C. Hunt, Ph.D., J.D., Registered Patent Attorney/Partner
KNOBBE, MARTENS, OLSON & BEAR LLP

Karoly Nikolich, Ph.D., Chief Executive Officer
AGY THERAPEUTICS INC.

Tod Woolf, Ph.D., President
SEQUITUR, INC.

Daniel A. Boehnen, J.D., Founding Partner
MCDONNELL BOEHNEN HULBERT & BERGHOFF



12:15 - 1:30 Luncheon

siRNA, ANTISENSE AND OTHER RNA THERAPEUTICS III

1:30 - 1:55

The Use of eliRNA for Target Validation and Therapeutics

We are developing an approach of using expressed long inhibitory dsRNA (eliRNA) for silencing gene expression in mice and ultimately, for use as a therapeutic. Using plasmids and a proprietary delivery system, we have been able to achieve rapid and long lasting silencing in adult mice. Pharmacokinetic analysis of the plasmid demonstrates that it enters tissues at low efficiency but once in the organism, remains for significant periods of time (greater than one year). The DNA distributes to all tissues analyzed with the exception of the brain and gonads. These eliRNAs have been used to successfully silence endogenous gene expression in adult mice without activating any component of the stress response pathway. Conversely, when long dsRNA or siRNA are delivered in a similar fashion, a strong induction of interferon is observed in mice. Viral silencing has been accomplished in cell culture and animal efficacy studies are being initiated and will be discussed.

Vincent R. Zurawski, Jr., Ph.D., President and CEO
NUCLEONICS, INC

1:55 - 2:20

Harnessing the Full Potential of RNAi: From High Throughput Research Tool to Pharmaceutical Composition

This presentation will show how RNAi-based technologies have been implemented in several systems including worms, flies, human cells and mice, to streamline and accelerate the path to new INDs: from genome-wide screens and detailed validation work to efficient development and optimization of pharmaceutical RNAi compositions.

Christophe J. Echeverri, Ph. D., CEO/CSO
CENIX BIOSCIENCE GMBH

2:20 - 3:15

A View from Pharma: Growth & Partnering Opportunities

Will RNA-based therapeutics developed by innovative biotechs become the subject matter of major deals with BIG Pharma? If yes, when? And in what therapeutic categories, for what indications?

Conversely, the adoption rate by BIG Pharma of novel biomolecular entities and technologies is not auspicious. Therapeutic antibodies, whether fully-human, humanized, chimeric or animal-derived polyclonals, are a valid proxy for the uptake rate of future RNA-based drugs. Although highly validated for many years, and now with 11 or more FDA-approved therapeutic antibodies on the market, most BIG Pharmas continue to decline to develop antibody products. Why?

Likewise, the general reluctance of BIG Pharma to embrace antisense-based therapeutics is foreboding; however, a few bright spots (after more than 10 years of development!) include Genta's \$480 million agreement with Aventis to jointly develop and commercialize Genasense™ (April 2002) for common types of cancer, and Isis Pharmaceuticals' wide-ranging \$200+ million deal with Eli Lilly for Affinitac™ in treating non-small cell lung cancer and to fund various discovery programs for metabolic and inflammatory diseases (August 2001).

Regardless, can biotechs developing siRNA-based therapeutics wait 5-10 years for partnerships with BIG Pharma, as most antibody and antisense biotechs have? Very unlikely. Most investors and biotech managers will flee from such a business model.

Or, is it different this time? Does BIG Pharma believe that siRNA drugs will show efficacy sooner? Pass through clinical trials more quickly? Have a higher success rate in the clinic? Will siRNA-based therapeutics be more commercially viable than antibodies or antisense? Is BIG Pharma developing siRNA drugs in-house, or will they partner into the field? How long before the first siRNA drugs pass FDA muster?

Besides therapeutics, is BIG pharma really interested in novel target discovery and validation by innovative biotechs? If yes, at what stage? At what scale of funding?

Learn all the above and more from the oracle of our BIG Pharma panel members, hand-picked by SRI to maximize trenchant commentary and witty repartee.

MODERATOR:

David Palella, MBA, President
BIOSCIENCE VENTURES, INC.

PANELISTS:

Jeff Southerton, Ph.D., MBA, Site Head, Strategic Alliances
PFIZER

Varavani Dwarki, Ph. D., Director, Technology Licensing and Alliances
AVENTIS PHARMACEUTICALS

Daniel Shoemaker, Ph.D., Research Associate, Department of Molecular Neurosciences
MERCK & COMPANY

Marianne De Backer, Ph.D., Director Technology Licensing
JOHNSON & JOHNSON PHARMACEUTICALS

Troy Wilson, Vice President, Business Development
GENOMICS INSTITUTE of the NOVARTIS RESEARCH FOUNDATION (GNF)



3:15 - 3:40

Refreshments, Exposition & Networking

To Register Call 1-888-666-8514 or 646-336-7030 or online at www.srinstitute.com/cs248

OTHER RNA-BASED TARGET VALIDATION, PROTEIN PROFILING & NUCLEIC ACID DELIVERY

3:40 - 4:05

The Interface between Protein Chips and siRNA

The moment of knocking out a gene must be followed by phenotype analyses, whether the experiment is done in cells or animals. Protein profiling with chips is potentially a wonderful way to observe the expected or unexpected impacts of knock outs. Dense chips are built to assay protein levels in biological samples, either blood or tissue extracts. The chips use photoaptamers as capture agents. Photoaptamers can be selected against proteins using robotics, leading to the possibility that our system will have very large feature densities. Chip parameters will be defined, with special emphasis on robustness, sensitivity (LOQs), and the likelihood that such chips will become available for mice and other model organisms. Menus for our first human chips will be described in detail. Finally, comparative data for ELISAs and our photoaptamer chips will be provided.

Larry Gold, Ph.D., CEO & Chairman of the Board
SOMALOGIC

4:05 - 4:30

Nucleic Acid Biotools: Accelerating the Discovery of Small Molecule Leads

A novel, patent-protected technology, Nucleic Acid Biotools, which is based on nucleic acid aptamers will highlight exhibiting binding characteristics comparable to or even better than monoclonal antibodies. Aptamers can be used as highly efficient inhibitors of protein function and subsequently as competitive probes in high-throughput screening (HTS) assays to identify functionally equivalent low molecular weight compounds. The advantage of this technology is the rapid, automated generation of sophisticated ligands against almost any target molecule and the convenient structural or chemical modification of the nucleic acid probes. In addition, the same probes used in the validation process can be applied immediately in high-throughput screening to identify a pharmaceutical lead compound. This direct linkage significantly streamlines the process of drug discovery.

Michael Blind, Ph.D., CSO
NASCACELL GMBH

4:30 - 4:55

Pathotropic Targeting Strategies for Nucleic Acid Drug Delivery

Targeted gene delivery has long been considered the "holy grail" of gene therapy. The classic vector targeting strategy for nucleic acid drug delivery involves cell-specific targeting by modification of the viral coat or envelope protein. This approach has failed to generate vectors that enhanced gene delivery in animal studies, thus, precluding their further progress into clinical trials. In recent years, we developed the alternative strategy of "pathotropic" targeting that enables gene vectors to selectively target the area of "pathology" or diseased tissues *in vivo*. This proprietary platform technology forms the basis of a Phase I/II clinical trial for metastatic cancer. Additional clinical applications of "pathotropic targeting" include nucleic acid drug delivery for cardiovascular disease, inflammatory disorders, and wound healing. Because the Epeius targeting system is a versatile platform technology, it can be adapted for strategic delivery of many therapeutic genes, recombinant proteins, and pharmaceutical agents owned by other companies.

Erlinda M. Gordon, M.D., CEO
EPEIUS BIOTECHNOLOGIES CORPORATION

4:55 **Chairpersons' Closing Remarks**

5:00 **Conference Concludes**

THANK YOU TO OUR EXHIBITOR



OligoEngine improves the process of drug development with innovative tools and technologies for specialized research applications. "Complete RNAi" is an open platform for new and emerging techniques, featuring the exclusive pSUPER RNAi System(tm) for stable suppression, Si2 custom silencing duplexes, and new high-throughput products - all powered by OligoEngine's RNAi software

THANK YOU TO OUR MEDIA PARTNERS




CanBiotech - A Portal and B2B Outsourcing Marketplace for the Biopharma industry. The site features the Request for Quote Outsourcing Marketplace, the Request for Partnership Marketplace, the IP-Out-licensing/In-licensing Marketplace, the Product Marketplace, and the Career Service. Publications include the Outsourcing and U-BioMed Newsletters. <http://www.canbiotech.com>



GenomicsProteomics.com is the main web information portal dedicated to the fields of genomics and proteomics. Featuring focused company, event and new product news it aims to keep researchers and business leaders up to date on what's happening in this important sector.



PharmacoGenomicsOnline.com is the main web information portal dedicated to personalised medicine. Featuring focused company, event and new product news it aims to keep researchers and business leaders up to date on what's happening in this important sector.



Kalorama Information

Innovative Life Science Market Research Reports with an Independent Voice

Biotechnology • Diagnostics • Medical Devices • Pharmaceuticals

Kalorama's comprehensive reports offer a valuable alternative to your current subscription services. We provide you with objective information, extensive primary research, and detailed analysis by highly qualified industry experts.

Recently published studies cover topics such as Stem Cells, Drug Delivery, Neurotherapeutics, Generic Drugs, and Dermatological Drugs, among others.

Let Kalorama give you the answers you're searching for. Visit www.KaloramaInformation.com today to view information and tables of contents for any of our studies. Or call 1-800-298-5603 to speak to one of our industry specialists.

www.KaloramaInformation.com

—Jim Madden,
Quest Diagnostics, Inc.

SPONSORSHIP & EXHIBITION OPPORTUNITIES

Leverage our strength in the siRNA, RNAi and antisense technology area to showcase your services and products to this very targeted group of pharmaceutical company scientists, business development and other senior management decision makers. Booths up to 10 x 10 may be accommodated. THIS YEAR'S EXHIBIT SPACE IS OPTIMAL; IT'S ALL LOCATED IN THE FOYER TO ENSURE CONTACT WITH YOUR TARGET MARKET!

Conference sponsors benefit from exposure far beyond those afforded exhibitors to showcase your company and gain much greater visibility, before and during the conference. The luncheons provide speaking opportunities during the functions themselves and giveaways, such as totebags and writing portfolios are valuable take-aways. Sponsorships may also be customized to meet your needs and max your exposure. Contact Kellie Swanstrom at kswanstrom@srinstitute.com or call 212-967-0095, x232.

To Register Call 1-888-666-8514 or 646-336-7030 or online at www.srinstitute.com/cs248

siRNA

Prospects for New Therapeutics & Commercial Opportunities for BIG PHARMA

SECTIONS:

siRNA IN TARGET VALIDATION & THERAPEUTICS

INTELLECTUAL PROPERTY

RELATED ANTISENSE TECHNOLOGIES

PARTNERING OPPORTUNITIES

PROTEIN PROFILING & NUCLEIC ACID DRUG DELIVERY

siRNA

www.srinstitute.com/cs248

REGISTRATION FORM

236 West 27th Street, 8th Floor, New York, NY 10001
Tel 646-336-7030 or 888-666-8514 • Fax 646-336-5891

- Please register the following delegate at the price of \$1195 (on or before FEBRUARY 3, 2003)
- Please register the following delegate at the price of \$1395 (after FEBRUARY 3, 2003)
- For group registration discount information, see page 2.
- Please register the following delegate at the Academic, Hospital and Government Discounted rate - \$695



236 West 27th Street, 8th Floor
New York, NY 10001

Return Service Requested

PRESORTED
FIRST CLASS MAIL
U.S. POSTAGE
PAID
BURLINGTON, VT
PERMIT NO.21

Name (please print)

Title

Company

Address

City/State/Zip Code

E-Mail

Phone

Fax

Payment enclosed Bill my company
Charge my: American Express Visa MasterCard Diners Club Discover
Card# _____

Expiration Date: Month _____ Year _____

Name (as shown on card)

CS248