

Blockbuster Follow Up to the Very
Successful March siRNA Meeting You Attended!

NUCLEIC ACID WORLD SUMMIT

TRANSFORMING
CUTTING-EDGE SCIENCE
INTO BUSINESS

Co-Sponsors:



September 15-17, 2003

The Radisson Hotel • Boston, MA

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WELCOME

Dear Colleague:

RNA interference (RNAi), with its power in selective gene silencing, has revolutionized functional genomics and ignited tremendous interest in therapeutic potential of small interfering RNAs (siRNAs) and varieties of RNAi-inducing oligonucleotides. Prior to the emergence of siRNA, tremendous efforts have been devoted in the development of oligonucleotide-based therapeutics through various approaches. The two most prominent ones are antisense and ribozyme. Yet both are still waiting for the first blockbuster drug.

Will siRNAs outshine their precedents and bring the first oligo-based blockbuster drug?

Or, while RNAi is an indisputable wizard in gene silencing, is RNAi-based therapeutics too early to call? Will Genasense™, now in late stage Phase III clinical trials, revive interest in antisense therapeutics? Or, will the much-awaited proof-of-concept blockbuster come from some low profile approach? After more than 15 years, will nucleic acid-based therapeutics take off in the next five years?

Besides all the touted potential of RNAi in therapeutics, will RNAi's proven power in target validation be enough to create a substantial market? Will the rising of RNAi have an adverse effect on market demand for companies providing other approaches for target validation? What business strategy shall a company facing the competition adopt? Will the demand for RNAi-related reagents grow exponentially as RNAi becomes a widely used research tool? How will the highly anticipated intellectual property war affect nucleic acid therapeutics and the technology industry?

Come to Strategic Research Institute's "Nucleic Acid World Summit" (NAWS) to hear opinions of growing RNAi companies, veteran antisense, ribozyme, and other nucleic acid-based companies, large and small, regarding business strategies, deal-making, market trends and prospects for new therapeutics and commercial opportunities for the nucleic acid-based industry, as well as the latest technology and clinical development.

Prepare for the opportunity! See you in Boston!

Sincerely,



Jing Xu, Ph.D., President
BIOMINERVA GROUP

THANK YOU TO OUR SPONSORS

LEAD SPONSORS:



Aventis Oncology is globally committed to addressing the tough challenges facing healthcare professionals and their patients. With cancer being a leading cause of death in the world today, innovative solutions in cancer care are critical. At Aventis Oncology, we share

this sense of urgency. That's why we strive for new solutions that will improve the lives of cancer patients. We've been pioneers in the development of new cytotoxic agents, including Taxotere® (docetaxel) for Injection Concentrate, and supportive-care products, such as Anzemet® (dolasetron mesylate) injection/tablets. Today, these agents play a major role throughout the world in the treatment of certain types of cancer, as well as in the management of side effects. We realize that the advances in cancer research will not only come from individuals, but from global communities of researchers sharing information and knowledge. For this reason, we've established a broad range of partnerships to optimize the use of currently available agents and to accelerate the introduction of the next generation of anticancer treatments.



Sirna Therapeutics is a biotechnology company that is focused on developing therapeutics based on RNA interference (RNAi) technology, a promising field in biology and medicine. The company uses its proprietary technology and expertise in nucleic acid technology to develop a new class of nucleic acid RNAi-based therapeutics that target human diseases. Sirna Therapeutics has over 10 years of experience in nucleic acid technology, and a broad portfolio of intellectual property in the nucleic acid technology field. The company believes that its intellectual property position and its nucleic acid expertise put Sirna Therapeutics in a leading position for the development of RNAi-based therapeutics.

CONFERENCE SPONSORS:



Ambion, The RNA Company, has products for the isolation, detection, and quantitation of RNA. Ambion offers a wide range of products including kits and reagents developed for RNAi and siRNA analysis, RNA isolation, microarray analysis, RT-PCR, tissue microarrays, Northern analysis, and premade Northern, RNAs and cDNAs.



(www.avatarps.com) **Avatar Pharmaceutical Services, Inc.** is a dynamic, innovative GMP contract research organization providing services and support to the pharmaceutical and biopharmaceutical industries with a specialty in oligonucleotides. Analytical services include ICH stability programs, methods development/validation, forced degradation studies, and material certification; regulatory services include auditing, regulatory submissions, documentation creation and review, quality systems development and instrumentation qualification; training services that incorporate assessment and certification in instrument and document processes.



BD Biosciences - BD Biosciences Clontech provides research reagents and assay kits with applications for genomics, proteomics, and drug discovery. Major product lines include arrays, fluorescent proteins, gene cloning and expression systems, PCR kits and enzymes, and signal transduction systems.



Dharmacon is the world's leading provider of innovative RNA interference research products. Dharmacon's superior 2'ACE® synthesis chemistry paired with powerful SMARTselection™ and SMARTpool™ algorithms deliver guaranteed siRNA mediated gene silencing. Dharmacon supplies the highest quality RNA oligonucleotides, and pre-made siRNA, as well as amidites, synthesizers, and reagents for in-house synthesis.



QIAGEN is the world's leading provider of innovative technologies for separating, purifying, and handling nucleic acids. QIAGEN offers a comprehensive range of integrated products for RNAi research that include custom and library siRNAs, transfection reagents, RNA purification kits, quantitative RT-PCR and microarray products.



Xenogen is the pioneer of biophotonic imaging, utilizing light (bioluminescence and fluorescence) to monitor biological processes, including gene expression that is both temporal and spatially defined, in live animals in real-time. This imaging technology is used to facilitate drug discovery in infectious disease, oncology, inflammation and drug metabolism.

EVENT SPONSORS:



Archemix Corp. (www.archemix.com) is a privately held biotherapeutics company based in Cambridge, Mass. Founded in May 2001, the company's mission is to discover and develop aptamer-based therapeutics. This technology derive from Archemix's proprietary and dominant intellectual property portfolio that encompasses over 300 patents and applications owned by or licensed to Archemix, and covers the selection of biologically active nucleic acid aptamers. To date the company has completed a \$51.75M Series A round of financing. Therapeutic aptamers, serum-stabilized agents derived through an entirely *in vitro* process, are under development for a wide range of disease areas, including many of those currently addressed by protein-based therapeutics.



CombiMatrix Corporation has produced a technology for the rapid production of customizable active biochips, which are semiconductor-based tools for use in identifying and determining the roles of genes, gene mutations and proteins. The CombiMatrix technology has a wide range of applications including multiplex DNA analysis, molecular diagnostics, siRNA production and gene

Register on the Web at: www.srinstitute.com/NAWS

CONFERENCE AT A GLANCE

SUNDAY SEPTEMBER 14, 2003

6:00 - 9:00 Exhibitor Set-Up

MONDAY, SEPTEMBER 15, 2003

8:00 - 8:55 Registration, Breakfast & Exposition - Breakfast Sponsored By COMBIMATRIX

8:55 - 9:00 Chairperson's Opening Remarks

TECHNOLOGY SHOWCASES

9:00 - 9:20 BD BIOSCIENCES

9:20 - 9:40 XENOGEN

9:40 - 10:00 AMBION

10:00 - 10:50 Refreshments, Networking & Exposition

10:50 - 11:10 DHARMACON

11:10 - 11:30 QIAGEN

11:30 - 11:50 AVATAR

11:50 - 1:20 Lunch Sponsored By SIRNA THERAPEUTICS

PLENARY SESSION

1:20 - 1:25 Conference Chair's Introduction

1:25 - 2:00 Keynote Address

2:00 - 2:35 Potent and Specific Inhibition of Human Immunodeficiency Virus Type 1 Replication by RNA Interference

2:35 - 3:10 Overview on Target Discovery and the Impact of Oligonucleotides

3:10 - 3:55 Refreshments, Networking & Exposition

3:55 - 4:30 High Throughput Target Identification and Validation with siRNAs

4:30 - 5:05 Discovery and Development of RNAi Therapeutics

5:00 - 5:10 Conference Chair's Day One Closing Remarks

5:10 - 7:00 Reception

TUESDAY, SEPTEMBER 16, 2003

7:15 - 8:00 Registration, Breakfast & Exposition - Breakfast Sponsored By ARCHEMIX CORP.

CONCURRENT TRACKS:	TRACK A: siRNA/RNAi	TRACK B: Oligo-based Therapeutics: Pre-Clinical, Clinical & Business Development	TRACK C: Nucleic Acid Delivery, RNA as Drug Targets & Other Related Technologies
8:00 - 8:05	Track Chair's Intro Dmitry Samarsky, Ph.D. <i>Director of Technology Development</i> SEQUITUR	Track Chair's Intro Jing Xu, Ph.D. <i>President</i> BIOMINERVA GROUP	Track Chair's Intro Joseph Heilig, Ph.D. <i>Senior Director, Science</i> SOMALOGIC
8:05 - 8:30	High-throughput RNAi Screens in Drosophila Cells	Preclinical and Clinical Pharmacology of Antisense Oligonucleotides	Issue in the Systemic, Non-Viral Delivery of Nucleic Acids
8:30 - 8:55	Target Identification & Validation Using RNA Interference Technologies	Second-Generation Antisense and Immunomodulatory Oligonucleotides	Novel Injectable Intra-tumoral Oligonucleotide Drug Delivery Applications
8:55 - 9:20	Development of a Robust Screen for Active siRNA Duplexes & Using siRNA Technology for Target Validation	Induction of Apoptosis in Tumours Using the Bcl-2 Antisense Oblimersen Therapeutic Approach to Cancer	Charge Reversible Liposomes for Systemic Delivery of Nucleic Acids
9:20 - 9:45	Genome-wide Knockdown Strategies - RNAi Applications	Challenges in the Clinical Development of Molecular Targeted Agents	Efficacy & Safety of an Injectable "Pathotropic" Retroviral Vector Bearing a Cytocidal Gene Construct (Rexin-G) as Therapeutic Intervention for Stage IV Pancreatic Cancer.
9:45 - 10:35	Refreshments, Networking & Exposition		
10:35 - 11:00	High Throughput Solutions to siRNA Design, Execution, and Analysis	Therapeutic Applications of Intracellularly Expressed siRNAs for AIDS and Cancer	Targeting RNA with Fluorescence and NMR Screens

Register on the Web at: www.srinstitute.com/NAWS

CONFERENCE AT A GLANCE

	TRACK A: (cont.)	TRACK B: (cont.)	TRACK C: (cont.)
11:00 - 11:25	Strategies for Design of Highly Functional, Stabilized siRNAs	Towards the Development of Novel Therapeutics on the Basis of Small Synthetic Double-Stranded RNAs (SIRPLEX)	A Two Million Atom Simulation of the 70s Ribosome in Explicit Solvent
11:25 - 11:50	The Usefulness of siRNA Based on Its Efficacy	Tumor Inhibition by RNAi-Mediated Anti-Angiogenesis Models in Xenograft Models	Targeting RNA: Fluorescence & NMR Techniques to Identify New Therapeutic Leads
11:50 - 12:15	Silence of the Genes: Viral Delivery of siRNA	Development of siRNA In Therapeutics	Telomerase Template Antagonist GRN163 as Targeted and Specific Potential Anti-Cancer Agent
12:15 - 1:45	Lunch Sponsored By AVENTIS		
1:45 - 2:10	siRNA Design and the Transcriptome	Activating Immunity by Stimulating TLR9 with CpG Oligos	Biophotonic Imaging as a Method for Monitoring Gene Expression in Live Animals in Real-Time, & its Applicability to RNAi Research In Vivo
2:10 - 2:35	Effective Nonviral Delivery of siRNA and siRNA-Expressing Vectors into Cells in Vitro and in Vivo	Clinical Development of a Double-Stranded RNA Therapeutic (Ampligen®)	Multiplexed Protein Quantification using Photoaptamer A
2:35 - 3:00	RNAi in the Drug Discovery Process: Validation of Targets and Leads	Ribozyme Reporters as Tools for Drug Discovery	Gene Quiescence by Locked Nucleic Acid
3:00 - 3:45	Refreshments, Networking & Exposition		
3:45 - 4:10	RNAi in Drug Development	Toxicity and Pharmacokinetics of Proliferating Cell Nuclear Antigen Ribozyme Against Cell Proliferation in Proliferative Vitreoretinopathy	Re-programming Gene Expression by RNA Trans-splicing
4:10 - 4:35	Express Track™ siRNA Drug Discovery Program: Integrating CombiMatrix's Programmable Synthesis Platform into a Streamlined siRNA Drug Development & Screening Program	Characterization and Pre-clinical Development of Chimeric Backbone Oligos as TLR9 Agonists	Aptamers as Tools for Drug Discovery: Translating Functional Knockdown Data into Lead Compounds
4:35 - 5:00	Arrayed Adenoviral Knock-Down Vectors for Target Discovery and Validation	Biostable Aptamers as Novel Therapeutic Agents	Improving the Odds of Therapeutic Efficacy: Blocking Angiotensin II
5:00 - 6:30	Reception		

WEDNESDAY, SEPTEMBER 17, 2003

7:15 - 8:10 **Breakfast, Networking & Exposition**

8:10 - 8:15 **Chair's Recap**

GENERAL SESSION

8:15 - 8:45 **Patentability & Maximum Protection and Valuation of Intellectual Property in Biotechnology**

8:45 - 10:00 **PANEL DISCUSSION: Strategies for Protecting siRNA/RNAi Related Intellectual Property**

10:00 - 10:30 **Refreshments, Networking & Exposition**

10:30 - 11:15 **PANEL DISCUSSION: Pharma & Biotech: Partnering & Growth Opportunities**

11:15 - 12:00 **PANEL DISCUSSION: Venture Capital & Financing Outlook in siRNA/RNAi**

12:00 **Conference Concludes**

Register on the Web at: www.srinstitute.com/NAWS

GENERAL SESSION

MONDAY, SEPTEMBER 15, 2003

8:00 - 8:50

Registration, Breakfast, & Exposition - Breakfast Sponsored By:



8:50 - 9:00

Conference Chair's Opening Remarks

TECHNOLOGY SHOWCASES

9:00 - 9:20

Viral Delivery of siRNA

RNA Interference (RNAi) is a powerful new technology that provides rapid, inexpensive suppression of a specific gene using small interfering dsRNA (siRNA). The two greatest challenges for effective RNAi is target sequence selection and siRNA delivery. While sequence selection is still a process of trial and error, viral expression systems can greatly increase the overall effectiveness of any functional siRNA by delivering the siRNA to ~100% of the target cell population. We will describe BDTM Knockout Adenoviral RNAi Systems and pSIREN adenoviral and retroviral vectors - the ultimate tools for transient and stable expression for your siRNAs in any cell type.

Linnea Hager, MS, Senior Product Manager, BD BIOSCIENCES CLONTECH



9:20 - 9:40

In Vivo Biophotonic Imaging and its Uses in Drug Discovery

Xenogen are pioneers of biophotonic imaging, a technology that utilizes light (bioluminescence and fluorescence) to monitor biological processes, including gene expression that is both temporal and spatially defined, in live animals in real-time. This imaging technology is currently being used to facilitate drug discovery in areas such as infectious disease, oncology, inflammation and toxicology. An overview of this technology will be presented along with examples in each of the above disease areas.

Kevin P. Francis, Ph.D., Director of Technical Applications, XENOGEN CORPORATION



XENOGEN
Discovery in the Living Organism™

9:40 - 10:00

RNA Manufacturing at Ambion: From High-Throughput siRNA Synthesis to RNA Therapeutics

Ambion has increased its capacity to deliver chemically synthesized RNA oligonucleotides, especially for the siRNA market. We now have the ability to synthesize over 800 siRNAs per day. Ambion is utilizing this capacity to synthesize siRNAs for every human gene based on the siRNA design algorithm of our partner, Cenix Bioscience GmbH. In addition to custom RNA oligonucleotide production, Ambion is identifying functional siRNAs by functional testing. Ambion has large-scale production capabilities that can produce gram quantities of a RNA in a single production run. To serve the therapeutics market, Ambion recently opened a GMP oligonucleotide production facility specifically geared toward RNA production.

David Dorris, PhD, Manager, Custom RNA Services, AMBION, INC.



10:00 - 10:50

Refreshments, Networking & Exposition

10:50 - 11:10

Rational Design of Functional siRNA Sequences and Guaranteed Gene Silencing

Short-interfering RNAs (siRNAs) are potent sequence-specific reagents designed to suppress gene expression. By systematically analyzing a panel of randomly generated functional and nonfunctional siRNA duplexes, we identified physical and sequence-related characteristics promoting active gene suppression. An algorithm for guiding rational siRNA design was then developed based on these characteristics. Termed SMARTselection, the algorithm effectively predicts highly functional siRNA sequences and eliminates those that are non-functional. Silencing effectiveness is further improved by pooling the selected siRNA into SMARTpool reagents. SMARTpool reagents are guaranteed to silence the target gene by at least 75%. SMARTselection and SMARTpool technologies enable functional siRNAs to be designed against any gene.

Anastasia Khvorova, Ph.D., Director of Biology, DHARMA CON INC.



11:10 - 11:30

New Tools for Your Gene Silencing Toolbox

With interest in gene silencing using siRNAs rapidly expanding, QIAGEN has developed many products to facilitate research in this area. The presentation will highlight our 4-for-Silencing siRNA Duplexes. Careful design of an siRNA sequence is critical for effective gene silencing. However, the efficiency of gene knockdown with a given siRNA is not fully predictable and there is a risk that a particular duplex will not result in effective silencing. The 4-for-Silencing siRNA Duplexes from QIAGEN minimize this risk by providing four individual siRNA duplexes, designed by QIAGEN against a target gene of the researcher's choice. Along with a brief discussion of the design strategies, siRNA-specific transfection technologies will also be discussed.

Sally Bee, Ph.D., Global Product Manager - siRNA, QIAGEN



11:30 - 11:50

Strategies for the Optimization and Validation of CGE Methods for the Analysis of Oligonucleotides

Although the general trend is to replace Capillary Gel Electrophoresis (CGE) with reversed-phase methodology, CGE is still one of the three standard techniques used for the analysis of oligonucleotides. This presentation will demonstrate strategies for optimizing CGE methods, including sample preparation and instrumentation tips. The result of implementing such strategies results in more robust methods, leading to more fluid validations and method transfers.

Judy Carmody, Ph.D., President, AVATAR PHARMACEUTICAL SERVICES



11:50 - 1:20

Lunch Sponsored By:



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MONDAY, SEPTEMBER 15, 2003

PLENARY SESSION

1:20 - 1:25

Conference Chair's Introduction

Jing Xu, Ph.D., *President*
BIOMINERVA GROUP

1:25 - 2:00

Keynote Address

Bob D. Brown, Ph.D., *Vice President, Research & Technology*
GENTA INCORPORATED

2:00 - 2:35

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 a test of this hypothesis, we have assessed the ability of RNAi to block HIV-1 replication in culture. I will present data obtained using siRNAs introduced by direct transfection, or transcribed from plasmids or lentiviral vectors, that show efficient inhibition of HIV-1 replication in human cells after targeting HIV-1 mRNAs directly or after targeting CCR5, a human receptor that is critical for HIV-1 infection but dispensable for host cell viability. Importantly, we have been able to show highly effective, stable inhibition of HIV-1 replication in primary cells, including primary macrophages.

Bryan Cullen, Ph.D., *Director, Duke University Center for Virology*
DUKE UNIVERSITY MEDICAL CENTER

2:35 - 3:10

Overview on Target Discovery and the Impact of Oligonucleotides

This presentation will review the area of target discovery including the provision of disease models, target identification and target validation. It will critically examine the existing strategies and the impact of different oligonucleotides technologies such as siRNA, antisense (phosphothioates, PNA, LNA) and discuss possible limitations to its application including the provision of delivery technologies.

Mark A. Lindsay, Ph.D., *Project Leader*
ASTRAZENECA

3:10 - 3:55

Refreshments, Networking & Exposition

3:55 - 4:30

High Throughput Target Identification and Validation with siRNAs

This presentation will discuss our development of high throughput *in vitro* target identification and validation by the application of siRNAs. This will include a discussion of specificity of gene targeting with these reagents, and the applicability of this technology to target-by-class analysis.

Donald N. Halbert, Ph.D., *Director, Genomics, Proteomics and Bioinformatics*
ABBOTT LABORATORIES

4:30 - 5:05

Discovery and Development of RNAi Therapeutics

This presentation will discuss the opportunity for siRNA therapeutics as a new drug class and the challenges of developing these new products.

John Maraganore, Ph.D., *President & CEO*
ALNYLAM PHARMACEUTICALS, INC.

5:05 - 5:10

Chair's Day One Closing Remarks

5:10 - 7:00

Reception

SPONSORSHIP & EXHIBITION OPPORTUNITIES:

Leverage our strength in the nucleic acid field to showcase your products and services to this very targeted audience of industry scientists and executive decision-makers.

Exhibit packages provide for booth space up to 10'x10', up to two full passes, your logo posted on the conference website and an ad or other promotional piece printed in the conference workbook.

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For more information, please contact Kellie Swanstrom at kswanstrom@srinstitute.com or call (973) 571-0867.

Register on the Web at: www.srinstitute.com/NAWS

CHOOSE FROM TRACKS A, B, C TUESDAY, SEPTEMBER 16, 2003

TRACK A: siRNA/RNAi IN DRUG DISCOVERY

TRACK B: OLIGONUCLEOTIDE-BASED THERAPEUTICS: PRE-CLINICAL & CLINICAL DEVELOPMENT

TRACK C: NUCLEIC ACID DELIVERY, RNA AS DRUG TARGETS & RELATED TECHNOLOGIES

7:15 - 8:00

Registration, Breakfast & Exposition

Breakfast Sponsored By:



8:00 - 8:05

Track Chair's Introduction

Dmitry Samarsky, Ph.D., Director of Technology Development
SEQUITUR

siRNA/RNAi IN TARGET VALIDATION

8:05 - 8:30

High-Throughput RNAi Screens in Drosophila Cells

To characterize gene functions on a genome-wide scale in Drosophila, we have generated a library of 21,300 double-stranded RNAs (dsRNAs) directed against all predicted open reading frames (ORFs). This resource can now be used to conduct high-throughput cell-based RNA interference (RNAi) screens to identify genes involved in various assays. These screens provide a powerful methodology to identify rapidly all the proteins encoded by the genome that interfere with a specific assay. We are applying this screening platform to further our understanding of the complexity of signal transduction pathways and cell biological questions. Clustering of genes with related RNAi phenotypes can serve to predict novel gene functions. Functional data generated by RNAi can be used as the primary tool to integrate the information from other existing genomic databases.

Norbert Perrimon, Ph.D., Department of Genetics, Howard Hughes Medical Institute
HARVARD MEDICAL SCHOOL

8:30 - 8:55

Target Validation Projects Using siRNA Technology

Art Brace, Ph.D., Senior Research Scientist
EXELIXIS, INC.

8:00 - 8:05

Track Chair's Introduction

Jing Xu, Ph.D., President
BIOMINERVA GROUP

ANTISENSE THERAPEUTICS

8:05 - 8:30

Preclinical and Clinical Pharmacology of Antisense Oligonucleotides

Frank Bennett, Ph.D., Vice President, Antisense Technologies
ISIS PHARMACEUTICALS, INC.

8:30 - 8:55

Second-Generation Antisense and Immunomodulatory Oligonucleotides

The principle behind antisense technology is simple and rational. However, it has become clear that in addition to stability, chemistry and nucleotide sequence of antisense oligonucleotides are critical for specificity. After gaining experience with PS-oligos, we have designed second-generation antisense oligos containing modified RNA and DNA, referred to as mixed backbone oligos (MBOs). MBOs possessed desirable pharmacokinetic, tissue distribution, and safety profiles. In addition, MBOs permitted oral administration of antisense oligonucleotides.

It has been well established that certain nucleic acid motifs activate the vertebrate immune system through Toll-like receptors 3 and 9. Based on the experience gained from antisense PS-oligos and MBOs, we have identified novel structural characteristics and synthetic nucleotide motifs for optimal recognition of the receptors and induction of desirable cytokine secretion profiles. The combination of these structural and nucleotide motifs resulted in more potent immunomodulatory oligonucleotide (IMO) agents than the conventional CpG DNAs. Human clinical trials are ongoing with antisense MBOs and IMOs.

Sudhir Agrawal, D. Phil., President and Chief Scientific Officer
HYBRIDON

8:00 - 8:05

Track Chair's Introduction

Joseph Heilig, Ph.D., Senior Director, Science
SOMALOGIC

NUCLEIC ACID DRUG / OLIGONUCLEOTIDE DELIVERY I

8:05 - 8:30

Issue in the Systemic, Non-Viral Delivery of Nucleic Acids

Non-viral nucleic acid delivery systems have the potential to yield therapeutics that can be administered systemically. In order to do so, numerous obstacles must be overcome. Barriers in extracellular and intracellular transport will be discussed, and emphasis placed on issues that need to be addressed in creating a functioning system. Examples will involve all types of nucleic acids including siRNA and plasmids.

Mark E. Davis, Ph.D., Professor
CALIFORNIA INSTITUTE OF TECHNOLOGY

8:30 - 8:55

Novel Injectable Intra-tumoral Oligonucleotide Drug Delivery Applications

Johanne D. Cashman, Ph.D., Head of Pre-Clinical Development
ARC PHARMACEUTICALS, INC.

TUESDAY, SEPTEMBER 16, 2003

8:55 - 9:20

siRNA: Target Validation & Beyond

Applications of RNAi starts with an effort to identify potent siRNA molecules working at low nM concentrations. This presentation addresses an approach for identifying potent siRNAs based on the characteristics of naturally occurring miRNA molecules that are also processed by Dicer and enters into the intermediates of the RNAi pathway. Utilization of siRNA molecules in a robust screening platform will also be described with the emphasis on how RNA interference departs from classical antisense approach in target validation.

Sumedha Jayasena, Ph.D., *Research Scientist*
AMGEN

9:20 - 9:45

Genome-wide Knockdown Strategies - RNAi Applications

RNAi was discovered in 1995 as a natural process that involves inactivating of genes via double-stranded RNA (dsRNA). Its versatility has resulted in a rapid assimilation into the drug discovery process. Devgen exploits the availability of the RNAi technology in *C. elegans* by conducting large-scale, comprehensive target identification and validation experiments in *in vivo* models of human disease. The talk will review Devgen's target hunt studies using *in vivo* models of metabolic disease and an overview of the application of RNAi in whole organisms for target validation will be addressed.

Thierry Boegart, Ph.D., *CEO*
DEVGEN NV

8:55 - 9:20

Induction of Apoptosis in Tumours Using the Bcl-2 Antisense Oblimersen Sodium (Genasense™) : A Promising Therapeutic Approach to Cancer

Bcl-2 is over-expressed in a range of tumour types and may be crucial for their continued survival, by protecting them from apoptosis. Elevated bcl-2 levels are responsible for the drug resistant state in a number of tumour types. Bcl-2 knockout mice are viable and demonstrate that bcl-2 is not a sole crucial factor in the survival of the great majority of normal cells. In several tumour types (e.g. haematological tumours and melanoma) the great majority of tumour cells do depend crucially on bcl-2 for their survival, and a reduction of bcl-2 protein leads to cell death by apoptosis. Oblimersen could be considered for monotherapy in these cases and Phase I/II clinical trials in CLL demonstrated activity with oblimersen-alone. This is consistent with responses seen in several pre-clinical studies both *in vitro* and with tumour xenograft models in mice. However, additive or synergistic effects have also been observed in animal models in combination with several chemotherapies in these tumour types, with a high level of complete remissions. Combination therapy has been the preferred initial clinical approach. There is a continuum of degrees of bcl-2 dependence across the tumour types, depending on the contributions of other pro- and anti-apoptotic factors involved in this core apoptosis control mechanism. At the other extreme there several tumour types which may have elevated levels of bcl-2, but are not dependent on this factor for their survival (e.g. some lung and breast cancers). Such tumours would not be expected to show strong responses to oblimersen alone. However, in combination with various chemotherapies, synergistic responses have been observed. The chemotherapies give some degree of selectivity for the tumours, and in the presence of their various proapoptotic actions bcl-2 again plays a controlling role in the survival of the cells. Bcl-2 reduction results in an amplification of the tumour apoptosis response. Phase I/II clinical data suggest similar response profiles to those in animal studies in a range of tumour types, and the results from three Phase III trials (melanoma, CLL, multiple myeloma) will be available in 2003.

Colin Gardner, Ph.D., *Sr. Manager, Oncology Disease Group*
AVENTIS PHARMACEUTICALS

9:20 - 9:45

Challenges in the Clinical Development of Molecular Targeted Agents

Anthony W. Tolcher MD FRCP(C), *Director Clinical Research*
INSTITUTE FOR DRUG DEVELOPMENT

8:55 - 9:20

Charge Reversible Liposomes for Systemic Delivery of Nucleic Acids

Lack of reliable and affordable delivery systems is recognized as today's major obstacle on the way to nucleic acid based drugs. Novosom has developed a proprietary class of liposome based carriers (Smarticles) that open novel business perspectives in the antisense or RNAi field as well as for human gene therapy. Smarticles are charge reversible liposomes and overcome traditional limitations of cationic lipids, while still maintaining a proven ability to transfect cells. Smarticles are fully compatible and stable in serum and do not form any aggregates. Smarticles facilitate uptake of functionally intact nucleic acids into liver, spleen, endothelia and sites of inflammation. Transfer of entire plasmids as well as oligonucleotides has been shown in animals.

Steffan Panzer, Ph.D., *CEO*
NOVOSOM AG

9:20 - 9:45

Efficacy and Safety of an Injectable "Pathotropic" Retroviral Vector Bearing a Cytocidal Gene Construct (Rexin-G) as Therapeutic Intervention for Stage IV Pancreatic Cancer.

Rexin-G is a pathology-targeted ("pathotropic") injectable retroviral vector bearing a cytotoxic dominant negative cyclin G1 construct that is authorized for systemic use by the U.S.FDA in a Phase I clinical trial for metastatic colon cancer and by the Philippine Bureau of Food and Drugs for Stage IV pancreatic cancer. Three patients with Stage IV pancreatic cancer participated in the clinical trial. The tumor response rate was 100% based on MRI or CT scan results. Further, Rexin-G infusions were not associated with nausea or vomiting, hair loss, hemodynamic instability, bone marrow suppression, liver or kidney damage over a 3-month observation period. Taken together, the results of these studies provide encouraging evidence of the safety and efficacy of intravenous Rexin-G for Stage IV pancreatic cancer.

Erlinda M. Gordon, M.D., *Medical Director*
EPEIUS BIOTECHNOLOGIES CORPORATION

9:45 - 10:35

Refreshments, Networking & Exposition

Register on the Web at: www.srinstitute.com/NAWS

ADVANCES IN siRNA/RNAi TECHNOLOGY

10:35 - 11:00

High Throughput Solutions to siRNA Design, Execution, and Analysis

In order to facilitate the utilization of RNAi technologies for drug discovery, QIAGEN has instituted a program to develop high throughput approaches to design, synthesis, and validation of siRNA. I will describe our efforts to develop the next generation in design algorithms, the use of these algorithms to develop large siRNA libraries, and a multi-institutional effort to validate the specificity and efficiency of these reagents. In addition, the automation of a high throughput RNA synthesis facility will be briefly described.

Eric Lader, Ph.D., Associate Director
QIAGEN

11:00 - 11:25

Strategies for Design of Highly Functional, Stabilized siRNAs

RNA interference is now established as an important biological strategy for gene silencing, but its application to mammalian cells has been limited by two principle factors: a low probability of identifying functional siRNAs sequences and the instability of the siRNA in biological environments. By analysis of a large number of functional and nonfunctional siRNAs coupled with a systematic high throughput screening approach we developed a method allowing identification of highly active siRNA's. Rational design significantly enhances the probability of selecting functional duplexes. More than 90% of rationally designed duplexes will cause greater than 75% gene silencing. The same systematic approach was used for screening and identification of modifications that enhance siRNA stability without interfering with the silencing efficiency. Additional biochemical and positional analysis of the tolerated nucleotide, backbone and sugar modifications provide important insight on the RNA interference mechanism.

Anastasia Khvorova, Ph.D., Director of Biology
DHARMACON INC.

11:25 - 11:50

The Usefulness of siRNA Based on Its Efficacy

The knockdown efficacy of a siRNA affects its usefulness in unraveling biological functions. We have simultaneously targeted multiple genes, each with a gene-specific, validated siRNAs. These experiments show that the number of genes that can be targeted per experiment is impacted by the efficacy of each siRNA. Additionally, we have targeted genes in complex biological pathways using validated siRNAs to confirm the accuracy of these pathways. siRNAs were used to knockdown two independent receptors and/or the common kinase in the pathway for these receptors. The resistance of cells to the ligands for these receptors after siRNA treatment demonstrates the utility of highly efficacious siRNAs.

David Dorris, PhD, Manager, Custom RNA Services
AMBION, INC.

RNAi-BASED THERAPEUTICS

10:35 - 11:00

Therapeutic Applications of Intracellularly Expressed siRNAs for AIDS and Cancer

We have taken advantage of the ability of mammalian cells to be programmed with small interfering RNAs to functionally destroy RNA targets of clinical importance, including the EWS/Fli1 and BCR/ABL fusion transcripts. In addition to these oncogene encoding RNAs, siRNAs targeting HIV-1 have been delivered to hematopoietic cells, including T-lymphocytes and hematopoietic progenitor cells. We have been able to demonstrate potent inhibition of HIV replication and selective survival of anti-HIV siRNA expressing cells. Experiments detailing these applications of siRNA will be presented along with new methods for expressing these small RNAs in mammalian cells.

John Rossi, Ph.D., Chairman and Professor
BECKMAN RESEARCH INSTITUTE

11:00 - 11:25

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., CEO
RIBOPHARMA AG

11:25 - 11:50

Tumor Inhibition by RNAi-Mediated Anti-angiogenesis in Xenograft Models

Intradigm has developed a propriety system for high-efficiency delivery in the xenograft tumor model, of various forms of RNAi. This delivery system enables the RNAi-mediated down regulation of endogenous genes, hVEGF165 and mVEGFR2, that play key roles in angiogenesis pathway. This paper will describe how this technology is being used to validate novel cancer targets ready for pre-clinical development of cancer therapeutics.

Martin Woodle, Ph.D., President
INTRADIGM CORPORATION

RNA AS DRUG TARGETS

10:35 - 11:00

Targeting RNAs with Small Molecules Using NMR and Fluorescence Screening

James Williamson, Ph.D., Professor; Department of Molecular Biology and the Skaggs Institute of Chemical Biology
SCRIPPS RESEARCH INSTITUTE

11:00 - 11:25

A Two Million Atom Simulation of the 70S Ribosome in Explicit Solvent

The ribosome is an important target for several classes of antibiotics. We have recently performed large-scale molecular dynamics simulations of the 70S ribosome in explicit solvent using the Los Alamos National Laboratory Q machine. The simulation is approximately 6.2 times larger than the largest to date and has set a new state of the art in biomolecular simulation. The preliminary results indicate that the highly conserved regions are more structurally stable than the variable regions. Preliminary findings on the dynamics and solvation shell of the ribosome will be discussed.

Kevin Sanbonmatsu, Ph.D., Staff Scientist, Theoretical Biology and Biophysics Group - Theoretical Division
LOS ALAMOS NATIONAL LABORATORY

11:25 - 11:50

Targeting RNA: Fluorescence & NMR Techniques to Identify New Therapeutic Leads

The development of specific inhibitors of protein-RNA complexes is of significant interest since these complexes can provide potential targets for regulating gene expression and inhibiting viral/bacterial infection. RNA-based drug discovery requires general approaches for detecting, quantifying and characterizing RNA interactions that can be used as the basis for high-throughput screening and for obtaining rapid structural information to guide rational drug design. Our laboratory has pursued a combination of fluorescence emission quenching and heteronuclear magnetic resonance (NMR) methods to identify and characterized low molecular weight compounds which bind specifically to RNA and inhibit RNA-protein interactions. To demonstrate our approach, results from fluorescence and NMR experiments used to identify and characterize novel antagonists of retroviral protein-RNA interactions critically involved in HIV-1 infection will be presented.

John P. Marino, Ph.D., Research Chemist, Center for Advanced Research in Biotechnology
NATIONAL INSTITUTE OF STANDARDS & TECHNOLOGY

TUESDAY, SEPTEMBER 16, 2003

11:50 - 12:15

Silence of the Genes: Viral Delivery of siRNA

RNA Interference (RNAi) is a powerful new technology that provides rapid, inexpensive suppression of a specific gene using small interfering dsRNA (siRNA). We will describe BDTM Knockout RNAi Systems and pSIREN vectors - the ultimate tools for both transient and stable expression for your siRNAs in any cell type. The BDTM Knockout Adenoviral RNAi Systems enable rapid, easy generation of siRNA-expressing adenoviruses, which efficiently infect both dividing and quiescent cells. For those requiring retroviral delivery, the pSIREN-RetroQ vectors can generate virus which can infect up to 100% of your target cells, allowing you to rapidly generate stable cell lines. The pSIREN vectors, the cornerstone of the BD Knockout Systems, may be used as standard expression vectors to test various siRNA sequences prior to generating adenovirus or retrovirus.

Brad Scherer, Ph.D., *Research Scientist*
BD BIOSCIENCES CLONTECH

11:50 - 12:15

Development of siRNA Therapeutics

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. Small interfering RNA molecules (siRNA), that may be chemically synthesized, mediate this process. Although the use of siRNA in cell culture has become a potent, robust and ubiquitous method for gene function studies, there remain challenges to the development of siRNA as a therapeutic. Key near-term challenges include stability, delivery and pharmacokinetics (PK). Sima Therapeutics has made significant progress in all three of these areas. Stability in serum and tissue on the order of days has been achieved by chemical modification with little or no loss of biological activity. These chemical modifications also improve the PK and tissue distribution of siRNA. Percent dose delivered to the liver has exceeded 5% at 24 hours, and siRNA can be detected in both tissue and plasma up to 96 hours post single administration. These stable, potent and targeted siRNAs are currently being developed for two indications, hepatitis C (viral RNA target) and age-related macular degeneration (VEGF pathway mRNAs). Animal efficacy and pharmacokinetic data will be presented.

Nassim Usman, Ph.D., *CSO & Vice President R&D*
SIRNA THERAPEUTICS

11:50 - 12:15

Telomerase Template Antagonist - GRN163 as Targeted and Specific Potential Anticancer Agent

Telomerase, the enzyme responsible for proliferative immortality, is expressed in essentially all cancer cells, but not in most normal human cells. Thus, specific telomerase inhibition is potentially a universal anticancer therapy with few side effects. We designed N3'@P5' thio-phosphoramidate (NPS) oligonucleotides as telomerase template antagonists and found that their ability to form stable duplexes with the telomerase RNA subunit was the key factor for anti-telomerase activity. In biochemical assays 11-13-mer NPS oligonucleotides demonstrated sequence- and dose-dependent inhibition of telomerase with IC50 values <1 nM. Optimization of the sequence, length, and bioavailability resulted in the selection of a 13-mer NPS oligonucleotide, GRN163, as a drug development candidate. GRN163 inhibited telomerase in a cell-free assay at 45±7 pM, and in various tumor cell lines at ~1 nM and ~0.3-1.0 µM in the presence and absence of carriers, respectively. GRN163 was competitive with telomeric primer binding, primarily due to hybridization to hTR. Tumor cells treated with GRN163 in culture underwent telomere shortening, followed by cellular senescence or apoptosis after a period of time that generally correlated with initial telomere length. In a flank DU145 (prostate cancer) xenograft model, parenterally administered GRN163 caused suppression of tumor growth in the absence of gross toxicity. These data demonstrate that GRN163 has significant potential for further development as an anticancer agent.

Sergei M. Gryaznov, Ph.D., *Director & Sr. Research Fellow; Nucleic Acid Chemistry*
GERON CORP

12:15 - 1:45

Lunch Sponsored By:



siRNA/RNAi IN DRUG DISCOVERY I

1:45 - 2:10

siRNA Design and the Transcriptome

In designing siRNAs to interfere with specific mRNAs in cells, accurate and complete information on the transcriptome is critical, particularly in order to guarantee specificity and appropriately incorporate alternative splicing. In collaboration with Novartis, Compugen has created a platform for the design of gene-specific and transcript-specific RNAi molecules. In the talk, we will discuss the RNAi platform and the underlying transcriptome database, and present results on RNAi specificity and related issues.

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

OTHER OLIGO-BASED THERAPEUTICS I

1:45 - 2:10

Activating Immunity by Stimulating TLR9 with CpG Oligos

Bacterial DNA stimulates innate and acquired immunity through a specific receptor, TLR9. These effects can be mimicked by synthetic oligodeoxynucleotides containing CpG motifs (CpG ODN). CpG ODN are extremely effective vaccine adjuvants and have shown therapeutic activity in animal models of infectious and allergic disease and cancer. CpG ODN 7909 has been well tolerated in phase I human clinical trials. As an adjuvant for a hepatitis B vaccine, CpG 7909 induces earlier seroconversion with the production of markedly increased immune responses, even in HIV-infected patients. Additional clinical trials in cancer patients are underway, with encouraging preliminary results.

Arthur M. Krieg, MD, *Chief Scientific Officer*
COLEY PHARMACEUTICALS

RELATED TECHNOLOGIES SPEEDING RNAi APPLICATIONS I

1:45 - 2:10

Biophotonic Imaging as a Method for Monitoring Gene Expression in Live Animals in Real-Time, & Its Applicability to RNAi Research In Vivo

To date, Xenogen's technology has been used predominantly to facilitate drug discovery in areas such as infectious disease, oncology, inflammation and toxicology. Recently, this technology has also been used to assess the capability of RNAi molecules to regulate gene expression in live animals, enabling researchers to rapidly assess whether an RNAi is being delivered to the target tissue to effectively reduce translation of a specific mRNA. We believe that Xenogen's technology will greatly facilitate research and development of RNAi in live animals and provides an insight into how small RNAi molecules might be better developed as human therapeutics.

David West, Ph.D., *Division VP, Preclinical Research*
XENOGEN CORPORATION

Register on the Web at: www.srinstitute.com/NAWS

TUESDAY, SEPTEMBER 16, 2003

2:10 - 2:35

Breaking Down Barriers: Nucleic Acid Delivery Using Novel Particles and Injection Methods

The lack of efficient *in vivo* delivery methods limits the use of antisense molecules, siRNA and expression plasmids. Mirus Corporation has developed novel intravascular injection procedures and recharged particle technologies that allow for delivery of nucleic acid molecules that are biologically active. Data will be presented illustrating the effectiveness of Mirus' delivery technologies in mammalian model systems.

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

2:35 - 3:00

RNAi in the Drug Discovery Process: Validation of Targets and Leads

RNAi has already changed the early stages of the drug discovery process, specifically the target validation phase. We are finding that RNAi has a significant role to play in the later stages of discovery as well, including characterizing lead compounds, secondary assays and pre-clinical studies. This talk will highlight some of the early and later stages of the drug discovery process that utilizing RNAi.

Steven Haney, Ph.D., *Sr. Scientist, Department of Genomics*
WYETH RESEARCH

2:10 - 2:35

Discovery and Development of Therapeutic Aptamers

Archemix develops aptamer-based therapeutics to treat a range of human diseases. Aptamers, the nucleic acid equivalent of antibodies, are macromolecules composed of nucleic acids that bind tightly to specific molecular targets to elicit their pharmacological effects. The therapeutic potential of aptamer-based drugs is supported through a range of *in vivo* efficacy studies in animal models of disease and through results from human clinical trials. Recent data for therapeutic aptamers in the Archemix discovery and development pipeline will be presented.

David Epstein, Ph.D., *Vice President, Biology*
ARCHEMIX CORPORATION

2:35 - 3:00

Clinical Development of a 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 Hemispherx's anti-viral pipeline are the 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 and Chairman*
HEMISPHERX BIOPHARMA (INVITED)

2:10 - 2:35

Multiplexed Protein Quantification Using Photoaptamer Arrays

Assessing protein expression is essential for evaluating effects of changes in gene expression induced by any means: mutation, RNAi, antisense, and other, non-genomic mechanisms including disease or therapeutic intervention. Photoaptamers provide a versatile, practical and effective way to quantitatively measure protein expression in serum, plasma or other biological fluids and tissues. We are generating photoaptamers and constructing photoaptamer arrays to facilitate rapid and accurate multiplexed measurement of proteins for any proteomic application. The photoSELEX process allows us to develop arrays with broad content for surveys of protein expression and biomarker discovery as well as arrays with customized content for specific applications. The performance of photoaptamer arrays as well as examples of their application will be discussed.

Joseph S. Heilig, Ph.D., *Senior Director, Science*
SOMALOGIC, INC.

2:35 - 3:00

Gene Quiescence by Locked Nucleic Acid

Locked Nucleic Acid (LNA) is a class of bicyclic nucleic acid analogues that is readily incorporated in nucleic acids and analogues hereof. Oligonucleotides containing LNA residues have greatly improved nucleic acid binding and are bio-stable. Thus, LNA oligonucleotides can be used in almost any oligonucleotide technology. In the presentation it will be shown that LNA greatly improves the potency of antisense oligonucleotides. IC50 values ranging from 0.5 - 1.0 nano molar were obtained by 14 - 16mer LNA oligonucleotides targeting several clinically relevant gene targets. *In vivo* studies are presented that demonstrate the therapeutically potential of LNA antisense oligonucleotides. In the presentation the use of LNA in other gene quiescence technologies such as RNAi is also discussed.

Troels Koch, M.Sc, Ph.D., *CTO & Director of Chemistry*
CUREON

3:00 - 3:45

Refreshments, Networking & Exposition

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For more information, please contact Kellie Swanstrom at kswanstrom@srinstitute.com or call (973) 571-0867.

Register on the Web at: www.srinstitute.com/NAWS

siRNA/RNAi IN DRUG DISCOVERY II

3:45 - 4:10

RNAi in Drug Development

RNAi technology plays dual roles in the drug development process. Indeed, RNAi compounds enable systematic drug target validation, and exhibit strong potential for development as a therapeutic modality. The data presented will demonstrate the applicability of RNAi compounds for drug target identification and validation through gene knock-downs in mammalian cells, and provide examples of phenotypic results in various disease model systems. We will then discuss the potentials of RNAi technology for therapeutic applications. In particular, we will address potency, stability, specificity and delivery of Sequitur's proprietary STEALTH™ RNAi compounds. We will conclude with the analysis of our most recent efforts of applying RNAi compounds *in vivo*.

Dmitry Samarsky, Ph.D., Director of Technology Development
SEQUITUR, INC.

4:10 - 4:35

Express TrackSM siRNA Drug Discovery Program: Integrating CombiMatrix's Programmable Synthesis Platform into a Streamlined siRNA Drug Development and Screening Program

CombiMatrix has integrated its semiconductor-based parallel oligonucleotide synthesis platform into a streamlined siRNA Drug Discovery Program for rapid identification of specific compounds with potential therapeutic value. The Express TrackSM siRNA Drug Discovery Program integrates the following functions: (1) gene target or pathogen identification, (2) bioinformatic construction of sequence libraries, (3) chip-based parallel synthesis of siRNA compounds, (4) parallel *in vitro* library screening, (5) optimization and validation of lead siRNA compounds using CombiMatrix's customizable gene expression microarrays. Rapid and parallel synthesis of different siRNA compounds permits cost effective screening of pools siRNA compounds. Small or large pools of siRNA compounds can be generated that specifically target single genes or entire genomes. Functional *in vitro* screening rapidly identifies the most suitable compounds for gene silencing. Finally, CombiMatrix's customizable gene expression microarrays determine specificity of gene silencing within target systems. CombiMatrix is initially applying the Express TrackSM Drug Discovery Program for identification of novel siRNA antiviral compounds against prevalent viruses such as HIV, Herpes, Hepatitis C and Influenza.

Michael W. Chansler, Director, Business Development
COMBIMATRIX CORPORATION

OTHER OLIGO-BASED THERAPEUTICS II

3:45 - 4:10

Toxicity and Pharmacokinetics of Proliferating Cell Nuclear Antigen Ribozyme Against Cell Proliferation in Proliferative Vitreoretinopathy

The toxicity of VIT-100 - a synthetic ribozyme for intra-vitreous administration during retinal repair, to treat or prevent Proliferative Vitreoretinopathy (PVR) - was evaluated in rabbits and pigs and its pharmacokinetics characterized in rabbits. VIT-100 a DNA-RNA chimeric oligonucleotide that inactivates the function of the cell division factor Proliferating Cell Nuclear Antigen (PCNA) was determined to limit cell growth and neo-membrane formation in a rabbit dispare model of PVR. A single dose toxicity study in rabbits after intra-vitreous injection at two concentrations 0.5 and 5 mg, showed no significant ocular changes with the exception of a transient retinal congestion and transient reduction in electroretinographic waveforms in animals treated at 5mg immediately after the intra-vitreous injection. In a pig study, at 0.5 and 5 mg, repeated intra-vitreous injections of VIT-100 showed retinal lesions such as vascular congestion, increased vascular tortuosity and hemorrhage at the high concentration. The ophthalmology findings correlated histopathologically with mild to moderate retinitis and optic neuritis in the injected eyes of animals treated with 0.5 and 5mg VIT-100. Minor kidney lesions were also reported after histologic examination. The half-life of VIT-100 was determined to be approximately one hour. VIT-100 was quickly taken up by the retina and cleared in both the retina and the vitreous. These studies support the clinical testing of VIT-100 as a therapeutic agent in the treatment of PVR delivered as a single intra-vitreous injection during retinal repair. VIT-100 has since entered in clinical trial, where 150 patients with recurrent PVR will be randomized and treated either with VIT-100 at 0, 1 or 5 mg/ml. At this time, no signs of toxicity have been reported in the 70 patients already treated.

Celia K. Habita, Ph.D.

Director of Pre-clinical and Product Development
IMMUSOL, INC.

4:10 - 4:35

Characterization and Preclinical Development of Chimeric Backbone Oligos as TLR9 Agonists

CpG oligos activate innate and acquired immunity by binding a specific receptor, TLR9. This receptor is selectively expressed on human B cells and plasmacytoid dendritic cells. Depending on the oligo backbone and sequence, preferential activation of either or both cell type can be induced. Several classes of CpG oligos have been identified, with differential immune effects that appear to be useful in the therapy of infectious and allergic disease and cancer.

Eugen Uhlmann, Ph.D., Vice President, Chemistry
COLEY PHARMACEUTICALS

4:35 - 5:00

RELATED TECHNOLOGIES

3:45 - 4:10

Re-programming Gene Expression by RNA Trans-splicing

Spliceosome mediated RNA trans-splicing (SMaRT™) re-programs pre-messenger RNA. Re-programming is achieved through the use of RNA molecules known as pre-trans-splicing molecules or PTMs. PTMs have three domains: a binding domain that is complementary to a specific sequence in a targeted pre-mRNA, a splicing domain and a coding domain, consisting of one or more exons that are spliced into the target to create a new mRNA. SMaRT™ has broad applications depending on the sequences in the coding domain. A gene encoding a fluorescent/luminescent protein results in real time molecular imaging. Other applications include RNA therapy (a new approach to molecular medicine), determination of alternate splice sites and molecular evolution.

Gerard J. McGarrity, Ph.D., President and Chief Executive Office
INTRONN, LLC

4:10 - 4:35

Aptamers as Tools for Drug Discovery: Translating Functional Knockdown Data into Lead Compounds

Highly specific nucleic acid ligands, so-called aptamers, are excellent tools for the functional validation of putative targets and the subsequent identification of small molecule lead compounds. These synthetic inhibitors are rapidly isolated by an automated *in vitro* selection process for almost any given protein. Used in disease models, aptamers have the ability to directly inactivate an endogenous protein in its natural environment. The most impressive feature of the aptamer technology is that the same molecule used in the target validation step can be immediately integrated into competitive high-throughput assays to identify functionally analogous small molecules. Due to the straightforward chemical modification of nucleic acids, they are compatible with almost any kind of industrial read-out format such as fluorescence polarization (FP), fluorescence intensity (FI) or bead-based assay systems. Aptamers are therefore excellently suited to design target independent, cost-effective, and universally applicable screening assays even for difficult targets when no biochemical or structural information is available. HTS systems with high reproducibility and Z'-values above 0.7, which led to the identification of biologically active small molecule lead compounds, will be presented. Nucleic acid biotools offer an elegant route to provide supplementary data to other knockdown technologies like RNA interference and to link them to the discovery of small molecule lead compounds.

Michael Blind, Ph.D., CSO
NASCACELL GMBH

4:35 - 5:00

Arrayed Adenoviral Knock-Down Vectors for Target Discovery and validation

Arrayed adenoviral cDNA expression libraries (knock-in, PhenoSelect™) in combination with cell-based screens have provided a powerful platform for discovery and validation of targets that are key regulators in a variety of disease processes (Michiels et al., Nat Biotech, 2002, November). We have now initiated the construction and use of knock-down arrayed adenoviral libraries (SilenceSelect™). This technology combines efficient *in vitro* delivery, including the vast majority of human primary cells, and long-term expression with siRNA based knock-down. Further the platform can be used for *in vivo* validation studies. Each individual virus expresses a short hairpin RNA that is processed to a siRNA targeting a specific mRNA. Libraries target all the known drugable gene classes, for example kinases. We will present data on the performance of adenoviral knock-down vectors first at the level of mRNA and at the gene function level. Level and duration of mRNA knock-down activity were studied using real-time PCR. We show efficient knock-down in primary human cells including HUVECs and keratinocytes. The SilenceSelect™ vectors and libraries are used to identify genes that induce phenotypic changes in disease relevant human cellular assays.

Dirk Pollet, Ph.D., VP of Business Development
GALAPAGOS GENOMICS NV

4:35 - 5:00

Biostable Aptamers as Novel Therapeutic Agents

Biostable aptamers (Spiegelmers™) are short single-stranded L-nucleotide oligomers which bind to their targets with high specificity and affinity and therefore inhibit protein-protein-interactions similarly to monoclonal antibodies. Since Spiegelmers are synthesized from L-nucleotides (the mirror image of natural nucleotides; German: Spiegel = mirror) they are extremely biostable because they cannot be degraded by naturally occurring nucleases. Chemical modification, such as PEGylation, enables Spiegelmers with enhanced pharmacokinetic properties to be developed for animal and human studies. During the past 6 months, NOXXON have automated much of their R&D process and are able to predictably generate Spiegelmer aptamers against oligopeptides and protein domains. NOXXON has Spiegelmer development projects underway against three oncology targets, the first of which will enter clinical trials during the second half of 2004. A further three targets are also in development in the field of metabolic diseases.

David Pearson, Ph.D., CEO
NOXXON PHARMA AG

4:35 - 5:00

Improving the Odds of Therapeutic Efficacy: Blocking Angiotensin II

We've found that all cardiovascular disease, all cancers except prostate, all autoimmune diseases, most viral diseases and TB, and several psychiatric diseases are associated with overactivity of ACE and hence production of angiotensin II. An ACE inhibitor or angiotensin II receptor blocker (ARB) ought therefore to increase the efficacy of any new treatment, including nucleic acid therapies.

David W. Moskowitz, MD, MA (Oxon.), FACP
Chairman, CEO and Chief Medical Officer
GENOMED, INC.

5:00 - 9:00ish Networking Reception, Dinner & Casino Night

This evening we'll take a respite from sessions to have some fun. A networking dinner and casino games are planned for you and your fellow speakers and attendees to enjoy. Leave your cash at home, the money's fake. The function is open to all speakers & attendees. Come join your colleagues for some fun!

CASINO NIGHT



WEDNESDAY, SEPTEMBER 17, 2003 **GENERAL SESSION**

7:15 - 8:10

Breakfast, Networking & Exposition

8:10 - 8:15

Chairperson's Recap

TRANSFORMING CUTTING-EDGE SCIENCE INTO BUSINESS

8:15 - 8:45

Patentability & Maximum Protection and Valuation of Intellectual Property in Biotechnology

The courts give mixed messages - the biotech patent world is a mess. Some courts find infringers exempt from infringement while others do not. Other courts allow certain research patents to be avoided. With this lack of direction there is no certainty. But, a well planned IP portfolio and strategy can significantly reduce these problems

Richard J. Warburg, J.D., Partner
FOLEY & LARDNER

8:45 - 10:00

Strategies for Protecting siRNA/RNAi Related Intellectual Property

RNAi is taking the biotech world by storm. Its robust performance stimulates an expectation that lab results will translate predictably into clinical results. What

considerations should companies have in mind when looking at emerging breakthrough biotechnologies such as RNAi? What can be said at this time about the patent issues that are likely to arise in relation to RNAi? How can a small company stay informed about the patent estates being created in the fast-moving world of RNAi? What about Big Pharma versus Small Biotech: How do their views of RNAi compare and contrast? These and other timely issues will be addressed this stellar panel of patent law experts.

MODERATOR:

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

PANELISTS:

Nick Slepchuk, J.D., Patent Counsel
PFIZER, INC.

Vineet Kohli, J.D., Assistant Patent Counsel
MERCK & COMPANY

O. Prem Das, Ph.D., Director, Office of Technology Licensing
HARVARD MEDICAL SCHOOL

Bharat M. Chowrira, Ph.D., J.D., Vice President, Legal Affairs, Licensing & Patent Counsel
SIRNA THERAPEUTICS

10:00 - 10:30

Refreshments, Networking & Exposition

Register on the Web at: www.srinstitute.com/NAWS

GENERAL SESSION

WEDNESDAY, SEPTEMBER 17, 2003

10:30 - 11:15

Pharma & Biotech: Partnering & Growth Opportunities

RNA-based therapeutics has revolutionized functional genomics and ignited tremendous interest in therapeutic potential of small interfering RNAs (siRNAs) and varieties of RNAi-inducing oligonucleotides. Prior to the emergence of siRNA, tremendous efforts have been devoted in the development of oligonucleotide-based therapeutics through various approaches such as antisense and ribozymes. The question is with RNAi's proven power in target validation be enough to create a substantial market? Will siRNA/RNAi drugs show efficacy sooner and pass through clinical trials quickly? Are pharmaceutical/biotech companies developing siRNA drugs in-house or will they partner into the field? Join us in this panel discussion as we will explore these ideas and see if nucleic acid-based therapeutics will take off in 5-10 years from now.

MODERATOR:

Keith Dionne, Ph.D., Vice President & General Manager

MILLENNIUM PHARMACEUTICALS

PANELISTS (INVITED):

NOVARTIS

AVENTIS PHARMACEUTICALS

JOHNSON & JOHNSON

PFIZER LA JOLLA

MERCK & COMPANY

View confirmed panelists on line at www.srinstitute.com/NAWS

11:15 - 12:00

Venture Capital & Financing Outlook in RNAi/siRNA

Douglas Fambrough, Ph.D., Venture Partner

OXFORD BIOSCIENCE VENTURES

Bennett Weintraub, Ph.D., Senior Analyst

BIOTECH TRACKER

Linda Powers, Ph.D., Co-Founding Partner & Managing Director

TOUCAN CAPITAL (Invited)

Robert Marshal, Ph.D., Partner

MILLENNIA PARTNERS

ADDITIONAL PANELISTS TBA

12:00

Conference Concludes

5

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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 30 days in advance by August 14, 2003 prior to the conference and stipulate that you will be attending the NAWS or SRI conference.

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