GTC
Global Technology Community

MAY 30-31, 2012 BOSTON, MA
HYATT HARBORSIDE HOTEL

3rd RNAi Research & Therapeutics

PLENARY KEYNOTE SPEAKERS

George Church, Ph.D.
Professor of Genetics, Director of the Center for Computational Genetics
Harvard Medical School

Craig C. Mello, Ph.D.
Nobel Laureate
Blais Professor, Molecular Medicine
University of Massachusetts Medical School
Howard Hughes Investigator
HHMI

G. Steven Burrill
Chief Executive Officer
Burill & Company

KEYNOTE SPEAKER

John J. Rossi, Ph.D.
Lidow Family Endowed Professor and Chairman
Molecular and Cellular Biology
Beckman Research Institute
City of Hope

FEATURED SPEAKER

Matthew Stanton, Ph.D.
Head, RNA Optimization
Merck

FEATURED SPEAKER

Rachel Meyers, Ph.D.
Vice President, Research and RLD
Alnylam

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Wednesday, May 30, 2012

8:00 Welcome & Opening Remarks

KEYNOTE PRESENTATION

8:05 Functional Analyses of RNAi Triggers

John J. Rossi, Ph.D., Professor & Chair, Division of Molecular Biology, ***Beckman Research Institute, City of Hope***

Small interfering RNAs trigger post-transcriptional gene silencing by serving as guides for Argonaute proteins which in combination with other proteins in the RNA induced silencing complex (RISC) are the effectors of gene silencing. Having guide sequences that are efficiently incorporated into the Argonaute effectors critically impacts of the efficacy of RNAi. We have been studying the functional differences and similarities between 19+2 siRNAs and asymmetric 25/27mer Dicer substrate siRNAs as well as Pol II and Pol III promoter expressed short hairpin RNAs (shRNAs). Our studies have investigated incorporation of these RNAs by the argonaute proteins via deep sequence analyses as well as more standard Northern blotting approaches. The presentation will summarize the results of these studies and provide insight into the factors that enhance incorporation into RISC and subsequent target knockdown .

RNAi Delivery Methods

Moderator: Devin Leake, Global Director of Research & Development, Genomics, Thermo Fisher Scientific

FEATURED SPEAKER

8:40 Recent Advances in Lipid Nanoparticle (LNP) Mediated siRNA Delivery

Matthew Stanton, Ph.D., Head, RNA Optimization, ***Merck Research Laboratories***

Lipid nanoparticles (LNP) represent the most advanced delivery platform for siRNA therapeutics. Our efforts in LNP mediated siRNA delivery have focused upon optimization of the individual lipid components within the LNP (chemical SAR), optimization of the formulation parameters (compositional and process SAR) and mechanistic understanding of LNP mediated delivery. This presentation will focus on the discovery of low MW cationic lipids as a novel class of siRNA delivery agents with improved in vivo tolerability and expanded therapeutic margins.

9:15 Novel Delivery Reagents for in Vivo Delivery of Low Dose of siRNA

Xavier de Mollerat du Jeu, Ph.D., Senior Staff Scientist, Research and Development, ***Life Technologies***

siRNA is poised to be the next therapeutic drug. However, delivery of these molecules to the appropriate tissue remains the major bottleneck. The goal of this study was to develop new in vivo delivery reagents to deliver siRNA in vivo by screening a library of lipid formulations complexed with siRNA. An siRNA targeting FactorVII (FVII) was complexed with each formulation and injected intravenously at a 1mg/kg to 0.0125 mg/kg doses. The formulations resulting in initial FVII knockdown were further optimized by mixture DOE and evaluated for their ability to deliver other siRNA as well as microRNA mimics and inhibitors. After a single intravenous injection of FVII siRNAs (0.050mg/kg) complexed with this new reagent, we observed more than 90% mRNA and protein level reduction in liver cells for more than 2 weeks and this silencing was dose dependent with an ED50 of 0.0125mg/kg. We also observed a reduction of Cholesterol, LDL and triglycerides when we silenced APOB using this reagent. In addition, we were able to knockdown 4 genes at the same time after a single injection of a mix of different siRNA complexed with this reagent. This reagent can also deliver other payloads such as antimirs and microRNA mimics. Finally, these new reagents are safe and did not trigger any sustained IFN response or liver toxicity.

9:40 Combinatorial Development of Synthetic siRNA Delivery Systems

Daniel G. Anderson, Associate Professor, Chemical Engineering,Harvard-MIT Division of Health Sciences & Technology, David H. Koch Institute for Integrative Cancer Research, ***Massachusetts Institute of Technology***

High throughput, combinatorial approaches have revolutionized small molecule drug discovery. Here we describe our work on high throughput methods for developing and characterizing siRNA delivery systems. Libraries of degradable polymers and lipid-like materials have been synthesized, formulated and screened for their ability to delivery siRNA, both in vitro and in vivo. A number of siRNA delivery formulations have been developed with in vivo efficacy, and show potential therapeutic application for the treatment of genetic disease, viral infection, and cancer.

10:05 Networking & Refreshment Break

10:30 The Development of Dynamic Poly Conjugates

Dave Rozema, Ph.D., Vice President, Chemistry,
Arrowhead Research

Safe and efficient in vivo delivery of siRNA to the appropriate target cell would be a major advance in RNAi therapeutics. Hepatocytes, the key parenchymal cells of the liver, are a particularly attractive target cell type for siRNA delivery not only for their central role in infectious diseases

and metabolic disorders, but also their accessibility through liver fenestrae. We have developed a vehicle for the delivery of siRNA to hepatocytes in vivo, which we have named Dynamic PolyConjugates. Key features of the Dynamic PolyConjugate technology include: a new class of membrane-active polymers, the ability to reversibly mask the activity of these polymers until they reach the acidic environment of endosomes, and the ability to target these modified polymers and their siRNA cargo specifically to hepatocytes in vivo after intravenous injection.

Attendees will learn latest developments in DPC technology
- size of therapeutic window
- duration of gene knockdown from single and repeat injections
- mechanism of targeting and intracellular delivery

10:55 Design and Production of Lipid Nanoparticle Systems for the Systemic Delivery of siRNA

Pieter R. Cullis, Ph.D., FRSC Director, NanoMedicines Research Group, Professor, Biochemistry and Molecular Biology, ***University of British Columbia***

RNAi-based drugs such as siRNA require sophisticated delivery systems in order to achieve therapeutic benefits. These delivery systems must protect encapsulated siRNA from degradation in the circulation, promote accumulation in target tissue and facilitate intracellular delivery into target cells. In order to be suitable for clinical use, these delivery systems must also be relatively non-toxic and must encapsulate siRNA efficiently into well-defined, reproducible nanomedicines using a scalable manufacturing process. Lipid nanoparticles (LNP) are currently the leading delivery systems for satisfying these demands. Efficient loading into LNP can be achieved using ionizable cationic lipids that are relatively non-toxic and can be optimized to achieve maximum intracellular delivery of siRNA following uptake into target cells. With regard to manufacture of LNP siRNA systems, formulation processes require rapid mixing of an aqueous stream, containing siRNA, with an enthanolic solution containing cationic lipid and PEG-lipid. We have devised scalable microfluidic mixing technology that results in the formation of LNP siRNA systems over the size range 20-100 nm with siRNA encapsulation efficiencies approaching 100%. It is shown that LNP siRNA systems containing optimized ionizable cationic lipids are highly potent and relatively non-toxic agents for silencing hepatocyte target genes following i.v. injection, achieving 50% or greater target gene silencing of 10 ?g siRNA/kg body weight with therapeutic indices of 1000 or higher. This is currently the world-leading “gold standard” for the potency of siRNA-based therapeutics in vivo.

11:20 TIGRs: Targeted Image-Guided RNA Therapies

Paloma H. Giangrande, Ph.D., Assistant Professor, Hematology, Oncology and Blood & Marrow Transplantation Faculty, ***University of Iowa***

Recent clinical trials of small interfering RNAs (siRNAs) have highlighted the need for robust delivery and detection techniques that will enable the application of these therapeutics to increasingly complex disease and organ systems. Recent evidence points to synthetic RNA ligands (aptamers) as an emerging class of pharmaceuticals with great potential for targeted diagnostics and therapy. While encouraging, the extended use of RNA aptamers as a delivery tool for siRNAs awaits the identification of RNA aptamer sequences capable of targeting and entering the cytoplasm of many different cell types. Here, we describe novel selection methodologies for the rapid identification and characterization of RNA aptamers capable of delivering siRNAs into the cytoplasm of target cells. We coupled these methodologies with state-of-the-art RNA chemistries and fluorescent technologies resulting in effective, targeted image-guided RNA reagents (TIGRs) that can be easily tracked in vivo. Importantly, these TIGRs may represent a crucial first step in the transition of siRNAs from the bench-side into the clinic.

11:45 Novel siRNA Delivery Technology Targeting STAT3 in Tumor and Tumor Microenvironment for Treatment of Cancer

Hua Yu, Ph.D., Associate Chair and Professor, Cancer Immunotherapeutics & Tumor Immunology, ***Beckman Research Institute at City of Hope Comprehensive Cancer Center***

STAT3 is persistently activated in many types of tumors. It plays a crucial role in tumor invasion and resistance to therapy, enabling tumor growth while turning off the body’s anti-tumor immune response. Silencing STAT3 could therefore have significant implications for improved cancer therapy. However, as a transcription factor lacking its own enzymatic activity, STAT3 is a challenging target for conventional small molecule drugs. While siRNA has been effectively used to silence a host of genes, delivering it to specific tumor or tumor stromal cells while avoiding unrelated cells, and thus unwanted side effects, has proven difficult. Dr Yu and colleagues have recently developed an in vivo targeted siRNA delivery technology - by covalently linking siRNA to the CpG moiety, they are able to deliver siRNA to those cells expressing the endosomal Toll-like receptor 9 (TLR9), which recognizes CpG, TLR9’s ligand. These include immune cells such as dendritic cells, macrophages and B cells, and a variety of tumor cells, including lymphoma and glioma. In addition to serving as a delivery vehicle for the siRNA, CpG’s binding and activation of the TLR9 receptor has its own anti-tumor immunostimulatory effects. The CpG-Stat3 siRNA serves as an ideal weapon against many cancers, delivering a dual blow by simultaneously activating immune cells in the microenvironment and promoting tumor self-destruction. Dr Yu and colleagues at City of Hope Comprehensive Cancer Center are moving this approach towards clinical trials.

12:10 Lunch On Your Own

Therapeutic, Diagnostics and Clinical Applications

Moderator: Ralph A. Tripp, Professor & GRA Chair, Infectious Diseases, University of Georgia

FEATURED PRESENTATION

1:40 RNAi Therapeutics: from Discovery to Clinical Development

Rachel Meyers, Ph.D., Vice President, Research and RLD, ***Alnylam***

2:05 Advances in Orally Administered RNAi Therapeutics

Richard T. Ho, M.D., Ph.D., Executive Vice President, Research and Development, ***Marina Biotech***

2:30 siRNA Therapeutics for Eye Diseases

Elena Feinstein, Chief Scientific Officer, ***Quark Pharmaceuticals***

Two of our three siRNA drug candidates that are currently in clinical development are being tested for ophthalmic indications. One of these siRNAs, PF-655, targets our proprietary gene RTP801, a stress-induced mTOR inhibitor. This drug has finished Phase IIa clinical trials in diabetic macular edema where dose dependent and substantial improvement of visual acuity has been observed. Relatively slow kinetics of the development of the observed therapeutic effects as well as data from animal models indicate that intravitral administration of siRNA targeting RTP801 causes both neuroprotection and stimulation of axonal outgrowth. Another siRNA, QPI-1007, targeting caspase 2 is in Phase I clinical trials in non-arteritic ischemic optic neuropathy (NAION). Intravitreal injections of this siRNA showed significant and substantial neuroprtection in five different animal models of retinal ganglion cell injury including the glaucoma. The intermediate analysis of human data points to the inhibition of further visual deterioration in NAION patients treated with single intravitreal injection of QPI-1007 within 2 weeks after the symptoms occur. In animal studies, both these siRNAs displayed a quick distribution throughout retinal layers following intravitreal injection, did not cause any type of local innate immune response including interferon response and elicited RNAi-dependent cleavage of target mRNAs.

The presented data:
(1) Confirms safety and RNAi activity of intravitreally delivered siRNA drugs;
(2) Confirms predictability of animal efficacy results with siRNA therapeutics in human trials;
(3) Demonstrates clinical efficacy of siRNA therapeutics in clinical trials with efficacy rather than with pharmacodynamic endpoints

2:55 Asymmetric, Hydrophobically-Modified RNAi Compounds: From Mechanism of Uptake to Clinical Development

James Cardia, Ph.D., Scientist II, Technology Development, ***RXi Pharmaceuticals***

RNAi-based therapeutics offer the potential to efficiently and specifically inhibit expression of any target gene in the human genome. To realize RNAi's full potential as a viable therapeutic, challenges in the delivery of RNAi compounds to target tissues and individual cells must be overcome. This presentation will provide an overview of our recent work using a medicinal chemistry approach to generate improved RNAi compounds that are readily taken up by human cells without any delivery vehicle or formulation. This novel type of RNAi compound, termed self-delivering rxRNAs (sd-rxRNA™), are extensively chemically-modified, asymmetric RNA duplexes, with a short duplex region of 11-15 bp and a fully phosphorothioated single stranded tail. As demonstrated by total internal reflection fluorescence (TIRF) microscopy, efficient cellular internalization of sd-rxRNA compounds occurs within minutes of exposure to cells. Uptake is driven by the RAB5/EEA1 associated branch of the endocytotic pathway. Preclinical data supporting RXI-109, the first clinical candidate based on the sd-rxRNA platform will also be presented. RXI-109 is designed to reduce the expression of CTGF (connective tissue growth factor), a critical regulator of several biological pathways involved in fibrosis, including scar formation in human skin. Pending FDA review, a clinical trial to evaluate RXI-109 for safety, tolerability and initial efficacy will be initiated in 2012.

- Describe a novel class of small asymmetric hydrophobically-modified RNAi compounds, which are active in vitro and in vivo in the absence of a delivery vehicle
- Data demonstrating mechanism of sd-rxRNA cellular uptake
- Describe RXI-109 - an anti-CTGF sd-rxRNA and new anti-fibrotic compound for the treatment of dermal anti-scarring
- Data characterizing RXI-109 efficacy in animal models

3:20 Networking & Refreshment Break

3:50 Pre-Clinical and Clinical Development of Atu027

Klaus Giese, Ph.D., Chief Scientific Officer, Research and Development, ***Silence Therapeutics***

Atu027, a novel RNAi therapeutic composed is currently being tested in a Phase 1 clinical trial in oncology. This investigational drug targets the expression of PKN3 in the vascular endothelium and shows strong anti-tumor and anti-metastatic activity in various pre-clinical models. Latest developments on Atu027 will be discussed.

- RNA interference
- Delivery systeme
- Oncology
- Clinical trial

4:15 siGENOME Discovery and Validation of Novel Anti-influenza Drugs

S. Mark Tompkins, Associate Professor, Infectious Diseases, ***University of Georgia***

Influenza A virus causes widespread infection in humans often with severe clinical manifestations, thus there is a need for vaccines and therapeutic drugs. As influenza virus relies on host cell proteins and their associated pathways to complete its life cycle, identifying the host molecules required for virus replication provides valuable new targets for antiviral therapy. In this study, we performed a genome-wide RNA interference (RNAi) screen in a human respiratory epithelial cell line infected with H1N1 viruses A/WSN/33, A/New Caledonia/20/99, or A/California/04/09 to identify host genes important for influenza virus replication. From the RNAi screen numerous host genes were found to be critical for influenza replication or act as host resistance genes using three assay endpoints that included influenza NP localization, viral genome replication, and infectious virus production. The key signaling pathways linked to these genes were identified and validated by reporter systems. MicorRNAs that regulate these pathways were also identified and shown to modulate viral replication. Pathway analysis showed that several genes functioned as apex genes in host cell pathway, and targeting these genes with re-purposed small molecule drugs phenotyped RNAi-based gene silencing and inhibition influenza virus replication. These novel druggable targets were sensitive to nanomolar levels of drugs in vitro and in mouse models of infection suggesting new disease intervention strategies with new classes of antiviral drugs for chemoprophylaxis and treatment.

BENEFITS
1. Use of RNAi for novel drug target discovery
2. Targeting host processes mitigates potential for viral escape mutants
3. The potential for viral use of common pathways may enable broad anti-viral activity
4. Pathway analysis identifies microRNAs that may serve as global regulators of infection
5. Potential for rapid development by repurposing existing compounds.

4:40 DsiRNA/EnCore Hepatocellular Carcinoma Program: Preclinical Delivery,Efficacy and Tolerability

Sujit K. Basu, Ph.D.,Vice President, Formulation, ***Dicerna Pharmaceuticals***

5:05 RNAi for Cancer Target Discovery and Cancer Therapy: Opportunities and Challenges
Yu Shen, Senior Group Leader, Cancer Research, **Abbott**

RNAi is not only an invaluable research tool for studying gene functions in cell and animals but also holds promise as a novel therapeutic modality. Over the last 10 years, we have been applying the RNAi technology for cancer target identification/validation and for the development of siRNA therapy. In this presentation, we will highlight the opportunities and challenges of using RNAi technology to help advancing oncology pipeline - with a focus on lessons learnt from our experience.

5:30 Networking Reception

Thursday, May 31, 2012

Plenary Keynote Session
Moderator: *Shidong Jia, Scientist,* ***Genentech***

KEYNOTE PRESENTATION

8:00 *Steven Burrill, Chief Executive Officer,* ***Burrill & Company***

Pharmaceutical R&D spending is falling, the demand for innovation is increasing, and the traditional business model for the industry is failing. What does innovation look like today in the new austerity and what will it take to be successful? What's required is creativity in raising money, making deals, and forging new business models. Burrill brings his 45 years of successful dealmaking, company building, and investing to this discussion.

KEYNOTE PRESENTATION

8:45 The Personal Genome Project - Open Access to Genome Sequences + Trait data.

George Church, Ph.D., Professor, Genetics; Director, Center for Computational Genetics, ***Harvard Medical School***

The PGP enables open observation and critique of a large cohort "test-driving" comprehensive participatory personalized medicine. Since 2004, we have helped push the cost of reading and writing DNA (and biological systems) down by a million-fold (5-fold faster exponential than Moore's law) and enabled fully open-access human Genome+Environment=Trait (GET) data, stem cells, and clinical community curation/interpretation tools (Evidence.PersonalGenomes.org). This involves inherited genomes plus day-to-day genomic variation -- cancers, microbes, allergens, vaccines, & subcellular-resolution epigenomics. We are also sequencing centenarians and long-lived mammals. Benefits include human genome engineering technologies for personalized diagnostics as well as stem cell, synthetic organ, microbiome and immunome transplantation therapies.

KEYNOTE PRESENTATION

9:30 RNAi and Immortality: Recognition of Self/non-Self Nucleic Acids

Craig C Mello, Ph.D., Nobel Laureate, Blais Professor in Molecular Medicine, ***University of Massachusetts Medical School****; Howard Hughes Investigator,* ***HHMI***

Organisms exhibit a fascinating array of gene-silencing pathways, which have evolved, in part, to confront invasive nucleic acids such as transposons and viruses. Not surprisingly, these pathways are highly active in the germline and can be elicited upon the introduction of transgenes. A key question raised by the existence of these pathways is how do they distinguish self- from non-self nucleic acids? Evidence exists for a number of cues that might facilitate the recognition of foreign sequences including, copy-number sensing, sensing of unpaired DNA, or the sensing of aberrant RNA (e.g. dsRNA). Here we report on a remarkable silencing pathway that can permanently silence even single-copy transgenes. We show that the initiation of silencing depends on the piwi Argonaute PRG-1 and its genomically encoded piRNA cofactors. Our findings support a model in which PRG-1 scans for foreign sequences while two other Argonaute pathways serve as epigenetic memories of "self" and "non-self" RNAs. These findings suggest that organisms utilize RNAi-related mechanisms to keep inventory of all genes expressed in the germ-line, and to recognize and silence foreign genes.

10:15 Networking & Refreshment Break

Target Discovery and Validation

Moderator: Benjamin Haley, Scientist, Genentech

10:45 RNAi Genetic Screening for Drug Target Discovery

Paul Diehl, Ph.D., Director, Business Development, ***Cellecta***

Phenotypic loss-of-function RNAi screens with complex lentiviral-based shRNA expression libraries that target and silence several thousand genes provide a realistic and workable approach to identify genes that functionally modulate a cellular response such as viability of cancer cells or apoptosis. As long as the shRNA libraries are properly constructed so that hairpin representation is well characterized and reasonably constrained, and changes in shRNA representation in selected vs. control cell populations can be efficiently measured by HT sequencing, pooled RNAi screens produce robust and reproducible results in a range of cell models.

We will present results from two analyses: one “drop-out” screen to identify genes essential for viability in a panel of leukemic cells, and a second “rescue” screen to identify genes required for FAS induced apoptosis. Both screens found a combination of known and novel signaling pathway and regulatory genes whose functions were confirmed to be required to produce the biological responses. In the case of the FAS-induced apoptosis, in vitro screening data also enabled us to select targets that protected mice from FAS-induced hepatic failure. These results demonstrate that complex pooled shRNA libraries provide a highly efficient, flexible, and cost-effective alternative to array-based RNAi screening methods for identifying genes regulating biological responses and possible new therapeutic targets.

11:10 Improving Reproducibility of Pooled Viral Screens - No shRNA Left Behind

Devin Leake, Global Director of Research& Development, Genomics, ***Thermo Fisher Scientific***

RNAi screens are an essential tool for gene discovery and validation. Two predominant RNAi screening strategies employ arrayed siRNAs or pooled shRNAs. In the former strategy, a large collection of siRNAs are arrayed across thousands of wells so that each well targets one gene. In the latter strategy, a large collection of lentivirus-expressed shRNAs target thousands of genes in a single well. Cells with shRNAs targeting certain genes respond differently to phenotypic selection and become enriched or depleted during the screen. Identifying the exact shRNA producing the phenotype is then determined using next generation sequencing of genomic DNA from the cell(s). However, many variables affect the reproducibility of this powerful screening strategy. For example, the size and composition of the shRNA collection impacts shRNAs representation in the pool (and in transduced cells). Further, the amount of genomic DNA needed for analysis is influenced by the amount of shRNA represented. Our results show that optimizing the level of shRNA by controlling the number of viral-transduced cells as well as the amount of genomic DNA dramatically increase the screens reproducibility.

- Value of conducting pooled RNAi discovery screening without automation
- Benefits of using lentiviral shRNA expression for target validation
- Techniques for increasing precision of shRNA discovery screening
- Experimental design that will improve discovery rate of pooled lentiviral shRNA collections

11:35 A Bioinformatics Method to Identify Off-target Effects in RNAi Screens

Randall W. King, M.D., Ph.D., Associate Professor, Cell Biology, ***Harvard Medical School***

Because off-target effects hamper interpretation and validation of RNAi screens, we developed a bioinformatics method, Genome-wide Enrichment of Seed Sequence matches (GESS), to identify candidate off-targeted transcripts from direct analysis of primary screening data. GESS identified a prominent off-targeted transcript in several screens, including MAD2 in a screen for components of the spindle assembly checkpoint. I will discuss how incorporation of the results of GESS analysis can enhance the validation rate in RNAi screens.

12:00 Discovering Novel Regulators of Tumor Angiogenesis through Integrated *in vivo* and *in vitro* Genetic Analyses

Benjamin Haley, Scientist, ***Genentech***

The survival benefits of antiangiogenic cancer therapies have been proven over the last decade. To better understand the gene networks that promote or maintain tumor angiogenesis, and potentially enhance clinical outcomes, we have developed a focused RNAi-based screen in cultured primary endothelial cells. Our approach makes use of an in vivo-validated genetic signature combined with real-time phenotypic analyses in vitro. I will discuss the results and significance of the screen, along with the unique challenges presented upon interpretation of real-time datasets.

12:25 Lunch Provided by GTC

MicroRNA and Diseases

Enal Razvi, Biotechnology Analyst, Nova Bioreports

1:30 [Oral Presentation from Exemplary Submitted Abstracts]
To be considered for an oral presentation, please submit an abstract here by April 30.

1:55 Respiratory Syncytial Virus (RSV) Modifies MicroRNA Gene Regulation during Infection Affecting RSV Replication

Ralph A.Tripp, Professor & GRA Chair, Infectious Diseases, ***University of Georgia***

Respiratory syncytial virus (RSV) causes substantial morbidity and life-threatening lower respiratory tract disease in infants, young children, and the elderly. Understanding the host response to RSV infection is critical for developing disease intervention approaches. The role of microRNAs (miRNAs) in post-transcriptional regulation of host genes responding to RSV infection is not well understood. In this study, we show that RSV infection of a type II lung epithelial (A549) cell line induces five miRNAs (let-7f, miR-24, miR-337-3p, miR-26b and miR-520a-5p) and represses two miRNAs (miR-198 and miR-595), and show that RSV G protein is a major inducer of let-7f. Luciferase-UTR reporters and miRNA mimics and inhibitors validated a subset of predicted target genes for let-7f, specifically showing let-7f regulates cell cycle genes (CCND1, DYRK2 and ELF4), a chemokine gene (CCL7), and a suppressor of cytokine signaling 3 (SOCS3) gene. Together, these results show that RSV G protein affects let-7f regulation of host gene networks, a feature that affects RSV replication.

A benefit of this talk will be a better understanding of the mechanisms that contribute to RSV disease and new pathways for RSV disease intervention.

2:20 *TBA*

2:45 Application of genome-wide RNAi screens for the identification of novel drug targets, combination therapies, and development of potential patient selection biomarkers

Attila Seyhan, Sr. Biomarker Discovery and Development Leader, Biotherapeutics Clinical R&D, ***Pfizer***

Neratinib (HKI-272) is a small molecule tyrosine kinase inhibitor of the ErbB receptor family currently in Phase III clinical trials. Despite its efficacy, the mechanism of potential cellular resistance to neratinib and genes involved with it remains unknown.

We undertook a genome-wide pooled lentiviral RNAi screen to identify synthetic lethal or enhancer genes that interact with neratinib in a human breast cancer cell line (SKBR-3).

We discovered a diverse set of genes and pathways whose inhibition selectively impaired or enhanced the viability of cancer cells in the presence of subeffective concentrations of neratinib. Examining the changes of these genes and their protein products also led to a rationale for clinically relevant drug combination treatments. Treatment of cells with either paclitaxel or cytarabine in combination with neratinib resulted in a strong antiproliferative effect. Notably, our findings support a paclitaxel and neratinib phase III clinical trial in breast cancer patients.

In addition, we performed an RNAi screen to identify genes involved in resistance to lethal concentrations of neratinib, using a long term survival study with pooled RNAi libraries and identified genes involved in chemoresistance to lethal concentrations of neratinib.

The identification of novel mediators of cellular resistance to neratinib could lead to the identification of new or neoadjuvant drug targets and their use as patient or treatment selection genetic biomarkers could make the application of anti-ErbB therapeutics more clinically effective.

- The study identified novel chemosensitizer and chemoresistance targets for an experimental cancer drug neratinib.
- The identification of novel targets and pathways to neratinib could lead to the development of novel selective therapies and combination therapies that overcome therapeutic resistance to neratinib and other ErbB2-targeted therapies.
- The screen also identified a set of novel genes whose silencing by RNAi caused long term chemoresistance to lethal concentrations of neratinib.
- The identification of novel mediators of cellular resistance to neratinib has profound implications for both basic and translational research.
- These genes can provide a rationale to stratify patients who may most likely benefit from neratinib therapy.

3:15 Conference Concludes

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