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December Meeting

The 901th Meeting of the Northeastern Section of the American Chemical Society

Northeastern Section
American Chemical Society

JOINT MEETING: NORTHEASTERN SECTION, ACS AND MEDICINAL CHEMISTRY GROUP

Symposium
RECENT DEVELOPMENTS IN RNAi THERAPEUTICS

Organized by the Medicinal Chemistry Section of the Northeastern Section, American Chemical Society

Thursday - December 10th, 2009
Marriott Hotel
One Burlington Mall Road, Burlington, MA.

3.00 pm	Refreshments
3.30 pm	Welcome *Raj (SB) Rajur, Program Chair, CreaGen Biosciences, Inc., Woburn, MA*
3.40 pm	Introductory Remarks *Norton P. Peet, Director of Chemistry, Microbiotix, Worcester, MA*
4.00 pm	**Novel, Chemically Modified RNAi Compounds with Improved Therapeutic Properties** *Pamela A. Pavco, Vice President Pharmaceutical Development, RXi Pharmaceuticals Corporation Worcester MA.*
4:45 pm	**Synthetic DNA- and RNA-based therapeutic agents: Paying tolls through TLRs** *Sudhir Agrawal, Idera Pharmaceuticals, President, Chief Executive Officer and Chief Scientific Officer, Idera Pharmaceuticals, Cambridge, MA*
5:30 pm	Social Hour
6:30 pm	Dinner
7:45 pm	**Chemical Strategies for Harnessing RNAi** *Muthiah Manoharan, Vice President of drug discovery, Alnylam Pharmaceuticals Pharmaceuticals, Cambridge, MA*

Dinner reservations should be made **no later than 12:00 noon on Saturday, December 5th , 2009.** Please contact Marilou Cashman at (800) 872-2054 or (508) 653-6329 or mcash0953@aol.com**.** Reservations not canceled at least 24 hours in advance must be paid. Anyone who needs handicapped services/transportation, please call a few days in advance so that suitable arrangements can be made.

Directions Burlington Marriott

Please use map quest to reach the hotel: Marriott Hotel is located on one Burlington Mall Road, Burlington, MA.

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Pamela A. Pavco

"Novel, Chemically Modified RNAi Compounds with Improved Therapeutic Properties"

Abstract: A major hurdle in the development of RNAi as a broad therapeutic class is delivery of the RNAi compound to the appropriate tissue and efficient intracellular uptake. Numerous delivery modalities are being explored in the field, most of which involve formulating the RNAi compound with additional components to form complex delivery vehicles. An alternative approach is to alter the structural and chemical composition of siRNA to create novel RNAi compounds that demonstrate efficient cellular uptake. These 'self-delivering' RNAi compounds (*sd*-rxRNA™) retain potent activity, stability, and reduced immune stimulation but are rapidly and efficiently taken up by cells without the requirement of a transfection reagent or delivery vehicle. Specific proprietary chemical modifications, precise number of chemical modifications and reduction in oligonucleotide content are required. Analyses of fluorescently-labeled *sd*-rxRNAs demonstrate efficient cellular internalization in a variety of cultured and primary cells *in vitro* and following direct administration *in vivo*. Significant reduction of targeted mRNA *in vivo* following local administration supports the use of *sd*-rxRNAs for clinical applications where direct administration is possible.

Dr. Pavco is currently Vice President, Pharmaceutical Development at RXi Pharmaceuticals in Worcester MA. Prior to joining RXi in 2007, Dr. Pavco was employed at Sirna Therapeutics / Ribozyme Pharmaceuticals for ~15 years. There she served in various leadership roles, including Director of Biology Research and Sr. Director R&D Project Management, and managed numerous corporate collaborations and internal programs developing oligonucleotides in a variety of therapeutic areas. She has authored numerous scientific articles and contributed to over 50 patents and patent applications. Dr. Pavco received a Ph.D. in Biochemistry from Virginia Commonwealth University and did post-doctoral work at Duke University.

Sudhir Agrawal

"Synthetic DNA- and RNA-based therapeutic agents: Paying tolls through TLRs"

Abstract: Synthetic DNAs and RNAs are being used as therapeutic agents based on various mechanisms of action, including antisense, siRNA, aptamer, ribozyme, decoy, and as agonists and antagonists of TLRs. Nucleotide base compositions and chemical modifications of DNA and RNA are key parameters for desired mechanism of action. Nucleic acid-based compounds are commonly taken up by cells by endocytosis and internalized in endosomal compartments. In Endosomal compartments four Toll-like receptor (TLR) 3, 7, 8, and 9 are expressed that recognize pathogen associated nucleic acid molecular patterns and induce immune responses. TLR3 recognizes viral and synthetic double-stranded RNAs, TLR7 and 8 recognize viral and synthetic single-stranded RNAs, and TLR9 recognizes bacterial, viral and synthetic DNA containing unmethylated CpG dinucleotide motifs. Based on our work on first and second generation antisense and insights gained, we have identified novel DNA-based compounds that act as agonists of TLR9 and RNA-based compounds that act as agonists of TLR7, TLR8 and dual TLR7 and 8. We have also identified novel DNA-based compounds that act as antagonists of TLR7 and TLR9. Agonists of TLR7, 8, and 9 have broad therapeutic applications including for cancer, asthma, allergies, and infectious diseases and as adjuvants with vaccines. Antagonists of TLR7 and 9 have applications for the treatment of autoimmune and inflammatory diseases, including lupus, rheumatoid arthritis, psoriasis, multiple sclerosis, and colitis.

Dr. Agrawal is currently President, Chief Executive Officer and Chief Scientific Officer at Idera Pharmaceuticals in Cambridge MA.

Since joining the Company in 1990, Dr. Agrawal has served in various capacities including Vice President of Discovery, Senior Vice President of Discovery, and Acting Chief Executive Officer. He was appointed Chief Scientific Officer in January 1993, President in February 2000, and Chief Executive Officer in August 2004. Dr. Agrawal has led the Company's transition into the discovery and development of targeted immune therapy based on Toll-like receptors.

Dr. Agrawal received his D. Phil. in Chemistry in 1980 and carried out his post-doctoral research at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, U.K. While working at Worcester Foundation of Experimental Biology, he carried out work in antisense technology with Paul Zamecnik, MD, and based on this technology, the Company was founded.

Dr. Agrawal has published over 275 research papers/reviews and has edited two volumes on oligonucleotide chemistry and one on antisense therapeutics. He has also authored over 300 patents, issued or pending worldwide.

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Muthiah Manoharan
” Chemical Strategies for Harnessing RNAi”

Dr. Manoharan currently vice president, drug discovery at Alnylam Pharmaceuticals Pharmaceuticals in Cambridge. He served as the Executive Director of Medicinal Chemistry at Isis Pharmaceuticals, Inc., a leading biotechnology company focused on nucleic acid-based therapeutics where he had a 12-year tenure. With a distinguished career as a world-leading nucleic acid and bioconjugate chemist, Dr. Manoharan is an author on over 130 publications and over 200 abstracts, as well as the inventor on over 115 issued U.S. patents. Prior to Isis Pharmaceuticals, he earned his Ph.D. in chemistry at the University of North Carolina-Chapel Hill and conducted post-doctoral work at Yale University and the University of Maryland