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December Meeting

The 883rd 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
Signal Transduction Targets and Drug Discovery

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

Wednesday - December 12th, 2007
Holiday Inn, 15 Middlesex Canal Park Road, Woburn, MA

3.00 pm	Refreshments
3.15 pm	Welcome *Raj (SB) Rajur, Program Chair, CreaGen Biosciences, Inc. Woburn, MA*
3.20 pm	Introductory Remarks *Norton Peet, International R&D consultant, North Andover, MA*
3.30 pm	**Discovery of MP-529: A Selective Inhibitor of Aurora 2 Kinase in Development for the Treatment of Cancer.** *Hariprasad, V, Director of Medicinal Chemistry, SuperGen, Inc. Salt Lake City, UT*
4:15 pm	**Hit To Lead Case Studies** *Adrian D Hobson, Group Leader, Global Pharmaceutical Discovery, Abbott Bioresearch Center, Worcester, MA*
5:00 pm	**The Discovery of Motesanib (AMG 706), a Multi-Kinase Angiogensis Inhibitor for Treatment of Human Cancers: From Crystal to Clinic** *Vinod F. Patel, Director of Medicinal Chemistry, Amgen Inc., Cambridge, MA*
5:45 pm	Social Hour
6:30 pm	Dinner
7:45 pm	**Exploring Chemical Space in Protein-Protein Interaction Drug Discovery: Bridging Nature to Breakthrough Medicines** *Tomi Sawyer, Chief Scientific Officer and Senior VP of drug discovery, Aileron Therapeutics, Cambridge, MA*

Dinner reservations should be made **no later than 12:00 noon on Thursday, December 6th, 2007.** To, 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. Members. Anyone who needs handicapped services/transportation, please call a few days in advance so that suitable arrangements can be made. Reservations not canceled at least 24 hours in advance must be paid. **Payment is made at the door by cash or check (no credit cards.) Members, $28.00; Non-members, $30.00; Retirees, $18.00;Students, $10.00.**

Directions to Holiday Inn Hotel

A. **From Boston - Cambridge - Points North:** Take Route I-93 to Route 95/128 West. After 1 mile, take Exit 35 South to Route 38 (Main Street).
***After about 500 feet at the traffic light, turn right into Middlesex Canal Street to the hotel entrance.**
B. From the West: Take Route 95/128 North to Exit 35 South (Route 38 - Main Street. **Follow directions from * above.**

THE PUBLIC IS INVITED

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Hariprasad V

Discovery of MP-529: A Selective Inhibitor of Aurora 2 Kinase in Development for the Treatment of Cancer.

One of the important targets for discovering new therapeutics for treating various cancer disease is represented by Aurora kinases, a family composed of three Ser/Thr protein kinases such as Aurora-A, B, and C. Aurora kinases play a crucial role in proper spindle formation at mitosis. Overexpression of Aurora-A leads to dysregulation of the centrosome cycle resulting in the formation of multipolar mitotic spindles. The resulting abnormal mitotic events lead to genomic instability which is an underlying process in tumorigenesis. Inhibition of the Aurora kinase activity in tumor cell lines typically leads to the accumulation of polyploidy cells, apoptosis, and block of proliferation. As a part of our oncology drug development program to identify small molecule kinase inhibitors, we have initially identified a very selective sub-nanomolar inhibitor of the pyrimido[4,5-*b*]indole class of Aurora A kinase using a *de novo* fragment-based design strategy by utilizing X-ray crystal structure of an Aurora-A kinase. To further validate the inhibitory effect of this initial lead molecule, it was subjected to several cell-based assays in which it exhibited activity in the mid- to high-micromolar range. These results suggest that the lead compound is effectively hitting the intended cellular target and that lead optimization will likely be required to produce greater cellular potency. Therefore, we have employed lead optimization and successfully synthesized several compounds that led to the identification of MP-529 potent and selective Aurora A kinase inhibitor that belong to pyrimido[4,5-*b*]indoles series. Based on its high Aurora-A selectivity and antiproliferative activity on different cancer cell lines, favorable chemicophysical and pharmacokinetic properties, and high efficacy in *in-vivo* tumor models, the compound MP-529 was ultimately selected for further development.

Dr. Hariprasad V received PhD degree in Pharmaceutical sciences UDCT, University of Bombay, India. He moved to US as a post-doctoral fellow in the labs of Professor Hurley, at College of Pharmacy, Arizona cancer center, Tucson AZ. Presently, he serves as Director of Medicinal Chemistry at SuperGen Inc. Salt lake city, UT. His research interest is in Synthesis of small Molecule Heterocyclics as Kinase Inhibitors and Topoisomerase-II and G-quadruplex interactive agents. Dr. Hariprasad has published over 50 peer reviewed articles in national and international journals and holds several patents.

Adrian Hobson

"Hit To Lead Case Studies".

The talk covers the formalization of the Hit to Lead process. Using case studies, with and without structural information, it demonstrates how parallel synthesis can be leveraged to expedite the HTL process."

Adrian Hobson received his PhD in organic chemistry from University of Sheffield (UK) under the supervision of Dr. C.M. Marson. He then joined Knoll Ltd as a principle scientist where he was responsible for the all the medicinal chemistry activities. In early 2000, Dr. Hobson accepted a team leader position at Abbott Bioresearch Center, Worcester where, over the next 5 years, he was mainly involved in the hit to lead generation program. Presently, he serves as group leader and manages Hit to Lead team.

Vinod F. Patel

The Discovery of Motesanib (AMG 706), a Multi-Kinase Angiogensis Inhibitor for Treatment of Human Cancers: From Crystal to Clinic

Structure-guided approach to the discovery of a potent and highly selective VEGF-R2 inhibitor, AMG 706 will be presented. The preclinical properties that led to its selection as a development candidate and the subsequent initial Phase I experience with AMG 706 will also be discussed.

Vinod Patel received a B.Sc. degree (First Class Honors) in Applied Chemistry from Leicester Polytechnic (UK) and a Ph.D. in Organic Chemistry from Nottingham University (UK) under the supervision of Professor Gerry Pattenden. He moved to the US as a postdoctoral fellow in the labs of the late Professor Dick Schlessinger at University of Rochester (NY), where he was engaged in the Total Synthesis of Natural Products. In 1990, Dr. Patel accepted a position at Eli Lilly & Co. (Indianapolis) where, over the next 9 years, he was principally involved in discovering and developing oncolytics. In early 1999, he returned to the east coast to join Kinetix Pharmaceuticals (Medford, MA), a start-up firm specializing in Kinase Research. In late 1999, Amgen acquired Kinetix and Vinod accepted the role of Head of Medicinal Chemistry at the newlyopened Amgen Cambridge Research Center (CRC). Over the past 7 years at AMA, he has contributed to the growth of the site, especially the medicinal chemistry group, and has had the privilege of leading the KDR program that discovered AMG 706. Presently, he serves as Director of Medicinal Chemistry and manages a group of medicinal chemists with interests in Neuroscience and Oncology drug discovery programs.

PLEASE POST

Tomi Sawyer
Exploring Chemical Space in Protein-Protein Interaction Drug Discovery:
Bridging Nature to Breakthrough Medicines

Protein-protein interactions have incredible scope in the modulaton of biological activities and disease mechanisms. Inhibition or mimicry of such protein-protein interactions with small-molecules or natural products has been incredibly challenging, whereas peptide/protein strategies have been limited by cell penetration and in vivo pharmacological properties. Nevertheless, there exists a significant potential to develop a new class of drugs that are capable of modulating proteinprotein interactions to switch "off" or "on", for example, signal transduction pathways in many disease states. Examples of therapeutic targets as well as pioneering research to advance drug discovery will be described. Exploring known proteinprotein interactions has revealed that alpha-helical protein ligand/receptor type binding mechanisms are key to such molecular recognition processes. Noteworthy has been recent investigations providing proof-of-concept that synthetic alphahelical peptides are capable to bind and modulate specific therapeutic targets utilizing protein-protein interaction. Furthermore, hydrocarbon bridging of key alpha-helical peptides has advanced a first-generation series of promising class of biologics possessing unique cell-penetrating and in vivo pharmacological efficacies. Examples of such "stapled" alpha-helical peptides that mimic the BH3 domain alpha-helix of BID, a pro-apoptotic BCL-2 family member will be highlighted with respect to their effective in vitro and in vivo anti-cancer activities for leukemias. The significance of this concept and technology platform to exploit chemical space in protein-protein interaction drug discovery suggests an extraordinary opportunity for bridging nature to breakthrough medicines.

Tomi Sawyer recently joined AILERON Therapeutics (Cambridge) as Chief Scientific Officer and Senior Vice-President of Drug Discovery and Innovative Technologies. He will lead AILERON's development of a first-generation of breakthrough medicines directed at intracellular protein-protein interaction targets by leveraging a proprietary "stapled peptide" technology platform with application for the treatment of cancer and other diseases. Tomi was previously Senior Director, Pfizer Research Technology Center (Cambridge) and concurrently served on Pfizer’s Global Chemistry Leadership Team. Prior to Pfizer, Dr. Sawyer held several leadership positions in drug discovery at ARIAD Pharmaceuticals including Senior Vice-President, Drug Discovery, where he led chemistry campaigns which successfully advanced the mTOR inhibitor AP23573 (recently partnered with Merck) and the second-generation Src/Abl kinase inhibitor AP24534 (a clinical candidate). He began his career at The Upjohn Company as a peptide chemistry and drug design scientist before moving on to a position at Parke-Davis/Warner-Lambert Company where he last served as Head, Structure-Based Design Chemistry. Dr. Sawyer is the recipient of several international academic and corporate awards for outstanding drug discovery and innovative technologies. He is an inventor of more than 60 issued or filed scientific patents and is an author of more than 200 scientific publications including books, reviews, commentaries and research articles. Dr. Sawyer currently holds academic and research advisory appointments at the University of Massachusetts Medical School and the University of Massachusetts-Amherst. He is the Founding Editor-in-Chief of Chemical Biology & Drug Design. Dr. Sawyer received a B.Sci. with Honors in chemistry from Moorhead State University and a Ph.D. with Distinction in organic chemistry from the University of Arizona.