December Meeting

The 865th Meeting of the Northeastern Section of the American Chemical Society

Northeastern Section
American Chemical Society

Symposium
NEW TRENDS IN ONCOLOGY (Part II)
Organized by the Medicinal Chemistry Section of the Northeastern Section, American Chemical Society

Thursday - September 21, 2006
Holiday Inn Select Hotel, 15 Middlesex Canal Park Road, Woburn, MA

3.00	Refreshments
3.15 pm	Welcome *Raj (SB) Rajur, Program Chair,* CreaGen Biosciences, Inc, Woburn, MA
3.20 pm	Introductiory Remarks *Norton Peet, International R&D Consultant,* North Andover, MA
3.30 pm	**Beyond Biomolecular Screening: A Multi-Paradigm Approach in Streamlining Early Oncology Drug Discovery** *Dennis Francis,* Vice President of oncology and lead discovery, ArQule, Inc. Woburn, MA
4:15 pm	**Toward Improved Topoisomerase I Inhibitor Anticancer Agents .** *Beverly A. Teicher, PhD ,* Vice President, Oncology Research Genzyme Corporation, Framingham MA
5:00 pm	**Novel Small-Molecule Inhibitors of Oncogenic Protein Kinases: Tackling Selectivity and Resistance** *Tomi Sawyer,* Senior-Vice President, Drug Discovery, ARIAD Pharmaceuticals, Cambridge, MA
5.45 pm	Social Hour
6.30 pm	Dinner
7.45 pm	**The Development of Selective Aurora A and B Inhibitors** *Michael Block,* Director of Chemistry, Cancer Research Center, AstraZeneca R&D site Boston, MA

Dinner reservations should be made **no later than 12:00 noon on Thursday, September 14, 2006.** If you prefer to pay at the door, 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, $28.00; Non-members, $30.00; Retirees, $15.00; Students, $10.00. Anyone who needs handicapped services/transportation, please call a few days in advance so that suitable arrangements can be made.

Directions to Holiday Inn Hotel
http://www.radisson.com/woburnma

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

Dennis France
Beyond Biomolecular Screening: A Multi-Paradigm Approach in Streamlining Early Oncology Drug Discovery

Traditional HTS campaigns have been somewhat variable in providing suitable hits for further lead optimization for oncology targets with compelling epidemiologic and pathophysiological rationales. We have explored alternative opportunistic approaches to initiate the lead discovery process for highly attractive oncology targets. In the case of Hsp90 inhibitors, we assembled available structural information and generated a number of hypothesis-driven compound sub-libraries. One sub-library yielded an initial hit with high micromolar potency that was subsequently optimized to low nanomolar biochemical and cellular potency after iterative rounds of hit explosion. For mutant BRAF kinase, a target implicated in melanoma and other cancers, a unique scaffold was identified from an archival kinase sub-library with initial micromolar activity. The subsequent optimization of this series against mutant BRAF yielded selective, potent, and cell-active compounds. Finally, the chemistry space was expanded around known HDAC inhibitors using available structural data and compounds were synthesized with picomolar activity against certain HDAC isoforms and exhibited cell kill against cancer cells at low nanomolar concentrations. The unique features and accelerated timelines of these and other discovery programs will be discussed in detail.

Dennis France joined the ArQule Institute for Biomedical Research as Vice-President of Oncology and lead Discovery in July 2004. Dennis' role focuses on molecular targeted approaches to cancer from target selection to IND submission. Before joining ArQule, Dennis rose through the ranks over a span of 17 years at Novartis, his last position as an Executive Director in the oncology disease area where he was responsible for early target-based oncology lead discovery. Prior to joining the pharmaceutical industry in 1987, Dennis worked at leading medical research labs, including the Dana-Farber Cancer Institute (DFCI), the Mt. Sinai School of Medicine and NYU Medical School. At Novartis, he served as a key liaison for the collaboration between Novartis and the DFCI and was also a co-investigator for several natural product drug discovery grants sponsored by the National Cancer Institute. Until recently, Dennis was also the Executive Chairman of the Laboratory Robotics Interest Group for over ten years and was recently recognized for his leadership in growing this group from 200 members to over 8,000 worldwide. Dennis has also been Chairman of the MipTec Conference for eight years, a leading European conference on enabling technologies for drug discovery. Dennis has received a number of awards, including the ISLAR Pioneer Award in Laboratory Robotics, The Association for Laboratory Automation Achievement Award, the Novartis Pharmaceuticals Corporation Pioneer Award, and the Sino-American Pharmaceutical Association of New England Contribution Award. Dennis has co-authored over 30 peer-reviewed scientific papers during his career ranging across such diverse areas as oncology, atherosclerosis, and drug discovery technologies.

Beverly Teicher
Toward Improved Topoisomerase I Inhibitor Anticancer Agents.

Toposiomerase I is a nuclear enzyme involved in unwinding DNA during replication. The Topo I enzyme binds directly to DNA and produces a single strand-break allowing strand passage and then relegation to restore the duplex DNA. Topo I is essential for cell proliferation but is very difficult to over-express in cells. Camptothecin is a natural product that inhibits Topo I in such a way that the cleaved DNA/enzyme/camptothecin complex forms a stable unit which is called the "cleavable complex", thus trapping the cell with DNA strand breaks, a lethal event. Two camptothecin derivatives, topotecan and irinotecan, are approved anticancer drugs. A limitation of these agents results from pH-sensitive opening of the lactone ring of the camptothecin structure. The ring-opened form of the molecules is toxic to normal tissue but is not an effective Topo I inhibitor. We are exploring the possibility that non-camptothecin Topo I inhibitors can be developed with an improved therapeutic index and increased broad spectrum anticancer activity.

Beverly A. Teicher is Vice President of Oncology Research at Genzyme Corporation, Framingham, MA. Upon completion of her PhD in Bioorganic Chemistry at the Johns Hopkins University, Dr. Teicher accepted a postdoctoral position at Yale University School of Medicine. Her postdoctoral training focused on the development of models to study the response of hypoxic cells to anticancer therapies and synthesis of potential hypoxic cell selective cytotoxic agents. Dr. Teicher joined the staff of the Dana-Farber Cancer Institute as an Assistant Professor of Pathology and rose to the rank of Associate Professor of Medicine and Radiation Therapy, Harvard Medical School at the Dana-Farber Cancer Institute and Joint Center for Radiation

Therapy. Dr. Teicher pioneered the application of perfluorochemical and hemoglobin oxygen delivery agents in cancer therapy and tumor imaging. Dr. Teicher also elucidated mechanisms by which solid tumors are resistant to antitumor agents especially antitumor alkylating agents. Dr. Teicher hypothesized that tumors growing in a host would develop drug resistance through mechanisms involving the host and established a model system where drug resistance in a solid tumor was developed in vivo, Dr. Teicher went on to incorporate antiangiogenic agents into solid tumor treatment paradigms. In July 1997, Dr. Teicher was appointed Research Advisor in Cancer Drug Discovery at Lilly Research Laboratories. While there she founded and chaired the Tumor Microenvironment Action Group, chaired the Cell Cycle Action Group and headed the In Vivo Tumor Models Group. Dr. Teicher joined Genzyme Corporation on January 2002. Dr. Teicher is a very active member of the international scientific community. She has authored or co-authored more than 400 scientific publications, has edited seven books, is senior editor for the journal Clinical Cancer Research and is series editor for the Cancer Drug Discovery and Development book series.

Tomi Sawyer

Novel Small-Molecule Inhibitors of Oncogenic Protein Kinases: Tackling Selectivity and Resistance

Oncogenic protein kinases are key therapeutic targets for drug discovery. X-ray crystallographic,biochemical and cellular studies have revealed both structural and mechanistic properties of several oncogenic protein kinases. In an increasing number of cases, resistance to inhibition has shown to involve critical amino acid mutations in the ATP or proximate binding sites for small-molecule inhibitors.These challenges are being addressed by both chemical biology and drug design strategies. A case example is T315I mutation of Bcr-Abl kinase and drug
discovery campaigns focused on the generation, optimization and development of novel small-molecule inhibitors of Bcr-Abl kinase and mutants thereof. The clinical signifance of selectivity and resistance will be discussed in terms of future directions.

Tomi Sawyer received a B.Sc. degree in Chemistry at Moorhead State University (now Minnesota State University–Moorhead) and Ph.D. in Organic Chemistry at the University of Arizona. His research has integrated synthetic chemistry, drug design, structural biology, chemoinformatics, biochemistry, cell biology and in vivo disease models with a focus on cancer. Tomi's drug discovery track record includes contributions to clinical candidates and/or noteworthy molecular tools for several therapeutic targets, including GPCR receptors (melanocortin), aspartyl proteases (renin and HIV protease), and protein kinases (Src and Abl). He has published more than 200 scientific articles, reviews, commentaries, monographs and books. Tomi is an inventor of more than 50 issued patents and patent filings. He worked at Upjohn Company and Parke-Davis/Warner-Lambert (now both Pfizer Global Research & Development), and is currently Senior-Vice President, Drug Discovery, at ARIAD Pharmaceuticals. He is concurrently Adjunct Professor, Chemistry as well as Biochemistry & Molecular Biology, University of Massachusetts and also Adjunct Professor, Cancer Biology, at University of Massachusetts School of Medicine. Tomi has served on the highlights advisory panel of Nature Reviews Drug Discovery and the editorial advisory boards of Trends in the Pharmacological Sciences, Expert Reviews in Molecular Medicine, Expert Opinion on Investigational Drugs, Journal of Medicinal Chemistry, Chemistry and Biology, Current Medicinal Chemistry (Anti-Cancer Agents), Current Organic Synthesis, Expert Reviews in Molecular Medicine, Expert Opinion on Therapeutic Patents (Oncology), Drug Design and Discovery, Pharmaceutical Research, Molecular Biotechnology, and Biopolymers (Peptide Science). Most recently, is appointed Editor-in-Chief, Chemical Biology & Drug Design.

Michael Block

The Development of Selective Aurora A and B Inhibitors

Aurora kinases are viewed as attractive potential targets for anti-cancer therapy. The three human sub-types, Aurora A, B and C, are serine / threonine kinases that are only expressed during mitosis and play a role in chromosome segregation and cytokinesis. Aurora A and B are over-expressed in parallel in multiple tumor types, whereas Aurora C is not. The presentation will outline the identification and optimization of quinazoline based inhibitors that are selective for either Aurora A or Aurora B.

Michael Block began his career with a 1st class honors degree in Chemistry from the University of Edinburgh in 1982 and then moved to the University of Cambridge to study for his PhD with Professor Alan Battersby working on the synthesis of Vitamin B_{12} biosynthetic precursors. From 1985 to 1987 he held a Nato Postdoctoral Fellowship, working with Professor David Cane at Brown University in the USA on synthesis of labeled biosynthetic precursors of the polyether antibiotic Monensin. In 1988 he joined ICI Pharmaceuticals as a medicinal chemist and has remained with the company as it first became Zeneca and then through a merger to become AstraZeneca. He has worked in a number of different disease areas, focusing in the early part of his career on cardiovascular and antibacterial therapy, and including two years in process research and development. From 1997 to 2002 he was involved in building research at AstraZeneca in the area of diabetes and obesity. In March 2002 he moved to Boston to help lead the newly established Oncology research group, and formally took up the position of Director of Chemistry for Cancer at the AstraZeneca R&D site in Boston in January 2004.