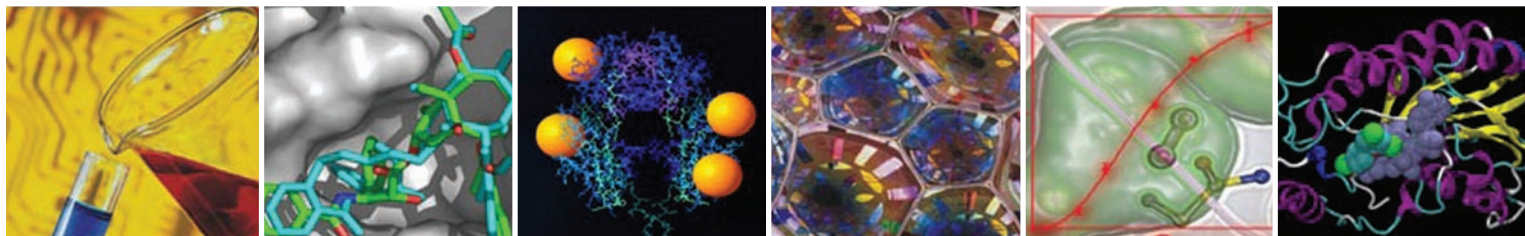


F I F T H A N N U A L S Y M P O S I U M



Institute of Chemical Biology & Drug Discovery

*Frontiers in Chemical Biology
and Drug Discovery*

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Friday, October 14, 2011
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Charles B. Wang Center



Message From Iwao Ojima, Director, Institute of Chemical Biology & Drug Discovery



The primary objective of the Institute of Chemical Biology & Drug Discovery (ICB&DD) is to establish a world-class “Center of Excellence” in chemical biology and drug discovery at Stony Brook University. The rapid and impressive advancements in chemical biology

during the last decade have clearly demonstrated that solutions for a vast majority of medical problems rely on the understanding of the molecular basis of diseases, therapeutic targets, drug actions, and drug resistance. ICB&DD promotes highly productive interdisciplinary and collaborative research among chemists, biologists, medicinal chemists, pharmacologists, and physicians to attack major biomedical problems to find solutions including the discovery of novel therapeutic drugs.

—Iwao Ojima, *Director, Institute of Chemical Biology & Drug Discovery*

Dr. Iwao Ojima received his B.S., M.S., and Ph.D. (1973) degrees from the University of Tokyo, Japan. He joined the Sagami Institute of Chemical Research and held a position of Senior Research Fellow until 1983. He joined the faculty at the Department of Chemistry, State University of New York at Stony Brook first as Associate Professor (1983), was promoted to Professor (1984), Leading Professor (1991), and then to Distinguished Professor (1995). He served as the Department Chairman from 1997 to 2003. He has been serving as the founding Director for the Institute of Chemical Biology and Drug Discovery (ICB&DD) from 2003. He has a wide range of research interests in synthetic organic and medicinal chemistry as well as chemical biology, including discovery and development of anticancer agents and antimicrobials, targeted drug delivery, catalytic methodologies and asymmetric synthesis. His awards and honors include Arthur C. Cope Scholar Award (1994), E. B. Hershberg Award for Important Discoveries of Medicinally Active Substances (2001), the Medicinal Chemistry Hall of Fame (2006) from the American Chemical Society; The Chemical Society of Japan Award (1999); Outstanding Inventor Award (2002) from the Research Foundation of the State University of New York; Fellows of J. S. Guggenheim Memorial Foundation, the American Association for Advancement of Science, the New York Academy of Sciences and the American Chemical Society.

ICB&DD History and Mission

The ICB&DD was established in 2004 with Stony Brook University’s institutional support as well as the NYSTAR Faculty Development Award. One of ICB&DD’s strengths is that it has been founded by reorganizing existing exceptional talents on campus, and thus the core of the institute is a well proven entity with an excellent track record: The core members of ICB&DD currently hold more than \$25M in NIH grants. ICB&DD is open to a wide range of collaborative research programs with pharmaceutical and biotechnology industrial firms. Members of ICB&DD are from the departments of Chemistry; Pharmacological Sciences; Physiology and Biophysics; Molecular Genetics and Microbiology; Biochemistry and Cellular Biology; Applied Mathematics and Statistics; Medicine, Oral Biology and Pathology; Center for Structural Biology; Center for Infectious Diseases; and Biology Department of Brookhaven National Laboratory. In addition, ICB&DD has two core laboratories located in the Chemistry Building: Analytical Instrumentation Laboratory and Discovery Chemistry Laboratory. There are also two Strategic Research laboratories for Cancer Stem Cell Research and Anti-Inflammatory Research.

ICB&DD has three programs: Structural and Computational Biology Program, Infectious Diseases Research Program, and Cancer Research Program. ICB&DD, in collaboration with the School of Medicine, is to establish the Translational Experimental Therapeutics Laboratory (TETL) to streamline the preclinical evaluations, leading to the Investigational New Drug (IND) filing to FDA. ICB&DD integrates the existing strengths at Stony Brook University in the basic medical sciences as well as medicinal chemistry and brings in complementary expertise from outside to explore drug discovery and development. At present, ICB&DD focuses on drug discovery in cancer therapeutics, infectious diseases, and therapeutics for diabetes. Through ICB&DD connections, a number of collaborative research teams have been created and research proposals have been submitted to NIH and other funding agencies. Currently, there are 26 ICB&DD-designated projects (Total funding: ca. \$22.7 million).

5th ICB&DD Annual Symposium

Frontiers in Chemical Biology and Drug Discovery

Friday, October 14, 2011

9:30 am to 9:45 am

Moderator: Dr. Peter Tonge (*Chair of the Organizing Committee*)

Opening Remarks

Dr. Wadie Bahou, *Professor of Medicine and Vice Dean for Scientific Affairs, School of Medicine, Stony Brook University*

Dr. Iwao Ojima, *Distinguished Professor and Director, Institute of Chemical Biology and Drug Discovery, Stony Brook University*

9:45 am to 10:30 am

Moderator: Dr. Maria Ryan

Dr. Kenneth Kaushansky, *Dean School of Medicine and Senior Vice-President of Health Sciences, Stony Brook University*

"Thrombopoietin: From Cloning to Clinic"

10:30 am to 11:15 am

Moderator: Dr. Jian Cao

Dr. Johanna Fowler, *Director of Biological Imaging, Medical Dept, Brookhaven National Laboratory*

"Imaging Drug Action in the Human Brain"

11:15 am to 12:00 pm

Moderator: Dr. Nicole Sampson

Dr. John Gerlt, *Gutgsell Chair, Center for Biophysics and Computational Biology, Depts of Biochemistry and Chemistry, University of Illinois at Urbana-Champaign*

"Discovering and Predicting New Functions in the Enolase Superfamily"

12:00 pm to 1:00 pm

Lunch

Chapel (*by invitation only*); Theatre Lobby (*students*)

1:00 pm to 1:45 pm

Moderator: Dr. Miguel Garcia-Diaz

Dr. Stephen V. Frye, *Director, Center for Integrative Chemical Biology and Drug Discovery, University of North Carolina*

"The Role of Academic Drug Discovery and Chemical Biology of Chromatin Regulation"

1:45 pm to 2:30 pm

Moderator: Dr. James Bliska

Dr. Deborah Hung, *Center for Computational and Integrative Biology, and Dept of Molecular Biology, Mass General Hospital; Dept of Microbiology and Immunobiology, Harvard Medical School; Broad Institute of MIT and Harvard University*

"Chemical Biological Approach to TB: Identifying New Drugs Targets"

2:30 pm to 3:15 pm

Moderator: Dr. Isaac Carrico

Dr. Russell Petter, *Vice-President Drug Discovery, Avila Therapeutics*

"The Resurgence of Covalent Drugs"

3:15 pm to 4:15 pm

Coffee Break and Student Poster Session

Theatre Lobby

4:15 pm to 5:00 pm

Moderator: Dr. Jessica Seeliger

Dr. Celia Schiffer, *Co-Director Institute of Drug Resistance, Dept of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School*

"Combating Drug Resistance: Lessons from the viral proteases of HIV and HCV"

5:00 pm to 5:45 pm

Moderator: Dr. Rob Rizzo

Dr. Carlos Simmerling, *Associate Director, Laufer Center for Physical and Quantitative Biology, Dept of Chemistry, Stony Brook University*

"Using Computer Simulations to Investigate Dynamic Aspects of Inhibitor Binding and Potency"

5:45 pm

Closing Remarks: Dr. Peter Tonge

5:50 pm to 6:30 pm

Reception and Poster Session (*two poster awards*)

Theatre Lobby

6:30 pm to 6:45 pm

Announcement of Poster Awards: Dr. Peter Tonge

Theatre Lobby

6:45 pm

Dinner

Chapel (*by invitation only*)

Speakers



Kenneth Kaushansky, M.D., M.A.C.P. earned his B.S. and M.D. degrees from the University of California, Los Angeles, and completed his Internal Medicine Internship, Residency and Chief Medical Residency, and Fellowship in Hematology at the University of Washington. He joined the faculty at the Univer-

sity of Washington as an Assistant Professor in 1987, was promoted to Associate Professor in 1991 and to Professor in 1995. Following his service as Hematology Section Chief at the University of Washington Medical Center, Dr. Kaushansky was named Helen M. Ranney Professor and Chair of the Department of Medicine at UC San Diego in February 2002. More recently, Dr. Kaushansky was named Senior Vice President for Health Sciences and Dean, School of Medicine at Stony Brook University.

During his career Dr. Kaushansky has been a successful teacher, clinician and biomedical researcher. His laboratory work has led to several significant discoveries, for which he received the Dameshek Award from the American Society of Hematology, awarded annually to the scientist who has provided the most seminal insight into the pathophysiology of hematological disorders, and the Outstanding Investigator Award from the American Society for Medical Research, the most prestigious award of the Society. Dr. Kaushansky is a past-president of the American Society of Hematology (2007-2008), the American Society for Clinical Investigation (2004 – 2005) and the Western Society for Clinical Investigation (1998 – 1999). He also served a 5 year term as Editor-in-Chief of the journal *Blood* (1998-2002) and as a major reviewer for the National Institutes of Health and many major scientific periodicals. Dr. Kaushansky has been recognized for his scientific and clinical contributions by election as a Master of the American College of Physicians, and to several honor societies and organizations, including the American Society for Clinical Investigation, the Association of American Physicians, the Institute of Medicine of the National Academies of Science and the American Academy of Arts and Sciences.

Dr. Kaushansky has conducted seminal research on the molecular biology of blood cell production. His team has cloned several of the genes important in the growth and differentiation of blood cells, including thrombopoietin, a key regulator of stem cell and platelet production. In recent years his group has established that thrombopoietin exerts a profound influence on hematopoietic stem cells, affects the expression of a number of transcription factors that influence stem cell fate decisions (HoxB4, HoxA9, c-Myb, HIF-1) and has unraveled the pathobiology of several congenital disorders of thrombopoiesis. He is an accomplished cli-

nician, and he has been a champion of the need to train more physician-scientists who can bridge the gap between the laboratory and the clinical arena, translating research discoveries into improved treatments and technologies for the prevention, diagnosis and management of disease.

“Thrombopoietin: From Cloning to Clinic”

The talk will focus on the clinical needs for an agent that stimulates blood platelet production, the successful search for the primary physiological regulator of the process, a "side trip" into its more complete biological effects including its somewhat surprising role in stem cell biology, its initial application to clinical medicine and its huge "shot in the foot", and ultimate resolution with the development of peptide and chemical mimics that potently affect clinical platelet production and reduce bleeding complications.



Joanna S. Fowler received her B.A. degree in chemistry at the University of South Florida and her Ph.D. in chemistry at the University of Colorado. She carried out post-doctoral research at the University of East Anglia (Norwich, England) and at the Department of Energy's Brookhaven National Laboratory.

She is currently a Senior Chemist and serves as Director of Brookhaven's Radiotracer Chemistry, Instrumentation and Biological Imaging Program. She is also an adjunct professor in the Departments of Chemistry and Biomedical Engineering at Stony Brook University and also Professor of Psychiatry at Mount Sinai School of Medicine. Along with other chemists at Brookhaven, Joanna developed ¹⁸F-FDG, a radiotracer for imaging brain function and tumor metabolism. Her current research centers on using radiotracer chemistry and PET to study the brain circuits which are disrupted in drug addiction. Some of her early studies include imaging the uptake and movement of cocaine in the human brain which shed light on why this drug is so powerfully reinforcing and addictive and the observation the smokers have reduced levels of monoamine oxidase (MAO) an enzyme which breaks down dopamine, the neurotransmitter which mediates reward.

“Imaging Drug Action in the Human Brain”

Positron Emission Tomography (PET) measures the concentration and movement of a positron emitting radioisotope in a volume element of living tissue. When the positron emitting isotope such as carbon-11 (t_{1/2}: 20.4 min) or fluorine-18 (t_{1/2}: 110 min) is incorporated into a molecule which is targeted to a specific cellular element (receptor, transporter, enzyme) or when it is incorporated into a drug molecule, PET can provide

Speakers

information on biochemical transformations or the drug pharmacokinetics and pharmacodynamics in the living human and animal body. This can provide unique new knowledge of biological pathways which are altered in disease and by drugs. The advancement of PET for biological applications requires innovation in radiotracer chemistry, particularly in the development of rapid synthetic methods for introducing the short-lived isotopes, carbon-11 and fluorine-18 into chemical compounds which are targeted to different cellular elements. In this presentation, we highlight some examples of development and applications of selective radiotracers to measure the pharmacokinetics and pharmacodynamics of drugs of abuse in the human brain. We will also highlight new radiotracers and imaging instrumentation which will serve as scientific tools for advancing knowledge of the human body in health and disease in the future.



John A. Gerlt received his B.S. in Biochemistry from Michigan State University in 1969. He received his Ph.D. in Biochemistry and Molecular Biology from Harvard in 1974 where he worked with Frank Westheimer on measuring the enthalpies of hydrolysis of phosphodiester models of 3',5' cyclic AMP. Following

one year of postdoctoral studies with Christian Anfinsen at NIH, John joined the Department of Chemistry at Yale University in 1975. In 1984, he moved to the Department of Chemistry and Biochemistry at the University of Maryland, College Park. Then, in 1994, John moved as Head to the Department of Biochemistry at the University of Illinois, Urbana Champaign; in 2003 he “retired” from administration and was named Gutsell Chair of Biochemistry. Since the late 1980s, John has focused on understanding the structural basis of divergent evolution of function in functionally diverse enzyme superfamilies and suprafamilies, including the enolase, enoyl CoA hydratase, and RuBisCO superfamilies and the orotidine 5'-monophosphate decarboxylase suprafamily. As genome sequencing has become routine, John's attention has turned to devising multidisciplinary strategies for predicting the functions of unknown/uncharacterized enzymes discovered in genome projects. For more details, see *Nature Chemical Biology* 2007, 8, 486-491; *Structure* 2008, 16, 1668-1677; and *Biochemistry* 2009, 48, 11546-11558.

“Discovering and Predicting New Functions in the Enolase Superfamily”

Determining the functions of proteins encoded by sequenced genomes is a major challenge in biology. We are implementing an integrated sequence structure-function strategy to facilitate functional assignment by

predicting the substrate specificities of unknown proteins in the mechanistically diverse enolase superfamily. The reactions are initiated by abstraction of a proton from a carbon acid substrate to generate a Mg²⁺ stabilized enolate intermediate. We are using three approaches: 1) operon context for unknowns encoded by bacterial genomes, 2) experimental screening of libraries of potential substrates, and 3) computational prediction by in silico docking of libraries of potential substrates to experimentally determined structures and homology models. This lecture will highlight functional assignments using these approaches. Our successes using computational prediction establish this approach as a viable strategy to facilitate functional assignment of unknown enzymes discovered in genome projects. Supported by 2R01GM071790 and 2U54GM093342.



Stephen Frye is Professor and Director of the Center for Integrative Chemical Biology and Drug Discovery at UNC-Chapel Hill. His research focuses on oncology drug discovery and the chemical biology of chromatin regulation. Before joining UNC in 2007, he served as worldwide Vice President for High

Throughput and Discovery Medicinal Chemistry at GlaxoSmithKline. During his 20 years at GSK, his creation and leadership of a department focused on oncology and protein kinases resulted in the discovery of several marketed drugs and he is also the inventor of Avodart, GlaxoSmithKline's drug approved for treatment of benign prostate disease.

“The Role of Academic Drug Discovery and Chemical Biology of Chromatin Regulation”

This lecture will briefly review data from a survey of US Academic Drug Discovery Centers to illustrate the emerging role of these efforts in US biomedical research. The second part of the lecture will focus on efforts to develop small molecule probes to modulate protein-lysine methyl transferases and methyl-lysine binding domains in order to progress biological understanding of the role of these targets in epigenetic regulation.

Speakers



Deborah Hung is a physician-scientist at the Broad Institute of MIT and Harvard, the Department of Molecular Biology at the Massachusetts General Hospital, and the Department of Microbiology and Molecular Genetics at Harvard Medical School. She received her Ph.D. in organic chemistry from

Harvard University under Stuart Schreiber at Harvard University and pursued her postdoctoral research under John Mekalanos at Harvard Medical School. She is combining chemical biological and genomic approaches to define host-pathogen interactions and to reveal essential *in vivo* gene functions of pathogens to explore new paradigms for anti-infective intervention. By deploying small organic molecules and genome-wide tools to both perturb and understand bacterial infection, she is working to provide insight into new approaches to a variety of devastating pathogens, including *Vibrio cholerae*, *Pseudomonas aeruginosa* and *Mycobacterium tuberculosis*.

“Chemical Biological Approach to TB: Identifying New Drugs Targets”

There is an urgent need for new drugs for treating tuberculosis (TB), particularly in the setting of rising drug and multi-drug resistance in *M. tuberculosis*. One of the major challenges of anti-TB drug discovery has been the identification of novel, validated *in vivo* targets that can be chemically disrupted, thus bearing true therapeutic potential. New molecules that hit novel targets in validated pathways have the dual advantage of a high likelihood of therapeutic efficacy based on a validated mechanism of action while overcoming the high levels of resistance to current inhibitors of the pathway. These factors immediately elevate the chemical class and target above the majority of other possible candidates, few as they are for TB, in potential for therapeutic development. We will discuss our efforts taking this type of strategy.



Dr. Petter is Vice President of Drug Discovery at Avila Therapeutics. Previous positions include Vice President of Research at Mer-sana Therapeutics, Director of Small Molecule Drug Discovery at Biogen, Section Head in Oncology Chemistry at Sandoz/Novartis, and Assistant Professor of Chemistry at

the University of Pittsburgh. Dr. Petter earned his PhD in organic chem-

istry at Duke University with Ned Porter and was a post-doctoral fellow in Ron Breslow’s group at Columbia University.

“The Resurgence of Covalent Drugs”

This lecture will provide some background on the history and prevalence of covalent drugs, describe the design challenges for modern targeted covalent inhibitors, and conclude by focusing on Avila’s drug discovery programs.



Celia A. Schiffer is a Professor in the Department of Biochemistry and Molecular Pharmacology, University of Massachusetts Medical School. She became Director of the UMMS Center for AIDS Research in December 2010. She is also the Co-Director of the Institute for Drug Resistance. Dr. Schiffer has a BA in

physics from the University of Chicago, Ph.D. in biophysics from University of California, San Francisco, with postdoctoral training at the ETH in Zurich, Switzerland and Genentech, Inc. She has published 70 peer reviewed journal articles, using a combination of experimental and computational biophysical techniques to obtain key biological insights. Her laboratory primarily studies the molecular basis for drug resistance in HIV and more recently Hepatitis C. Through her research, she has developed a new paradigm for avoiding drug resistance that likely translates to other diseases – by putting drug resistance first in development of drug design strategies, inhibitors can be developed that are more robust against drug resistance. Through this research she conceptualized an interdisciplinary approach to avoid drug resistance and co-founded the Institute for Drug Resistance.

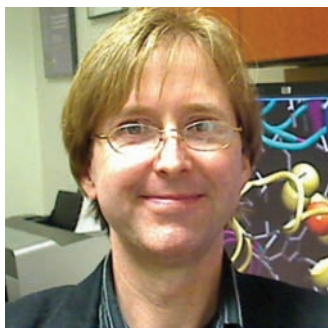
“Combating Drug Resistance: Lessons from the viral proteases of HIV and HCV”

Drug resistance negatively impacts the lives of millions of patients and costs our society billions of dollars by limiting the longevity of many of our most potent drugs. Drug resistance can be caused by a change in the balance of molecular recognition events that selectively weakens inhibitor binding but maintains the biological function of the target. To reduce the likelihood of drug resistance, a detailed understanding of the target’s function is necessary. Both structure at atomic resolution and evolutionary constraints on its variation is required. “Resilient” targets are less susceptible to drug resistance due to their key location in a particular pathway. This rationale was derived from our lab’s experience with substrate recognition and drug resistance in HIV-1 protease and Hepatitis C (HCV)

Speakers

NS3/4A. Both HIV-1 protease and HCV NS3/4A protease are potentially “resilient” targets where resistant mutations occur outside of the substrate binding site. These principals are likely more generally applicable to other quickly evolving diseases where drug resistance is quickly evolving.

Carlos Simmerling received his B.A. in chemistry in 1991, followed by his PhD in physical chemistry in 1994 at the University of Illinois at Chicago. He carried out postdoctoral research at the School of Pharmacy, University of California at San Francisco. He is currently a Professor in the Department of Chemistry at SUNY Stony Brook, and is Associate Director of the Laufer Center for Physical and Quantitative Biol-



ogy. Dr. Simmerling has received several awards, including the AMDeC “Young Investigator in Women’s Cancer”, Research Corporation “Cottrell Scholar”, the SUNY Chancellor’s “Excellence in the Pursuit of Knowledge”, and he was the 2007 recipient of the annual “Humanitarian Impact Innovation

Award” given by Microsoft, HP and Intel. Dr. Simmerling is a Councilor for the ACS Division of Computers in Chemistry and serves on the NSF’s Scientific Advisory Board for supercomputing. His research involves new algorithms for computer simulation of complex biomolecular systems; in collaboration with 4 other labs, he develops the Amber molecular simulation software that is licensed to over 900 research sites worldwide. He also uses these tools to study how dynamic aspects of structure are related to molecular recognition and drug resistance. Dr. Simmerling is very passionate about community outreach and sharing the excitement of scientific discovery with future scientists. He mentors ~5 high school students each year, resulting in 6 Intel Science Talent Search and 6 Siemens Competition semi-finalists, 3 Intel national finalists, winner of a Davidson Fellowship, the biochemistry “best in category” winner at the 2011 International Science and Engineering Fair, and the 2009 national first-prize winner in the Siemens Competition.

“Using Computer Simulations to Investigate Dynamic Aspects of Inhibitor Binding and Potency”

Many important drug targets are flexible and are known to change conformation when ligands bind, presenting challenges for accurate virtual screening as well as obtaining experimental structural and mechanistic data. Perhaps the most well-characterized example is HIV-1 protease, in which a large conformational change is observed between crystal structures of bound and free enzyme. Furthermore, no direct structural data is

available for the open form which is presumed to be required for binding substrate proteins into the active site. Design of inhibitors that overcome resistance would be greatly facilitated by an accurate model of the dynamic behavior of HIV-PR in both the bound and unbound states, along with a deeper insight into the mechanistic events associated with binding of substrates and inhibitors. This seminar will describe the development of simulation models that are used to study HIV-PR and validated against crystallographic and EPR solution data. The work is also extended to gain insight into the behavior of other retroviral proteases. Most recently, we have also extended the work to the study of slow-onset enzyme inhibitors, in which a structural rearrangement is believed to accompany binding. Lack of experimental data for the rearrangement transition state prevents rational optimization of inhibitor binding kinetics. Simulation models can help fill this gap and facilitate development of more potent inhibitors.

Please note: This event is being photographed and/or videotaped and your image may be used in connection with the advertising and promotion of Stony Brook University and/or Stony Brook University Medical Center.



INSTITUTE OF CHEMICAL BIOLOGY & DRUG DISCOVERY

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