Institute of Chemical Biology & Drug Discovery

“Frontiers in Chemical Biology and Drug Discovery”

Friday, October 6, 2017

Charles B. Wang Center
From the Director

The primary objective of the Institute of Chemical Biology & Drug Discovery (ICB&DD) is to establish and sustain 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 tackle major biomedical problems to find solutions including the discovery of novel therapeutic drugs and innovative diagnostic tools.

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

ICB&DD’s 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. 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, Medicine, Molecular Genetics and Microbiology, Biochemistry and Cellular Biology, Physiology and Biophysics, Applied Mathematics and Statistics, Oral Biology and Pathology, Cancer Center, Center for Structural Biology, Center for Infectious Diseases, and Biosciences 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.

ICB&DD has three major programs: Structural and Computational Biology Program, Infectious Diseases Research Program, and Cancer Research Program. In addition, ICB&DD has two strategic Research Laboratories on Cancer Stem Cell Research and Anti-inflammatory Research. ICB&DD, in collaboration with the School of Medicine, has established the Translational Experimental Therapeutics Laboratory (TETL) to streamline the preclinical evaluations, leading to the Investigational New Drug (IND) filing to FDA. ICB&DD collaborates with the Stony Brook University Cancer Center to develop a Cancer Therapeutics Program. 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 therapeutics for cancer, infectious diseases, neurodegenerative diseases and inflammation. Through ICB&DD connections, a number of collaborative research teams have been created and research proposals have successfully acquired grants from NIH and other funding agencies. (Total grant funding > 47M). Currently, there are 19 ongoing ICB&DD-designated projects (Total funding: $17.7M).

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), ACS Award for Creative Work in Fluorine Chemistry (2013) 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; Elected Fellow of J. S. Guggenheim Memorial Foundation, the American Association for the Advancement of Science, the New York Academy of Sciences, the American Chemical Society and the National Academy of Inventors.
ICB&DD 11th Annual Symposium
“Frontiers in Chemical Biology and Drug Discovery”
Friday, October 6, 2017

9:15 am to 9:30 am
Opening Remarks
Dr. John Haley, Research Associate Professor of Pathology, Chair, Symposium Organizing Committee
Dr. Scott L. Friedman, Dean of Therapeutic Discovery, Icahn School of Medicine at Mount Sinai
Dr. Kenneth Kaushansky, Dean, Stony Brook University School of Medicine
Dr. Iwao Ojima, Distinguished Professor and Director, Institute of Chemical Biology and Drug Discovery, Stony Brook University

9:30 am to 10:15 am
Moderator: Dr. Elizabeth Boon
Dr. Ming-Ming Zhou, Dr. Harold and Golden Lamport Professor and Chairman, Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai
“From Epigenetic Structural Mechanism to Targeted Therapy”

10:15 am to 11:00 am
Moderator: Dr. John Haley
Dr. Jingfang Ju, Professor, Department of Pathology, Stony Brook University School of Medicine
“The Development of miRNA-Based Therapeutics for Colorectal Cancer”

11:00 am to 11:45 pm
Moderator: Dr. Maurizio del Poeta
Dr. Dusan Bogunovic, Assistant Professor, Department of Microbiology, Icahn School of Medicine at Mount Sinai
“Broad Spectrum Antivirals – Human Genetics Leading Therapy”

11:45am to 12:30 pm
Moderator: Dr. Martin Kaczocha
Dr. Arvin Dar, Assistant Professor, Department of Oncological Sciences and Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai
“A Whole Animal Platform to Advance a Clinical Kinase Inhibitor into New Disease Space”

12:30 pm to 1:15 pm
Lunch
Chapel (invited faculty only) Zodiac Gallery (students)

1:15 pm to 2:00 pm
Moderator: Dr. Scott Laughlin
Dr. Nicole Sampson, Professor, Department of Chemistry, Stony Brook University.
“Cholesterol Metabolic Pathways in M. tuberculosis: Opportunities for Tuberculosis Drug Discovery and Diagnosis”

2:00 pm to 2:45 pm
Moderator: Dr. Robert Rizzo
Dr. Dima Kozakov, Assistant Professor, Department of Applied Mathematics and Statistics, Faculty Member, Laufer Center for Physical and Quantitative Biology, Stony Brook University
“Modeling and Modulation of Protein Interactions”

2:45 pm to 3:30 pm
Coffee Break and Student Poster Session
Theatre Lobby and Zodiac Gallery

3:30 pm to 4:15 pm
Moderator: Dr. Jarrod French
Dr. Michael Airola, Assistant Professor, Department of Biochemistry and Cell Biology, Stony Brook University
"Structure, Function, and Inhibition of Lipid Metabolism in Cancer"

4:15 pm to 5:00 pm
Moderator: Dr. Adam Rosebrock
Dr. Michael Lazarus, Assistant Professor, Department of Pharmacological Sciences, Icahn School of Medicine at Mount Sinai
“The Incredible ULKs: Structure and Inhibition of Autophagy Kinases”

5:00 pm to 5:05pm
Closing Remarks: Dr. Elizabeth Boon

5:05 pm to 6:00pm
Reception and Poster Session (three poster awards)
Theatre Lobby and Zodiac Gallery

6:00 pm to 6:15 pm
Announcement of Poster Awards: Dr. Jarrod French
Theatre Lobby

6:15 pm
DINNER, Chapel (by invitation only)
Gene expression of the human genome in response to physiological and environmental stimuli is dictated by chemical modifications of the DNA and the DNA-packing histones, as well as transcription factors that work in concert to direct gene activation or silencing in an ordered fashion. This highly complex biological system that operates with a large number and different combinations of such chemical modifications in chromatin has defied a full investigation of its basic regulatory mechanisms. In this talk, I will present our latest structural and mechanistic study of protein-protein interactions involving master transcription factors and core histones that play an important role in epigenetic control of gene transcription cell proliferation and lineage-specific differentiation. I will discuss the functional implications of our new findings of the basic principles that govern the molecular interactions and regulation in gene expression and strategies for developing new targeted epigenetic therapy for human diseases, including cancer and inflammation.

“The Development of miRNA-Based Therapeutics for Colorectal Cancer”

Research involved in the translational regulation of suspected genes in cancer has come to a new frontier in recent years. Mounting evidence showed that post-transcriptional and translational controls mediated by various regulatory molecules, such as RNA binding proteins and non-coding RNAs (e.g. miRNAs), are critically important. We uncovered a novel mechanism that a number of miRNAs were regulated by tumor suppressor p53 in colon cancer. Such a regulatory mechanism was important in regulating cell proliferation and cell cycle control. To investigate the impact of miRNAs in chemoresistance to fluoropyrimidines and antifolates, we discovered that miR-192 and miR-215 suppresses the expression of both thymidylate synthase and dihydrofolate reductase. In addition, the expression of miR-192 and miR-215 were directly regulated by p53. The expression of miR-215 was significantly associated with colorectal cancer patient survival. We also discovered the superior stability of miRNAs in archival FFPE to establish a foundation for miRNA based biomarker discovery. Our recent studies have shown that miR-129 acts as a tumor suppressor to inhibit several important targets such as E2F3, TS, and BCL2 in colorectal cancer. We have developed a unique miR-129 mimic with superior stability, efficacy, and ease of delivery. miR-129 mimic was able to eliminate 5-FU resistant colon cancer stem cells. miR-129 mimic can block colon cancer metastasis in vivo. Given the significant role of miRNAs in many aspects of tumor development such as proliferation, autophagy, cell cycle control, invasion, EMT and maintained tumor stem cell phenotype, we remain hopeful that miRNA based therapeutics, diagnosis and prognosis may emerge in the near future to benefit patients.
Dr. Dusan Bogunovic is an Assistant Professor in the Department of Microbiology, Department of Pediatrics and Mindich Child Health and Development Institute at the Icahn School of Medicine at Mount Sinai. He completed his Ph.D. thesis in Immunology at New York University Medical School. He identified an algorithm which uses immune and mitotic parameters to predict survival in metastatic melanoma. There, he also studied the innate immune signaling in dendritic cells as a function of their ability to mount an adaptive immune defense against melanoma. This work has inspired two clinical trials. Subsequently he was a Postdoctoral Fellow at The Rockefeller University where he studied how host genetics contributes to susceptibility to infectious diseases. Since Dr. Bogunovic started his lab, his group has defined an essential role for free intracellular ISG15 and USP18 in regulation of Type I Interferon induced inflammation which was reported in Nature in 2015. More recently, his group identified USP18 deficient individuals and detailed the molecular mechanisms behind the Type I IFN inflammation they presented with which was reported in Journal of Experimental Medicine in 2016. Recently, his group discovered that ISG15 deficient individuals have augmented antiviral responses which they reported in Nature Comm. in 2016. They are currently developing drugs to inhibit ISG15, to be used as broad-spectrum antivirals. Scientific American has placed this discovery in its "top ten with the potential to change the world". In 2015, Dr. Bogunovic received the Milstein Award for Young Investigators from the International Cytokine and Interferon Society, in 2016, the Young Investigator Award from the American Society for Microbiology and in 2017, the Lamport Research Award from the Icahn School of Medicine at Mount Sinai. In July, 2017, he also served as an advisor to Mr. Bill Gates on the current state of antivirals.

“Broad Spectrum Antivirals – Human Genetics Leading Therapy”

Using next-generation sequencing we have recently discovered humans who have augmented protection against viral infections. These individuals have loss-of-function mutations in ISG15, a negative regulator of Type I interferon (IFN) pathway. Clinically, ISG15 deficient individuals are largely asymptomatic, but functionally have low-level, persistent transcription of IFN stimulated genes (at about 1% of peak levels). We have recently demonstrated that this small amount of IFN stimulated gene transcripts confers increased protection against a broad spectrum of viruses including, but not limited to: Nipah virus, the human immunodeficiency virus, Zika virus, herpes simplex virus type 1, Rift Valley fever virus and influenza A virus. Pharmacologically, inhibition of ISG15 in WT individuals would temporarily mimic an inherited ISG15 deficiency and provide increased broad spectrum antiviral protection. To identify and characterize candidate inhibitors of ISG15 axis, we are combining virtual small molecule screen (Schrodinger in silico modeling suite), with our established in vitro, ex vivo and biochemical assays.

Dr. Arvin Dar is an Assistant Professor of Oncological Sciences and Pharmacological Sciences at the Icahn School of Medicine at Mount Sinai. He completed his B.Sc. in Chemistry from the University of Western Ontario, and in 2006, his Ph.D. in Structural Biology at the University of Toronto. His Ph.D. thesis was done in the laboratory of Dr. Frank Sicheri, where he studied the structure and regulation of protein kinase complexes and viral inhibitors that play important roles in protein synthesis. Dr. Dar then conducted his postdoctoral studies with Kevan M. Shokat, Ph.D. at the University of California, San Francisco, where he developed small molecule tools to control kinase structure and signaling in normal and cancer cells. In 2012, Dr. Dar started his laboratory at Mount Sinai with a research focus on the use of target-based and systems pharmacology approaches to generate new classes of small molecule modulators for Ras-dependent cancers.

“A Whole Animal Platform to Advance a Clinical Kinase Inhibitor into New Disease Space”

In the Dar laboratory, we study signal transduction networks at multiple levels: structurally, biochemically, within cells, and also within whole animals. A goal of our lab is to build the tools that will allow us to modulate signaling networks within the context of cells and animals for therapeutic applications. In this talk, I will describe our recent work employing methods from synthetic organic chemistry, X-ray crystallography, informatics, biochemistry and model organism genetics to develop novel kinase inhibitors.
Dr. Nicole S. Sampson is a Professor in the Department of Chemistry at Stony Brook University. She has a Ph.D. in Chemistry and has expertise in chemical biology, enzymology, organic synthesis, inhibitor discovery, and metabolic profiling. She has served in many leadership roles at Stony Brook, including Chair of the Chemistry Department from 2012 to 2017. She is the co-founder and co-Director of the NIH-funded T32 Chemical Biology Training Program that has been funded by NIH since 2010. Professor Sampson has received over $16 million in research support from Federal and private agencies. She has published approximately 100 peer-reviewed articles, reviews, and issued patents. Professor Sampson’s honors and awards include the Camille and Henry Dreyfus New Faculty Award, a National Science Foundation CAREER Award, the Arthur C. Cope Scholar Award and the Pfizer Award in Enzyme Chemistry, both from the American Chemical Society, the Research Foundation of SUNY Research and Scholarship Award and the New York State NYSTAR Faculty Development Award. In 2017, she was selected as a Fellow of the Stellenbosch Institute for Advanced Study (STIAS) and she was elected a Fellow of the American Chemical Society. She serves on the editorial advisory boards of Accounts of Chemical Research, Biochemistry, and the Journal of Organic Chemistry, as well as Chemical & Engineering News. A primary interest of Dr. Sampson’s research program is to develop improved therapeutics and diagnostics for treating tuberculosis through understanding Mycobacterium tuberculosis. In addition, her laboratory studies protein-protein interactions that occur during mammalian fertilization. Currently, she is investigating the receptors on the sperm responsible for initiating the membrane remodeling (acrosome) reaction utilizing glycopolymer conjugate flow cytometry-based assays. Her work with polymers in fertilization led to the development of new methodology for the synthesis of polymers by ring-opening metathesis polymerization. Most notably, these methods enable the synthesis of precisely alternating polymers that are presently being applied to expand synthesis of new materials for technology applications.

**“Cholesterol Metabolic Pathways in M. tuberculosis: Opportunities for Tuberculosis Drug Discovery and Diagnosis”**

Tuberculosis (TB) is the number one killer from infectious disease in the world. Current drug regiments are lengthy and toxic, and new approaches to TB treatment are needed. Moreover, existing diagnostic tools fail to confirm TB in most children, who typically have disease with low bacterial counts. *Mycobacterium tuberculosis* (*Mtb*), the causative agent of TB, infects and divides inside human immune cells. The ability of *Mtb* to metabolize human cholesterol is critical for the maintenance of the *Mtb* infection in these cells. Building on our extensive biochemical foundation of how cholesterol is metabolized, my laboratory has identified potential avenues for both diagnosing TB disease more readily, particularly in children, and for improving treatment of TB.

Dr. Dima Kozakov received an M.S. in Applied Mathematics and Physics at the Moscow Institute of Physics and Technology, and his Ph.D. in Biomedical Engineering at Boston University. Currently, he is Assistant Professor at the Department of Applied Mathematics and Statistics at Stony Brook University. He is also an affiliated faculty member of the Laufer Center for Physical and Quantitative Biology. Before joining Stony Brook University, Dr. Kozakov was a Research faculty at Boston University. Dr. Kozakov has been active in method development for modeling of biological macromolecules, with emphasis on molecular interactions and drug design. Dr. Kozakov’s automated docking approaches were ranked the best, in the latest evaluation of worldwide blind protein docking experiment CAPRI. His research has been funded by the National Science Foundation, and the National Institutes of Health.

**“Modeling and Modulation of Protein Interactions”**

Modulating protein interactions for therapeutic purposes has become one of the modern frontiers of biomedical research. My talk will focus on understanding the key principles of disrupting protein-protein interactions using small molecules, macrocycles or other compounds. This will be done by introducing the concept of hot spots of protein-protein interactions, i.e., regions of surface that disproportionately contribute to binding free energy. Hotspots will be determined by modeling the interaction of proteins with a number of small molecules used as probes. This method is a direct computational analogue of experimental techniques, and uses the FFT based sampling approach. I will demonstrate that the hot spots provide information on the “druggability”, i.e., on the ability to bind drug-like small molecules of protein-protein interactions and allosteric sites.
**Speakers**

**Dr. Michael Airola** majored in Chemistry as an undergraduate at Occidental College. He received his Ph.D. in Chemical Biology at Cornell University working with Dr. Brian Crane, where he studied bacterial transmembrane signaling. In his postdoctoral work, he began to study lipid-modifying enzymes involved in cancer and neurological disorders with Dr. Yusuf Hannun. In 2017, he started his own lab in the Department of Biochemistry and Cell Biology at Stony Brook University. Dr. Airola’s research focuses on a mechanistic understanding of lipid metabolism, primarily using structural biology and lipid biochemistry techniques. His laboratory is currently focused on enzymes in triglyceride metabolism and metabolic disease, as well as several cancer therapeutic enzymes in sphingolipid and phospholipid signaling.

“Structure, Function, and Inhibition of Lipid Metabolizing Enzymes in Cancer”

During the past thirty years, the perceived role of lipids has shifted from simple structural components of cell membranes to bioactive molecules that regulate critical cellular and pathological processes. The enzymes that generate and breakdown these bioactive lipids have emerged as novel therapeutic targets for treating the leading causes of diseases in the United States, including cancer. This talk will present new insight into how two key enzymes in sphingolipid metabolism work at the molecular and structural level. These include the colon cancer therapeutic target human Neutral Ceramidase, and the membrane-associated enzyme neutral sphingomyelinase 2, which has established roles in neurodegeneration, metastasis and intracellular communication.

**Dr. Michael Lazarus** is a chemical and structural biologist who recently began his independent career. Dr. Lazarus received his Ph.D. in 2010 from Harvard University, working in the labs of Dr. Suzanne Walker and Dr. Daniel Kahne. In his graduate work, Dr. Lazarus learned about crystallography and solved the first structure of the nutrient sensing human glycosyltransferase OGT. After completing his work there, he then did a postdoctoral fellowship in the lab of Dr. Kevan Shokat, where he was a Helen Hay Whitney postdoctoral fellow. It was there that he learned about kinases and first became interested in autophagy. In 2016, he began his independent career at Mount Sinai. His lab currently focuses on how cells respond to changes in nutrients in cancer and diabetes, through structural understanding of the key enzymes involved in these pathways and developing chemical tools to probe these pathways.

“The Incredible ULKs: Structure and Inhibition of Autophagy Kinases”

Autophagy is a fundamental cellular pathway conserved from yeast to humans. It is necessary for development and normal cellular function. However, it has been shown that cancer cells can take advantage of autophagy for promoting tumor growth and resisting chemotherapy. We are working on developing small molecule inhibitors against the key enzymes that initiate autophagy, a family of kinases called ULKs. These enzymes diverged from the yeast kinase Atg1 and have more complex roles in mammalian cells in general and in cancer in particular. We solved the first structure of ULK1 and are developing inhibitors to probe the therapeutic value of targeting autophagy alone or as a combination treatment for numerous malignancies. These compounds show that targeting ULK1 and ULK2 could be beneficial for cancer treatment. Our latest work on other ULK family members shows an increasing complexity in their dual roles in development and in cancer.
Acknowledgments

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