Institute of Chemical Biology & Drug Discovery

“Drug Discovery for COVID-19 and Other Emergent Coronaviruses”

Thursday, October 7, 2021  ◆ Via Zoom

Distinguished Speakers

Dr. Sara Cherry, University of Pennsylvania
Dr. Rolf Hilgenfeld, University of Lübeck
Dr. Carolyn Machamer, Johns Hopkins University School of Medicine
Dr. Stanley Perlman, University of Iowa
Dr. Carlos Simmerling, Stony Brook University
Dr. David Veesler, University of Washington
Dr. Susan Weiss, University of Pennsylvania

Poster Sessions  ◆ Poster Awards

For more information, please visit
http://ws.cc.stonybrook.edu/icbdd/

Stony Brook University/SUNY is an affirmative action, equal opportunity educator and employer. 10090247
From the Director

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, antimicrobials, and targeted drug delivery systems. 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), and E. Guenther Award in the Chemistry of Natural Products (2019) 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, the National Academy of Inventors and the European Academy of Sciences.

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 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 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 > 69M). Currently, there are 11 ongoing ICB&DD-designated projects (Total funding: $25M).
ICB&DD 15th Annual Symposium
Thursday, October 7, 2021 via Zoom

Join Zoom Meeting https://stonybrook.zoom.us/j/97710676606?pwd=NTFLZzFmTkRDSDdjYUFnNGY4QUxFQT09

Drug Discovery for COVID-19 and Other Emergent Coronaviruses

9:15 am to 9:30 am Opening Remarks
Dr. Carlos Simmerling, Professor, Department of Chemistry, Marsha Laufer Professor of Physical and Quantitative Biology, Stony Brook University, Chair, Symposium Organizing Committee
Dr. Richard Reeder, Vice-President for Research, Stony Brook University
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. Patrick Hearing
Dr. Susan Weiss, Professor, Department of Microbiology, University of Pennsylvania, Perelman School of Medicine
“History and Biology of Coronaviruses: What this Teaches us About Targets for Therapeutics”

10:15 am to 11:00 am
Moderator: Dr. Peter Tonge
Dr. Rolf Hilgenfeld, Professor, University of Lübeck, Institute of Molecular Sciences, Lübeck Germany
“The Main Protease of SARS-CoV-2: Structures, Inhibitors, and Mutations”

11:00 am to 11:45 am
Moderator: Dr. Hwan Kim
Dr. Stanley Perlman, Professor, Department of Microbiology and Immunology, University of Iowa, Carver College of Medicine
“Animal models for COVID-19”

11:45 am to 1:00 pm Lunch and Poster Session via Zoom

1:00 pm to 1:45 pm
Moderator: Dr. Carol Carter
Dr. Carolyn Machamer, Professor Department of Cell Biology, Johns Hopkins University School of Medicine
“Assembly and Egress of Coronaviruses”

1:45 pm to 2:30 pm
Moderator: Dr. Erich Mackow
Dr. Sara Cherry, Professor, Department of Microbiology, University of Pennsylvania, Perelman School of Medicine
“COVID-19: Antiviral Discovery Pipeline”

2:30 pm to 3:30 pm Student Poster Session via Zoom

3:30 pm to 4:15 pm
Moderator: Dr. Janet Hearing
Dr. David Veesler, Associate Professor, Department of Biochemistry, University of Washington
“Structure-Based Design of a Coronavirus Vaccine”

4:15 pm to 5:00 pm
Moderator: Dr. Robert Rizzo
Dr. Carlos Simmerling, Professor, Department of Chemistry, Marsha Laufer Professor of Physical and Quantitative Biology, Stony Brook University
“Developing a Model of the Membrane Fusion Mechanism of Coronavirus Spike Glycoproteins”

5:00 pm to 5:05 pm Closing Remarks: Dr. Patrick Hearing

5:05 pm to 5:10 pm Announcement of Poster Awards: Dr. Janet Hearing

5:10 pm to 5:30 pm Short Presentations by the Award Winners
Dr. Susan Weiss obtained her PhD in Microbiology from Harvard University working on paramyxoviruses and did postdoctoral training in retroviruses at University of California, San Francisco. She came to Penn as an Assistant Professor in 1980, and is currently Professor and Vice Chair, Department of Microbiology and Co-director of the Penn Center for Research on Coronaviruses and Other Emerging Pathogens at the Perelman School of Medicine at the University of Pennsylvania. She previously served as Associate Dean for Biomedical Postdoc Programs (2010-2019). She has worked on many aspects of coronavirus replication and pathogenesis over the last forty years, making contributions to understanding the basic biology as well as organ tropism and virulence. This work included the murine coronavirus (MHV) infection of the central nervous system disease, a mouse model of multiple sclerosis. More recently she has work on MERS-CoV and since 2020 also on SARS-CoV-2. Her work for the last ten years has focused on coronavirus interaction with the host innate immune response and viral innate antagonists of double-stranded RNA induced antiviral pathways. Her other research interests include activation and antagonism of the antiviral oligoadenylate-ribonuclease L (OAS-RNase L) pathway, flavivirus-primarily Zika- virus-host interactions and pathogenic effects of host endogenous dsRNA.

“History and Biology of Coronaviruses: What this Teaches us About Targets for Therapeutics”

I will describe the history of human coronaviruses, leading up to the SARS-CoV-2 pandemic. This includes the early research beginning in the late 1970s on coronavirus replication and pathogenesis, mostly on animal coronaviruses, that was crucial to identifying and understanding the emerging lethal human coronaviruses SARS-CoV, MERS-CoV and SARS-CoV-2. In addition, I will discuss the different genera of coronaviruses and possible origins of SARS-CoV-2. The second part of the talk will focus on the biology of coronaviruses and how this informs us on antiviral strategies. I will describe the two entry pathways utilized by coronaviruses and the different host proteases involved in each pathway, that may serve as targets for antivirals. In addition, I will discuss the unique mechanisms of RNA and protein expression utilized by coronaviruses. This includes the many conserved proteins encoded by all coronaviruses, that provide potential targets for antivirals. Finally, I will discuss the SARS-CoV-2 variants, how they arise and why they are of concern.

Dr. Rolf Hilgenfeld was the Director of the Institute of Biochemistry at the University of Lübeck, Germany, from 2003 to 2020. Since April 2020, he has held a Senior Professorship at the Institute of Molecular Medicine of the same university. Following his PhD in chemistry and macromolecular crystallography at the Free University of Berlin and postdoctoral training at the Biocenter in Basel, he joined the pharmaceutical company Hoechst AG in Frankfurt, where he established protein crystallography and structure-based drug design. Here he worked on inhibitors of HIV protease and elongation factor Tu. He led the design of a long-acting insulin, which has now annual sales around 2 billion Euros under the name Lantus®. In 1995, he accepted the chair of Structural Biochemistry at the University of Jena, where he was Director of the Institute of Molecular Biotechnology from 1998 to 2000. Following his move to Lübeck in 2003, he determined the crystal structure of the coronavirus main protease and designed early inhibitor leads against the SARS virus. Later, his group published the crystal structure of the Zika virus protease and more recently, that of the SARS-CoV-2 main protease. His research group follows an integrated approach towards antiviral drug discovery, which includes comparative molecular biology, X-ray crystallography, drug design, and chemical synthesis of inhibitors. In 2009, Rolf Hilgenfeld was awarded an honorary doctorate from the University of South Bohemia, Budweis (Czech Republic), and from 2010 to 2012, he was a Chinese Academy of Sciences Visiting Professor with a co-affiliation at the Shanghai Institute of Materia Medica. In 2015, he received the Ge Hong Medal of the Wuhan Institute of Virology. The focus of his present research is on the structure-based design and chemical synthesis of coronavirus and enterovirus protease inhibitors.

“The Main Protease of SARS-CoV-2: Structures, Inhibitors, and Mutations”

The main protease (M^pro) of SARS-CoV-2 is a major target for the discovery and development of antiviral drugs. We have published the crystal structure of the enzyme in early 2020. We used this structure to optimize our pre-existing alpha-ketoamide inhibitors of coronavirus M^pro, which we had designed on the basis of our early structural work on homologous enzymes of alpha- and betacoronaviruses. This resulted in a peptidomimetic inhibitor, compound 13b. This compound has the P3 - P2 amide bond hidden within a pyridone ring in order to increase its half-life in plasma. Pharmacokinetic experiments in mice revealed sufficient bioavailability of 13b when administered via subcutaneous injection, inhalation, or the peroral route. We have since managed to improve the diastereomeric purity of the compound, resulting in a considerable increase in inhibitory activity (IC_50 = 140 nM). We will also present novel derivatives of our parent alpha-ketoamide, with the best one achieving now an IC_50 of 60 nM. In another series of compounds derived from boceprevir, our lead inhibitor displays IC_50 = 13 nM. Experiments in small-animal models of COVID-19 are underway. Unavoidably, application of direct-acting inhibitors will lead to the emergence of resistance mutations in the RNA genome of the virus. To analyze these, it will be important to understand the natural background of the mutations that occur in the absence of inhibitors. We will present an analysis of the evolution of the viral M^pro as our prime target of antiviral drug discovery since the beginning of the COVID-19 pandemic.
Dr. Stanley Perlman received his Ph.D. in Biophysics from M.I.T., Cambridge, Massachusetts and his M.D. from the University of Miami, Miami, Florida. He was trained in Pediatrics and Pediatric Infectious Diseases at Boston Children’s Hospital, Boston, Massachusetts. He is a member of the VRBPAC of the FDA and the COVID-19 Advisory Committee of the ACIP (Advisory Committee on Immunization Practices). His current research efforts are focused on coronavirus pathogenesis, including virus-induced demyelination and the Severe Acute Respiratory Syndrome (SARS), the Middle East Respiratory Syndrome (MERS) and COVID-19. His laboratory has developed several novel animal models useful for studying pathogenesis and evaluating vaccines and anti-viral therapies. His studies are directed at understanding why aged patients and mice developed more severe disease than younger individuals after infection with SARS-CoV or SARS-CoV-2 and also on why there is a male predominance in patients with more severe disease after infection with SARS-CoV, MERS-CoV or SARS-CoV-2. He and his colleagues demonstrated that transduction of mice with an adenovirus expressing the human receptor for MERS-CoV, DPP4, rendered them sensitive to infection, providing the first rodent model useful for studying MERS. Similar approaches have been used to develop several mouse models for COVID-19. Among other topics, his research is now focusing on the loss of sense of smell (anosmia) and taste (ageusia) observed in patients with COVID-19. He is a member of the VRBPAC of the FDA and the COVID-19 Advisory Committee of the ACIP (Advisory Committee on Immunization Practices).

“Animal models for COVID-19”

As the COVID-19 pandemic continues around the world, greater understanding of the immune response to the virus and pathogenesis are required. Experimentally infected animal models of COVID-19 are required for these purposes. Over the past few months, we have developed several mouse models for COVID-19. Mice are naturally resistant to the original strains of SARS-CoV-2, so either the mouse needs to be sensitized for SARS-CoV-2 infection or the virus needs to be modified to use the mouse host cell receptor. To obtain mice useful for studying COVID-19, we used several approaches. In a first approach, we sensitized mice for infection by transduction with an adenovirus vector expressing human ACE2, the virus receptor. We also used K18-hACE2 mice that we developed during the SARS epidemic. Most recently, we isolated a mouse-adapted SARS-CoV-2 that causes severe disease in young and old BALB/c mice, and in aged C57BL/6 mice. Disease is confined to the lungs but our preliminary results suggest that inflammatory changes are widespread, even in organs that are not infected. Mice infected with this virus are not only useful for studies of pathogenesis of COVID-19 in the lungs, but also for other manifestations, including anosmia and ageusia.

Dr. Carolyn Machamer is a Professor of Cell Biology at the Johns Hopkins University School of Medicine. She received her Ph.D. at Duke University in Microbiology and Immunology working with Peter Cresswell on class II MHC antigen assembly and trafficking. Her postdoctoral work was at the Salk Institute and Yale University with Jack Rose, where she studied viral protein processing and trafficking. Since starting her own lab in 1988, Dr. Machamer has focused on the structure and function of the Golgi complex. The work in her lab uncovered mechanisms for targeting of Golgi membrane proteins and a role for Golgi-localized caspases in stress and apoptotic signaling. The other main topic of interest of her lab is the assembly and egress of coronaviruses, which bud intracellularly at pre-Golgi membranes. These late steps of the infection cycle are less well studied than earlier steps and are thus promising targets for novel antiviral therapeutics.

“Assembly and Egress of Coronaviruses”

SARS CoV-2, the virus that causes COVID-19, is a member of the family of coronaviruses that cause respiratory and gastrointestinal disease in vertebrates. Coronaviruses are enveloped RNA viruses that assemble by budding into the ER-Golgi intermediate compartment. After budding, virus particles must make their way out of the infected cell, a process that has not been well-studied. Our work has focused on virus assembly and egress from infected cells. The three envelope proteins (S, M and E) are targeted to the assembly compartment after synthesis in the ER. They interact with each other and with the N protein-wrapped RNA genome to form virions that bud into the lumen of the ER-Golgi intermediate compartment. Virus particles (120 nm) are much larger than most endogenous cargoes in the secretory pathway, and virion release is less efficient than enveloped viruses that bud from the plasma membrane. How do coronaviruses traverse the cell for secretion? For the model coronavirus infectious bronchitis virus, the small E protein neutralizes the pH of the Golgi lumen. Although this slows host membrane traffic, it prevents aberrant proteolysis of the S protein, which is essential for infection. Interestingly, SARS CoV-1 also neutralizes Golgi pH, but uses a different protein (ORF3a) and a different mechanism. Thus, neutralization of acidic compartments may be a universal feature of CoV infection and suggests a novel target for antiviral therapeutics.
Dr. Sara Cherry is a Professor in the Department of Pathology and Laboratory Medicine at the University of Pennsylvania, Scientific Director of the High-throughput Screening Core and Director of the Chemogenomic Discovery Program in the School of Medicine. She obtained her BS with Dr. Peter Schultz at Berkeley, her PhD with Dr. David Baltimore at MIT and her postdoctoral fellowship with Dr. Norbert Perrimon. Upon starting her laboratory at Penn, she has applied High-throughput Screening technology to discover mechanisms by which emerging viral pathogens hijack cellular machinery while evading defenses. She has identified innate immune mechanisms and cellular interactions between viruses and cells comparing and contrasting viral families. More recently, she has uncovered new insights into the interplay between metabolic regulation, the microbiota and immune defense. Given the recent pandemic, her laboratory has now applied her screening platform to study the emerging coronavirus, SARS-CoV-2 identifying new antivirals active in the respiratory tract.

“COVID-19: Antiviral Discovery Pipeline”

The ongoing COVID-19 pandemic has highlighted the dearth of approved drugs to treat viral infections, with only ~90 FDA approved drugs against human viral pathogens. To identify drugs that can block SARS-CoV-2 replication, extensive drug screening to repurpose approved drugs is underway. We screened ~20,000 drugs for antiviral activity using live virus infection in human respiratory cells. Dose-response studies validate ~150 drugs with antiviral activity and selectivity against SARS-CoV-2. amongst these drug candidates are innate immune modulators, one of which is a STING agonist which potently blocks SARS-CoV-2 infection in vitro and in vivo in small animal models. In addition, we identified 16 nucleoside analogs, the largest category of clinically used antivirals. This included the antiviral Remdesivir approved for use in COVID-19, and the nucleoside Molnupirivir, which is undergoing clinical trials. RNA viruses rely on a high supply of nucleoside triphosphates from the host to efficiently replicate, and we identified a panel of host nucleoside biosynthesis inhibitors as antiviral, and we found that combining pyrimidine biosynthesis inhibitors with antiviral nucleoside analogs synergistically inhibits SARS-CoV-2 infection in vitro and in vivo suggesting a clinical path forward. We will discuss these inhibitors and our pipeline to further develop small molecule therapeutics.

Dr. David Veesler is an Associate Professor at the University of Washington. He received his PhD from Aix-Marseille University where he determined the X-ray structures of the tails and associated components of tailed bacteriophages. Dr. Veesler received his postdoctoral training at the Scripps Research Institute where he analyzed virus maturation and virus-receptor interactions using cryo-electron microscopy. His lab published a high-resolution structure of the pre-fusion form of the mouse hepatitis virus spike glycoprotein in 2016 using single-particle cryo-EM and has since made major contributions to the understanding of spike-receptor binding, conformational changes in the spike protein during virus entry, and immune evasion by SARS-CoV-2 variants. In a partnership with SK Bioscience, he has developed a COVID-19 vaccine candidate consisting of self-assembling spike protein nanoparticle that is in Phase III clinical trial. Dr. Veesler is the recipient of numerous awards including a 2017 Pew Biomedical Scholar Award, 2018 Burroughs Wellcome Fund Investigator Award, 2020 NIH Director’s Pioneer Award, and a 2021 Howard Hughes Medical Institute Investigator Award.

“Structure-Based Design of a Coronavirus Vaccine”
Dr. Carlos Simmerling obtained his Bachelor’s degree (1991) and PhD (1994) in Chemistry at the University of Illinois at Chicago, performing early research on methods for computer modeling of biomolecules such as proteins. He went on to a post-doctoral fellowship in Pharmaceutical Chemistry at UCSF, where he became a lead developer of the Amber biomolecular simulation software that is used in thousands of research labs worldwide. In 1998 Prof. Simmerling joined the Chemistry department at Stony Brook University, where he is currently a Professor and Associate Director of SBU’s Laufer Center for Physical & Quantitative Biology. His research is funded by the USA’s National Institutes of Health, National Science Foundation, and Department of Energy. His work focuses on development of improved molecular simulation methods and models, and use of these tools to study biomolecular recognition mechanisms. His articles on improving the physics underlying biomolecular modeling have been cited nearly 10,000 times. Prof. Simmerling is the Marsha Laufer Chair of Physical & Quantitative Biology at Stony Brook University and a Fellow of the American Chemical Society.

“Developing a Model of the Membrane Fusion Mechanism of Coronavirus Spike Glycoproteins”

The coronavirus spike is a class I viral fusion glycoprotein that extends from the viral surface and is responsible for viral entry into the host cell. The spike is the primary target of neutralizing antibodies, and spike-based vaccines are highly effective. However, the resulting antibodies bind to the spike surface, which varies among coronaviruses, and immunity to one coronavirus does not provide immunity to another. Furthermore, genetic evolution of the virus is expected to lead to resistant variants. In contrast, the interior of the spike tends to be highly conserved among coronaviruses, suggesting a potential for pan-coronavirus treatments based on spike structure and function. Cryo-EM experiments have revealed spike structures in a variety of states, including the free and bound pre-fusion spike, as well as the post-fusion state that adopts a dramatically different conformation. However, little is known about how this important change is triggered by receptor binding, and the lack of detail impedes development of mechanism-based therapeutics. The lecture will present an analysis of key spike features across > 200 experimental structures; these data guide strategic all-atom spike simulations involving over 1 million atoms. Our work provides new insight into the energy landscape of spike dynamics, how it can be modulated by amino acid substitutions or binding of small molecules, and the coupling between receptor binding and membrane fusion.
Acknowledgments

SCHOOL OF MEDICINE, STONY BROOK UNIVERSITY
OFFICE OF THE VICE PRESIDENT FOR RESEARCH, STONY BROOK UNIVERSITY
DEPARTMENT OF CHEMISTRY, STONY BROOK UNIVERSITY
CHEMBIO DIAGNOSTICS SYSTEMS INC.
HOFFMAN AND BARON LLP