Breakthroughs

Feinberg School of Medicine Research Office

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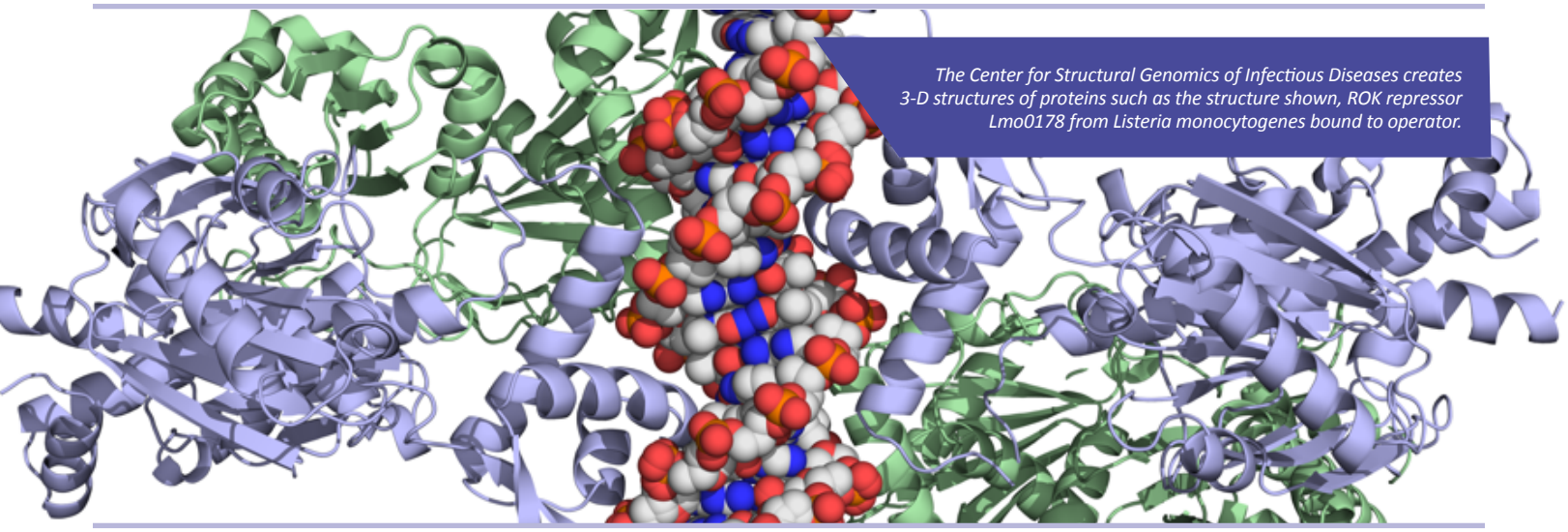

The Center for Structural Genomics of Infectious Diseases creates 3-D structures of proteins such as the structure shown, ROK repressor Lmo0178 from Listeria monocytogenes bound to operator.

Satchell to Lead Major Infectious Diseases Grant

By Michelle Mohney

The art (and science) of war against the world's most dangerous infectious diseases is approached by an international team of scientists with an adage from the ancient Chinese military leader Sun Tzu: Know your enemy.

In this case, the Center for Structural Genomics of Infectious Diseases (CSGID), based at Northwestern University Feinberg School of Medicine, and its sister center, the Seattle Structural Genomics Center for Infectious Disease (SSGCID), map the atomic structure of proteins or other molecules that have an important biological role in human pathogens and infectious diseases. Funded by the National Institute of Allergy and Infectious Diseases (NIAID), the CSGID began its third five-year contract on September 1, with new leadership from Feinberg's Karla Satchell, PhD, professor of Microbiology-Immunology.

She will co-direct the CSGID with Andrzej Joachimiak, PhD, director of the Structural Biology Center and the Midwest Center for Structural Genomics at the Argonne National Laboratory. Joachimiak is also a senior fellow of the Institute for Genomics and Systems Biology at the University of Chicago. Wayne Anderson, PhD, professor of Biochemistry and Molecular Genetics, who headed the Center since its 2007 launch, is stepping down, transitioning towards retirement.

The centers are especially focused on emerging and re-emerging infectious diseases in NIAID Category A-C priority lists, which include Ebola, dengue virus and antimicrobial-resistant pathogens, as well as other organisms responsible for dangerous infectious diseases, such as Clostridium difficile and Zika virus.

"I met with all of the Center co-principal investigators and was inspired by their enthusiasm to have an expert in microbiology assume the leadership," said Satchell, who is also a member of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University. "Indeed, I have found over the past year that there is great strength in the structural biology expertise of the Center and an opportunity to revitalize the infectious disease focus."

Satchell explained that Joachimiak will lead technical implementation, while she will focus on streamlining the center administration, broadening outreach and expanding partnerships with the microbiology research community. Among Satchell's primary goals for the CSGID is to integrate advances in next-generation sequencing into the structural biology platforms of the Center.

"In particular, I want the Center to better encompass the changes in technology that have dramatically transformed microbiology and how microbiologists view genomics and proteomics," Satchell said. "For instance, we rarely think in terms of 'species' anymore, but rather how variants within a species can cause a spectrum of disease."

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CSGID Grant

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Next-generation technology allows scientists to sequence a specific bacterial genome from a sample microbial community, or sequence the whole genome of numerous pathogens simultaneously in one run. This genome data is instrumental for examining pathogenesis -- the biological mechanisms of diseases -- identifying drug resistance relationships and investigating a range of mutational studies, including the co-evolution of hosts and parasites, and genetic mutations that increase the virulence of pathogens.

The CSGID currently boasts over 10,000 proteins active its database, according to Satchell. The scientific community requests approximately one-third of the protein targets. Coincidentally, Satchell requested the very first community target solved by the center in 2009 for research related to the activation of a toxin in the bacteria Vibrio cholerae.

"Most recently, we utilized the center to solve the structure of a protein that has potential impact related to cancer treatment," Satchell said.

Consortium members each specialize in a particular part of the assembly line to process and crystallize the proteins and apply computational methodology to produce the structures.

"Northwestern is a major site for protein production, crystallization and structure determination, accounting for about 40 percent of all structures solved," Satchell said.

Satchell's lab is collaborating with CSGID scientists to improve the successful crystallography of proteins that are intrinsically unfolded and fold only upon interaction with ligands -- molecules that bind to a site on a target protein. The advances will make such proteins more viable candidates for successful synchrotron imaging and structure determination.

The new CSGID leadership team also includes investigators from Sanford Burnham Prebys Medical Discovery Institute, University of Calgary, University of Chicago, University of Texas Southwestern Medical Center, University of

Karla Satchell, Ph.D., professor of Microbiology-Immunology, named co-director of CSGID, effective Sept. 1.

Virginia and Washington University School of Medicine. New member, Purdue University, will bring expertise in cryo-electron microscopy, virology and screening of ligands.

One of the primary activities CSGID engages in is using a technique called X-ray crystallography to create 3-D models of proteins' atomic structures at the Argonne National Laboratory's Advanced Photon Source (APS). After a protein is cloned and expressed, it is crystallized and positioned within the path of the APS's synchrotron X-ray beam. Images are generated through diffraction patterns recorded when the intense light bounces off the atoms, giving a detailed view of the position of and distance between atoms.

Protein structures determined by the Center are then deposited into the Protein Data Bank. The CSGID recently achieved the milestone of completing 1,000 structures. "Determining a single protein structure took several years when I was a graduate student," Anderson said. "The CSGID was able to average 100 structures per year."

Recent breakthroughs have been published in journals such *Nature Chemical Biology* and *Antiviral Research*. A recent study published in *Nature Microbiology* examined each of the proteins involved in a previously unknown metabolic pathway in Listeria (the cause of listeriosis, which is the result of eating contaminated food products).

"The structures allowed us to define the activities and biological functions of each protein, which led to the discovery of how the system provided an advantage to Listeria in the competition with other bacteria for nutrients in the human gut, enabling their growth and initiating an infection," Anderson said.

CSGID protein structures are freely available to the research community, in addition to data related to protein-ligand complexes, clones, peptides, purifications and molecular screening of complex proteins. Academic, not-for-profit, industry and government investigators may also request protein gene-to-structure services from the center. Proposals for targets submitted by the community are reviewed and approved by NIAID staff.

If you are interested in submitting a community target request to the CSGID, please visit csgid.org to review NIAID criteria and submission guidelines.

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