Scientists achieve milestone against deadly diseases

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Investigators at the Center for Structural Genomics of Infectious Diseases, a multi-institutional collaboration, have determined their 500th pathogen protein structure since beginning in 2007. Scientists at the Computation Institute, a joint effort of the University of Chicago and Argonne National Laboratory, contributed more than 200 structures to the CSGID's effort.

Led by Wayne Anderson, professor of molecular pharmacology and biological chemistry at Northwestern University's Feinberg School of Medicine, researchers at the CSGID used X-ray crystallography to examine the atomic details of proteins from major human pathogens, including Bacillus anthracis, Yersinia pestis, Salmonella enterica and Vibrio cholera, which are responsible for anthrax, the plague, salmonellosis and cholera, respectively. Emerging or re-emerging pathogens such as multi-drug resistant Staphylococcus aureus (MRSA), Clostridium difficile, the Dengue virus and the Influenza virus were also studied.

The CI's effort involved eight researchers working over the last five years, said Andrzej Joachimiak, a CI senior fellow and Argonne distinguished fellow. "All of these structures have been solved using the Advanced Photon Source and the Structural Biology Beamlines at APS," Joachimiak said, referring to CSGID's collective work.

A multi-institutional, international consortium, the center is funded by the National Institute of Allergy and Infectious Diseases, a part of the

National Institutes of Health. The NIAID also funds the Seattle Structural Genomics Center for Infectious Disease, which also recently determined its 500th protein structure — bringing the total to 1,000 structures of human pathogen proteins determined by the NIAID Structural Genomics Centers in less than five years.

The protein structures represent a selection of proteins with biomedical relevance and potential therapeutic benefits.

“We are laying the groundwork for drug discovery,” Anderson said. “Determining protein structures can help researchers find potential targets for new drugs, essential enzymes and possible vaccine candidates.”

One of the major challenges in medicine is fighting bacteria that have become drug-resistant. Methicillin-resistant Staphylococcus aureus, commonly known as MRSA, is incredibly difficult to treat because it has developed a resistance to antibiotics, including penicillin and cephalosporins. Determining the protein structure of the bacterium helps researchers better understand how to treat it.

“We can look at how the atoms are arranged in space and in relation to one another and how they interact,” Anderson said. “Then researchers can see how the bacterium developed drug resistance and figure out what to change in the drug so that the bacteria will not recognize it.”

When the center originally received NIH funding, it planned to determine 375 proteins in five years. However, it passed 375 determined structures last summer and currently has more than 6,000 proteins in process. The speed is partially due the efficiency of the team and partly to do with advancing technologies.

The investigators that make up the CSGID have led efforts to develop

and apply rapid-processing structural biology methods. Each institution in the consortium contributes to different aspects of the high-throughput CSGID pipeline, which include selecting proteins for study, cloning the genes that code for proteins, protein production, purification, data collection at the APS and structure determination.

“It used to take four years to determine one structure,” Anderson says. “Now we can do about three per week.”

One-third of the protein targets are being worked on by request from the infectious disease research community. “We work these structures and collaborate with other laboratories on the function of these enzymes and their inhibition for designing drugs,” Joachimiak said.

Members of the scientific community interested in nominating protein targets for structural determination can complete a request form on the CSGID website. This service is limited to pathogens of Categories A, B, C, and those causing emerging and re-emerging diseases that are listed on a NIAID priority list. It is offered free of charge to the scientific community.

CSGID and CI scientists conduct their own research on the protein structures, but they also make their data publicly available to the scientific community, Joachimiak said. In addition to structure determination, CSGID also provides the scientific community with the protein expression systems that are deposited in the Biodefense and Emerging Infections Research Resources Repository.

After the proteins are decoded, they are deposited into the NIH-supported Protein Data Bank. They are also uploaded on the CSGID website (click here for the list of structures).