Milestone in fight against deadly disease

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Scientists at Seattle Biomedical Research Institute (Seattle BioMed) and Northwestern University Feinberg School of Medicine have reached a major milestone in the effort to wipe out some of the most lethal diseases on the planet. As leaders of two large structural genomics centers, they've experimentally determined 500 three-dimensional protein structures from a number of bacterial and protozoan pathogens, which could potentially lead to new drugs, vaccines and diagnostics to combat deadly infectious diseases. Some of the structures solved by the centers come from well-known, headline-grabbing organisms, like the H1N1 flu virus.

Portraits of these protein structures, ranging from the plague, cholera and rabies to H1N1 can been seen on the websites www.csgid.org and www.ssgcid.org.

The Center for Structural Genomics of Infectious Diseases (CSGID), which is led by Wayne Anderson, Professor of Molecular Pharmacology and Biological Chemistry at Feinberg (Chicago, IL), and the Seattle Structural Genomics Center for Infectious Disease (SSGCID), led by Peter Myler, Full Member at Seattle BioMed and Affiliate Professor of Global Health and Medical Education & Biomedical Informatics at the University of Washington, were created in 2007 through contracts from the National Institute of Allergy and Infectious Diseases (NIAID), part of the National Institutes of Health (NIH). The Centers' mission is to apply genome-scale approaches in solving protein structures from biodefense organisms, as well as those causing emerging and re-emerging diseases.

"By determining the three-dimensional structure of these proteins, we can identify important pockets or clefts and design small molecules which will disrupt their disease-causing function," said Myler. "Each solved structure provides an important piece of new knowledge for scientists about a wide variety of diseases."

Recently, scientists from the Seattle group, which includes Emerald BioStructures, the University of Washington and Pacific Northwest National Laboratory in addition to Seattle BioMed, provided structural data that offered insight into how specific differences in one of the RNA polymerase proteins in the swine flu virus changed the way it interacts with host cells, allowing it to infect humans. This information could provide a basis for future antiviral agents that could be used to prevent replication of the flu virus.

Other structures solved come from little known or emerging pathogens that cause disease and death, but have been less well studied by the research community. For example, the SSGCID solved the first protein structure from Rickettsia, bacterial pathogens carried by many ticks, fleas and lice that causes several forms of typhus and spotted fever.

Recently, scientists at CSGID determined the structure of a crucial enzyme in the shikimate pathway of Clostridium difficile, which is the most serious cause of antibiotic-associated diarrhea in humans and can lead to pseudomembranous colitis, a severe infection of the colon often resulting from eradication of the normal gut flora by antibiotics. The shikimate pathway is essential for plants and bacteria like C. difficile, but is not present in animals, making this enzyme an attractive antibiotic target. CSGID researchers have also determined the structures of numerous proteins from other disease-causing organisms such as Bacillus anthracis (anthrax), Salmonella enterica (salmonellosis food poisoning), Vibrio cholerae (cholera), Yersinia pestis (plague), and Staphylococcus aureus (staph infections).

The CSGID is a consortium which includes researchers from the University of Chicago (Chicago, IL), the J. Craig Venter Institute (Rockville, MD), University College London (London, United Kingdom), the University of Toronto (Toronto, Canada), the University of Virginia (Charlottesville, VA), the University of Texas Southwestern Medical Center at Dallas (Dallas, TX), and the Washington University School of Medicine (St. Louis, MO), in addition to Northwestern University.

Mapping the structures of drug-resistant bacteria is also a priority for the two centers. "Drug-resistant bacteria are an increasing threat to us and we need to get new drugs to stay ahead of them," said Anderson, Principal Investigator of CSGID. "The recent years have brought not only an avalanche of new macromolecular structures, but also significant advances in the protein structure determination methodology that are now making their way into drug discovery. We provide the structural information so that in the future companies can develop new drugs to overcome resistance."

The structures solved by the Centers are immediately made available to the international scientific community through the NIH-supported Protein Data Bank (www.pdb.org), providing a "blueprint" for development of new drugs, vaccines and diagnostics.

The Centers are on track to ultimately identify nearly 500 more structures by the end of the current five-year NIH contract in 2012. Apart from the protein structures, the two Centers make available to the scientific community all the clones and purified proteins that they produce in order to facilitate a global collaboration in the fight against deadly diseases.

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