Protein biologists find new chink in staph's armor

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(PhysOrg.com) -- The battle against deadly staph infections is closer to victory as Illinois researchers have uncovered secrets of how the bacterium protects itself from human immune attacks, which could lead to more effective anti-staph therapies.

Using powerful X-ray beams from the Advanced Photon Source (APS) at the U.S. Department of Energy's Argonne National Laboratory, scientists from the University of Illinois at Urbana-Champaign documented how a key enzyme enables staph to make a coating that protects the bacteria from human white blood cells. Armed with details about how the chemistry works, researchers hope to find drugs that can interfere with the process, leaving the bacteria vulnerable to immune system attacks.

"More people in the United States die of staph infections each year than from HIV/AIDS," said Eric Oldfield, the Illinois chemistry professor who co-led the team of researchers from the University of Illinois and from Taiwan who made the discovery. "We need to come up with new antibiotics."

Using X-ray diffraction available at the APS, the researchers were able to watch how a key drug target, the staph enzyme dehydrosqualene synthase (CrtM), functions. They discovered the bacterium uses a two-step reaction involving two active sites on the enzyme, so finding a way to block both sites would stop the reaction and kill an infection.

"The leads that people have been developing for inhibiting these sorts of enzymes really haven't had any structural basis," said Oldfield, who also is a professor of biophysics. "Now that we can see how the proteins work, we're in a much better position to design molecules that will be more effective against staph infections." Inhibitors used in the project have been licensed to AuricX Pharmaceuticals, a start-up company that has a grant from the Texas Emerging Technology Fund to do preclinical testing in staph infections.

The knowledge might also be applied to fight some parasitic diseases and even lower cholesterol levels because the same sorts of enzymes are involved in those processes as well.

Helping researchers reveal the structures of proteins and how they interact dynamically with one another is an ongoing function of the APS, and progress has accelerated as APS researchers and their academic collaborators have automated the process of refining proteins and crystallizing them so they can be studied with X-ray diffraction.

Seven years ago, scientists using the APS characterized 162 protein structures in a year, said Andrzej Joachimiak, director of the Structural Biology Center and Midwest Center for Structural Genomics at Argonne. In 2009, that number was up to 1,493.

Such increased efficiency stems from installing robotic systems that now quickly handle tedious operations once done by hand. Joachimiak said that further automation, such as a system that could quickly locate tiny crystals in droplets of liquid, will further reduce time and expense required to tease out nature's secrets of protein structure and function.

An advanced protein crystallization facility to be built adjacent to the APS is in the design phase now, and Joachimiak said that construction may begin late this year or early in 2012. The state of Illinois is helping

to fund the facility, which is intended to further boost the output of information about proteins.

Many drug companies as well as academic researchers use APS beamlines to characterize proteins, and as more information becomes available, the industry moves closer to its goal of designing drugs based on knowledge of the structure of biological targets.

Since 2006, researchers of the Argonne's Midwest Center for Structural Genomics (MCSG) and Northwestern University Center for Structural Genomics of Infectious Diseases (CSGID), funded by the National Institutes of Health, have mapped out over 1,300 3-D protein structures from bacterial and protozoan pathogens, making the information available to scientists designing therapies and diagnostics. By the end of next year, these consortia are on track to have 2,000 such structures mapped.

"In addition to the aim of providing a starting point for structure-based drug discovery, we can also use this research as a way to learn more about these pathogens and how they cause diseases, how they get around the immune system, how we defend ourselves against them and how they interact with their host," said Wayne Anderson, a Northwestern University professor of molecular pharmacology and biological chemistry and principal investigator of the CSGID project.

Provided by Argonne National Laboratory