NIH funds center at Arizona State to battle infectious diseases

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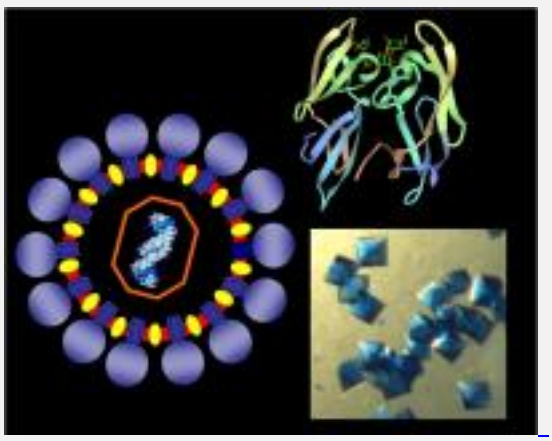
TEMPE, Ariz. Arizona State University has been awarded a $7.7 million grant for the next five years from the National Institute of General Medical Sciences, part of the National Institutes of Health, to unravel the structures of membrane proteins that play a key role in protection against infectious diseases.

As part of the Protein Structure Initiative (PSI:Biology), ASU's Department of Chemistry and Biochemistry in the College of Liberal Arts and Sciences will be home to one of nine new national centers for structure determination of membrane proteins. The centers are focused on the discovery of the structure and function of membrane proteins.

Membrane proteins catalyze essential life functions, like respiration, photosynthesis, cell communication, import and export out of a cell and they play an essential role in the host-pathogen interaction.

"The impact of this work on human health and the battle against infectious diseases will be huge," explained Petra Fromme , a professor in chemistry and biochemistry and the director of the new ASU Center for Membrane Proteins and Infectious Diseases (MPID).

The cell membrane surrounds and protects the cell's interior like a skin. The membrane proteins, which are embedded in the membrane, in turn guard all transport in and out of the cell.



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For example, when a virus enters the body, it docks to membrane proteins at the cell surface and subsequently tricks the cell into allowing the virus inside, like a Trojan horse. Once in the cell, its genetic information is released and the virus reprograms the human enzymes (or complete cell machinery) to produce thousands of new virus particles.

Elucidation of the membrane protein structures involved in docking and cell entry would enable the development of new drugs that specifically block the pathways into the cell. The virus (or the bacterial pathogen) could be "caught" and neutralized before it even starts its destructive actions.

Solving the specific membrane protein structure is like finding out the exact shape of a lock once that is known, a key that fits the lock and thereby blocks the docking process can be designed, according to Fromme. The discovery of the structure of these key proteins involved in pathogen-human cell interaction will therefore have a huge impact on human health and pave the way for structure-based rationally designed drugs that fight infectious diseases - diseases that kill millions of humans each year worldwide.

Sixty percent of all current drugs are targeted to membrane proteins, yet only three human membrane protein structures are known despite their medical relevance. The centers will develop highly efficient methods for solving the structures of these elusive yet critically important proteins.

"The ASU center is the only one of the new centers focused specifically on membrane proteins from viral and bacterial pathogens," said Ward Smith, Ph.D., PSI director. "By determining these proteins' structures, the center will provide important clues for understanding infectious disease pathways that could point to new ways to treat and prevent infectious diseases."

"A critical step in understanding the complex processes that are catalyzed by membrane proteins is an understanding of their structure, dynamics and function, "said Fromme. Our knowledge of processes catalyzed by membrane proteins suffers greatly from a lack of information concerning their molecular-level structures. While more than 60,000 structures of soluble proteins have been solved only 250 membrane protein structures have been determined to date. The reason why membrane proteins are so intransigent is that they "live" in biological membranes, and so are not soluble in water. This makes them extremely difficult to isolate, purify and, in particular, to crystallize.

"Researchers at the ASU center will target membrane proteins of key viral and bacterial pathogens, their infectious pathways and molecules involved in host defense against the pathogens," Fromme said. "This theme is unique and the results and structures determined by the center will be highly relevant for human health worldwide."

Fromme is an expert in protein structure elucidation. Her group has succeeded in crystallizing and solving the structures of two of the most complex and difficult membrane protein structures to be determined so far, photosystems I and II. These photosystems perform the first and most important step of photosynthesis, the conversion of solar energy into chemical energy, making them the source of energy for all higher life forms on Earth.

The ASU center will feature an interdisciplinary team that includes faculty from the department of chemistry and biochemistry, School of Life Sciences, department of physics and the Biodesign Institute. International membrane protein expert professor Martin Caffrey, of Trinity College, Dublin, Ireland, also is involved in the center.

Biodesign's Joshua LaBaer, whose PSI:Biology - Materials Repository -- http://psimr.asu.edu [3] has a valuable plasmid repository with immediate broadly available access, will play an important role in the work. Having been the first to publish in this area, LaBaer's group has the experience necessary to provide the needed high throughput of protein expression and screening.

"The protein structure initiative is a response to one of the grand challenges of biological and medical sciences today," said William Petuskey, chair of chemistry and biochemistry. "Its products will have far reaching impact and we expect that our new center will play a key role in these important advances."

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