Argonne NATIONAL LABORATORY

News Release

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For immediate release

Argonne protein structure may lead to treatment for infection targeting Cystic Fibrosis patients

ARGONNE, Ill. (June 9, 2006) – Researchers at the U.S. Department of Energy's Argonne National Laboratory have determined the structure of a key protein believed to play a role in a deadly infection that afflicts the lungs of patients with cystic fibrosis. This finding, published in today's issue of *Science*, may lead to a new drug to treat the bacterial infection.

Pseudomonas aeruginosa, a pathogen that infects more than 80 percent of cystic fibrosis patients, is a leading cause of these patients' deaths. *P. aeruginosa* is difficult to treat because it is resistant to many drugs.

While working through a number of pathogenic proteins, Argonne protein crystallographer Marianne Cuff's keen eye caught a glimpse of a bagel-shaped pore. Closer inspection revealed a six-sided ring that she believed "might be involved in transferring toxins into cells," she said.

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"I thought it would be an important structure," she said. "The ring is very stable and unusual and nature usually has a purpose for these stable forms."

Cuff, who is a co-author of the *Science* paper, deposited the structure of the protein, called Hcp1, into the Protein Data Bank, a resource used by biologists worldwide to find information about the proteins they are studying.

While exploring the Protein Data Bank, Harvard Medical School researchers who were also studying *P. aeruginosa* in the laboratory of John Mekalanos recognized that the amino acid sequence of Hcp1 in *P. aeruginosa* closely resembled that of Hcp1 in *Vibrio cholerae.* The Mekalanos lab had previously discovered that the Hcp1 protein of *V. cholerae* is released from the bacterium via a novel secretion pathway.

Because Hcp1 proteins from both pathogens belong to the same protein family, *Science* paper lead-author Joseph D. Mougous, wondered whether the *P. aeruginosa* Hcp1 might also be secreted via this pathway. Researchers at Harvard and Argonne quickly formed a collaboration and confirmed the hypothesis. They then turned their attention to Hcp1 in cystic fibrosis patients to gain more insight in the role of Hcp1 during infection.

“Pathogenic bacteria such as *P. aeruginosa* use protein secretion systems to cause disease in their hosts,” said Mougous, a research fellow in the Harvard Medical School Department of Microbiology and Molecular Genetics. “In the case of *P. aeruginosa*, the host may be a cancer patient with a weakened immune system, a burn patient or a person with cystic fibrosis.

“Cystic fibrosis patients are particularly susceptible to *P. aeruginosa*,” Mougous said. “The bacterium thrives in the excess mucus that accumulates in their lungs. Once the infection in a cystic fibrosis patient's lung has been established, these hardy bacteria are difficult or impossible to clear, which over many years eventually results in death of the patient.”

Working with cystic fibrosis patients at Children's Hospital Boston, the Harvard Medical School researchers sought and found Hcp1 in the sputum of patients with *P. aeruginosa.* They also found Hcp1 antibodies in the patients' blood – further proof that Hcp1 plays a critical role in the infection. The human immune system creates antibodies to pathogens it is exposed to.

"This finding provides a possible drug target to fight the infection in cystic fibrosis patients," explained Andzrej Joachimiak, director of Argonne's Structural Biology Center and of the Midwest Center for Structural Genomics based at Argonne, where the protein structure research was performed.

Determining and imaging the structure of the protein Hcp1 was part of the routine structural biology research Argonne biologists are performing on pathogens with funding from the National Institute of General Medical Sciences (NIGMS) Protein Structure Initiative. This initiative funds researchers to determine a number of unique protein structures to serve as a base of knowledge from which other structures and functions can be inferred.

"This research is an example of how the Protein Structure Initiative was designed to work," explained Joachimiak. "A structure we determined led researchers to design an experiment to provide key information about how a pathogen works. New treatments could be developed from this starting point."

The protein crystallography research was performed at Argonne by researchers in the Argonne-led Midwest Center for Structural Genomics, funded by NIGMS. Following the protein cloning, expression, purification and crystallization, the protein crystallography data were collected at Argonne's Structural Biology Center at this hemisphere's most brilliant source of X-rays for research – the Advanced Photon Source. Cuff converted the data into three-dimensional models that revealed the six-sided pore with the 40-Angstrom wide center.

Cystic Fibrosis – add three

The nation's first national laboratory, Argonne National Laboratory conducts basic and applied scientific research across a wide spectrum of disciplines, ranging from high-energy physics to climatology and biotechnology. Since 1990, Argonne has worked with more than 600 companies and numerous federal agencies and other organizations to help advance America's scientific leadership and prepare the nation for the future. Argonne is managed by the University of Chicago for the U.S. Department of Energy's Office of Science.

Harvard Medical School has more than 7,000 full-time faculty working in eight academic departments based at the School's Boston quadrangle or in one of 47 academic departments at 18 Harvard teaching hospitals and research institutes. Those Harvard hospitals and research institutions include Beth Israel Deaconess Medical Center, Brigham and Women's Hospital, Cambridge Health Alliance, the CBR Institute for Biomedical Research, Children's Hospital Boston, Dana-Farber Cancer Institute, Forsyth Institute, Harvard Pilgrim Health Care, Joslin Diabetes Center, Judge Baker Children's Center, Massachusetts Eye and Ear Infirmary, Massachusetts General Hospital, Massachusetts Mental Health Center, McLean Hospital, Mount Auburn Hospital, Schepens Eye Research Institute, Spaulding Rehabilitation Hospital, and VA Boston Healthcare System.

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Editors note: A high-resolution image and video of the Hpc1 structure are available online at www.anl.gov/Media_Center/News/2006/news060609.html.