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Discovery holds potential in destroying drug-resistant bacteria

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Through the serendipity of science, researchers at the University of Pittsburgh have discovered a potential treatment for deadly, drug-resistant bacterial infections that uses the same approach that HIV uses to infect cells. The National Institutes of Health-supported discovery will be described in the June issue of the journal *Antimicrobial Agents and Chemotherapy*. It is especially promising in the development of a potential treatment for lung infections in people with cystic fibrosis.

"The discovery of this new antibiotic was an unexpected result of basic research on HIV proteins," said senior author Ronald Montelaro, Ph.D., professor and co-director of Pitt's Center for Vaccine Research (CVR). "As a result of studying these proteins, we discovered novel structures that turn out to work very well against bacterial infections, including the complicated bacterial populations in lung infections in cystic fibrosis patients."

Cystic fibrosis is a genetic disorder that leads to thick, viscous secretions in the lungs and other organs in about 30,000 children and adults in the United States, according to the Cystic Fibrosis Foundation. Lung infections resistant to antibiotics often are deadly for people with cystic fibrosis. About 80 percent of cystic fibrosis patients have at least one antibiotic-resistant infection in their lungs by age 18.

"Infections with progressively resistant bacteria in the lung shorten the lives of people with cystic fibrosis," said Joseph M. Pilewski, M.D., co-director of the Adult Cystic Fibrosis Center at UPMC. "What happens is

the genetic defect predisposes patients to infections that drive the production of mucus that then blocks the airways and makes it difficult to breath."

Dr. Montelaro and his colleagues found that a particular sequence of amino acids on the tail end of HIV allow the virus to "punch into" and infect cells. The team manufactured a synthetic and more efficient version of this sequence – called engineered cationic antimicrobial peptides, or "eCAPs" – that laboratory tests have shown to rapidly destroy bacteria that are otherwise resistant to most standard antibiotics.

The eCAPs can be assembled in a laboratory setting from the amino acids arginine and tryptophan and manufactured to the shortest effective length, giving the resulting antibiotic treatment maximum potency while reducing costs.

The discovery was featured in April at two prestigious gatherings intended to put scientists in touch with business developers—the BIO International Convention in Chicago, and the University Research & Entrepreneurship Symposium (URES) in Boston.

"At both symposia, we received a lot of interest from pharmaceutical-related companies," said co-author Jonathan Steckbeck, Ph.D., M.B.A., post-doctoral associate at CVR. "It was a particular honor to be recognized at URES as one of the year's 10 breakthroughs in life sciences."

Pitt has taken out several U.S. and international patents on this discovery.

"We have an unmet clinical need for treatment of hospital-acquired infections where the bacteria are extremely resistant to antibiotics," said co-author Yohei Doi, M.D., Ph.D., assistant professor of medicine in

Pitt's School of Medicine. "We have patients with no treatment options left. The fact that these eCAPs are completely engineered puts them at an advantage because they can be manufactured easily, and they give us some hope for a quick-acting treatment in these dire circumstances."

Traditional antibiotics typically work by poisoning important metabolic processes after being taken up by the target bacteria, a process that may take hours, or days, to clear a bacterial infection. In contrast, the eCAPs are specifically attracted to the surface of target bacteria where they disrupt the bacterial membrane, causing death within seconds, or minutes.

Laboratory tests indicate that the eCAPs work well against biofilms, which are bacterial communities that develop very high levels of resistance to antibiotics by working together to protect the film's inner bacteria from traditional treatments. The eCAPs seem to push through the outer layers of biofilms to destroy the entire bacterial community.

"It's like a pin bursting a balloon; it's a very rapid action," said Dr. Montelaro. "While cystic fibrosis patients are our initial target and a very high-priority target, we also could look at infections associated with burns or indwelling medical devices, such as venous catheters. We could even look to the biodefense realm, in terms of a rapid, handheld nebulizer treatment that soldiers could use in the case of exposure to a bioterrorism agent."

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