Scientists decipher mechanism behind antimicrobial 'hole punchers'

September 20 2007

In the battle against bacteria, researchers have scored a direct hit. They have made a discovery that could shorten the road to new and more potent antibiotics.

The rapid development of bacterial resistance to conventional antibiotics (such as penicillin or vancomycin) has become a major public health concern. Because resistant strains of bacteria can arise faster than drug companies can create antibiotics, understanding how these molecules function could help companies narrow their focus on potential antibiotics and bring them to market sooner.

As reported in a paper accepted for publication in the *Journal of the American Chemical Society* and posted on its Web site, researchers have now deciphered the molecular mechanism behind selective antimicrobial activity for a prototypical class of synthetic compounds.

The compounds, which mimic antimicrobial peptides found in biological immune systems, “function as molecular ‘hole punchers,’ punching holes in the membranes of bacteria,” said Gerard Wong, a professor of materials science and engineering, physics, and bioengineering at the U. of I., and a corresponding author of the paper. “It’s a little like shooting them with a hail of nanometer-sized bullets – the perforated membranes leak and the bacteria consequently die.”

The researchers also determined why some compounds punch holes only in bacteria, while others kill everything within reach, including human

cells.

“We can use this as a kind of Rosetta stone to decipher the mechanisms of much more complicated antimicrobial molecules,” said Wong, who also is a researcher at the university’s Beckman Institute.

“If we can understand the design rules of how these molecules work, then we can assemble an arsenal of killer molecules with small variations, and no longer worry about antimicrobial resistance.”

In a collaboration between the U. of I. and the University of Massachusetts at Amherst, the researchers first synthesized a prototypical class of antimicrobial compounds, then used synchrotron small-angle X-ray scattering to examine the structures made by the synthetic compounds and cell membranes.

Composed of variously shaped lipids, including some that resemble traffic cones, the cell membrane regulates the passage of materials in and out of the cell. In the presence of the researchers’ antimicrobial molecules, the cone-shaped lipids gather together and curl into barrel-shaped openings that puncture the membrane. Cell death soon follows.

The effectiveness of an antimicrobial molecule depends on both the concentration of cone-shaped lipids in the cell membrane, and on the shape of the antimicrobial molecule, Wong said. For example, by slightly changing their synthetic molecule’s length, the researchers created antimicrobial molecules that would either kill nothing, kill only bacteria, or kill everything within reach.

“By understanding how these molecules kill bacteria, and how we can prevent them from harming human cells, we can provide a more direct and rational route for the design of future antibiotics,” Wong said.

Source: University of Illinois at Urbana-Champaign