Natural antibiotics yield secrets to atom-level imaging technique

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Frog skin and human lungs hold secrets to developing new antibiotics, and a technique called solid-state NMR spectroscopy is a key to unlocking those secrets.

That's the view of University of Michigan researcher Ayyalusamy Ramamoorthy, who will discuss his group's progress toward that goal March 3 at the annual meeting of the Biophysical Society in Baltimore, Md.

Ramamoorthy's research group is using solid-state NMR to explore the germ-killing properties of natural antibiotics called antimicrobial peptides (AMPs), which are produced by virtually all animals, from insects to frogs to humans. AMPs are the immune system's early line of defense, battling microbes at the first places they try to penetrate: skin, mucous membranes and other surfaces. They're copiously produced in injured or infected frog skin, for instance, and the linings of the human respiratory and gastrointestinal tracts also crank out the short proteins in response to invading pathogens.

In addition to fighting bacteria, AMPs attack viruses, fungi and even cancer cells, so drugs designed to mimic them could have widespread medical applications, said Ramamoorthy, who is an associate professor of chemistry and an associate research scientist in the Biophysics Research Division.

While researchers have identified hundreds of AMPs in recent years,

they're still puzzling over exactly how the peptides wipe out bacteria and other microbes. Unlike conventional antibiotics, which typically inhibit specific bacterial proteins, AMPs get downright physical with invaders, punching holes into their membranes. But they're selectively pugnacious, targeting microbes but leaving healthy host cells alone.

"They're like smart bombs," Ramamoorthy said. "We'd like to exploit their properties to design super-smart bombs, but before we can do that, we need to understand how these AMP smart bombs interact with membranes to destroy bacteria. We need to know how they're shaped before, during and after the process of attaching to bacteria and how they attach."

Solid-state NMR spectroscopy is an ideal tool for answering such questions because it provides atom-level details of the molecule's structure in the complex and challenging cell membrane environment, Ramamoorthy said. "Just as an MRI produces a detailed image of our internal organs, solid-state NMR spectroscopy is used to construct a detailed image of a peptide or protein and to reveal how it sits in the cell membrane," providing clues for modifications that might make synthetic AMPs even more effective in overcoming ever-increasing bacterial resistance. For instance, rearranging parts of the molecule might make it fit into the membrane better, resulting in greater effectiveness with smaller amounts of AMP.

"Our overall mission is to use the kind of basic physical data we obtain from solid-state NMR spectroscopy to help interpret biological functions," Ramamoorthy said. The work is highly interdisciplinary, involving not only Ramamoorthy's lab and several other groups in the Chemistry Department, but also researchers from the College of Engineering, the School of Dentistry, the Medical School and the Biophysics Research Division, as well as collaborators in Canada, Japan, India and the U.S. pharmaceutical companies Genaera Corporation and

Eli Lilly and Company. Ramamoorthy was awarded support from the National Institutes of Health and the National Science Foundation, through an NSF Faculty Early Career Development Award.

A leader in this area of research, he has organized two major international symposia on the field at the University of Michigan, edited a special issue in the journal BBA-Biomembranes, published a number of papers in leading journals, and brought out a book on NMR Spectroscopy of Biological Solids. Ramamoorthy says that this area of research will grow considerably at U-M from implementing plans to set up a high magnetic field solid-state NMR spectrometer facility and an NIH-funded program.

Source: University of Michigan