Bacterial hole puncher could be new broad-spectrum antibiotic

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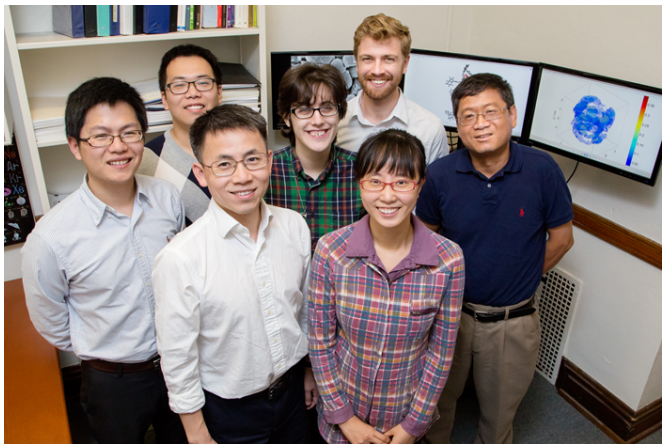

A team of researchers developed a new broad-spectrum antibiotic that kills bacteria by punching holes in their membranes. Front row, from left: materials science and engineering professor Jianjun Cheng and postdoctoral researcher Yan Bao. Back row, from left: postdoctoral researcher Menghua Xiong, graduate students Ziyuan Song and Rachael Mansbach, materials science and engineering professor Andrew Ferguson, and biochemistry professor Lin-Feng Chen. Credit: L. Brian Stauffer

Bacteria have many methods of adapting to resist antibiotics, but a new class of spiral polypeptides developed at the University of Illinois targets one thing no bacterium can live without: an outer membrane.

The polypeptides, which are short protein chains, act as bacterial hole-punchers, perforating the bacterial membrane until the cell falls apart. The antimicrobial agents are dressed for their mission in a positively charged shell that lets them travel in body fluids, protected from interacting with other proteins, and also attracts them to bacterial membranes.

Led by U. of I. materials science and engineering professor Jianjun Cheng, the researchers published their findings in the *Proceedings of the National Academy of Sciences*.

"When you have an infection, it can be very difficult for a doctor to know which bacteria is infecting you," said postdoctoral researcher Menghua Xiong, a co-first author of the paper. "Many antimicrobial agents can only cure one class of bacteria. A doctor may try one class, and if that doesn't work, try another class. We need more broad-spectrum antimicrobial agents."

The new antimicrobial polypeptides are specially designed to fold into a rigid spiral resulting in a rodlike structure, ideal for punching holes in the bacterial membrane.

"We use a very set mechanism to puncture the bacterial membrane," Cheng said, "so the polypeptides don't really care whether the bacteria are gram positive or gram negative. They just kill the bacteria independent of their other surface properties."

Such structures have been investigated for various medical applications, but because they do not like water, they do not travel well in bodily fluids. In addition, other molecules in the cell could interact with the polypeptide to disrupt the spiral structure, making it ineffective in puncturing the membrane.

The Illinois researchers and their collaborators addressed these challenges by attaching positively charged ions to the backbone of the spiral, creating a protective shell around the polypeptide so that it is both water soluble and shielded from cross-reactions. The shielded spiral structures are inured to changes in temperature or pH, so they have a stability and predictability that similar agents lack, Cheng said. Furthermore, the positive shell has the advantage of targeting bacterial membranes while decreasing interaction with human cells.

"At the molecular level, there are big differences between bacterial and human cells in the membranes," Xiong said. "The cell membrane lipids in bacteria have a lot of negative charges, and this polypeptide is positive, so it interacts with the negatively charged bacterial membrane. But with human cells, the interaction is weaker."

Many drugs are very targeted, interacting with a particular protein or interfering with a particular pathway in the bacterial cell. Bacteria can develop resistance to the antibiotic by circumventing the specific target. Since the spiral structures simply poke holes in the physical structure of the membrane, it would be much harder for bacteria to form resistance, Xiong said. In addition, the new antimicrobial agents could be coupled with other, targeted drugs to enhance their effectiveness.

"The polypeptides punch holes in the membrane, which makes it very easy for other drugs to go through and bypass some of the drug-resistant mechanisms," Cheng said. "Together, they work even better than a single agent. "

Because the proteins have a preset design, Cheng predicts that scaling up production would not present significant challenges. The precursor elements are already manufactured at large scales and available commercially.

Next, the researchers will continue to improve the antimicrobial polypeptides, further decreasing interaction with human cells, and working to more specifically target pathogenic bacteria.

More information: Menghua Xiong et al. Helical antimicrobial polypeptides with radial amphiphilicity, *Proceedings of the National Academy of Sciences* (2015). DOI: 10.1073/pnas.1507893112