Reseachers discover new insights for antibiotic drug development

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University of Minnesota and University of Michigan researchers have discovered a new method of developing antibiotics, an important step in fighting the growing number of drug-resistant infections.

In two articles published in the current online issue of *Nature Chemical Biology*, researchers describe an approach that is more efficient--and environmentally friendly--in developing new antibiotics, those needed to kill the increasing number of infections resistant to multiple drugs.

"We're striving to create new drugs that can have a positive impact on the growing threat of infectious diseases," says Robert Fecik, Ph.D., an assistant professor of Medicinal Chemistry at the University of Minnesota College of Pharmacy and one of the lead authors of the study. "This type of research can help us make new antibiotic molecules."

Officials at the Centers for Disease Control and Prevention have called antibiotic resistance one of the world's most pressing public health problems. Once only found in hospitals, these "superbugs" are now being found in community settings, including schools, nursing homes, and locker rooms.

These infections don't respond to common antibiotics such as erythromycin, which belong to a ring-shaped class of antibiotics called macrolides. Nearly all antibiotics in use today are natural molecules made by bacteria to kill their enemies. The bacteria use specialized proteins called enzymes to carry out the chemical steps in making these

ring-shaped antibiotic molecules.

One way to increase the number of antibiotics for fighting infections is to start where nature stopped and engineer the enzymes to produce new molecules, and thus new antibiotics. But to do this more effectively, scientists need a clearer picture of how the enzyme molecules act upon the precursor to the antibiotic.

The interdisciplinary team of scientists, including research professors David H. Sherman and Janet L. Smith from the University of Michigan's Life Sciences Institute and Fecik of University of Minnesota College of Pharmacy, is the first to crystallize an enzyme in the process of closing the antibiotic ring, which illustrates exactly how the ring is formed.

Their work creates important opportunities for drug discovery to stay one step ahead of the superbugs.

"Having the tools to make the next generation of macrolide antibiotics is crucial because these drugs are so well tolerated and have so few side effects," Smith said. "They are really a great class of antibiotics, so we need more of them."

These macrolide antibiotics are of particular interest because bacteria make them in a way that potentially allows for thousands of slightly different compounds to be synthesized and tested for antibiotic activity.

The structure of macrolides is a large ring, itself constructed from a linear molecule, which is built in an assembly-line fashion from smaller molecules. An enzyme at the end of the chain triggers the ring formation that results in antibiotic formation.

"These findings are likely to enable the development of powerful new methods to build structural diversity into large ring systems that are a

key component of many types of macrolide antibiotic molecules. This will provide yet another strategy to stay ahead of the emerging and persistent antibiotic resistance threat," Sherman said.

In traditional drug development, researchers start with an existing antibiotic and chemically manipulate it to develop a new version of the original drug. With the new approach outlined in the article, researchers describe a method that can be used to get the bacteria itself to produce new compounds that turn into the ring structure and may be useful as new drugs.

Typical drug development involves chemical manipulations that result in chemical waste, which can be difficult to dispose of and is hazardous to the environment.

This research implies it is realistic to develop a more environmentally friendly way to discover more potential drug compounds with less chemical manipulation, and thus less chemical waste.

Source: University of Minnesota