Cloning techniques produce FDA-approved antibiotic

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The successful synthesis of an antibiotic in a non-native host has provided a team of researchers at the University of Illinois at Urbana-Champaign with the potential for developing new treatments for bacterial infections.

The rapid rise of antibiotic resistance poses a serious threat to human health, and demands new treatments effective against resistant pathogens. Fosfomycin is a natural antibiotic approved by the Food and Drug Administration for the treatment of various bacterial infections, and has proven effective for the treatment of infections that have become resistant to the antibiotics penicillin and vancomycin.

Fosfomycin is a member of a class of compounds called phosphonic acids because they contain a carbon-phosphorous bond. Fosfomycin functions by inactivating an essential enzyme involved in the formation of the bacterial cell wall.

"Phosphonic acids are underexploited bioactive compounds with great potential for treating human disease," said Huimin Zhao, a U. of I. professor of chemical and biomolecular engineering. "We hope to understand the complete pathway for how fosfomycin is made."

In a paper to appear in the Nov. 27 journal *Chemistry and Biology*, Zhao and U. of I. chemistry professor Wilfred A. van der Donk report the first successful synthesis of fosfomycin in a non-native host.

Fosfomycin is produced by various species of bacteria, but generally in low yields. Using a cloning method developed by Illinois microbiologist William W. Metcalf, the researchers were able to clone the essential genes for fosfomycin synthesis and then produce it in a non-native host, potentially in much larger quantities.

After isolating the genetic information from fosfomycin's native host, Streptomyces fradiae, certain genes were inactivated, and the ability of a non-native host Streptomyces lividians to produce fosfomycin was assessed.

With the help of graduate students Ryan Woodyer and Zengyi Shao, Zhao and van der Donk were able to determine not only the minimal set of genes required for fosfomycin biosynthesis, but also the function of some of these genes.

"Our goal now is to produce fosfomycin in Escherichia coli so that we can use various protein and metabolic engineering tools to manipulate the fosfomycin biosynthetic pathway," said Zhao, who also is an affiliate of the university's Institute for Genomic Biology. "Eventually, we should be able to produce fosfomycin in a cost-effective manner and create more potent derivatives of it."

Previously, four essential genes and a portion of fosfomycin's biosynthetic pathway had been proposed, but researchers were unable to produce fosfomycin in a non-native host. Zhao's findings indicate that the presence of additional genes that result in a revised mechanism is crucial for successful fosfomycin biosynthesis.

Source: University of Illinois at Urbana-Champaign