

The Scripps Research Institute

News Release

Scripps Florida Scientists Uncover Drug Resistance Mechanism that Could Impact Development of Two Antibiotic Drug Candidates

JUPITER, FL, February 20, 2014 – The use of antibiotics is often considered among the most important advances in the treatment of human disease. Unfortunately, though, bacteria are finding ways to make a comeback. According to the Centers for Disease Control, more than two million people come down with antibiotic-resistant infections annually, and at least 23,000 die because their treatment can't stop the infection. In addition, the pipeline for new antibiotics has grown dangerously thin.

Now, a new study by scientists from the Florida campus of The Scripps Research Institute (TSRI) has uncovered a mechanism of drug resistance. This knowledge could have a major impact on the development of a pair of highly potent new antibiotic drug candidates.

"Now, because we know the resistance mechanism, we can design elements to minimize the emergence of resistance as these promising new drug candidates are developed," said Ben Shen, a TSRI professor who led the study, which was published February 20, 2014 online ahead of print by the Cell Press journal *Chemistry & Biology*.

Bacteria Versus Bacteria

The study centers around a kind of bacteria known as *Streptomyces platensis*, which protects itself from other bacteria by secreting anti-bacterial substances. Interestingly, *Streptomyces platensis* belongs to a large family of antibiotic-producing bacteria that accounts for more than two-thirds of naturally occurring clinically useful antibiotics.

The antibiotic compounds secreted by *Streptomyces platensis*, which are called platensimycin and platencin and were discovered only recently, work by interfering with fatty acid synthesis. Fatty acid synthesis is essential for the production of bacterial cell walls and, consequently, the bacteria's existence. Platencin, although structurally similar to platensimycin, inhibits two separate enzymes in fatty acid synthesis instead of one.

The question remained, though, of why these compounds killed other bacteria, but not the producing bacteria *Streptomyces platensis*.

The Path to Resistance

The scientists set out to solve the mystery.

"Knowing how these bacteria protect themselves, what the mechanisms of self-resistance of the bacteria are, is important because they could transfer that resistance to other bacteria," said Tingting Huang, a research associate in the Shen laboratory who was first author of the study with Ryan M. Peterson of the University of Wisconsin, Madison.

Using genetic and bioinformatic techniques, the team identified two complementary mechanisms in the bacteria that confer resistance to platensimycin and platencin. In essence, the study found a pair of genes in *Streptomyces platensis* exploits a pathway to radically simplify fatty acid biosynthesis while bestowing an insensitivity to these particular antibiotics.

"Understanding how these elements work is a big leap forward," added Jeffrey D. Rudolf, a research associate in the Shen lab who worked on the study. "Now these bacteria have shown us how other bacteria might use this resistance mechanism to bypass fatty acid biosynthesis inhibition."

In addition to Shen, Huang, Peterson and Rudolf, the study, "Mechanisms of Self-Resistance in the Platensimycin and Platencin Producing *Streptomyces Platensis* MA7327 and MA7339 Strains," was authored by Michael J. Smanski of the University of Wisconsin, Madison.

The study was supported by the National Institutes of Health (Grant Numbers AI079070 and GM08505).

About The Scripps Research Institute

The Scripps Research Institute (TSRI) is one of the world's largest independent, not-for-profit organizations focusing on research in the biomedical sciences. TSRI is internationally recognized for its contributions to science and health, including its role in laying the foundation for new treatments for cancer, rheumatoid arthritis, hemophilia, and other diseases. An institution that evolved from the Scripps Metabolic Clinic founded by philanthropist Ellen Browning Scripps in 1924, the institute now employs about 3,000 people on its campuses in La Jolla, CA, and Jupiter, FL, where its renowned scientists—including three Nobel laureates—work toward their next discoveries. The institute's

graduate program, which awards PhD degrees in biology and chemistry, ranks among the top ten of its kind in the nation. For more information, see www.scripps.edu.

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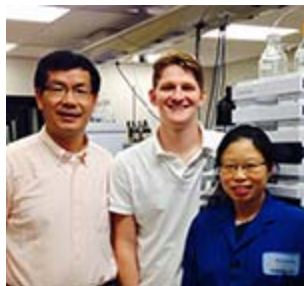
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Authors of the new study include (left to right) Professor Ben Shen, Research Associate Jeffrey Rudolf and Research Associate Tingting Huang of The Scripps Research Institute.

– For a high-resolution image see: http://www.scripps.edu/news/press/images/shen_ben/shen_group.jpg