Scientists reveal unique mechanism of natural product with powerful antimicrobial action

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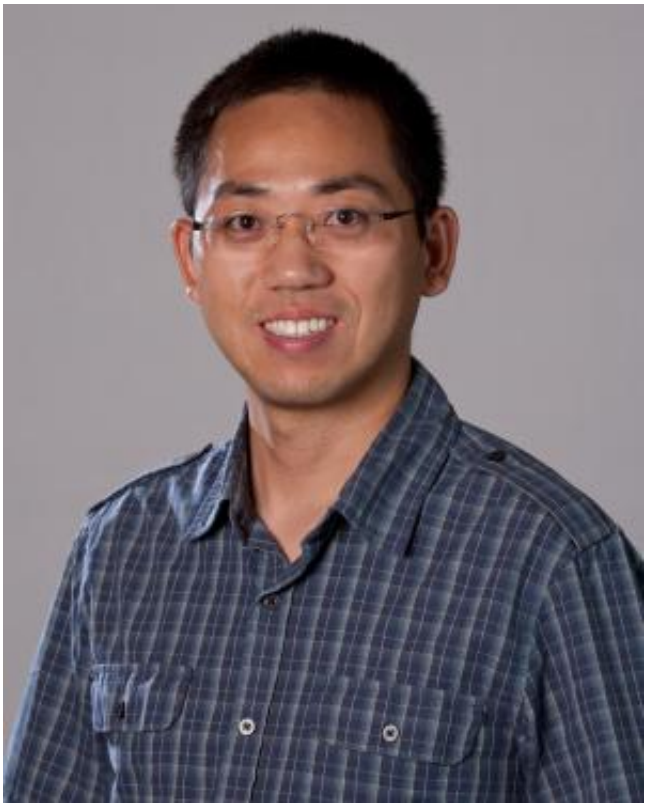

Min Guo, Ph.D.. Credit: The Scripps Research Institute.

Scientists from the Florida campus of The Scripps Research Institute (TSRI) have uncovered the unique mechanism of a powerful natural product with wide-ranging antifungal, antibacterial, anti-malaria and anti-

cancer effects.

The new study, published online ahead of print by the journal *Nature Communications*, sheds light on the natural small molecule known as borrelidin.

"Our study may help the rational design of compounds similar to borrelidin with a range of useful applications, particularly in cancer," said Min Guo, a TSRI associate professor who led the study.

Powerful Medicines

Guo and his colleagues were interested in borrelidin, because it inhibits a specific type of enzyme known as threonyl-tRNA synthetase (ThrRS), ultimately impeding protein synthesis.

Compounds similar to borrelidin have been used as treatments for microbial infections. For example, the natural product mupirocin is approved as a topical treatment for bacterial skin infections and febrifugine (the active component of the Chinese herb Chang Shan (Dichroa febrifuga Lour)) has been used for treating malaria-induced fever for nearly 2,000 years.

Previous studies from the collaborator Professor Christopher S. Francklyn of the University of Vermont College of Medicine and others have shown that borrelidin impedes angiogenesis, the growth of new blood vessels critical for the spread of malignant tumors, as well as increasing apoptosis in certain types of leukemia.

"It is probably the most potent tRNA synthetase inhibitor on Earth,"said Research Associate Pengfei Fang, co-first author of the study and member of the Guo lab at Scripps Florida. "It is also the earliest known tRNA synthetase inhibitor, discovered in 1966—just a few years after

people learned the existence of tRNA synthetase and genetic code."

Research Associate Xue Yu, also co-first author of the study and a member of the Guo lab, emphasized, "While little is known about how borrelidin works, the fairly widespread use of these types of inhibitors highlights their tremendous potential in a number of medical applications."

Winning at Musical Chairs

In the new study, the scientists set out to conduct a detailed structural and functional analysis of the binding of borrelidin to both human and bacterial (E. coli) ThrRS in the hope of identifying its unique mechanism.

The researchers succeeded, and the new study shows for the first time that borrelidin occupies four distinct subsites on both the bacterial and human tRNA synthetase, including all three subsites for its normal binding substrates and an extra one that is created when the compound binds. In this way, borrelidin crowds out all natural partners that would otherwise bind those sites and fuel the process of protein synthesis.

In that sense, borrelidin more or less wins the game of molecular musical chairs by taking over everyone's seat well before the music starts, even including the aisles.

Because each of the subsites is essential for its activity, the fact that borrelidin occupies four subsites within ThrRS, an apparent inhibitory overkill, was a quite surprise, and indeed accounts for its potency as validated by further experiments done in both in vitro and in cells.

"This has never been seen in any other tRNA synthetase inhibitors, including the ones sold as medicines," said Guo. "This finding

establishes a new inhibitor class and highlights the striking design of this natural compound that inhibits tRNA synthetases in two of the three kingdoms of life."

More information: Structural Basis for Full-Spectrum Inhibition of Translational Functions on a tRNA Synthetase, *Nature Communications*, 2015.

Provided by The Scripps Research Institute