

Keeping ribosomes stuck may stop virulent bacteria strain in its track

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Compounds that stop a cellular rescue operation for stuck ribosomes may bolster the nation's defenses against biowarfare and bioterrorism, as well as create alternative antibiotics to handle increasingly resistant pathogens, according to a team of researchers.

In a study of animal cells and macrophages, researchers used two inhibitors—KKL-10 and KKL-40—to stop the proliferation of *Francisella tularensis*, [bacteria](#) that the U.S. Centers for Disease Control classifies as a tier 1 select agent because the strain is highly infective and easily spread, said Kenneth Keiler, professor of biochemistry and molecular biology, Penn State.

The [compounds](#) target ribosomes in the translation phase of the bacteria's genetic process, he added. For bacteria to grow and proliferate, protein-generating ribosomes, like engines rolling down a track, must travel down the messenger RNA (mRNA) to translate additional proteins. However, when the ribosomes become stuck, the bacteria dispatches ribosome rescue factors - tmRNA, ArfA and ArfB—to free the ribosome.

Keiler said that KKL-10 and KKL-40 were able to halt this [rescue operation](#) in the bacteria without damaging host cells.

"At the beginning of the study, we identified compounds that block rescue of ribosomes that are stuck on mRNA, and these have antibiotic activity against a number of pathogens that we can test in the lab," said

Keiler. "In this study, first, we wanted to test the compounds against a pathogen that is important for biodefense and we also wanted to make sure that these compounds would work inside eukaryotic cells."

Francisella tularensis can cause fatalities in up to 60 percent of the cases if left untreated, said Girish Kirimanjeswara, assistant professor, veterinary and biomedical sciences, Penn State, who worked with Keiler. It was also stockpiled as a biowarfare agent during the Cold War.

"In today's world of terrorism, it is essential that we are well-prepared to defend ourselves and our military personnel against biowarfare agents," said Kirimanjeswara. "In that regard, finding new targets and antibiotics against these agents is critical and our research shows that these compounds may be very."

After decades of using antibiotics to kill pathogens, more and more diseases have become resistant to conventional drugs and treatments, according to the researchers, who report their findings in *Antimicrobial Agents and Chemotherapy*, currently available online. This has increased the urgency to find new drugs and new ways of stopping pathogens.

"There are many pathogens that are resistant to all existing antibiotics—if you are infected with one of these totally resistant strains and show up in the clinic there's nothing the doctors can do for you," said Keiler. "If your immune system can fight off the infection, you'll survive and if it can't, you die. It's back to pre-1940s-era medicine. If we don't develop [new drugs](#) and the resistant genes are going to continue to spread, more and more diseases will become untreatable."

He suggests that because the researchers are using a new compound and targeting a new pathway, *Francisella tularensis*—and possibly other pathogens—may struggle to adapt resistance to the treatment.

"One of the good things about our compounds is this is a new chemical, so it's unrelated to any of the existing drugs, which means maybe there may not be enzymes out there to modify those drugs and inactivate them," said Keiler. "Although we won't know that until we get into the clinic."

Kirimanjeswara said that *Francisella tularensis* is difficult to stop because it can survive both outside and inside the cell, as well as in different compartments of host cells.

"This strategy allows bacteria to survive and escape from host immune responses, for example, within the host cells, and there are not many antibiotics that can target a bacterium in all these compartments," said Kirimanjeswara. "In that regard, these compounds were effective outside the cells, in the various stages of endocytic vesicles, and in the cytoplasm, making it a very attractive way to treat bacterial diseases."

The next steps for the research will be to experiment on delivery designs and to test the compounds in animals.

Provided by Pennsylvania State University

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