The Big Idea

Jesse Coker - Stephenson Life Sciences Research Center

AS BACTERIA BECOME TOUGHER TO DEFEAT, OU UNDERGRADUATE RESEARCHER JESSE COKER IS GAINING GROUND ON A "SUPERBUG" ANTIBIOTIC.

By Anne Barajas Harp

They don't call CRE the "killer bacteria" for nothing. Carbapenem-resistant enterobacteriaceae is fatal to more than 40 percent of people it infects in hospitals and nursing homes, and scientists have declared all-out war against this superbug.

Helping to lead the charge is a fresh-faced University of Oklahoma junior named Jesse Coker. Surprising? Not at the Stephenson Life Sciences Research Center.

"Jesse's research experience right now is ahead of what you would actually expect to find in a first-year graduate student," says Coker's supervisor, Adam Duerfeldt, an assistant professor of chemistry and biochemistry at the OU Institute for Natural Products Applications and Research Technologies, or INPART.

"It was completely unexpected when I first got to OU," says Duerfeldt, who previously worked at the prestigious Scripps Research Institute. "But the longer I am here, the more I realize that this is an undergraduate research powerhouse."

That powerhouse is fueled by opportunity. Twenty-year-old Coker is one of dozens of undergraduates gaining crucial experience in OU labs, where they are tackling some of science's most perplexing problems.

"There has been a noticeable increase in antibacterial resistance in the last decade. Outbreaks of CRE in hospitals have caused a lot of fear and frustration," says Coker, a Nolensville, Tennessee, native who twice has been selected as a Vanderbilt University summer research intern.

"The problem with bacteria is they reproduce so fast that even if one or two bacteria survive a treatment with an antibiotic, suddenly there's a whole new strain of bacteria that is resistant." Coker adds that bacteria often go dormant and cannot be destroyed by available antibiotics. "They evolve to develop mechanisms of defense extremely quickly."

The toughest bacteria, such as CRE, are called "gram negative." Their defense mechanisms include a two-layer cell wall and a gel-like inner space full of bacterial enzymes and proteins that either destroy or pump out antibiotics.

Coker likens gram-negative bacteria cell walls to a World War I No-Man's Land. "The antibiotic never gets into the cell and does its thing, because it never actually makes it into the bacteria," he says. "Antibiotics don't have a chance."

Researchers may have found a way to trick bacteria into destroying itself. An enzyme called Caseinolytic Protease-P (ClpP) occurs naturally in bacteria and has the job of eating old, obsolete cell proteins. "You can turn ClpP on by binding a small molecule to it and ClpP goes crazy and eats everything," Coker says. "If you can flip that switch on permanently, it kills bacteria from the inside out."

Until now, scientists have only been able to flip the switch in less dangerous, "gram-positive" bacteria. But Coker has identified an activator that turns ClpP on in gram-negative bacteria. And it comes from nature.

The activator is produced by Aspergillus sclerotiorum, a plant-eating fungus. Coker identified the activator by searching a unique library of compounds from soil samples collected throughout the United States by INPART Director and OU Regents Professor Robert Cichewicz.

In just one week, Coker had screened ClpP against 500 compounds Cichewicz's staff had isolated from soil samples. He knew what he was looking for. "If you treat ClpP with a compound that activates it, ClpP 'eats' protein substrate and releases fluorescence," he says. "ClpP is turned on and carries out its digestion."

The mysterious fungus compound, which Coker says would be "almost impossible" to recreate in a lab, turns on ClpP purified from a strain of gram-negative bacteria. The next step will be to test the compound against live gram-negative bacteria cells. Meanwhile, Coker will continue screening ClpP against 7,000 additional soil compounds. The winning candidate could be synthesized and optimized in the first steps of developing a new antibiotic.

"We need to see if it can make it over No-Man's Land," Coker says. "If we can validate the 'hit' and make it a little bit better with some chemistry, this could be a new way to kill bacteria and target dormant, non-dividing bacteria as well, which would make it effective against the scarier strains that have been invading hospitals.

"We're a long way from that, at least a couple of years," he admits. "But it is a very promising start."

The same could be said of Jesse Coker.

Anne Barajas Harp is assistant editor of Sooner Magazine.

As a researcher at OU INPART, Jesse Coker is looking to nature for ways to develop new compounds for medical use. The OU junior already has identified a promising lead that could one day be used to battle “superbug” bacteria.

Photo by Theresa Bragg