Molecule shows ability to thwart pathogens' genetic resistance to antibiotic

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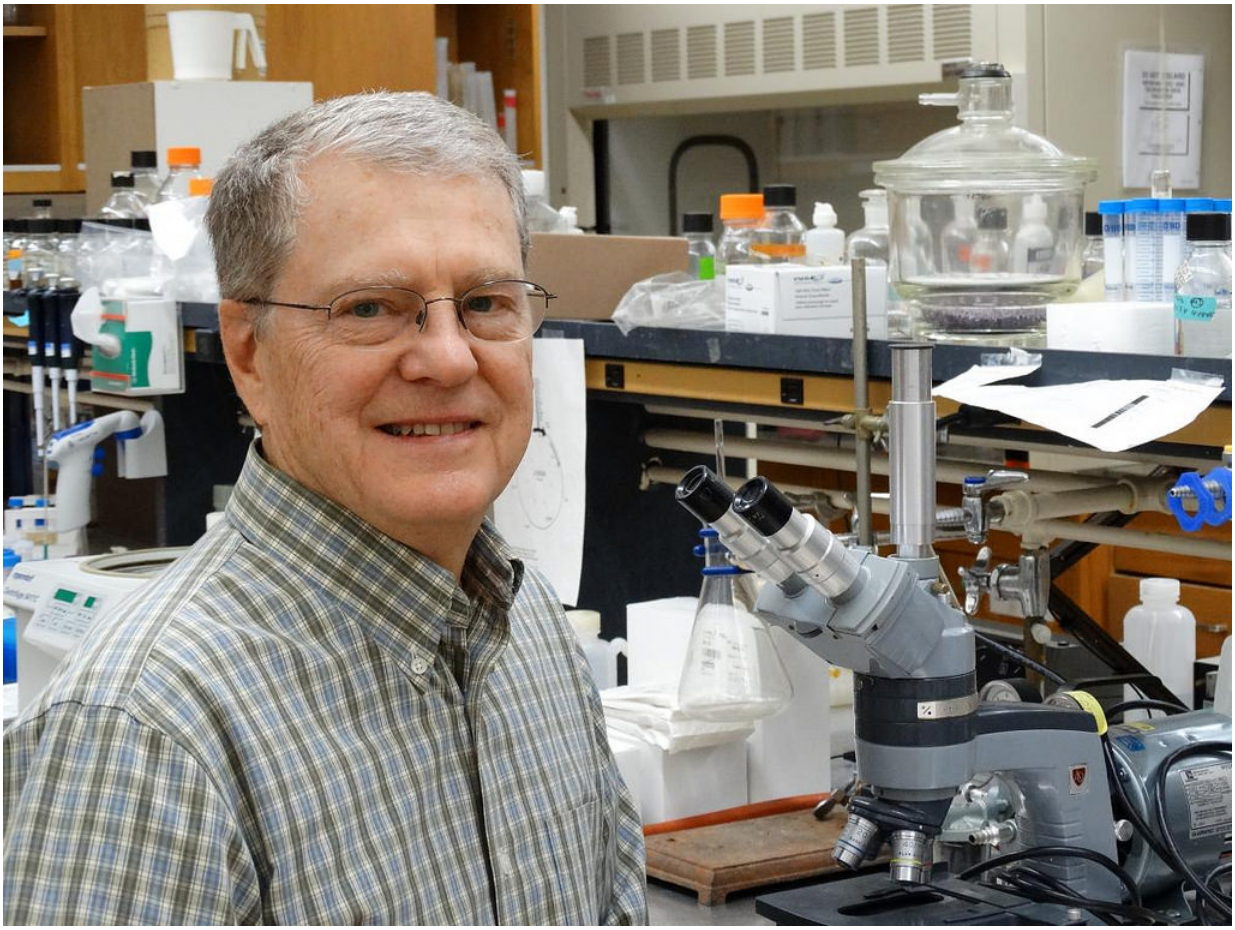

Bruce Geller. Credit: Oregon State University

Oregon State University researchers have developed a new weapon in the

battle against antibiotic-resistant germs - a molecule that neutralizes the bugs' ability to destroy the antibiotic.

Scientists at OSU were part of an international collaboration that demonstrated the molecule's ability to inhibit expression of an enzyme that makes bacteria resistant to a wide range of penicillins.

The molecule is a PPMO, short for peptide-conjugated phosphorodiamidate morpholino oligomer. The enzyme it combats is known as New Delhi metallo-beta-lactamase, or NDM-1, and it's accompanied by additional genes that encode resistance to most if not all antibiotics.

"We're targeting a resistance mechanism that's shared by a whole bunch of pathogens," said Bruce Geller, professor of microbiology in OSU's College of Science and College of Agricultural Sciences, who's been researching molecular medicine for more than a decade. "It's the same gene in different types of bacteria, so you only have to have one PPMO that's effective for all of them, which is different than other PPMOs that are genus specific."

The Oregon State study showed that in vitro the new PPMO restored the ability of an antibiotic—in this case meropenem, an ultra-broad-spectrum drug of the carbapenem class—to fight three different genera of bacteria that express NDM-1. The research also demonstrated that a combination of the PPMO and meropenem was effective in treating mice infected with a pathogenic strain of E. coli that is NDM-1 positive.

Results of the study, supported by a grant from the National Institutes of Health, were recently published in the *Journal of Antimicrobial Chemotherapy*.

Geller says the PPMO will likely be ready for testing in humans in about

three years.

"We've lost the ability to use many of our mainstream antibiotics," Geller said. "Everything's resistant to them now. That's left us to try to develop new drugs to stay one step ahead of the bacteria, but the more we look the more we don't find anything new. So that's left us with making modifications to existing antibiotics, but as soon as you make a chemical change, the bugs mutate and now they're resistant to the new, chemically modified antibiotic."

That progression, Geller explains, made the carbapenems, the most advanced penicillin-type antibiotic, the last line of defense against bacterial infection.

"The significance of NDM-1 is that it is destroys carbapenems, so doctors have had to pull out an antibiotic, colistin, that hadn't been used in decades because it's toxic to the kidneys," Geller said. "That is literally the last antibiotic that can be used on an NDM-1-expressing organism, and we now have bacteria that are completely resistant to all known antibiotics. But a PPMO can restore susceptibility to antibiotics that have already been approved, so we can get a PPMO approved and then go back and use these antibiotics that had become useless."

More information: Erin K. Sully et al, Peptide-conjugated phosphorodiamidate morpholino oligomer (PPMO) restores carbapenem susceptibility to NDM-1-positive pathogensand, *Journal of Antimicrobial Chemotherapy* (2016). DOI: 10.1093/jac/dkw476

Provided by Oregon State University

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