Finding new life for first-line antibiotics

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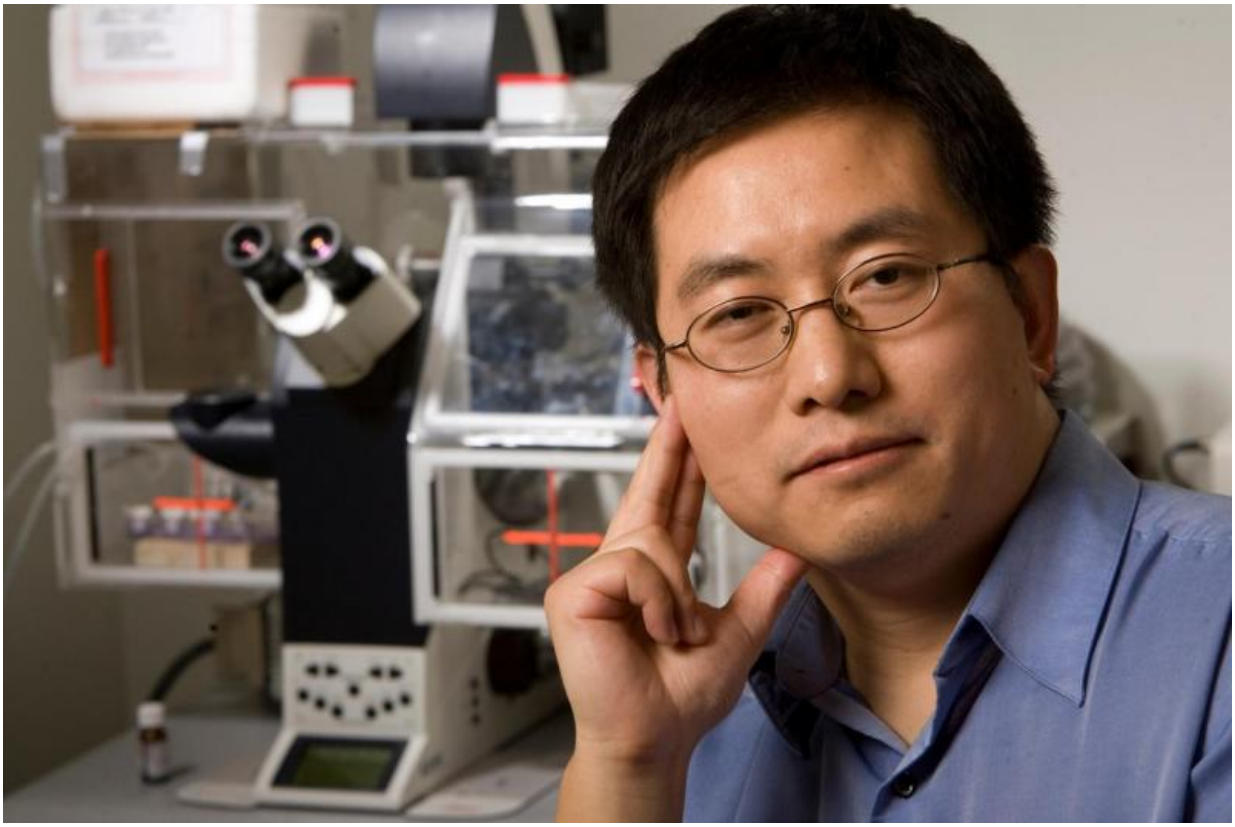

Lingchong You, the Paul Ruffin Scarborough Associate Professor of Biomedical Engineering at Duke University. Credit: Duke University Photography

Duke University researchers have identified a single, simple metric to guide antibiotic dosing that could bring an entire arsenal of first-line antibiotics back into the fight against drug-resistant pathogens.

A computer simulation created by Hannah Meredith, a biomedical engineering graduate fellow at Duke, revealed that a regimen based on a pathogen's recovery time could eliminate an otherwise resistant strain of bacteria. In theory, a database of recovery times for bacterial and antibiotic combinations could allow first-line antibiotics to clear many resistant infections.

Meredith has already begun lab work to create such a database, and early tests are confirming her model's predictions.

The study appears in *PLOS Computational Biology* on April 23, 2015.

"Bacteria are forming resistance to antibiotics faster than we can make new ones, so there is a real need to use the antibiotics that are already on the market more efficiently," said Meredith. "We hope this research will help hospitals improve patient outcomes while also making our antibiotics last as long as possible."

The computer simulation models the relationship between bacteria, antibiotics and a method of resistance called beta-lactamase—an enzyme that degrades beta-lactam antibiotics, one of the largest and most-used classes of antibiotics. Many beta-lactam antibiotics are currently disregarded out of concern for the infection being completely resistant to that type of antibiotic—even if the antibiotic appeared to be effective in the lab. The new model, however, reveals that the bacteria might be temporarily sensitive to the antibiotic before the beta-lactamase degrades the drug and allows the infection to recover.

"You can think of this as a race between the cells and the antibiotics," said Lingchong You, the Paul Ruffin Scarborough Associate Professor of Biomedical Engineering at Duke and Meredith's adviser. "Before their beta-lactamase degrades the antibiotics, the cells are still sensitive and can be killed. But the antibiotics degrade faster than the cell

population declines, allowing some cells to survive and repopulate."

When clinicians realize an infection is resistant, they often skip straight to some of the strongest antibiotics available. But the study indicates that if they instead changed the dosing frequency of first-line antibiotics so that each dose is delivered while the bacteria are weakened during their recovery period, some infections could be cleared without skipping to the last resort.

Doctors also need to be careful, however, not to wreck native populations of bacteria vital to human health. A database detailing the responses of different strains to different antibiotics could allow Meredith's computer model to determine the most efficient regimen to keep total exposure to a minimum. It could also indicate if multiple doses would not work, letting clinicians know when it is time to call in the heavy artillery.

"There's already a lot of work being done to determine antibiotic dosing schedules," said You. "But that typically involves building a model based on many complex biological mechanisms. This takes a lot of time, and there are thousands of constantly evolving bacterial strains, making it impossible for researchers to catch up. We're trying to see if this one, easy-to-test metric of recovery time can make a good enough prediction without years of study."

Meredith has already begun laboratory work to answer this question and validate her computational model. She has received 80 well-known antibiotic-resistant bacteria strains from Duke Medicine and is putting her theory to the test.

And the early results are promising.

"Our preliminary data have confirmed many of the clinical aspects of

the model's predictions, so we are tremendously excited by those," said Meredith. "If this strategy is successful, it could potentially reintroduce a large number of first-line antibiotics for patient treatment."

More information: "Bacterial Temporal Dynamics Enable Optimal Design of Antibiotic Treatment," Hannah R. Meredith, Allison J. Lopatkin, Deverick J. Anderson, Lingchong You. *PLOS Computational Biology*, 2015, 11(4): e1004201. DOI: 10.1371/journal.pcbi.1004201

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