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New Software Predicts Superbugs' Countermoves to New Drugs

In the fight against drug-resistant bacteria, new drugs are urgently needed, but so are ways to maximise the effective lifespan of these drugs. Researchers at Duke University in the U.S. have developed open-source software that can predict a constantly-evolving infectious bacterium's counter-moves to a new drug before the drug is tested on patients.

The team used their program to identify the genetic changes that will allow methicillin-resistant Staphylococcus aureus (MRSA) to develop resistance to a class of new experimental drugs. In tests on live live bacteria with the new drug, two of the genetic changes occurred, as predicted by the algorithm.

Knowing the germ’s resistance mutations will allow development of pre-emptive strategies while the drugs are still in the design phase.

Because bacteria reproduce so rapidly -- growing and dividing from one cell to two in less than an hour -- drug-resistant bacteria are constantly evolving, and researchers have to constantly develop new ways to kill them.

The proportion of infections caused by Staphylococcus aureus that have proven resistant to treatment has risen from just over 2 percent in 1975 and 29 percent in 1991 to more than 55 percent today.

"For some antibiotics, the first drug-resistant bacterial strains don't appear for decades after the drug is introduced, and in others all it takes is one year," Duke graduate student Pablo Gainza-Cirauqui, co-author of the paper, said.

The current approach of looking up possible mutations from "libraries" of resistance mutations that have been observed previously does not work when it comes to anticipating how bacteria will adapt to new drugs, where the microbes can't be counted on to change in repeatable, predictable ways, co-author Bruce Donald, a professor of computer science and biochemistry at Duke, said.

The research team, led by Donald at Duke and Amy Anderson at the University of Connecticut, used a protein design algorithm they developed, called OSPREY, to identify DNA sequence changes in the bacteria that would enable the resulting protein to block the drug from binding, while still performing its normal work within the cell.

The team focused on a new class of experimental drugs that work by binding and inhibiting a bacterial enzyme called dihydrofolate reductase (DHFR), which plays an essential role in building DNA and other processes. Propargyl-linked antifolates are a promising treatment for MRSA infections, but have not been tested in humans.

From a ranked list of possible mutations, the researchers focused on four tiny differences, called single nucleotide polymorphisms (SNPs), that would confer resistance in theory. While no mutation they identified had been reported previously, experiments with live bacteria proved that their predictions were right.

When they treated MRSA with the new drugs and sequenced the bacteria that survived, more than half of the surviving colonies carried the predicted mutation that conferred the greatest resistance -- a tiny change that reduced the drugs' effectiveness by 58-fold.

The team is are now using the algorithm to predict resistance mutations to other drugs designed to combat pathogens such as E. coli and Enterococcus. Donald speculates that they migt be able to coax a pathogen into developing mutations that mean it can not only avoid one drug, but make it susceptible to a second drug.

Their approach could be used to forecast drug resistance mutations in other diseases, such as cancer, HIV and influenza, where raising resistant cells or strains in the lab is more difficult to do than with bacteria, the researchers say.

OSPREY, the software, is open-source and freely available for any researcher to use.

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