

Putting bacterial antibiotic resistance into reverse

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The use of antibiotics to treat bacterial infections causes a continual and vicious cycle in which antibiotic treatment leads to the emergence and spread of resistant strains, forcing the use of additional drugs leading to further multi-drug resistance.

But what if it doesn't have to be that way?

In a presentation at the American Society for Biochemistry and Molecular Biology's annual meeting, titled "Driving backwards the evolution of antibiotic resistance," Harvard researcher Roy Kishony will discuss his recent work showing that some drug combinations can stop or even reverse the normal trend, favoring bacteria that do not develop resistance. The talk will be in Anaheim Convention Center Room 304D, on Sunday April 25 at 3:30 pm PST.

"Normally, when clinicians administer a multi-drug regimen, they do so because the drugs act synergistically and speed up bacterial killing," Kishony explains. However, Kishony's laboratory has focused on the opposite phenomenon: antibiotic interactions that have a suppressive effect, namely when the combined [inhibitory effect](#) of using the two drugs together is weaker than that of one of the drugs alone.

Kishony and his team identified the suppressive interaction in *E. coli*, discovering that a combination of tetracycline - which prevents bacteria from making proteins - and ciprofloxacin - which prevents them from copying their DNA - was not as good as slowing down [bacterial growth](#)

as one of the antibiotics (ciprofloxacin) by itself.

Kishony notes that this suppressive interaction can halt bacterial evolution, because any bacteria that develop a resistance to tetracycline will lose its suppressive effect against ciprofloxacin and die off; therefore, in a population the bacteria that remain non-resistant become the dominant strain.

While such a weakened antibiotic combination is not great from a clinical standpoint, the Kishony lab is using this discovery to set up a [drug screening](#) system that could identify novel drug combinations that could hinder the development of resistance but still act highly effectively.

"Typical drug searches look for absolute killing effects, and choose the strongest candidates," he says. "Our approach is going to ask how these drugs affect the competition between resistant versus sensitive bacterial strains."

To develop such a screen, Kishony and his group first had to figure how this unusual interaction works.

"Fast growing bacteria like *E. coli* are optimized to balance their protein and DNA activity to grow and divide as quickly as the surrounding environment allows," Kishony explains. "However, when we exposed *E. coli* to the ciprofloxacin, we found that their optimization disappeared."

"We expected that since the bacteria would have more difficulty copying DNA, they would slow down their protein synthesis, too," Kishony continues. "But they didn't; they kept churning out proteins, which only added to their stress." However, once they added the tetracycline and protein synthesis was also reduced in the *E. coli*, they actually grew better than before. They then confirmed the idea that production of

ribosomes - the cell components that make proteins - is too high under DNA stress by engineering *E. coli* strains that have fewer ribosomes than regular [bacteria](#). While these mutants grew a more slowly in normal conditions, they grew faster under [ciprofloxacin](#) inhibition of DNA synthesis.

Kishony notes that their preliminary work on the development of a screen for drugs that put resistance in a disadvantage looks promising, and hopes that it would lead to the identification of novel drugs that select against resistance.

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