Programming DNA to reverse antibiotic resistance in bacteria

June 4 2015

At its annual assembly in Geneva last week, the World Health Organization approved a radical and far-reaching plan to slow the rapid, extensive spread of antibiotic resistance around the world. The plan hopes to curb the rise caused by an unchecked use of antibiotics and lack of new antibiotics on the market.

New Tel Aviv University research published in *PNAS* introduces a promising new tool: a two-pronged system to combat this dangerous situation. It nukes antibiotic resistance in selected bacteria, and renders other bacteria more sensitive to antibiotics. The research, led by Prof. Udi Qimron of the Department of Clinical Microbiology and

Immunology at TAU's Sackler Faculty of Medicine, is based on bacterial viruses called phages, which transfer "edited" DNA into resistant bacteria to kill off resistant strains and make others more sensitive to antibiotics.

According to the researchers, the system, if ultimately applied to pathogens on hospital surfaces or medical personnel's hands, could turn the tide on untreatable, often lethal bacterial infections. "Since there are only a few pathogens in hospitals that cause most of the antibiotic-resistance infections, we wish to specifically design appropriate sensitization treatments for each one of them," Prof. Qimron says. "We will have to choose suitable combinations of DNA-delivering phages that would deliver the DNA into pathogens, and the suitable combination of 'killing' phages that could select the re-sensitized pathogens."

Reprogramming the system

"Antibiotic-resistant pathogens constitute an increasing threat because antibiotics are designed to select resistant pathogens over sensitive ones," Prof. Qimron says. "The injected DNA does two things: It eliminates the genes that cause resistance to antibiotics, and it confers protection against lethal phages.

"We managed to devise a way to restore antibiotic sensitivity to drug-resistant bacteria, and also prevent the transfer of genes that create that resistance among bacteria," he continues.

Earlier research by Prof. Qimron revealed that bacteria could be sensitized to certain antibiotics—and that specific chemical agents could "choose" those bacteria more susceptible to antibiotics. His strategy harnesses the CRISPR-Cas system—a bacterial DNA-reprogramming system Prof. Qimron pioneered—as a tool to expand on established principles.

According to the researchers, "selective pressure" exerted by antibiotics renders most bacteria resistant to them—hence the epidemic of lethal resistant infections in hospitals. No counter-selection pressure for sensitization of antibiotics is currently available. Prof. Qimron's strategy actually combats this pressure—selecting for the population of pathogens exhibiting antibiotic sensitivity.

"We believe that this strategy, in addition to disinfection, could significantly render infections once again treatable by antibiotics," said Prof. Qimron.

Prof. Qimron and his team are now poised to apply the CRISPR/phage system on pseudomonas aeruginosa—one of the world's most prevalent antibiotic-resistant pathogens involved in hospital-acquired infections—and to test whether bacterial sensitization works in a more complex microbial environment: the mouse cage.

Provided by Tel Aviv University