Discovery of essential genes for drug-resistant bacteria reveals new, high-value drug targets

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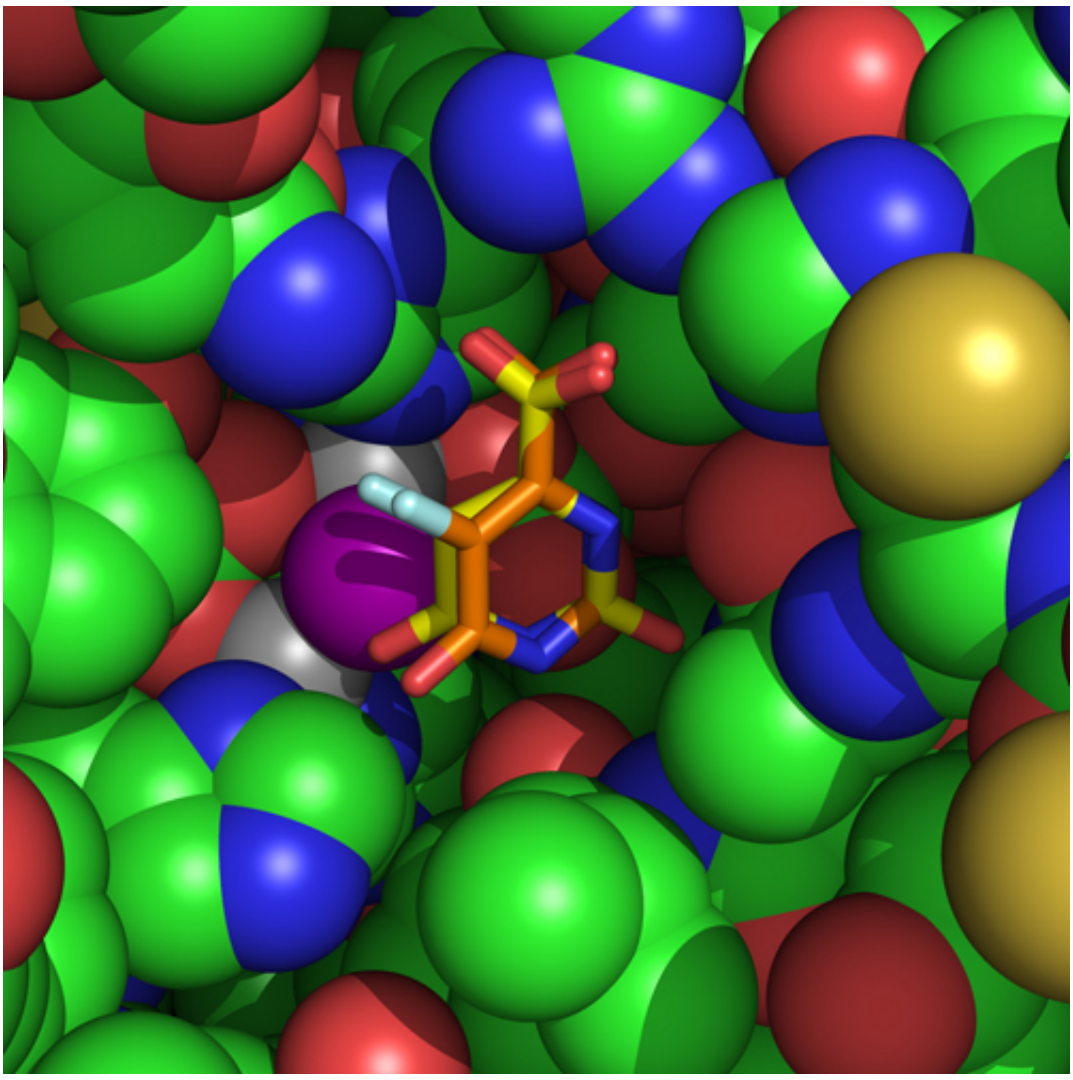

This schematic picture shows a potential drug against the resistant bacteria, *A. baumannii*, interacting with a drug target identified by the UB and HWI

researchers. Credit: Tim Umland and Tom Russo

(Phys.org)—Biomedical scientists collaborating on translational research at two Buffalo institutions are reporting the discovery of a novel, and heretofore unrecognized, set of genes essential for the growth of potentially lethal, drug-resistant bacteria. The study not only reveals multiple, new drug targets for this human infection, it also suggests that the typical methods of studying bacteria in rich laboratory media may not be the best way to identify much-needed antimicrobial drug targets.

The paper focuses on a Gram-negative bacteria called *A. baumannii*. It is published in the current issue of *mBio*, as an 'editor's choice' paper. The findings may be relevant to other Gram-negative bacteria as well.

A. baumannii is responsible for a growing number of hospital-acquired infections around the world. It can be fatal to patients with serious illnesses, the elderly and those who have had surgeries. Infections also have been seen in soldiers returning from Iraq and Afghanistan with battlefield injuries.

"Generally, healthy people don't get infected," explains lead author Timothy C. Umland, PhD, research scientist at Hauptman-Woodward Medical

Research Institute (HWI) and professor of structural biology in the University at Buffalo School of Medicine and Biomedical Sciences. "But what's challenging about *A. baumannii* is that it can survive in the hospital environment and is very hard to eradicate with common disinfectants, leading to healthcare-associated infections."

Typically, the way that essential genes for microbial pathogens are found

is by growing the bacteria under optimal conditions, says co-author Thomas A. Russo, MD, professor in the UB departments of medicine and microbiology and immunology. Genes found to be essential for growth are then entered into the Database of Essential Genes (DEG), which contains genes considered essential for the sustenance of each organism.

The researchers at HWI and UB decided to try to better understand what *A. baumannii* needs in order to grow when infecting patients.

"Laboratory conditions create a different type of environment from what happens in patients," Umland says, "where certain nutrients the bacteria need will be present in very low amounts and where the bacteria encounter immune and inflammatory responses. We were purposely trying to test for genes that are important for growth in these more realistic environments."

The team performed a genetic screen designed to identify bacterial genes absolutely required for the growth and survival of *A. baumannii* in human ascites, a peritoneal fluid that accumulates under a variety of pathologic conditions.

"We found that nearly all of these 18 genes had not been identified as essential in the DEG because they weren't necessary for growth in an ideal laboratory environment," explains Russo. "This is a large set of genes that has been flying under the radar."

He adds: "The biggest concern is that quite a few strains of *A. baumannii* are resistant to nearly all anti-microbial drugs and some strains are resistant to all of them. To make things worse, there are no new agents being tested for human use in the drug pipeline that are active against *A. baumannii*. This is a huge problem."

Not only do the new genes suggest brand new, high-value drug targets for *A. baumannii* infections, but the genes that have been identified may be relevant to other Gram-negative infections.

"So far, our computational models show that these genes seem to be conserved across Gram-negative infections, meaning that they may lead to new drugs that would be effective for other drug-resistant infections as well," says Umland.

The researchers who collaborated on the study are now pursuing antibacterial drug discovery efforts focused on the newly identified bacterial targets.

More information: Paper: http://mbio.asm.org/content/3/4/e00113-12

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