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Microbiology

Red in Tooth and Claw: another weapon against antibiotic resistance

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Bacteria are an integral part of human life. These organisms are on your skin, in your mouth, your ears, and your gut. After birth, a diverse population is acquired by the age of three and remarkably the population is quite similar and just as diverse in adulthood, practically remaining unchanged. Although the microbiome is essential to our survival, the world of bacteria is incredibly complex. While most bacteria do not harm us and they often protect us, pathogenic bacteria cause harm of their hosts. By understanding how these organisms function and interact with their surroundings is critical to identifying new ways to treat harmful bacterial infections and has been one of the most important scientific advances in achieving a long healthy life for members of society.

Competition and natural selection in nature are rampant, and bacteria as well have their own means of outcompeting other organisms: one is through the production of natural products (or small molecules). A notable and well-known natural product is penicillin. Penicillin was the very first antibiotic discovered when Alexander Fleming noticed that mold had contaminated his colonies of Staphylococcus aureus inhibiting their growth. Shortly following, he identified penicillin, resulting in a new family of compounds that have been undeniably one of the most important discoveries of the twentieth century. Commonly encountered infections could be treated simply by use of this antibiotic.

Although penicillin paved the way for antibiotic development, another highly important family of antibiotics came with the discovery of vancomycin in 1956. Vancomycin is unique as it targets fundamental cell wall building blocks (unlike penicillin) present across bacteria that affects the integrity of their cell wall. Think of stones required to build a castle. Without a proper castle wall, the insides are compromised. For bacteria, this results in death. Because of how vancomycin works, it is highly difficult for bacteria to develop a resistance. This makes vancomycin quite efficacious and it is employed when penicillin cannot get the job accomplished, resulting in it being a "last-resort" drug for nearly 50 years in the clinic.

Despite vancomycin's efficaciousness and long-standing utility in the clinic, there has been a rise in resistant bacterial strains towards vancomycin. Hospitals are now confronted with the frightening reality that drugs to treat such infections are sometimes not only ineffective, but might also result in breeding pathogenic bacteria that are even more resistant to any prescribed drug. Particular strains of bacteria are now a major threat and hospitals need a general solution. Thus, it is not surprising that vancomycin-resistant strains have recently been identified by the World Health Organization among those that pose the greatest threat to worldwide human health.

Researchers within our lab sought to address this problem. How do we design an antibiotic that is not only potent against vancomycin-resistant strains, but that might also "stand" the test of time? That is, can we change vancomycin in such a way that results in an antibiotic not only effective against vancomycin-resistant strains, but are also not prone to bacteria developing resistance to the drug. Can we design a truly durable antibiotic? Through experimentation, we identified how to synthetically change vancomycin such that it can

now attack bacteria on multiple fronts simultaneously. One change overcomes the molecular basis of vancomycin resistance. Two additional changes each introduced new independent ways in which the compound could prevent productive bacterial cell wall assemblage (the castle's wall). By employing such a strategy, these vancomycin-resistant strains were shown to be unable to create a counter-strategy (namely to develop resistance) towards our vancomycin analogue that can kill bacteria by three independent mechanisms of action. This concept was so effective, that we anticipate this being a general strategy in the future of antibiotic drug development.

Although still at an early stage of development, we are exceedingly excited about the potential. Our goals are to further study and understand if this new vancomycin analogue is efficacious and safe when given to an infected host. We also anticipate developing new ways to produce the new vancomycin analogues so that their cost and availability will not be a barrier to their use. There is still much to do and we are merely at the trail-head of our journey.