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Counter Attack: Developing New Weapons in the Battle Against Antibiotic Resistance

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Developing new weapons in the battle against antibiotic resistance

by Amy Oprean

In the course of human medicine, few discoveries have been as far-reaching and successful as the development of antibiotics in the 20th century. Introduced to mainstream medicine in the 1940s, these drugs have been utilized to vanquish a vast array of bacterial infections, relieving the suffering and saving the lives of millions of people. But antibiotics aren't the surefire defense they used to be. A drop in research over the past several decades in developing new antibiotics, coupled with bacteria's evolutionary drive to develop resistance, has caused the number of effective antibiotics to diminish, and with increasing speed.

Christine Chow, Ph.D., professor of Chemistry in Wayne State's College of Liberal Arts and Sciences, is leading a research team in developing a novel strategy to get an edge over bacteria's relentlessly evolving defense mechanisms. "Resistance is a huge problem," Dr. Chow said. "There are now strains of bacteria that are completely resistant to every known drug. We want to create something new that isn't as easy for bacteria to resist."

The key to Dr. Chow's research lies in ribonucleic acid, or RNA, a nucleic acid that consists of a long chain of nucleotide units, chemically similar to DNA, but consisting of one chain of nucleotides instead of DNA's double helix. RNA has a diverse set of functions, but one of the basic and most well-known is its job of containing the genetic "recipe" for synthesizing proteins. RNA's role has been highly conserved throughout evolution – organisms from bacteria all the way to humans depend on its functions.

Being such an important aspect of all life also makes RNA an incredibly useful target for antibiotics. The RNA of bacteria is one of the two most common targets for antibiotics – the other being enzymes that synthesize bacteria's cell walls – for several reasons, Dr. Chow explained. First, RNA is more chemically and structurally diverse than other possible target areas, such as DNA, meaning RNA has an abundance of unique structures for an antibiotic to "latch on to." It's also more accessible than DNA, and doesn't have the defense enzymes that protect DNA. Lastly, RNA comprises the physical structure of the ribosome, RNA-protein complexes that are found in all living organisms. Ribosomes perform the essential function of synthesizing all the proteins in an organism. Like RNA itself, these protein-making machines can be found from bacteria all the way up to humans, and are important to maintaining all life. Because of this importance, ribosomes are already one of the most common targets of antibiotics – one of simplest ways to eliminate unwanted bacteria is to shut down its ribosomes.

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Chow's strategy for battling antibiotic resistance takes the tried and true method of targeting a bacteria cell's ribosomes and aims to improve it, by targeting sites that are particularly vulnerable and attacking with a compound the bacteria has never seen before. "If your antibiotics are derived from natural compounds, there has already been time for the bacteria to evolve resistance mechanisms, and that's why we have this big problem with antibiotic resistance," she said. "So we want to find compounds that don't look like anything from nature. That way, resistance mechanisms will hopefully take longer to develop."

Selecting a target

Just like DNA, RNA's "genetic code" is subject to modifications – changes in either its chemical make-up or structure that enable it to carry out vital functions. With her lab, Chow has selected regions of RNA with six different natural modifications as potential antibiotic targets. Chosen for their importance to ribosome function, Chow's lab is synthesizing these modified portions of RNA, using miniaturized versions of the full scale RNAs so that individual nucleotides can be monitored more closely. All six modified portions of RNA are located at different places on the physical structure of the ribosome, and are believed to control such vital processes as the maintenance of protein assembly and control of turning protein synthesis on and off. "We wanted to target areas that are very essential for the survival of cells," she said.

Finding the weapon

With the targets of the "protein machine" chosen, Chow's task at hand is finding a chemical "monkey wrench" that will bind to a ribosome and shut down its protein production. The process will involve several steps, beginning with finding a compound that has an affinity for one of the modified sites, and will bind to it. "If there is a strong interaction, that means the compound has potential to be a drug," Dr. Chow said. "The next step is to look and see if it affects the ribosome function. In other words, does it stop protein synthesis? If that does happen, that's great, but there is still another question, which is, can this compound get into cells? If the drug never gets into the cells, then it can't kill them."

To find additional information on the nature of bacterial RNA, Chow is also performing these trials on the corresponding modified RNA sites in human ribosomes, looking for any functional or structural differences that will further her understanding of bacterial RNA at these modified sites. "We want to know if the function of these modifications is the same in both organisms" she said. "We believe that even though the modifications occur in both, they might have slightly different roles or effects on the RNA. And what we really want to do is determine the differences so that we can take advantage of them for drug targeting."

Even with the advantage of brand new chemical compounds, however, Chow knows that bacteria may still develop resistance to the antibiotics she develops. She is collaborating with Phil Cunningham, Ph.D., associate professor of biology in WSU's College of Liberal Arts and Sciences, to utilize the genetic system Cunningham developed that predicts "functional mutants" – the potential mutations bacterial RNAs are likely to take on. "We're trying to do a screening to find compounds that bind to functional mutants, so once the bacteria develops a mutation to an antibiotic, we'll already have a drug ready," she said.

In the meantime, Chow is hard at work looking for a drug that will be a new challenge for bacteria to defend against. "Our hope is to find a lead compound, something that could potentially lead to an antibiotic," she said. "If not, we'll at least learn a lot about the rules for how compounds bind and that would help other people to design new drugs."

About Dr. Christine Chow: Dr. Chow received an A.B. in environmental studies and chemistry from Bowdoin College and an M.A. in organic chemistry from Columbia University. She studied inorganic chemistry with a focus on the interactions of transition metal complexes with RNA at the California Institute of Technology, where she earned a Ph.D. She then became a National Institutes of Health postdoctoral fellow at the Massachusetts Institute of Technology, studying the interactions of proteins with DNA modified by the anticancer drug Cisplatin. She joined Wayne State University in 1994.

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