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Researchers develop novel method to find new antibiotics

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Bacteria are a cunning foe; at a worrisome rate, they are developing resistance to the current arsenal of antibiotic drugs. Without new drugs, society may be approaching a world reminiscent of the pre-antibiotic era, when coming down with a bacterial infection was often a matter of life or death.

The seemingly obvious solution lies in finding more microbe-killing compounds, but University of Wisconsin-Madison bacteriologist Marcin Filutowicz is taking another approach: He plans to search for new antibiotics that render virulent bacteria harmless without killing them.

"Bacteria evolve quickly; some have already acquired resistance to all clinically relevant antibiotics," says Filutowicz, professor of bacteriology in the College of Agricultural and Life Sciences. "We microbiologists have to respond with new ideas and new technologies to outsmart the evolving bugs."

Filutowicz has developed a novel method of searching for this untapped class of antimicrobial compounds. He is seeking a patent for what he plans to call "The No-Kill Strategy to Manage Infectious Disease." His invention disclosure — a key step in obtaining a patent — was recently approved by the Wisconsin Alumni Research Foundation (WARF) and the UW-Madison Graduate School, and WARF plans to file a patent application on his behalf in early 2007.

Filutowicz's approach involves looking for new drugs that render

bacteria harmless by blocking the replication of — and thus eliminating — some of their DNA.

Bacterial DNA comes in two forms: chromosomal DNA, which is required for life, and plasmid DNA, which is not. The nonessential plasmid DNA contains many undesirable bacterial genes, including those that confer antibiotic resistance or lead to the production of toxins.

Filutowicz is seeking antibiotics that would selectively disrupt the replication of plasmid DNA, so that when bacteria reproduce, they would produce plasmid-free offspring that are harmless or susceptible to traditional antibiotics.

Such compounds could dramatically alter the character of some of our nastiest microbial adversaries.

"In Bacillus anthracis, the causative agent of anthrax — and some other bacteria that are used as bio-weapons — all the virulence is plasmid-encoded. So if you get rid of the plasmids, you can actually drink a cup of [the bacteria] and you'd be fine," says Filutowicz.

The best source of drugs to treat bacterial infections is bacteria themselves. Bacteria contain genes that produce antibiotics that they use to fight and communicate with other bacteria as they compete for food and other resources.

To maximize his chances of finding these plasmid-busting compounds, Filutowicz's method makes use of groundbreaking technology called metagenomics, which was developed and patented by Jo Handelsman, a UW-Madison professor of plant pathology.

Metagenomics allows access to vast amounts of bacterial genetic material that was previously inaccessible.

Before the advent of metagenomics, researchers could study only those bacteria amenable to growth in the laboratory, a mere 2 to 3 percent of known bacterial species. Metagenomics makes it possible to study those bacteria that refuse to grow under artificial laboratory conditions, allowing access to a vast reservoir of bacterial genes - including the genes of countless soil microbes.

Access to these genes is vital because, Handelsman says, "At the same time that the treatment of infectious diseases is intensifying, the discovery of new antibiotics has slowed virtually to a crawl."

Filutowicz is confident that the vastly expanded pool of genes in Handelsman's metagenomic libraries will yield new compounds that selectively inhibit replication of plasmid DNA in bacteria. These antimicrobial agents may well constitute the next generation of antibiotic drugs.

Source: by Nicole Miller, University of Wisconsin-Madison