

Outsmarting the Toughest Bacteria

Can an antibiotic that works in cows be modified to solve resistance in humans?

SUPERBUGS, THE DISEASE-CAUSING BACTERIA THAT ARE RESISTANT TO EVEN the most high-powered antibiotics, are becoming more commonplace. One dangerous strain called methicillin-resistant *Staphylococcus aureus* (MRSA), once restricted to hospital wards, is turning up in soccer fields and gym lockers. Doctors are having a hard time keeping up. ¶ Although several new antibiotics to MRSA became available a few years ago, “we’re already starting to see resistance to those,” says



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NATALIE STRYNADKA

Natalie C. J. Strynadka, an HHMI international research scholar at the University of British Columbia in Canada. “You always need a couple more bullets in your arsenal to stay ahead of the game.”

In fact, what Strynadka and her Vancouver team would prefer to more bullets is a *better* bullet—an antibiotic not so readily foiled by bacteria. In their effort to develop one, the researchers focused on an antibiotic called moenomycin. “It’s been used in huge quantities in cattle feed,” Strynadka says, “and yet we’ve seen very little resistance.”

In fact, says Andrew Lovering, a postdoc in Strynadka’s lab, the drug appears to be “resistant” to resistance.

The problem, however, is that moenomycin doesn’t work in people. “It’s a really complex molecule and is not absorbed well in our bodies,” Lovering explains. “We wanted to see if we could change it to make it still effective but amenable to uptake in humans.” As a first step, he and his labmates set out to capture a precise atomic picture of moenomycin in midattack on its bacterial target, a membrane-anchored enzyme called penicillin binding protein 2 (PBP2).

As its name suggests, PBP2 is also the protein targeted by penicillin, methicillin, and a host of other conventional antibiotics. The dumbbell-shaped enzyme, tethered by one of its lobes to the bacterial cell membrane, is a molecular knitting machine. It stitches together the cell wall—a dense meshwork of polysaccharide and peptide threads that forms the bacterium’s protective outer shell.

Both ends of the enzyme contribute to get the job done. The part anchored to the membrane, called the GT domain, first stitches the sugars into chains that form the main fabric of the cell wall. The other end, called the TP domain, then crosslinks the sugar strands with short peptide chains. Penicillin-type drugs attack the TP domain. Moenomycin is the only well-characterized antibiotic that directly cripples the more mysterious GT domain. In either case, the sabotaged cell wall becomes so weak that the bacterium dies.

Lovering, Strynadka, and their colleagues sought to purify and crystallize moenomycin-bound PBP2 to determine the three-dimensional structure of the complex by x-ray crystallography. By understanding how moenomycin binds and interacts with PBP2, explains Strynadka, “we could ask what is really important in the moenomycin molecule for inhibition, and what can we get rid of to make this a smaller compound,

with better pharmacokinetic properties so it will work in humans?”

Proteins like PBP2 are notoriously difficult to extract from their membranes in a way that preserves their native structure. Lovering and research assistant Liza H. de Castro persevered for three years to find just the right conditions to purify and crystallize the protein, on top of an additional two years invested by Daniel Lim, a postdoc previously in the lab. The long-anticipated results, reported in the March 9, 2007, issue of *Science*, offer drug designers a wellspring

of information. “Our structure tells us exactly what the key components are that allow moenomycin to bind to the GT domain,” says Strynadka. It also enables them to define the smallest possible part of moenomycin that will react with PBP2, key to reducing the antibiotic’s size for use in humans.

The researchers also found that the bacterial membrane, which caused so much

frustration, might be a large factor in helping the moenomycin-PBP2 reaction fend off resistance, Strynadka says. “From what our structure shows, the GT enzyme activity appears to work within the membrane. And perhaps that protects the enzyme from modifications that would normally be part of a resistance phenomenon.”

Sounds like the makings of a better bullet against the toughest germs. ■

—PAUL MUHLRAD

ENZYME FREEZE-FRAME

A structural model of the penicillin binding protein 2 (PBP2) engaged with the antibiotic moenomycin. The strands and helical ribbons represent the “backbone” of the PBP2 chain, while the surrounding shapes represent the entire protein structure.

