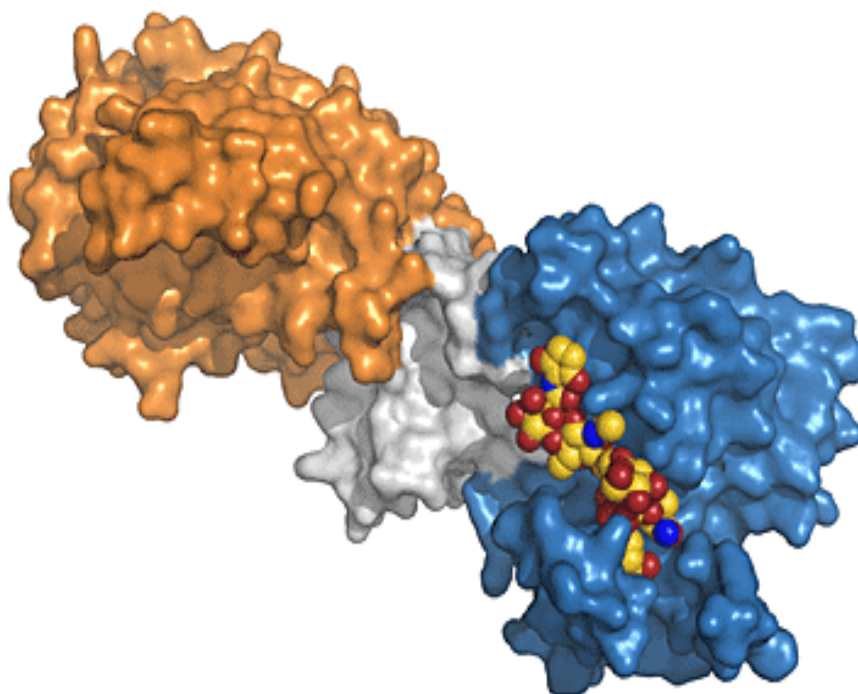


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## Bacterial Walls Come Tumbling Down



**Image Title:** The image shows a substrate based inhibitor in the GT region (blue) of the PBP2 enzyme that blocks bacterial cell wall synthesis. The GT region of the PBP2 enzyme is responsible for creating a sugar chain from the individual lipid II molecules. - Courtesy of Natalie Strynadka

The first detailed images of an elusive drug target on the outer wall of bacteria may provide scientists with enough new information to aid design of novel antibiotics. The drugs are much needed to treat deadly infections initiated by *Staphylococcus aureus* and other bacterial pathogens.

The research team, led by Natalie Strynadka, a Howard Hughes Medical Institute (HHMI) international research scholar at the University of British Columbia in Vancouver, Canada, published its findings in the March 9, 2007,

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Penicillin and many newer antibiotics work by blocking a piece of the machinery bacteria use to construct their durable outer walls. Without these tough, protective coatings, bacteria die. The enzymatic machinery (known as PBP2) studied by Strynadka's group has two main parts: One end assembles long sugar fibers; the other end stitches them together with bits of protein to form a sturdy interlocking mesh shell.

Strynadka's team has provided a long-awaited look at the portion of the enzyme used in the first step of the biochemical pathway that initiates assembly of the sugar coating. The second step is targeted by penicillin and has been well studied.

Although scientists have spent many years identifying bacterial components whose structural features might have weaknesses that can be exploited by antibiotics, progress in turning up bona fide drug targets has been slow. The cell wall enzymes in particular have tantalized scientists, Strynadka said. "The cell wall has all the hallmarks of a great drug target," she explained. "It is essential to the survival of all bacteria. The enzymes that create the cell wall are unique to bacteria. And it is accessible; you don't have to get the antibiotics into the cell."

In their structural studies, the researchers focused on *Staphylococcus aureus*, a notorious human pathogen. An epidemic strain of the bacteria known as methicillin-resistant *Staphylococcus aureus* is resistant to several common antibiotics, including penicillin and amoxicillin, and is a great cause for concern among hospital infectious disease staff. Postdoctoral fellow Andrew Lovering, who is first author on the paper, hopes the group's three-dimensional pictures of the sugar-building enzyme from *S. aureus* will accelerate the search for an effective weapon against the infamous superbug.

The images produced by Strynadka's team show the enzyme frozen in place by a powerful antibiotic called moenomycin. Moenomycin has been used for decades in animal feed to promote livestock growth. Bacteria have shown very little evidence of resistance to this antibiotic so far, and scientists think related compounds may be promising candidates for use in humans.

"This enzyme is an awesome target for antibiotics," said Strynadka. "We have a totally new understanding of how the enzyme works and how a very good animal antibiotic inhibits the enzyme." Although moenomycin is poorly absorbed by the human body, the new understanding of exactly how it interferes with bacterial enzyme function should help scientists design modified versions that are more suitable for use in people.

Understanding the structure of this enzyme should also speed up screening and design of new antibiotics, which are in constant demand as microbes continually evolve new ways to evade the drugs that researchers design to thwart them. The time it takes for bacteria to develop resistance to new antibiotics has been as short as one year for penicillin V and as long as 30 years for vancomycin.

Researchers attempting to solve the structure of this enzyme have struggled to recreate its cellular environment in the laboratory. But after much tinkering with different combinations of detergent, ions, and chemical additives, Strynadka's team was able to crystallize the enzyme so that it would diffract x-rays into a pattern that would ultimately reveal its natural structure. They then were able to repeat the feat to reveal the crystal structure of the enzyme combined with the animal antibiotic.

Their findings help reveal how the enzyme prepares to assemble the bacteria's sugar-coating by plucking sugars from a fat-sugar package known as lipid II. The antibiotic, which is another kind of sugar-lipid, probably mimics the lipid II molecule by tucking into a fold in the enzyme and taking up the space needed to bind to lipid II, the researchers believe. "We would like to see the enzyme in a complex with its natural substrates as well as with inhibitors," Lovering said. In the meantime, scientists now have the details of its shape and key contact points between enzyme and antibiotic.

The enzyme structure is the first ever solved of a member of a family of enzymes that remove sugars from lipids and attach them to other sugars. This process is used in a wide range of biochemical reactions, including allergic responses and cell signaling in cancer.