

Penicillin Tactics Revealed by Scientists

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Introduction. Penicillin, the wonder drug discovered in 1928, works in ways that are still mysterious almost a century later. One of the oldest and most widely used antibiotics, it attacks enzymes that build the bacterial cell wall, a mesh that surrounds the bacterial membrane and gives the cells their integrity and shape. Once that wall is breached, bacteria die -- allowing us to recover from infection. That would be the end of the story, if resistance to penicillin and other antibiotics hadn't emerged over recent decades as a serious threat to human health. While scientists continue to search for new antibiotics, they still don't understand very much about how the old ones work.

To find out, Bernhardt and Hongbaek Cho, a postdoctoral fellow in the Bernhardt Lab and lead author of the Cell paper, used a specific derivative of penicillin that targets only one enzyme in cell-wall assembly. Their trick was to genetically manipulate their study subject *E. coli* to make this enzyme dispensable for the life of the cell. To their surprise, the scientists saw that targeting the nonessential enzyme with the penicillin still killed the cell. This finding was quite a conundrum. The enzyme could be removed from cells completely without harm. Yet, when it was present and bound by the drug, the cells would die. The investigators discovered that the root cause of the problem was that the drug not only inhibited the enzyme, but it also caused it to malfunction in such a way that its activity became toxic. They found that the bacteria still made new cell wall strands, but because linking was blocked, they were immediately degraded, which set up a futile cycle of building up and breaking down the cell wall. This suggested that while the cell has many molecular machines building the wall, the drugs need to hit only a few of them to drain resources from the rest.

Conclusions. Penicillin is powerful, but it's still vulnerable to resistance. When the cell walls of bacteria are disintegrating, they fight back with enzymes called beta-lactamases that slice the beta-lactam molecules and keep them from attaching to their targets. Now it has been directly shown to cause the futile cycle of building and degrading new cell-wall material, creating the alarm signal the bacterium uses to start the production of beta-lactamases. Knowing in greater detail just how *Slt* recruits beta-lactamases may lead to ways to block this form of resistance.

References:

1. The above story is based on materials provided by Harvard Medical School. The original article was written by Elisabeth Cooney.
2. Harvard Medical School. "Penicillin tactics revealed by scientists." // ScienceDaily. 5.12. 2014. <www.sciencedaily.com/releases/2014/12/141205114011.htm>.
3. Hongbaek Cho, Tsuyoshi Uehara, Thomas G. Bernhardt. Beta-Lactam Antibiotics Induce a Lethal Malfunctioning of the Bacterial Cell Wall Synthesis Machinery. *Cell*, 2014; 159 (6): 1300 DOI: 10.1016/j.cell.2014.11.017