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Press Release

New strategies for “old” antibiotics

Tübingen researchers say new components in medicine could help conventional antibiotics overcome resistant bacteria

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The spread of multi-resistant pathogens is of increasing concern to medical researchers and laypeople alike. Yet it is expensive and time-consuming to develop new antibiotics. Researchers at the Universities of Tübingen and Konstanz are now looking at ways to save time by making current treatments more effective.

A team headed by Professor Christoph Mayer, of the Interfaculty Institute of Microbiology and Infection Medicine, in collaboration with the Graduate School of Chemical Biology in Konstanz, has discovered how pseudomonas bacteria recycle an important building-block in their cell envelope – thereby avoiding the effects of the broad-spectrum antibiotic fosfomycin. Having isolated this point of resistance, the researchers have now found new approaches toward making the antibiotic more efficient.

Pseudomonas and acinetobacter bacteria can infect wounds and lead to life-threatening pneumonia, meningitis and septicemia. They are highly resistant to many antibiotics. The bacterial cell envelope is structured differently from human cell membranes, being made of peptidoglycan, a macromolecule composed of sugars and amino acids. Peptidoglycan forms large networks, giving the cell a high mechanical stability, and is essential to these bacteria. It is therefore a target for antibiotics aiming to stop the bacteria from forming new cell walls and reproducing.

For example, the antibiotic fosfomycin prevents growth of the bacterial cell envelope by inhibiting peptidoglycan production in its early stages. But the researchers found that pseudomonas bacteria did not always produce the preliminary building-blocks of peptidoglycan – instead recycling existing ones and bypassing the point at which fosfomycin could inhibit cell reproduction. This greatly reduced the effectiveness of the antibiotic. The researchers calculated that roughly half of the early stages of peptidoglycan were being made of recycled material.

The researchers isolated two new genes in pseudomonas bacteria which were needed for this recycling process and switched them off in the

laboratory, overcoming this internal resistance to fosfomycin. The relevant genes, it turns out, are present in many bacteria, including many which cause disease in humans. It is possible that all of them could use the recycling technique to reduce the effectiveness of fosfomycin.

Unfortunately it is not so easy to switch off bacterial genes once they have attacked a person. However, enzymes could provide new targets for future medication. “We now have important starting-points from which to optimize the effectiveness of fosfomycin. It would make sense to supplement the antibiotic with an appropriate component which would inhibit peptidoglycan recycling,” says Christoph Mayer. He believes that such new combinations of well-known antibiotics are the way forward to new and possibly more effective treatments for bacterial infections. The pharmaceuticals maker Dr. Kade sponsors this work via a Dr. Marietta Lutze grant.

Original publication:
Jonathan Gisin, Alexander Schneider, Bettina Nägele, Marina Borisova, Christoph Mayer (2013) A cell wall recycling shortcut that bypasses peptidoglycan *de novo* biosynthesis. *Nature Chemical Biology*, 9: 491-93, doi 10.1038/nchembio.1289.

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