

Super-antibiotics that could overcome antibiotic-resistance

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The WHO has designated resistance against antimicrobials to be one of the world's top ten risks to humankind. The ability of bacteria and fungi to defeat the drugs that are formulated to kill them is called antibiotic resistance. Antibiotic-resistant illnesses are predicted to claim ten million lives every year by 2050 leaving world economics with severe losses. There is an increasing list of bacteria that are resistant to treatment against all known antibiotic alternatives and just a few new medications are in the pipeline causing new antibiotic classes to be of critical need regarding public health protection. It is important to establish a creative, two-pronged approach for developing novel compounds that can eliminate illnesses that are difficult to treat and simultaneously improve the natural host immune response. Apart from targeting nuclear and protein synthesis, the existing antibiotics target important bacterial processes such as the formation of the cell membrane and metabolic processes. Focusing on the metabolic pathway of bacteria would help in the production of more powerful antibiotics than the existing ones.

The biosynthesis of isoprenoids, which are necessary for cell survival in most pathogenic bacteria, is carried out by methyl-D-erythritol phosphate (MEP) or the non-mevalonate pathway. In order to prevent this process and kill the bacteria, the enzyme IspH (4-hydroxy-3-methylbut-2-enyl diphosphate reductase) was targeted, which is an important enzyme in isoprenoid biosynthesis. In the bacterial world, the broad occurrence of IspH can lead to this approach that is significant for a large array of bacteria. Computer modelling techniques were used to screen several million commercially obtainable compounds for their ability to bind with the enzymes, selecting the most powerful compound that inhibited IspH as the starting point for medical research. Because inhibitors of IspH which were previously available were unable to penetrate the bacterial wall, the search for novel molecules for the inhibition of IspH started, which would be able to penetrate inside the bacteria. In the clinical trials of antibiotic-resistant bacteria, including the vast variety of pathogenic Gram-negative and Gram-positive bacteria, the IspH inhibitors were seen to be more powerful and specific in the bacterial killing activity than existing best-in-class antibiotics. These super antibiotics open new scope to protect humans against bacterial antibiotic resistance threat.

Keywords: Antimicrobial resistance, Super-antibiotics, MEP pathway, ISpH inhibitors, Immune response, Bacterial pathogens

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