Antimicrobial Resistance and Antibiotics Research in Switzerland

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Resistance of bacterial pathogens to commonly used antibiotics has reached alarming levels worldwide leading to calls for global action to tackle the problem.[1] In analogy to EU and US, the Swiss government has published in 2016 the ‘Swiss Antibiotic Resistance Report’ as a combined national report on the comprehensive monitoring of antibiotic resistance and antibiotic consumption in human and veterinary medicine.[2] With the ‘one health approach’ in mind, the knowledge that human health is closely connected to the health of animals and the environment, the Swiss government proposed a list of action items with the aim to limit antimicrobial resistance development and its spread in the environment. 36 topics were defined which fall under eight different areas. Monitoring prevalence of resistance is key to understand its spread. Prevention of resistance emergence is essential and can be achieved through the prudent use of antibiotics and through combating and eliminating existing resistances. An important role plays the cooperation between disciplines as well as information and education of stakeholders which is helped by the regulatory and political environment.

And last but not least research and development of novel antibiotic drugs effective against multi drug resistant pathogens is of high urgency.

Recently, an update about the progress of the program was published by the Swiss government.[3]

Historically, the Swiss pharmaceutical industry had played an important role in the discovery of novel antibiotics. Especially the development of Ceftriaxone (Rocephin®) in the 1980 was a success, for the patients and also commercially. In the meantime, the situation in the pharmaceutical industry has changed. Requirements for the admission of novel medicines have significantly increased, together with costs. Prices for antibiotics are low compared to other indications. From an economical point of view the development of an antibiotic nowadays is not interest-

Fig. 1. Reversion of ETH resistance in tuberculosis-infected mice. Source: Science 2017, 355, 1206-1211. Reprinted with permission from AAAS

BioVersys has discovered a class of compounds named SMART (small molecules aborting resistance) that induce an alternative bioactivation pathway and thus reinstall susceptibility to ETH as shown in a murine infection model (Fig. 1). Co-administration of such a SMART-compound should render the pathogens sensitive to ETH again and thus prolong the lifetime of this important drug against M. tuberculosis.

Recent publications by Actelion Pharmaceuticals document their research programs targeting bacterial topoisomerases.[5,6] These enzymes, called DNA gyrase and TopoisomeraseIV are essential enzymes in Gram-positive and Gram-negative pathogens, regulating the topological state of DNA during replication. Topoisomerases are the targets of fluorquinolone antibiotics (i.e. ciprofloxacin and moxifloxacin) which over the last 20 years have played an important role in the treatment of severe infections predominantly caused by Gram-negative bacteria. Unfortunately, emergence of resistance has severely limited the utility of this class of drugs. At least three other binding sites and therefore unrelated modes of inhibition have been discovered.[6-8] Actelion worked on two different binding sites: the ATP binding site[6] and the site at the interface of DNA and enzyme where the so-called ‘Novel Bacterial Topoisomerase Inhibitors (NBTI)’ are known to bind.[7] Actelion described how they managed to extend the activity of inhibitors with a mainly Gram-positive spectrum towards Gram-negative pathogens by
modulating the physicochemical properties of the inhibitors (Fig. 2).

The systematic investigation of the parameters influencing the intracellular concentration of antibiotics has only recently been acknowledged as crucial for the development of novel agents active on Gram-negative pathogens. It has become clear that penetration into cells as well as efflux by specific pumps are the most important limiting factors for the development of novel antibacterial agents acting on a cytoplasmic target.

The problem of cell permeability was circumvented by Polyphor by choosing a target located in the outer bacterial membrane. Optimization of their PEM (Protein Epitope Mimetics) library has led to the discovery of POL7080 (murepavadin), a macrocyclic peptide selectively acting on Pseudomonas aeruginosa, one of the most difficult to treat Gram-negative pathogens. Researchers at Polyphor and the University of Zurich could show that POL7080 targets the outer membrane barrel LptD, which is a novel target in antibacterial drug discovery. The compound has successfully completed Phase 2, start of Phase 3 is planned for 2018. A recent review article describes strategies for the design and generation of large macrocyclic libraries and highlights the potential thereof for drug discovery (Fig. 3).

The global spread of resistant pathogens as well as the inherent obstacles for the development of novel treatment options ask for innovative approaches and perseverance. We are glad to see that Swiss biotech companies take this challenge!

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Fig. 3. The protein epitope mimetic (PEM) approach, reprinted from A. Luther et al., Current Opinion in Chemical Biology, 2017, 38, 45. Copyright (2017), with permission from Elsevier.