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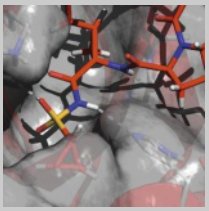

Medicinal Chemistry and Chemical Biology Highlights

Division of Medicinal Chemistry and Chemical Biology

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The World Needs Novel Antibiotics – and so does Switzerland

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This article is an excerpt of the synthesis report that was drafted in the context of the National Research Programme 'Antimicrobial Resistance' (NRP 72) of the Swiss National Science Foundation. The full report was published on the 15th November 2022 and can be found on the NRP 72 homepage (https://www.nfp72.ch/en/OdKdigE5p7Kb8Mu/page/findings).

Antimicrobial resistance (AMR) is a growing problem of global dimension (https://www.who.int/publications/i/item/9789240027336). Antibiotics belong to the most important discoveries of medicine, and patient safety in hospitals and in particular in intensive care units critically depends on functioning antibiotics. It is well recognized that the extent of the global AMR crisis has its roots in the massive misuse of antibiotics over several decades, both in veterinary and in human medicine. To slow the spread of AMR, industrialized countries including Switzerland have significantly reduced antibiotics usage in both veterinarian and human medicine and pertinent antibiotic stewardship programs have been implemented (https://www.star.admin.ch/star/de/home.html).

However, reduced antibiotics consumption will only slow down, but not stop, the spread of AMR. Therefore, it does not suffice to implement more decisive or even radical antibiotic stewardship programs to overcome the AMR crisis. Instead, it is imperative to discover and develop novel antibiotics and alternative antimicrobial treatments.[1]

The Swiss National Science Foundation launched the National Research Programme 'Antimicrobial Resistance' (NRP 72) on behalf of the Federal Council in 2017, which received a total of CHF 20 million of funding. In this context, a handful of projects aiming at the discovery of novel antibiotics were carried out at Swiss universities (Fig. 1).

Antibiotics discovery projects in the context of the NRP 72 aimed at i) improving the efficacy and safety profile of aminoglycosides and thereby overcoming resistance mechanisms,[2] ii) generating artificial peptide dendrimers not found in nature that exhibit antimicrobial activity against multi-resistant *Pseudomonas aeruginosa*;[3] iii) engineering phage-derived enzymes called endolysins to effectively target intracellular *Staphylococcus aureus*;[4] iv) the development of chimeric peptidomimetic antibiotics that target the essential outer membrane protein BamA of gram-negative pathogens;[5] v) genome-mining to discover biosynthesis pathways for novel antibiotics in microorganisms living on sponges and plants.[6]

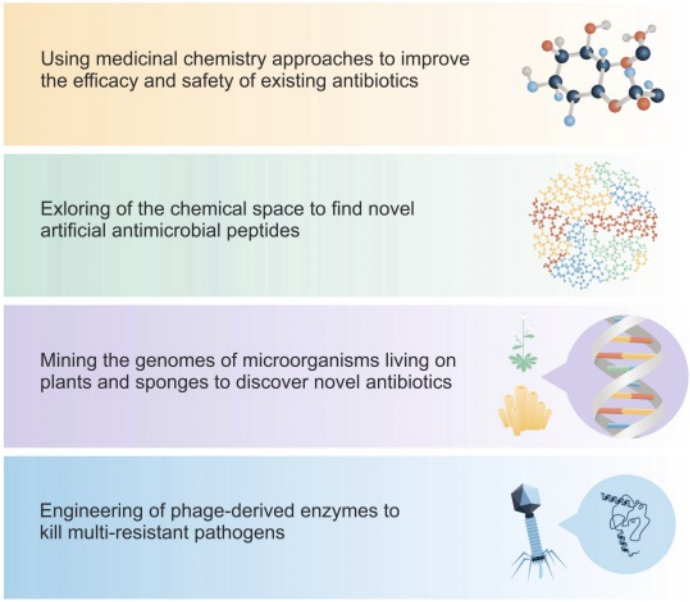

Fig. 1. Innovative antibiotic discovery projects conducted in the framework of the NRP 72 at Swiss Universities. Copyright picture: NFP 72 / Vaudeville Studios.

These excellent research findings demonstrate the opportunities offered by basic research to discover and engineer novel antimicrobials. Regrettably, further clinical development of these lead compounds proved to be challenging. The main reason behind this shortcoming is the poor economic attractiveness of the antibiotics market, which results in a severe lack of private investments in the clinical development of antibiotics (Fig. 2). Historically, prices for antibiotics have been low, and antibiotic stewardship programs demand for a prudent and thus rare use of novel last resort antibiotics. Furthermore, the AMR crisis is not equally severe across the globe; in Switzerland, the number of yearly deaths caused by AMR is estimated to amount to around 270 and thus is still comparatively low as compared to the estimated 1.27 million deaths caused by AMR worldwide.[7,8]

In recent years, governments across the globe made major investments in supporting antibiotics research by means of so-called 'push-incentives', namely, to boost innovations mainly at research universities. More recently and driven by international initiatives such as CARB-X and the Novo Repair Action fund, substantial push funding was targeted towards translational research and early development SMEs. Of note, Swiss SMEs active in the development of novel antibiotics were very successful in securing competitive funds from CARB-X in the past ten years.

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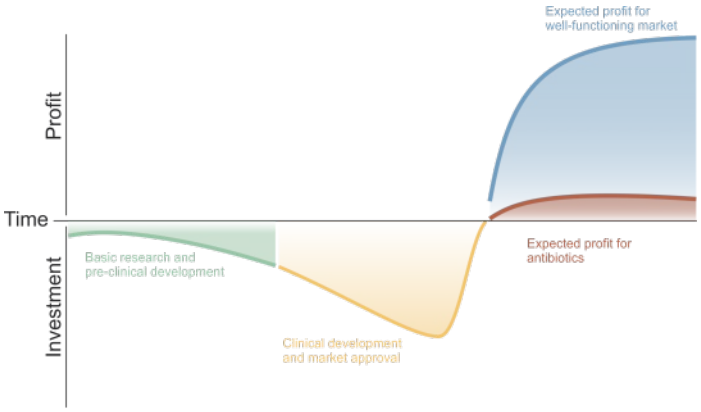

Fig. 2. Failed market for antibiotics. Investments carried out during the clinical development of novel antibiotics are not rewarded with commensurate profits. This explains the low number of novel antibiotics reaching market approval. Copyright picture: NFP 72 / Vaudeville Studios.

Unfortunately, while these investments are very important and need to be sustained, they do not suffice on their own to fix the problem of the broken antibiotics market. Therefore, the implementation of so-called 'pull-incentives' is currently discussed, but not yet implemented at an adequate scale (https://beam-alliance.eu/beam-proposal-eu-incentives/). The basic concept behind pull-incentives is to delink revenues from sales volume of antibiotics, for example by subscription models, thereby complying with the concept of antibiotic stewardship.

While some European countries such as Sweden or the UK play a pioneering role in running pilot programmes on pull-incentives, Switzerland has thus far played a passive role that neither represents Switzerland's capacity in drug innovation and development nor does it reflect the country's economic power or its aspiration for leadership in global health security.

The NRP72 synthesis working group therefore strongly advocates the Swiss Government to take an active role in fighting the global AMR crisis by improving the economic framework conditions for the development of novel antibiotics and by significantly increasing its financial engagement in this domain. Further, the Swiss Government is asked to increase its financial contributions towards well-established international actors such as Geneva-based GARDP and US-based CARB-X.

As a wealthy country hosting several international organizations dedicated to fight AMR, excellent research institutions and a strong life science sector, including numerous SMEs and one large pharma company standing at the international forefront of clinical development of antibiotics, Switzerland is in a unique position to actively contribute to one of the biggest global challenges of the 21st century.

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