Phage Lysins as a Promising Alternative Class of Antibiotics: a Metagenomics-Driven High-Throughput Platform for the Discovery of Novel Lysins

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The rapid emergence and dissemination of multi- and extensively drug-resistant bacteria pose a significant public health concern. Antibiotic-resistant bacteria are projected to kill 10 million people by 2050. Moreover, there has been a lack of introduction of new antibiotic classes for over five decades and the once successful Waksman platform for the discovering novel antibiotics has been largely depleted. Consequently, this all have resulted in a limited array of therapeutic options. Hence, there is an urgent need for the development of new discovery platforms to identify novel antibacterials and replenish the antibiotic portfolio.

Lysins, or bacteriophage-encoded peptidoglycan hydrolases, represent a promising and alternative class of antibiotics. They are highly specific at the species level, resulting in a narrow spectrum of activity. Yet, we and other experts claim that more novel lysin candidates must be discovered and engineered to feed the (pre)clinical pipeline.

Several promising approaches have emerged within the field of metagenomics. Here I will elucidate two concepts that have been the focus of my research. Their main idea rests upon the premise that the largely unexplored metagenome derived from uncultivable bacteriophages represents an essentially infinite reservoir of potentially potent lysins. The aim is to build an efficient discovery platform specifically tailored for novel lysin-based antibiotics, employing functional and sequence-based metagenomic methodologies.