

LS17-029 - bac-PROTAC: Developing proteolysis-targeting small molecules for the selective elimination of bacterial proteins

Abstract

Bacterial infections cause hundreds of thousands of deaths every year, and antibiotic resistance is becoming increasingly common, making the development of new antibiotics crucial. In the present project, we have developed a new type of antibiotic called BacPROTACs, which can selectively target and degrade bacterial proteins. Our BacPROTACs consist of two linked head groups that physically tether a specific target protein to a molecular shredder inside bacteria. As a result, the targeted protein is degraded, potentially leading to the bacterial death. The modular structure of BacPROTACs is versatile and can thus be adjusted to different target proteins and different bacterial species. We provide proof-of-concept data that BacPROTACs can reprogram the degradation devices in Gram-positive bacteria and mycobacteria, including prominent pathogens such as MRSA and Mycobacterium tuberculosis. In conclusion, BacPROTACs have the potential to boost antibiotic discovery, providing a platform to develop not only a single but a whole family of anti-bacterial agents. Moreover, the BacPROTAC induced elimination of specific proteins allows researchers to understand the roles of that specific proteins play in the bacterial cell.

Scientific disciplines:

Chemical biology (40%) | Biochemistry (30%) | Structural biology (30%)

Keywords:

PROTAC, targeted protein degradation, modulatory small-molecules, XL-MS

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Further links to the persons involved and to the project can be found under

<https://www.gmbh.wwtf.at/funding/programmes/ls/LS17-029/>