WWTF Project LS17-029

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

Abstract

The AAA protease ClpCP constitutes the core of the protein quality control system in Gram-positive bacteria, removing damaged proteins during stress situations. Aberrant proteins that need to be degraded are labeled by McsB, a protein kinase unique in phosphorylating arginine residues. The resulting pArg degradation mark is recognized by the N-terminal domain (NTD) of the ClpC unfoldase, which then translocates the captured client protein into the proteolytic cage formed by ClpP. The described pArg-ClpCP degradation system represents a simple, bacterial version of the eukaryotic ubiquitin-proteasome pathway. In this project, we will pursue a Chemical Biology approach to address the unique mechanistic features of the ClpCP protease. Guided by the structure of the recognized pArg mark, we will synthesize chemical substrate-mimics of ClpCP and characterize their binding mode by biochemical, mass spectrometric and crystallographic studies. Elucidating structural details of the pArg-dependent targeting mechanism holds great potential for developing a bac-PROTAC methodology that would allow for targeted, small molecule-induced protein degradation in bacteria. This system may be employed in basic microbial research as well as an alternative chemotherapeutic strategy against pathogenic bacteria, which still represent a major threat to human health.

Scientific disciplines:
104004 - Chemical biology (40%) | 106002 - Biochemistry (30%) | 106041 - Structural biology (30%)

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

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Further links about the involved persons and regarding the project you can find at
https://archiv.wwtf.at/programmes/life_sciences/LS17-029