Call: 6th transnational call for the JPIAMR within the ERA-NET JPI-EC-AMR:
Innovations against antibiotic-resistant bacteria: New targets, compounds and tools

Title: Fighting antibiotic-resistant superbugs with anti-persister compounds targeting the stringent response

Acronym: Anti-Persistence

Consortium composition

Type	Name	Institute	Country
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Abstract
Pathogenic antibiotic-resistant "superbugs" are increasing at an alarming pace. Persistence to antibiotics favours the emergence of resistance as mutations increasing antibiotic tolerance favour selection of resistance mutations. Persisters constitute subpopulations of cells that can withstand bactericidal antibiotics and are considered as a primary source of infections since they are difficult or impossible to eradicate with conventional antibiotics. Persister bacteria are encountered in a variety of chronic pathologies, including cystic fibrosis, pneumonia and tuberculosis. Thus the impact of persistence on public health is enormous and there is a pressing need to develop treatments to kill persisters. The existence of a causal link between persisters and persistent infections was demonstrated for *S. typhimurium*, whose survival inside the host relies on ppGpp. Compounds capable of killing persisters could sterilise *S. aureus* cultures and cured methicillin-resistant *S. aureus* (MRSA)-infected mice. Thus targeting the enzymes that regulate ppGpp is an interesting and unexplored route to develop new antibiotics active against persisters. This project aims to target key steps in the mechanism of ppGpp synthesis and hydrolysis in a variety of pathogenic bacteria. In an integrative biochemistry, structural and cellular biology based approach we will uncover novel mechanistic aspects of persistence, deliver novel metabolic biosensors for single-cell analysis and methodologies to study persisters in human pathogens, and discover and validate novel compounds with anti-persister action.