

**ACRONYM:** Combinatorials

**Title:** Novel drugs and drug combinations against bacterial growth, survival and persistence; from high-throughput screening to mechanism of action

**Keywords:** Combinatorial treatments; High-throughput screen; PK/PD modelling; Novel targets; Resistance; Persistence; Competence; Bactericidal; Mechanism; Mode-of-action; Animal studies; Drug discovery

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**Abstract:**

Control of bacterial infections is threatened by the rapid emergence of drug resistance, drug tolerance that mitigates antimicrobial efficacy, and the lack of new antibiotics in recent years. Combination treatments and/or re-purposing of known drugs can provide a cost- and time-efficient solution. We propose a comprehensive and powerful strategy to repurpose or improve FDA-approved drugs including neglected/disused (ND) antibiotics, and identify combinations to re-sensitize resistant/tolerant bacteria. Using high-throughput screening (HTS), we will test thousands of pairwise drug combinations on bacterial growth, viability and bacterial persistence in three clinically relevant pathogens: uropathogenic *Escherichia coli* (UPEC), *Staphylococcus aureus* (Sa), and *Streptococcus pneumoniae* (Sp). Our scope thus spans the Gram-negative/-positive divide, and targets several bacterial states implicated in both acute and chronic infections, including pneumonia, pyelonephritis, bacteremia and endocarditis. To optimize antimicrobial treatment, we will use state-of-the-art and further advance translational pharmacokinetic (PK)/ pharmacodynamic (PD) modeling. This will prioritize and validate lead combinations, which will be tested in several toxicity and animal models. In vivo PK/PD modeling will be also performed for our top leading combinations. Together, these approaches will provide invaluable pre-clinical data that will inform future drug development. In parallel, we will systematically probe for modes of action of our top 100 synergistic drug combinations using HT reverse genetic screens to provide the framework for subsequent in-depth mechanistic studies targeting processes such as the role of redox and iron homeostasis, membrane permeability/stability, drug efflux/influx and bacterial metabolism and stress responses in antimicrobial activity. We have assembled a strong team with extensive expertise in the cellular processes directly related to antimicrobial activity. For this project, we will combine HT chemical and genetic screening, large-scale data analysis, mechanistic biology, PK/PD modelling and infection models to discover and exploit antimicrobial combination therapy. The breadth and scope of our ambitious strategy will undoubtedly significantly advance the quest for novel treatment strategies against bacterial infections.