ACRONYM: JumpAR

Title: A multi-scale approach to understanding the mechanisms of mobile DNA driven antimicrobial resistance transmission.

Keywords: Multi-drug resistant bacteria, Resistance gene transfer, Mobile genetic elements, Metagenomics, Molecular mechanism, Animal studies, Clinical survey

Consortium composition:

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Abstract:

Antimicrobial resistance (AMR) spreads at an alarming pace resulting in continuous emergence of more virulent pathogens and multidrug-resistant 'superbugs'.Mobile genetic elements (MGE) provide a major mechanism to transfer AMR genes in hotspots of microbial interaction, including the bacterial communities in the human gut. However, the dynamics and mechanisms of movement of such 'jumping genes' are poorly understood. It is unclear how often they move, which natural and man-made compounds influence their movement, and how their movement occurs at the molecular level.

Here we propose (i) to annotate and characterize MGEs in available bacterial genomes and metagenomes in order to characterize their genetic cargos and dynamics of transfer; (ii) to study the impact of antibiotic treatment on MGE-mediated gene transfer in human patients with antibiotic resistant infections; (iii) to analyse the influence of natural microbial compounds and diverse clinically applied drugs on AMR transmission; and (iv) to dissect the structure and functioning of the underlying molecular machinery.

This work will elucidate AMR transfer at all scales from atomic resolution through bacterial and animal models to gut ecosystems in human patients individually and at the population level. To achieve these ambitious aims, our multidisciplinary consortium brings together leading scientists with complementary expertise in metagenomics, infection biology, infection medicine, molecular genetics, chemical biology, and structural biology.

By drawing on available genomic and metagenomic data, we will gain a global picture of the prevalence and distribution of MGEs, their AMR gene cargos, and transmission potential. Using clinical samples, including available data and a novel specialized cohort, we will chart the effects of antibiotics and other human drugs on MGE-borne AMR transmission, which will enable predictions on the likelihood of transfer in different settings. Using in vivo and in vitro models, we will obtain molecular level insights into the mechanisms and extent of active AMR transmission. Using unbiased high-throughput screening (HTS) in bacterial cultures, we will scout unanticipated environmental modulators of AMR transmission, which we will validate in animal models and identify their mode of action in in vitro tests and structure-function studies.

Integration of these insights will vastly expand our knowledge on the mechanisms and dynamics of MGE-borne AMR dissemination, opening doors to the development of novel intervention strategies and preventive measures aimed at reducing active transfer of AMR genes. In particular, our genomic surveys will help us develop risk assessment approaches relying on accurate prediction of AMR gene mobility, and our data on transfer enhancers and inhibitors will allow to design revised treatment guidelines for AMR colonized patients to prevent further transmission of resistance. Furthermore, we expect that the knowledge acquired here will lead to additional clinically relevant outcomes on the longer term, including design of specific inhibitors to prevent MGE-mediated AMR transfer, and development of diagnostic tools for AMR gene mobility.