Sujet: "BIOLOGICAL EFFECTS OF THE SUBINHIBITORY CONCENTRATIONS OF BACTERICIDAL ANTIBIOTICS ON BACTERIA

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Antibiotic resistance is a major public health problem. By seriously challenging our ability to treat bacterial infections it creates substantial mortality and morbidity as well as a significant economic cost. Therefore, a better understanding of the evolution of antibiotic resistance in bacterial populations is required for its prediction and control. Without such knowledge the responses to the antibiotic resistance problem will always be reactive, rather than proactive.

Vast majority of the studies evaluate effects of the above-minimal inhibitory concentration of antibiotics on bacteria. However, bacteria very frequently encounter very low concentrations of antibiotics in their environments, which also significantly influence emergence and dissemination of antibiotic resistance. Our project aims to examine biological effects of the subinhibitory concentrations of bactericidal antibiotics on bacteria, and in particular the impact on the induction of stress responses, horizontal gene transfer and mutation rates in Escherichia coli.

This is of major importance because induction of stress responses can increase intrinsic resistance to antibiotics, while increased mutagenesis and horizontal gene

transfers enhance probability of acquiring antibiotic resistance.

Our proposal is structured in three complementary tasks:

1) Characterization of the physiological state of bacteria exposed to the subinhibitory concentrations of different antibiotics.

2) Characterization of the modulation of the gene expression profiles of bacteria exposed to the subinhibitory concentrations of different antibiotics.

3) Characterization of an impact of the exposure of bacteria to the subinhibitory concentrations of different antibiotics to induction of persister state.

For this project, we envisage combining genetic, molecular biology and biochemical approaches with novel experimental methods allowing the study of individual bacterial cells. Our laboratory possess a fully automated robotic set-up allowing high throughput analysis and microfluidic platform coupled with automated fluorescent microscope, which will allow studying real-time analysis of living individual cells.

Our study will provide knowledge allowing risk assessment for the development of resistance to different antibiotics in bacteria exposed to very low concentrations of antibiotics. This is a key issue for the design of new drugs with low risk of resistance development and for the regulation of drug usage, because one needs to understand in order to be able to predict antibiotic resistance evolution."