Titel des Themas

Overcoming antibiotic resistance - an urgent global challenge Identification of highly effective alternative target specific biological and chemical approaches

Schlagworte

Antibiotics; Resistance; Bacteriophages; Drugs; Antimicrobial Drugs; Novel targets

Kurzfassung des Themas

Along with the consequences of climate change, dementia and cancer, antimicrobial multidrug resistance is seen as one of the greatest challenges facing worldwide society in the coming years. Millions of people die annually as a result of antimicrobial resistance (AMR). Therefore, new strategies are urgently needed to combat such infections, which may also occur as a secondary consequence of primary infections. To avoid multidrug resistance, these strategies must be target specific, i.e., directed at the bacteria causing the disease. Advances in classical antibiotics, which are the cause of AMR, do not provide a basis for successful treatment of bacterial infections. Great hopes are currently placed in biological (e.g. peptides) and biocompatible chemical antibacterial approaches, which are indeed targeted to specific bacteria, but which can be transferred to other bacteria in a modular manner. In addition, novel natural or synthetic compounds that target the bacterial redox metabolism via ROS formation or inhibition of specific defense mechanisms hold promise to tackle AMR. The proposed project is dedicated to these different strategies in an interdisciplinary network. As explained below, Berlin's scientific institutions offer excellent conditions for successfully addressing the topic, both from their complementary composition and from their globally respected, already existing expertise.

a) Inwiefern stellt das Thema eine globale Herausforderung von hoher aktueller und zukünftiger gesellschaftlicher Relevanz dar?

According to a recent study on antimicrobial resistance (AMR) in the journal 'The Lancet' (January 19, 2022; DOI: 10.1016/S0140-6736(21)02724-0), the leading causes of death worldwide include infections with antibiotic-resistant bacteria. In 2019, 4.95 million people lost their lives to diseases associated with antibiotic resistance, and many more underwent severe hospitalization. Of these, about 1.3 million deaths were the direct result of AMR, more deaths than caused by AIDS or Malaria (in 2020, 680,000 HIV/AIDS and 627,000 Malaria). Among these, the six deadliest bacterial pathogens (Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa, Escherichia coli) accounted for nearly three-quarters of all resistance-related deaths. About 200,000 people died in 2019 as a result of infection with antibiotic-resistant E. coli alone. Children under the age of five were most at risk. However, the number of deaths from a particular pathogen varies significantly by region. In places where people with high incomes live, half of those who died from AMR were due to S. aureus and E. coli. Each year, according to the RKI and the ECDC, there are an estimated 400,000 to 600,000 nosocomial infections in Germany and about 10,000 to 20,000 deaths from them.

b) Welches wissenschaftliche Erkenntnisinteresse wird aufgegriffen und ist anschlussfähig für exzellente, internationale Forschung?

Biological and biocompatible chemical antibacterial approaches offer promising strategies to circumvent AMR. The former includes, bacteriophages, which undergo naturally a lytic or lysogenic cycle upon infection of bacteria. However, it is now possible to introduce specific genetic modifications to bacteriophages that can exert a specific mode of action on bacteria and thus also inhibit their infection potential or disrupt biofilm formation. Biocompatible chemical approaches are particularly dedicated to the disruption of the bacterial cell wall or membrane. These can be structural disruptions, inhibition of essential transport proteins for nutrient uptake, or target sensing and signal transduction systems of the bacteria. Equally hopeful are chemical polymer structures that have a profound effect on contact behavior, such as biofilm formation. Initial approaches reported in the literature confirm the hopes placed in them, even if they are still far from practical application. In addition, novel natural or synthetic compounds that target the bacterial redox metabolism via ROS formation or inhibition of specific defense mechanisms hold promise as alternative treatment options of multi-resistant pathogens. The successful exploration of this topic requires expertise in cell and molecular biology as well as microbiology, genetics, chemistry and mathematical-theoretical modeling of structures and systems biology with applications ranging from basic and applied medical research.

c) Inwieweit ist das Thema durch die Expertise der Berliner Wissenschaft und Gesellschaft inter- und transdisziplinär bearbeitbar und/oder lösbar?

Two SFBs - SFB 765 and 1449 – and the SFB/TR84 (Berlin-Marburg/Giessen) are to be mentioned as examples for the potential of the Berlin scientific community to successfully deal with this topic in full breadth. These SFBs and the SFB/TR84 illustrate in their interdisciplinary composition and expertise the necessary prerequisites described under b) for a successful exploration of the topic. The recently completed SFB 765 'Multivalency as a Chemical Organization and Action Principle: New Architectures, Functions and Applications' has developed, among other things, new polymeric structures and modified phages that specifically inhibit the interaction of respiratory viruses with their host cells in a target-specific manner. These structures and phages form an excellent basis for their specific functionalization directed against bacteria. The SFB 'Dynamic Hydrogels at Biointerfaces' addresses the fundamentals of the interaction of pathogens with biological surfaces. In addition, the SFB/TR84 Innate Immunity of the Lung: Mechanisms of Pathogen Attack and Host Defense in Pneumonia' investigates the defense mechanisms of respiratory pathogens against the host innate immune system as well as host-pathogen interactions, providing leads for novel bacterial drug targets, which are important for survival of infections. At the same time, these SFBs prove that this topic has every chance of being successfully approved for another SFB.

Welche weiteren, bislang noch nicht genannten, Argumente sprechen für Ihr Thema?

Since the discovery of penicillin by Alexander Flemming, it is well known that each novel antibiotic causes soon after the application novel resistance mechanism in the bacteria, leading to the prevalence of multi-resistant pathogens with limited treatment options. Thus, it is urgently needed to (i) better understand the defense mechanisms of bacteria against the host immune defense to identify novel drug targets and (ii) to develop and to explore novel biological and biocompatible chemical approaches as well as ROS-producing drugs as alternative treatment options against multi-resistant bacteria to tackle the antibiotic crisis.