The discovery of antibiotics was revolutionary for the management of infectious diseases, but their widespread use has rendered them ineffective for the treatment of many bacterial infections. This phenomenon is known as antimicrobial resistance (AR). If a bacterium carries AR towards more than one antibiotic, this bacterium is considered to be multidrug-resistant (MDR). Currently, the most threatening human bacterial pathogens are **Gram-negatives that continuously, starting from the first published WHO report on Bacterial Priority Pathogen List in 2017, are still designated as critical priority group.** In the latest WHO report from 2024, Gram-negative bacterial pathogens maintain their critical status. Carbapenem-resistant *Acinetobacter baumannii* (CRAB), carbapenem-resistant Enterobacterales (CRE) and third-generation cephalosporin-resistant Enterobacterales (3GCRE) received the highest scores. The development of AR has reached a crisis level currently, jeopardizing our well-being and causing significant economic burden to our society. Development and use of novel antibiotics seem to be the most obvious way to overcome AR. However, there are very few new antibiotics being developed. Therefore, feasible approaches are critically needed to increase the number of therapeutic options. Inspired by the paradigm of the combination of clavulanic acid and β-lactam antibiotics, diverse antibiotic adjuvants have been extended either to enhance the efficacy of antibiotics or to defer the emergence of resistance. **Thus, we hypothesized that the development of broad-spectrum antibiotic adjuvants, exerting their adjuvant activity with multiple classes of existing antibiotics, would greatly benefit the treatment of bacterial infections. Based on our many years of experience (almost 20 years) of research on antimicrobial photodynamic inactivation (aPDI), we want to present aPDI as a non-antibiotic treatment modality that may undoubtedly serve as a broad-spectrum antibiotic adjuvant, resensitizing critical priority pathogens to clinically important antibiotics.** The most potent adjuvant is believed to share the following features, i.e., leading to membrane permeabilization, efflux pump inhibition, enzyme inactivation, quorum sensing inhibition and recruitment of immune cells to infection site. We are able to demonstrate that aPDI may exert all mentioned-above effects towards microbial cells, displaying very potent and broad-spectrum antibiotic adjuvant. During aPDI, molecules called photosensitizers (PS) are excited by light with a specific wavelength in the presence of oxygen, leading to the production of reactive molecular species (RMS). RMS could kill bacteria by oxidatively damaging their biomolecules, especially those constituting the external structures of bacteria, such as the cell membrane and cell wall, which are thus well-accepted as the major targets of aPDI. Moreover, RMS could impair the protein synthesis process, induce DNA mutation, and activate pro-cell-death factors when they penetrate into the internal structures of bacteria. Due to such a multitargeted nature of RMS, aPDI can possibly inactivate bacterial strains regardless of their AR levels and mechanisms, and more importantly, has less potency to induce AR compared to antibiotics. Likewise, RMS generated by aPDI are effective in damaging the bacterial biofilms which might be refractory to the most aggressive regimens of antibiotics. As antibiotics and aPDI are two essential and promising antibacterial therapies, investigations on developing a new, safe and effective approach against MDR bacterial pathogens by combining antibiotic and aPDI are emerging.

The project aims at giving the answers for the following research questions:

(1) It is unknown if the aPDI-induced resensitization of drug resistant bacteria to clinically important antibiotics is PS specific and depends on the microbial growth status.
(2) It is unknown if the aPDI-induced resensitization of drug resistant bacteria to clinically important antibiotics would cover all the most prevalent genotypes expressing various antimicrobial resistance mechanisms.
(3) The molecular mechanisms of aPDI adjuvant activity is still poorly understood.
(4) It is unknown whether the aPDI/antibiotics combination therapy leads to evolution and transmission of antimicrobial resistance.
(5) It is unknown whether the aPDI/antibiotics combination therapy exerts cyto- and genotoxicity effect toward prokaryotic and mammalian cells.