DESCRIPTION FOR THE GENERAL PUBLIC

Before a new substance will become a drug in pharmaceutical industry, it must be comprehensively characterized by many chemical methods during initial tests in the lab. Based on that early phase, researchers hope to identify a promising drug candidate to further *in vitro* biological study, *in vivo* research on animal models (preclinical), and then in people (clinical trials). Besides the hard work of many research groups and financial aspects, there is one essential ingredient - idea and development of the original chemical molecules with biological activity, which is the underlying driving motivation for the success. So now, what is the significance of design and development potential new medicines? What path have to be followed by chemicals from "bench-to-bedside", from laboratory experiments through clinical trials to point-of-care patient applications? During drug development process, the selection of the biological targets for a potential medicine and disease state is one of the basic problem. Vaccines, antibiotics, natural substances or even a simple chemical such as aspirin over the years have changed the face of pharmacotherapy. However, the received wisdom is that nature abhors a vacuum, and one of the greatest challenges that will face health systems globally in the 21st century is the increasing burden of cancer diseases. This is mainly related with the biology of cancer - its heterogeneity, invasiveness and metastasis. Moreover, one of the important features of cancer is the high resistance to traditional therapy, including both intrinsic and acquired (therapy-induced) chemoresistant behaviors of the cancer cells. Accordingly, such "reconnaissance" and analysis of traits responsible for therapy failure can help to fight the enemy more efficiently using new innovative anticancer strategy.

One of the promising alternative methods of cancer treatment is photodynamic therapy (PDT), which in recent years has entered the mainstream of the treatment of tumors. PDT allows the selective killing of cancer cells without damaging surrounding healthy tissues. An important role in this method plays a properly chosen photosensitizing drug with favorable physicochemical properties and high biological efficiency. The photosensitizer absorbs light, becomes activated and is transformed to electronically excited triplet state that can reacts with molecular oxygen in targeted cells by electron or hydrogen transfer or energy transfer with the formation of highly cytotoxic reactive oxygen species. There are three main mechanisms that make PDT an effective anticancer procedure: direct cells killing by ROS, tumor-associated vascular damage and activation of antitumor immune response. Our team under long-term research on new drugs for PDT in collaboration with the University of Coimbra, developed one of bacteriochlorin-based photosensitizer LUZ11 for an application for clinical trials in Europe. The clinical trial proposal was approved by all the regulatory agencies and LUZ11 (INN name Redaporfin) is the first innovative drug developed in Polish and Portuguese universities that reached clinical trials (II phase) for the treatment of cancer. Our experience and research on understanding the mechanisms underlying the effectiveness of PDT allowed to design a library of new potential drugs. In this project we want to test them against most invasive tumors, resistant to chemotherapy and PDT mediated by commercially available photosensitizers. In order to overcome resistance mechanisms we propose not only the appropriate structural modifications by targeting moieties of potential drugs but also we design nanoparticle-based strategy with responsive polymeric nanomicelles. Such small drug delivery systems penetrate tumor tissue more easily than normal tissue due to the enhanced permeability and retention effect and then are able to release their therapeutic payloads. Moreover, according to another hallmark of cancer such as acidic pH, which is markedly different from blood pH, we will use the pH-responsive nano-sized PDT-agents that can be controlled release in tumor microenvironment. Thereby, by targeted delivery we will improve the selectivity and effectiveness of the treatment.

By analyzing the influence of several structural modifications of photoactive drugs on their photochemical profile and photobiological activity, we will be able to select potential medicines against another most worrying threats to public health in recent years, that means the spread of multi-resistant bacterial strains. In view of the prediction of the "end of the antibiotic era", antimicrobial photodynamic therapy can be evaluated as a promising strategy in the treatment of resistant infections. In this context, we plan to use genetic engineering and molecular biology methods to prepare bioluminescent bacteria. That approach enable us to develop monitoring bacterial infection followed by bioluminescence imaging in a non-invasive fashion in individual wounds and soft-tissue abscesses mice in real time. We will also explore the therapeutic potential of newly, most promising "lead" compounds for application in aPDT toward bacterial infections. The results of our research will not only provide knowledge on structure-biological activity relationship (SAR) of potential drugs for photodynamic therapy, but also will help us to understand the drug- and antibiotic- resistance, and in consequence suggest the novel possibility for its overcoming. Recognition of the underlying mechanisms of drug resistance both in cancer and microbes is critical to develop new effective treatments. Carrying out all of preclinical studies such as molecules screening, toxicology studies, establishing predictive translational models based on a thorough disease and treatment understanding as well as identifying biological markers with crucial role in development of resistance may help us to select the most promising drugs for modern phototherapy and create effective PDT/aPDT regimens that can be used in clinical practice in the future.