

Age-related diseases constitute a considerable socioeconomic burden to modern societies. As the mean lifespan of human populations is steadily increasing, age-related diseases, such as Alzheimer's disease (AD) and Parkinson's disease (PD), are increasing in pandemic proportions. Finding new effective therapies hampering the development of these diseases can bring new hope to individuals affected and reduce the cost of healthcare.

As AD progresses, the loss of reasoning ability, language, decision-making ability, judgment and other critical skills make navigating day-to-day living impossible without help from others, most often a family member or friend. PD is recognized as the second most common neurodegenerative disorder after AD and affects 1% of the population worldwide after the age of 65 years. The main symptoms of PD are disturbances including slow movements, stationary tremor and increased tension of plastic-type muscles. There are no drug treatments that can cure AD and PD. However, medicines have been developed for these diseases that can temporarily alleviate symptoms, or slow down their progression, in some patients. Search for effective neuroprotectors is therefore extremely important.

Oxidative stress (OS) and nitrate stress (NS) accompanies inevitably these diseases and plays a key role in activation of many signaling pathways contributing to the development of AD and PD. Under conditions of OS, the production of ROS increases remarkably and endogenous antioxidants fail to protect adequately vital biomolecules against reactive oxygen species (ROS) damage. Prevention of OS injuries is an important current research issue, believed to provide candidates for new drugs.

Several antioxidants showed efficiency in inhibiting the progress of AD and PD in preclinical studies. The effects of application of antioxidants, which are a normal diet components are limited, however, and new, more effective substances are searched for.

A dynamic development of nanotechnology is being observed recently. Nanotherapeutics are more and more often employed in medicine and pharmacy as systems transporting various active substances to strictly defined tissues of the body. Thanks to the application of nanoparticles, pharmacodynamic and pharmacokinetic parameters of drugs are improved, including bioavailability and release time of active components.

Our previous studies have demonstrated different efficiency of various nitroxides in preventing protein glycation and peroxynitrite reactions, which gives a basis for choice of the most efficient compounds. However, the life time of nitroxides *in vivo* is limited since they are subject to intracellular reduction and, as low-molecular weight compounds, to rapid elimination. It can be expected that newly developed oral redox polymer nanotherapeutics containing covalently bound nitroxides (nitroxide containing nanoparticles, NCN) will prolong the life time of nitroxides in the body, increase their efficiency and provide optimal protection of cells against OS/NS, ameliorating the course of AD and PD.

The aims of the project are: (i) synthesis of nano-antioxidants, nanoparticles containing covalently bound nitroxyl free radicals, (ii) analysis of their entry into cells, (iii) evaluation of their cytotoxicity and (iv) evaluation of their efficiency in counteracting OS and its consequences. The main aim of the project will be assessment of the toxicity and efficiency of two chosen NCN in ameliorating the sequelae of pathological changes in the animal models of AD and PD. We will also get insight into the mechanism of the antidegenerative action of NCN in neurons. We strongly believe that our proposed studies will not only be a step toward a better understanding the molecular mechanisms of NCN activity in cells might also be the starting point for the development of the synthesis of new NCN agents of optimal structure and after testing *in vivo* in the preclinical and clinical studies, may become in the future a new class of therapeutic agents. This can contribute to the improvement of the pharmacological competitiveness of Poland in designing new drugs.