DESCRIPTION FOR THE GENERAL PUBLIC

All of us would like to live long, happy and in a good health. Unfortunately, this is not always possible and – paradoxically – the most serious of the tasks facing the modern medicine is not as much an extension of human life, but making it lasted in a relatively good health until the last days. One of the biggest threats to good mental and physical health in the elderly are diseases involving the irreparable loss of nerve cells - **neurodegenerative diseases**. These include **Parkinson's disease** manifested by tremor of the limbs, impairment in walking and maintaining posture, muscle stiffness. It proceeds implicitly over many years and neural loss begins long before the first clinical symptoms appear (usually when approx. 80% of cells is already lost), thus even a prompt diagnosis at this stage provides very little opportunity for further effective treatment. We do not know the cause of Parkinson's disease, and in a small proportion of cases evoked by different genetic mutations scientists still argue about its exact course at the level of intracellular mechanisms. As a consequence, currently available pharmacotherapies are based on disease symptomatology, and, although they do alleviate the typical symptoms, they do not restore neuronal function nor prevent neuronal loss.

Nerve cells that degenerate in Parkinson's disease are called the **dopaminergic system**, which consists of the cells that produce dopamine. Dopamine is an important neurotransmitter in the brain whose deficiency is directly related to the symptoms of the disease. However, it is known that neurodegeneration in Parkinson's disease also affects other neurotransmission systems, including cells that synthesize other important neurotransmitter: noradrenaline (**noradrenergic system**). Since they are not directly responsible for the symptoms, this phenomenon for many years was neglected. Recently, in a study conducted on material taken from the brains of people who died of Parkinson's disease, it was shown that the neurodegeneration of the noradrenergic system may overpass and precedes neurodegeneration of dopaminergic system. A hypothesis emerged, that noradrenaline itself may have neuroprotective properties for dopaminergic cells, which in terms of its lack are more susceptible to any harmful environmental cues. Animal studies seem to confirm the validity of this hypothesis: noradrenaline-deficient mice react much more strongly to neurotoxins that cause Parkinson's disease, and *vice versa* – mice with elevated levels of this neurotransmitter are more resistant to their effects.

Hence, the purpose of this project is to investigate this issue by replicating the conditions of progressive noradrenergic neurodegeneration in a transgenic mouse model. Namely, by introducing a specific genetic construct we will initially evoke **progressive degeneration of cells in the noradrenergic system**. Then, in coming months we will examine the changes of dopaminergic system functioning. The model will be created upon so called **conditional inducible gene targeting system**, which means that the site of removed cells (noradrenergic system) will be determined by a properly designed genetic construct and the launch of the mutation will be possible only after the administration of a special compound, at the moment chosen by the experimenter. Thus, obtained model will closely resemble the human disease, where the loss of neurons is started not before the adulthood.

Preliminary studies have shown that indeed, mice with a loss of noradrenergic cells after a couple of weeks start to express some **dysfunction of the dopaminergic system**. However, the pilot model possessed many caveats which made thorough research not possible. In-depth and profound analysis of spontaneous changes in the dopaminergic system (the system not affected by introduced mutation) evoked spontaneously by noradrenergic neurodegeneration will cover i.e. evaluation of motor skills of the animals, screening of the progressive development of neurodegeneration, interrelations between noradrenergic and dopaminergic systems, and exploration of processes and pathways at the intracellular level responsible for neurodegeneration by assessment of advanced molecular biology methods.

Observed mechanisms preceding degeneration of the dopamine system may have significant potential for early diagnosis of Parkinson’s disease. Moreover, because – contrary to all existing, genetic models of Parkinson’s disease – the mutation will not directly affect dopaminergic neurons, this model should allow to test potential neuroprotective pharmacotherapies, not only restricted to the compounds that delay the onset of neurodegeneration. The far-reaching results may provide opportunity for creation of new strategies for drug development and their implementation in the pharmaceutical industry. Thus, this study may provide valuable findings that may have direct impact the healthcare system of the aging population in industrialized societies, where the prevalence of neurodegenerative diseases is rapidly growing.