

MicroRNAs in blood as biomarkers for Alzheimer's disease: a molecular signature for personalized therapy

Alzheimer's disease (AD) is an aging-related, progressive process of degeneration and loss of brain neurons, which is the most common cause of dementia in the elderly. About 250,000 people currently suffer from AD in Poland, and the number of patients in the world reaches 47 million. Specialists are alarming that due to the increase in life expectancy, in the near future AD may constitute the largest health crisis in the world.

In most cases, AD arises sporadically, and the causes of the emergence are complex and not fully explained. This results in a lack of preventive methods and medications to eliminate the causes of AD. Since 1996, however, drugs which can act on AD symptoms have been available. Unfortunately, before symptoms of dementia occur, the disease develops asymptotically for many years. There are currently no biomarkers identifying complex pathways contributing to the development of AD and responsible for various subtypes of the disease, especially in the initial stage of AD. This is particularly evident in the light of the failure of previous clinical trials of new AD therapies carried out either in the late stages of AD or in groups of patients with various subtypes and stages of the disease. Thus, advances in AD prevention and therapy require the identification of biomarkers suitable for the detection of early, complex disease mechanisms and indicative for future individualized therapies. It is also desirable that such biomarkers occur in readily available diagnostic tissues such as blood.

We undertake this project to respond to these needs. The starting point for the proposed research is our recently published and patented discovery of changes in the level of 6 different microRNA molecules (miRNAs) in the blood plasma of patients in early AD stage compared to the control group (patent pending PCT/IB2016/052440). MiRNA molecules sustain a recently discovered group of molecules involved in the regulation of many important cellular processes. The two miRNAs of our AD plasma panel that appear to be the most significant indicators of early-stage AD are hsa-miR-483-5p and hsa-miR-200a-3p. Very little is known about the cellular functions of these two miRNAs and their role in the pathogenesis of AD. Therefore, the immediate goal of the proposed research is to explain the role of these two miRNAs in the AD pathogenesis. Using bioinformatics tools, we identified the molecules and cellular processes potentially regulated by these miRNAs. We will use biochemical as well as molecular and cellular biology methods to verify these assumptions.

The proposed research is innovative and pioneering. The project aims to investigate unknown mechanisms in the pathology of AD, in which two miRNA molecules participate (hsa-miR-483-5p and hsa-miR-200a-3p). The results of the project will indicate whether these miRNAs could be further investigated for therapeutic applications. Furthermore, the proposal for this project is based on our original pioneering hypothesis that the molecular signature of the miRNAs in the blood reflects in a better way complex AD pathogenesis, and therefore that miRNAs are more suitable for the diagnosis of this multifactorial disease than any other existing tests. The project will clarify whether the increase in the level of these miRNAs in the blood plasma signals the activation of specific molecular factors contributing to the development of the disease and may therefore enable the diagnosis of a specific subtype of the disease. Such diagnosis would be the basis for choosing the right prevention strategy or personalized therapy. A future blood test based on the use of these miRNAs as AD biomarkers would be non-invasive and more available in clinical settings than any existing AD tests, such as CSF or brain imaging (PET, MRI, CT). Such a test based on non-invasive methodology may revolutionize future AD diagnostics enabling early prevention or individualized therapy.