Lipids are a very diverse group of hydrophobic and amphipathic biomolecules, showing a wide range of biological activity. The basic components of almost every lipid group representative are fatty acids (FA). Their more accurate analysis is advisable, because the changed lipids content may underlie many pathological phenomenons. In 2017 team of Rafal Ploski discovered new disease IKSHD (*ichthyotic keratoderma, spasticity, mild hypomyelination and dysmorphic features*). Genetic research revealed that this disease is caused by the mutation in gene coding fatty acid elongase 1 (*ELOVL1*), one of the ELOVLs enzymes, involved in fatty acids elongation. Interestingly, for the first time our research team discovered a mutation in ELOVL1 gene, that was later confirmed by German researchers. The *ELOVL1* mutation results in reduced synthesis of very long chain fatty acids (VLCFA) containing 24-26 carbon atoms as well as the accumulation of shorter VLCFAs containing 20 – 22 carbon atoms. The symptoms of this mutation make it similar to peroxisomal diseases. However, it seems that the basis of IKSHD and the pathophysiological mechanism is different. At present, it is not clear how the *ELOVL1* mutation causes the symptoms of the discovered disease, including distinct ichthyotic keratoderma and an early progressive neurological disease associated with mild hypomyelination, high frequency hearing loss, photophobia and narrowed visual field. Another disease, whose skin symptomes are similar (fish scale disease) is also characterized by a disturbance in the levels of VLCFA, however, the VLCFA content is much higher than in control healthy group. What is more, the colorectal cancer (CRC) research performed by our team, showed elevated levels of VLCFA and ELOVL1 overexpression in cancer tissue, A common pathology for these diseases / conditions are altered VLCFA levels. Therefore, the aim of the project is to discover the pathophysiological significance of the alterations in VLCFA levels and ELOVL1 gene expression. The mice model of IKSHD was obtained by a team of one of our contractors, professor Andrzej Dziembowski. It should be emphasized that the creation of an animal model of a newly discovered disease is a unique achievement in our country.

Series of other research will be conducted, including lipidomics and transciptomics to precisely evaluate changes in lipidome in mice with the *ELOVL*1$^{p.Ser165Phe}$ mutation, and in order to better understand the consequences of the decrease of VLCFA caused by examined mutation for metabolism in tissues of mice (brain and skin) with the *ELOVL1p.Ser165Phe* mutation and characterize IKSHD, as well as discover the mechanism of formation of the symptoms of the IKSHD. To check, if the molecular mechanism leading to the onset of symptoms caused by the *ELOVL1* mutation is based on the altered substrate specificity of the enzyme mutating towards the synthesis of shorter VLCFAs that accumulate, experiments will be performed that will verify the activity of the mutant enzyme against labelled stearate. Finally, by using the primary cell culture from various tissues obtained from these mice we will check, how supplementation of VLCFA and decreased levels of shorter VLCFA (C20:0) impact on oligodendrocytes (brain), fibroblasts (connective tissue), keratinocytes (skin), pneumocytes (lungs), where the symptoms of IKSHD are observed. Also, in CRC cells, that are characterized by ELOVL1 overexpression, we will study the effects of ELOVL1 inhibition. Many fatty acids exhibit high biological activity and affect the expression of genes associated with metabolism. Studies on the mice model will allow to verify changes in the VLCFA profile caused by the mutation tested. VLCFAs, the amount of which decreases as a result of mutations, will then be administered to the cell cultures and mice with mutation, in order to determine their effect on survival and cell function.

The results of the planned research will determine the mechanism of development of the disease caused by the *ELOVL1* mutation, as well as the effect of excess/deficiency of VLCFA on the organism. Also, the planned research may provide information on the unknown to date lipid disorders that play a role in the development and treatment of not only skin, but also neurodegenerative diseases or cancer. Confirmation of the effectiveness of long VLCFAs in reversing the symptoms of IKSHD will give strong grounds for their application in therapy of diseases related to elongases mutations. VLCFA are responsible for stiffening cell membranes and are neural signalling molecules. Their lack may cause cell disintegration, neurodegenerative diseases, muscle and optic atrophy, and perhaps, dysfunction of other organs, where overexpression of ELOVL1 is detected (lung, kidneys, stomach, pancreas). Both in patients with all types of inborn ichthyosis, and in IKSHD patients the epidermal permeability barrier is damaged. Its dysfunction has significant clinical consequences. Recent study on CRC demonstrated enhancement of FA elongation in CRC tissue and overexpression of ELOVL1 in CRC. The underlying mechanism of the role of elevated FA elongation in CRC tissue is still to be understood. Many studies, mainly in rodents, indicate the impact of VLCFA excess or deficiency on living organisms, but in humans it is still a poorly studied subject. This research can reveal new relationships between genetic disorders, lipid and transcriptome alterations that influence cell differentiation and development of the cells in nervous system and skin, and also, so far unexplored effects of deficiency of VLCFA in other organs.