Due to low birth rates and increasing life expectancy inhabitants of Europe constitute a rapidly ageing population. Currently, 16% of Europeans are over 65 and this figure is expected to reach 25% by 2030. The aging of developed countries causes that the number of people suffering from neurodegenerative diseases increases every year. These diseases affect not only patients, but also their companions and caregivers, and generate high costs for both individuals and society, and will impose increasing workload and financial pressures on healthcare systems. This highlights the age-related neurodegenerative diseases as one of the leading medical and societal challenges faced by EU countries, including Poland. The civilization diseases, related to the lifestyle of present societies, is also a wide-spreading problem, having a great impact on public health. One of such diseases is Type 2 diabetes (T2DM). In the past 4 decades the prevalence of T2DM has risen dramatically in countries of all income levels, from 108 million in 1980 to 422 million in 2014 (World Health Organization). About 2 million deaths are attributed each year to diabetes and kidney disease caused by diabetes. In the United States 96 million people aged 18 years or older (38% of the adult US population) have prediabetes (crude estimates for 2017–2020, National Diabetes Statistics Report). The World Health Organization recognized diabetes as a global epidemic.

Type 2 diabetes and neurodegenerative diseases have a related etiology. In both cases the disease is connected with the assembly of protein molecules into gradually growing clusters (oligomers), which then results in the deposition of amyloids. Currently, there is no effective method for either preventing the development or treating amyloidogenic diseases. Advances of the recent years introduced targeted protein degradation (TPD) as a novel therapeutic approach, which enables the depletion or reduction of a disease-causing protein *via* hijacking the endogenous protein degradation machinery. In the past 5 years, the field of TPD has expanded dramatically, with dozens of substrates exemplified as being amenable to this mechanism. Nevertheless, compounds called PROTACs, capable of sending target proteins into the degradation pathway, have been developed so far only for 3 of the 49 proteins with aggregation properties linked to pathological conditions. PROTACs are constructs comprising in their structures an element that recognizes a target protein and an element that allows a tag to be attached to that protein. This tag is a signal for the proteolytic system to degrade such a protein. The goal of our project is to develop efficient methods for the controlled removal of two selected proteins, human islet amyloid polypeptide (hIAPP or amylin) and human amyloid A protein (hSAA), using PROTACs and targeted protein degradation approach.

Amylin is a hormone co-secreted with insulin by pancreatic β-cells. Insulin resistance, which often develops as a consequence of obesity, as well as in pre-diabetic conditions caused by other factors, results in an overexpression of insulin, which is accompanied by hyperproduction of amylin. Excessive secretion of SAA by hepatocytes is triggered by any inflammatory condition and is particularly problematic in chronic diseases, such as rheumatoid arthritis, cancer or diabetes. Both amylin and SAA have aggregation propensity and, when present in excess, form progressively larger oligomers, which are then deposited as amyloids. Aggregation of amylin occurs mainly in cells of the pancreas, but also in other organs, including the heart, kidneys, and brain, where amylin can reach with blood. Similarly, SAA aggregates have been found not only in the liver, but also in organs accessible to blood, such as the spleen, heart, and kidneys. Recent studies indicate that amylin co-aggregates with Aβ peptide and is present in amyloid deposits detected in people with Alzheimer's disease. Likewise, SAA has been found in cerebrospinal fluid as well as in amyloid deposits in the Alzheimer’s disease brains. These findings connect amylin and SAA with neurodegeneration and suggest that they may play a role of aggregation seeds for other proteins. Selective and effective removal of excessive amylin could reduce the risk of developing Alzheimer's disease, as well as curb the plague of type 2 diabetes, which develops due to the death of pancreatic β-cells, in response to the accumulation of oligomeric amylin. Selective removal of secreted in excess SAA may provide a way to bring under control both the aggregation of this protein and caused by it stimulation of neuroinflammation, which worsens the brain condition of Alzheimer's patients.