Abstract for the general public

Inside our cells, many essential processes take place in tiny droplets made of proteins. These droplets are not surrounded by a membrane, yet they work like miniature reaction chambers. In healthy cells they stay fluid, but in many brain disorders they slowly harden and eventually turn into harmful aggregates. This transformation is seen in conditions such as Alzheimer's and Parkinson's disease, but we still do not understand how and when it begins.

For decades researchers believed that a protein must adopt a fixed three-dimensional shape in order to function. However, we now know that many important proteins, especially in human cells, behave very differently. They are flexible and constantly changing shape. These **intrinsically disordered proteins** do not fold into a single structure, yet they are essential for cell regulation, signaling and stress responses. Their flexibility is often an advantage: it lets them rapidly switch partners and take part in many different interactions.

This same flexibility also allows such proteins to gather into liquid-like droplets by a process known as **liquid–liquid phase separation (LLPS)**. Under normal conditions these droplets are reversible and dissolve when the cell no longer needs them. But if this regulation fails, the droplets may slowly "mature", become more solid, and in some cases form toxic **amyloid fibrils** — highly ordered protein aggregates strongly associated with neurodegenerative diseases. Importantly, experiments show that even though these proteins look disordered overall, they contain short segments that can temporarily adopt shapes such as helices or □-strands. These structural elements may guide how droplets form and how they later convert into amyloids.

To uncover these early molecular events, we need tools that can capture both large-scale dynamics and subtle local structural changes. Classical all-atom molecular dynamics (MD) computer simulations provide high resolution but cannot reach the required time and size scales, while simplified coarse-grained MD models can follow droplet formation but usually miss local structural transitions

Our project aims to bridge this gap by using Martini 3 IDP simulations combined with a dynamic contact map inspired by our GōMartini 3 model, enabling us to follow the earliest molecular steps of structural change inside condensates. By integrating available biophysical experiments with advanced computer simulations, we will track how flexible protein chains behave in crowded environments and how they reorganize over time. Focusing on amyloid-β and α-synuclein, two proteins central to Alzheimer's and Parkinson's disease, we aim to identify the molecular events that drive the transition from dynamic liquid droplets to solid amyloid assemblies.

Understanding this process may reveal why some proteins become toxic while others remain functional, and could point to entirely new strategies for slowing or preventing the formation of disease-related aggregates. The results will strengthen modern research in Poland and contribute to the global effort to understand the molecular origins of neurodegeneration.