Aggregates of toxic polyglycine protein: in the spotlight.
Understanding of formation and degradation processes.

Microsatellite repeats are short DNA sequence motifs repeated at least few times. When number of repeats increases above a normal range, microsatellite expansion diseases develop. Common feature of these diseases is a presence of toxic proteins which accumulate and aggregate in neurons, leading to their death. One of microsatellite expansion diseases is Fragile X-associated tremor/ataxia syndrome (FXTAS) caused by increased number of CGG repeats in *FMR1* gene. Symptoms of FXTAS usually appear around the age of 60 and include tremor, gait ataxia, dementia, alternations in brain. Moreover, large inclusions of unknown origin are observed in FXTAS patients' neurons. The explanation of the origin of these inclusions seems to be crucial for understanding the basis of disease development at the cell level.

Less than 10 years ago, it was shown that CGG repeats in FXTAS contribute to the formation of a toxic protein composed of a tract of single amino acid, glycine. This protein is found in inclusions in patients with FXTAS and also forms aggregates by itself. Moreover, it has been shown to be toxic to cells. This suggests that it is the polyglycine protein that is the starting point for the formation of inclusions, and thus for the development of the disease.

Despite the supposedly crucial role of polyglycine protein in the development of FXTAS, very little is known about the processes involved in their aggregation and degradation. The aim of this project will be to investigate these mechanisms in depth. In addition, it is planned to conduct a high-throughput screening of low molecular weight compounds looking for those that will limit the aggregation process.

In the first stage of the project, cell models very similar to neurons, producing the toxic polyglycine protein, will be prepared. As a result, the studied processes will take place in an environment similar to that found in patients' neurons. A probe will also be synthesized that will allow the visualization of aggregates in cells. Then, with the use of these tools and advanced microscopic techniques, the following will be checked: the role of time and protein concentration in the aggregation process, the exact course and location of the aggregation and degradation processes in time in living cells, and the role of the cellular machinery responsible for removing defective and redundant proteins in these processes. The final step will be to conduct high-throughput screening and identify low molecular weight compounds limiting polyglycine protein aggregation.

Studying the processes of aggregation and degradation of the toxic polyglycine protein will allow us to learn about the causes of inclusion formation in the neurons of patients with FXTAS and the development of the disease. The identified small-molecule compounds can be used for further research on the aggregation process, and in the future also for the development of therapies against FXTAS and other related diseases.