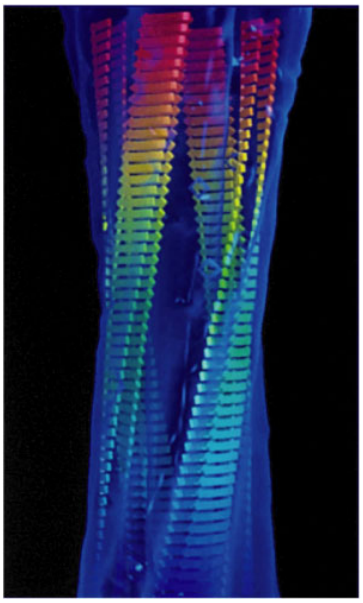
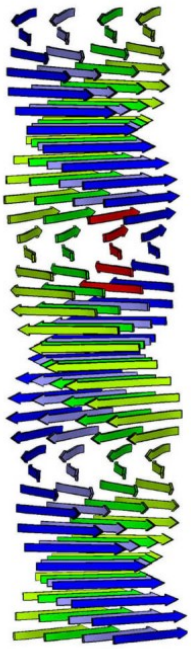
Examensarbete

Rational redesign of amyloid-like fibrils



Misfolding of proteins sometimes leads to the formation of certain type of aggregates, amyloids, which can cause diseases such as Alzheimer's, Parkinson┌s, type II diabetes and Creutzfeldt-Jakob. Due to their central role in disease, significant research efforts are targeted towards interfering with the process of amyloid formation. But amyloids have also sparked an interest in nanotechnology because of their unique biophysical properties. The same reasons that make amyloids lethal in biology make them useful as biomaterials (such as their superior stability). However, their use as biomaterials is limited by our lack of rational control of their structural and biophysical properties. Today, we have to work with the variety provided by naturally occurring amyloid fibrils. In this project our approach is to develop novel biomaterials based on the structure-based redesign of amyloid-like fibrils with the ultimate goal being the creation of a conducting protein nanowire.



Amyloid fibrils are formed by normally soluble proteins, which sometimes aggregate to form long fibers. When this happens in human cells, amyloid formation is often coupled to disease. A well-known example is Alzheimers disease, which is a amyloid disease caused by fibril formation of a protein called Abeta. There is no atomic structure of any complete amyloid fibril but biophysical experiments have shown that it contains two or more filaments with continuous β-sheet structure. A breakthrough in the field was the determination of the three-dimensional structure amyloid-like fibril formed by a small peptide from yeast. Even if its not a real amyloid fibril, the structure is an excellent structural model system for the formation of continuous β-sheets in amyloids. The peptides in the fiber are hydrogen bonding to form a continuous β-sheet with a polar interface formed by two filaments of peptides, which is called a "steric zipper".

Apart from its interesting role in disease amyloids have also stirred up a lot of interest in bionanotechnology. Because they are very strong, stable and regular they are excellent scaffolds for functional nanowires. Proteins can be attached to the outside of the fibers to result in wires that catalyze chemical reactions, they can be made to bind to metals and can be used as molds for casting metallic nanowires. Researchers typically use proteins and peptides from systems that are known to form amyloids. There is currently no good method to rationally alter the function of amyloid fibers for use in bionanotechnology. Our goal is to design amyloid-like fibrils on an atomic level to create new functional materials. The ultimate goal is to create protein-like fibrils that can cnduct electricity.

In this project you will characterize peptides that have been designed on an atomic level to form peptides with completely novel structure. We have recently shown that one of these designed peptides is able to form nice looking fibrils with properties that are consistent with the model of the peptide in the computer. First, your work will be to further characterize this peptide using biophysical methods to understand what atomic structure it adopts. Second, you will then design and make new variants of this peptide and add function to the fibrils by attaching chemical groups or proteins.

In this master thesis project you will learn:

I) Expression and purification of peptides.
II) How to make novel synthetic peptides
III) Biophysical characterization of peptides and amyloid fibrils using a variety of techniques
IV) State-of-the-art structural modeling using computational tools

Don't hesitate to contact me, ingemar.andre@biochemistry.lu.se, for further information about the project!