NeuroCampus – Inside Out:

Daniel Otzen

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Otzen's Lab investigates the behavior and kinetics of proteins, particularly α-synuclein, during aggregation. They examine how these processes can be neutralized or reversed in neurodegenerative diseases such as Parkinson's.

Daniel Otzen. Photo: Karoline Klitgaard

Can you describe your research in a nutshell?
In my lab we investigate the aggregation of the protein α-synuclein (α-syn) in neurodegenerative diseases such as Parkinson's' disease. α-syn is an intrinsically disorganized protein, which means that it only becomes structured when it binds to something else like membranes or other copies of itself, *i.e.* aggregates in the form of fibrils or amyloid. These amyloids are associated with neurodegeneration, and are, due to their very regular and strong structures, difficult to get rid of.
The aggregation of α-syn does however not always result in amyloid. Sometimes the proteins instead group as oligomers, which are smaller clusters of only 30 molecules. These α-syn oligomers have turned out to be much more cytotoxic than the more researched amyloids and are thus an important object for investigation.
Our research is shaped by an underlying biophysical perspective and is mostly conducted *in vitro* in test tubes. We measure spectroscopic changes, equilibrium constants and rate constants and use this to investigate how the proteins behave, both when behaves and when it misbehaves. In our test tubes we can create α-syn oligomers, purify them and stabilize them.

What translational impact may your research have for people?
Understanding how proteins fold and misfold leading to amyloids and oligomers is essential for understanding and potentially treating neurodegenerative diseases. We work with questions such as: Can we discover a way to keep the proteins monomeric, so that they do not aggregate? Can we neutralize the aggregation once it has happened? Or can they be coated in different molecules so that they do not become toxic?
Over the last few years, we have developed monoclonal antibodes and nanobodies that have high affinity for α-syn oligomers. Together with Mads Hartvig Clausen from DTU we are currently screening for compounds capable of interfering with the oligomers' harmful behavior. This could be a crucial step in targeting Parkinson's disease. Moreover, it is important to understand the biophysical aspects of protein folding e.g. the kinetics to know which therapeutics will be relevant at different points in disease progress.

How did you end up where you are today?
I originally did a degree in chemistry and biotechology, which shaped the biophysical approach of my research, and from there I narrowed my focus and did a PhD in protein folding and folding kinetics. For years, I only studied proteins with a non-clinical focus, until I was approached by the pharmaceutical company Wyeth, who inspired me to start working with α-syn and its role in neurodegeneration.

What does a (local) strong neuroscience research network mean for you and your research?
Local collaboration is crucial for our research. Our own area of expertise is pretty compact, and it essential that we reach out to people with different kinds of expertise. In addition to Mads Hartvig Clausen at DTU, we have a strong local collaboration centered around Parkinson's research including, among others, Marina Romero-Ramos, Per Borghammer, Poul-Henning Jensen and Jørgen Kjems, who have very different perspectives and expertise in different fields and methods.

If you had unlimited resources to conduct a big, multidisciplinary neuroscience project, what would you like to do?
When it comes to understanding the role of proteins in neurodegenerative diseases, we can only get so far in the test tubes. Hence, I would like to study the molecular mechanisms within the actual cell using single-molecule type measurements.
In vivo investigation is especially important, but also especially difficult, in neurons since they are quite unique cells that do not divide on their own. We may however be able to study the processes in vivo using single molecule measurements. In my lab we are starting to work with fluorescence assisted cell-sorting (FACS), in which we produce two types of α-syn which are each linked to two different types of fluorescent signals. When they get close to each they crosstalk via FRET. This means that when they aggregate, you get a signal that you would not otherwise get. This could make it possible to study the aggregation as well the effects of our different compounds at a single-molecule level.

In addition to studying protein aggregation for its clinical purposes, I would like to investigate the potential useful aspects of amyloids as biofilm. The strong and resistant structure of amyloid is used by bacteria for flocking together and creating antibiotics resistance, and I believe that there is a great potential for biofilm solutions, e.g. when it comes to capturing carbon dioxide or degrading toxic compounds.

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