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## **Degree project/Research training/Project work on Protein misfolding and its prevention by BRICHOS domains**

- When:** Anytime
- Where:** Structural and Molecular Biology Program at the Department of Cell and Molecular Biology (ICM), Knight lab ([Knight Lab - Department of Cell and Molecular Biology - Uppsala University, Sweden \(uu.se\)](#))
- Credits:** (15, 20 hp research training), 30 or 45 hp degree project (preferable)

### **Research topic**

The formation of amyloid deposits, characterized by fibrillar structures, is intricately linked to debilitating diseases with significant socio-economic impact. Notable examples include Alzheimer's disease (AD), Parkinson's disease (PD), and type 2 diabetes (T2D). Nature, through millions of years of evolution, has grappled with the challenges of correctly folding proteins even under adverse conditions where there is an increased potential of misfolding leading to protein misfolding diseases. The observation that the number of protein misfolding diseases is nevertheless quite limited suggests that current living organisms likely possess inherent quality control mechanisms to mitigate these challenges.

One such remarkable defense mechanism is the recently identified anti-amyloid chaperone domain BRICHOS, with a broad spectrum of substrates. Our recent discoveries have revealed that BRICHOS proteins can be classified into 13 families, produced by metazoan species ranging from worms to humans. Intriguingly, despite limited overall amino acid sequence similarities—approaching those of unrelated proteins—this classification implies related but distinct functions and mechanisms for individual BRICHOS domains. Thus, these domains represent a largely unexplored reservoir of natural defense molecules against amyloid-related pathologies.

The kinetics of amyloid aggregation adheres to nucleation-dependent microscopic events recently defined. In primary nucleation, soluble monomers associate to form a nucleus, initiating fibril elongation. The surface of existing fibrils catalyzes the formation of new nuclei from free monomers, resulting in exponential fibril growth—referred to as secondary nucleation—coupled with monomer-independent fibril breakage. The monomer-dependent secondary nucleation pathway predominantly produces toxic oligomeric species. Notably, BRICHOS chaperone domains, in spite of very low sequence similarity, can inhibit secondary nucleation of unrelated amyloids.

This project has dual objectives: 1) to identify highly effective chaperones against diverse protein misfolding types and assess their efficacy in mitigating neurotoxic effects of protein aggregates; and 2) to unravel the structural determinants governing surface-catalyzed

secondary nucleation and its inhibition by BRICHOS, providing crucial insights for therapeutic interventions.

### ***Requirements***

- Background knowledge in fundamental biochemistry and molecular biology techniques, e.g., recombinant protein expression and purification, characterization chromatography, SDS-PAGE, EM, Circular Dichroism and protein aggregation assay.
- Interest and strong motivation in protein aggregation and prevention, and structural biology.

### ***Our offer***

- Research training on an exiting research topic in an active and friendly research environment. We will also offer relevant training in different techniques involved in each project, such as chromatography, SDS-PAGE, Circular Dichroism, amyloid formation monitoring assay and mathematical modelling of amyloid aggregation.
- A chance to be involved in groundbreaking discoveries about a protein involved in neurodegenerative disease such as Alzheimer's disease
- A great Master's Thesis topic

### ***Contact***

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