Molecular insights into the misfolding pathways of antibody light chain proteins

Even though LC misfolding in systemic AL amyloidosis has been studied for 50 years, many structural aspects are not well understood and the misfolding pathways remain elusive. In the first funding period, we could establish and apply methods to investigate the structure and aggregation kinetics of amyloid fibrils derived from lambda-light chains and resolve the influence of selected point mutations in the misfolding process. We will combine NMR experiments and MD simulations to provide molecular insights into the misfolding pathways of ex vivo amyloid fibrils derived from lambda- and kappa-light chains. The work program will address the following aims: (i) Characterize three crucial steps in misfolding: Dimerization, local unfolding of the light chain, and formation of oligomeric intermediates (ii) Characterization of the stability and dynamics of AL fibrils. (iii) Modulation of amyloid structure by cellular components. (iv) Comparison of the aggregation behavior of lambda- and kappa-light chains. In summary, this project aims to resolve the structural dynamics of all species along the misfolding pathways from monomer to fibrils and to investigate the influence of mutations in the misfolding process. We expect that our combined NMR/MD simulation approach will yield molecular insights into the mechanism of light chain misfolding.

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Proposed collaboration within ArchiFun network (not mandatory at this stage): -

Proposed list of secondments (not mandatory, but recommended if known already):
European Synchrotron Radiation Facility, Grenoble, France
Fida Biosystems ApS, Copenhagen, Denmark
Randall at King's College London

Main ArchiFun theme involved:

Neurodegenerative and autoimmune diseases;

Neurosciences and cognition.