

INTERNSHIP PROPOSAL

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Research project title: Structural aspects of TPPP/p25 leading to microtubule stability and amyloid fiber formation observed in human Parkinson's disease.

5 Keywords to describe the project:

TPPP/p25, proteinopathy, fiber, microtubules

Description of the project (aims, experimental techniques, recommended background):

We are investigating the possible pathogenic roles of the microtubule (MT) associated protein TPPP/p25 which may be related to a loss of its native function, leading to altered dynamics of neuronal MT network, and/or to a gain of toxic function leading to formation of filamentous protein aggregates encountered in Parkinson's disease patients, similar to other proteinopathies linked to other neurodegenerative diseases. We are looking for an M2 candidate for the pursue of the characterization of the effect of wild-type and deletion mutants of TPPP/p25 on the dynamic properties of MTs in cells expressing GFP-Tubulin and the binding dynamics by FRAP of GFP-TPPP/p25 and its various domains once bound to cellular MTs. Reconstitute the minimal TPPP-tubulin complex for biophysical and structural studies taking advantage of the use of designed ankyrin repeat protein (DARPIN, D2) which strongly inhibits MT polymerization. D2 is capable of binding two tubulin dimers, mimicking the lateral arrangement of tubulin dimers in two adjacent MT protofilaments. As predicted by our cell-based data, our expectation is that TPPP/p25 will be able to crosslink two D2-tubulin complexes, facilitating either the crystallization of the complex and/or to the understanding of the conformational impact on TPPP/p25 resulting from TPPP/p25-tubulin complex formation in solution by NMR.

Justification that the internship's subject fits with the general theme of GRAL:

The proposed project is going to follow methodological approaches that combine integrated biochemical, structural, combined with cell biology approaches, to answer questions regarding the pathogenic role of loss and/or gain of function TPPP/p25 which is linked to Parkinson's disease.

Relevant publications of the team:

DeBonis S., Neumann E., Skoufias D.A. Self protein-protein interactions are involved in TPPP/p25 mediated microtubule bundling. Scientific Reports 2015 Aug 20;5:13242.