Cross-seeding at a molecular level: can amyloids breed?

Protein aggregation into amyloid fibrils is the hallmark of many diseases including Alzheimer's disease (AD), Parkinson's disease (PD) and type 2 diabetes (T2D). Amyloid fibrils contain a universal "cross-β" core structure composed of arrays of β-sheets and can be formed by a variety of peptides or proteins without any evident sequence similarity. Different amyloid-based diseases are typically characterized by the aggregation of specific proteins. For instance, the tau protein is involved in AD, α-synuclein is involved in PD and the islet amyloid polypeptide (IAPP) plays an important role in T2D. Strikingly, cross-talks between aggregation of different proteins have been highlighted in various disease contexts [1]. As a hormone, IAPP enters the bloodstream to reach different targets, including the brain. In postmortem AD and PD patients, IAPP has been found in brain tissues alongside Tau and α-syn [2]. At a molecular level, this cross talk occurs through cross-seeding in which fibrils composed of one protein are capable of enhancing the aggregation of a different protein.

This project aims at studying cross-seeding between three proteins: tau, αSyn and IAPP. We endeavor to reveal the mechanisms underlying cross-seeding, *e.g.* primary or secondary nucleation, and to show whether or not structural features can be transferred through cross seeding.

We will first analyze aggregation kinetics of the three proteins alone and in the presence of seeds using Thioflavin T fluorescence. The data will be fitted according to previously established models [3], allowing to derive kinetic and thermodynamic parameters. We will then apply TEM, AFM and AFM-based infrared nanospectroscopy (nanoIR) to study aggregates morphology and structure of the obtained fibrils. All proteins are available in CBMN and the student will express tau or αSyn recombinantly in bacteria, depending on our stocks. Preliminary data obtained by a co-supervised M1 student show that pre-made aggregates of tau enhance aggregation of IAPP (Figure 1).

This project is a collaboration between 3 teams of CBMN (http://www.cbmn.u-bordeaux.fr/) (Cecile Feuillie (BioAFM team), Lucie Khemtemourian (SIMBA team) and Yann Fichou (NMR team)).

The student could start in January or February depending on the university and the internship will last 6 months.

Please send your CV and cover letter to Yann Fichou y.fichou@iecb.u-bordeaux.fr .

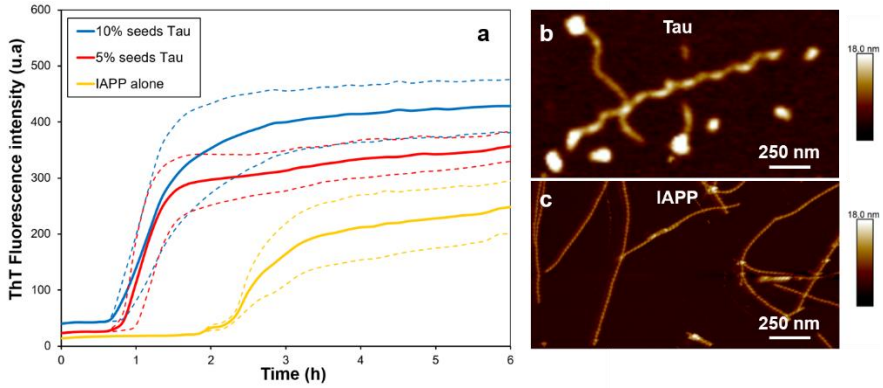

Fig. 1: (a) Kinetics of IAPP fibril formation alone (yellow) and in the presence of Tau seeds (red, blue); AFM height images of (b) Tau and (c) IAPP fibrils

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[3] G. Meisl, J. B. Kirkegaard, P. Arosio, T. C. T. Michaels, M. Vendruscolo, C. M. Dobson, S. Linse and T. P. J. Knowles, *Nat. Protoc.*, 2016, **11**, 252–272.