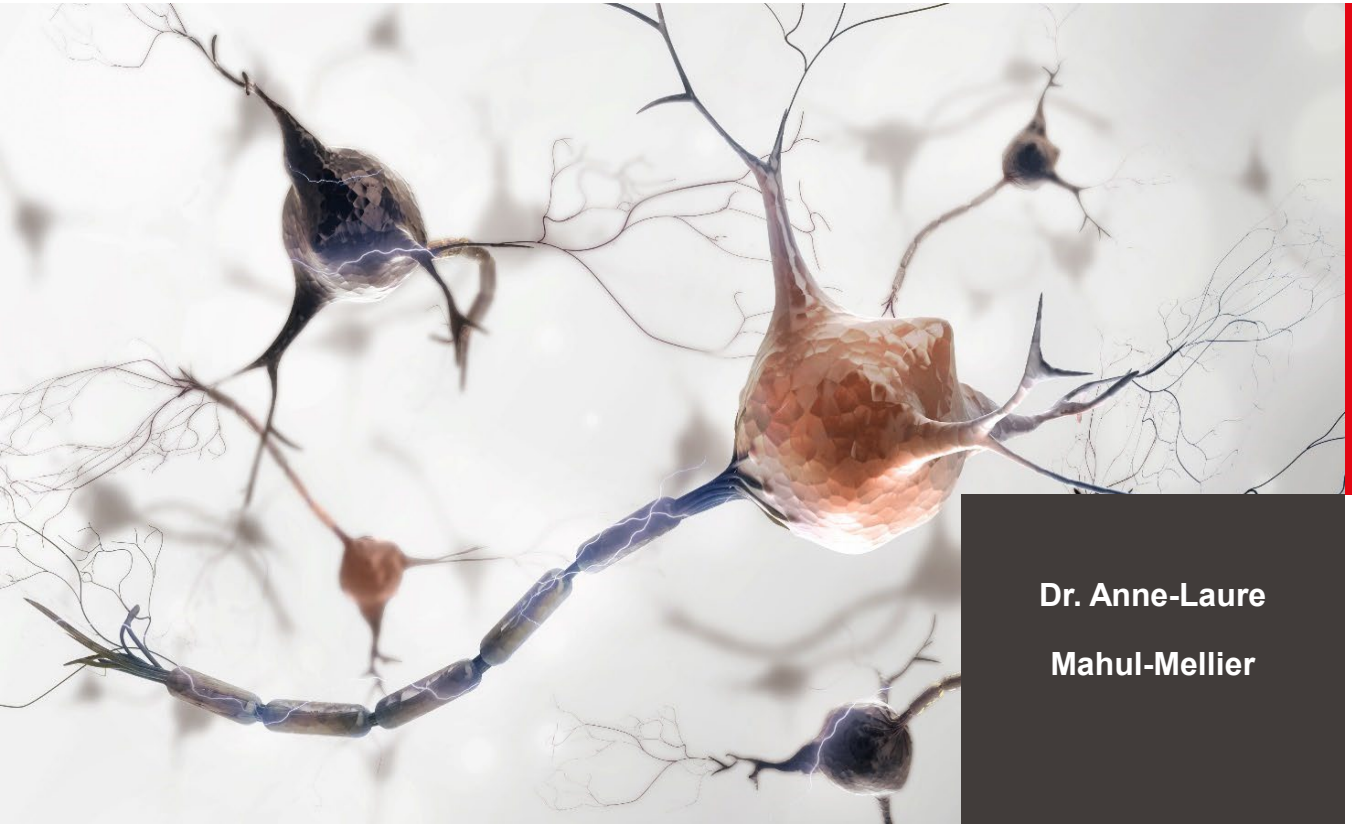
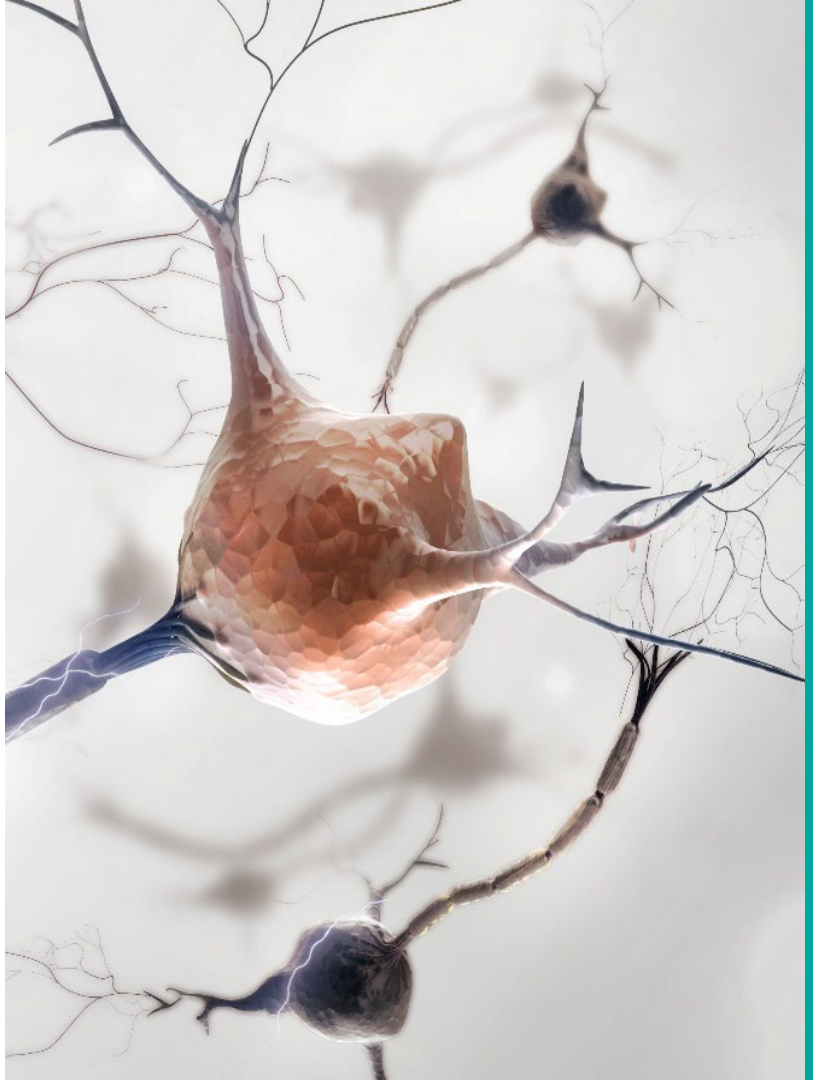


NDDs: prion-like diseases

Dr. Anne-Laure Mahul-Mellier



BIO480- Neurodegenerative disease (NDDs) lectures at glance

2. Overview of the Bio480 course contents

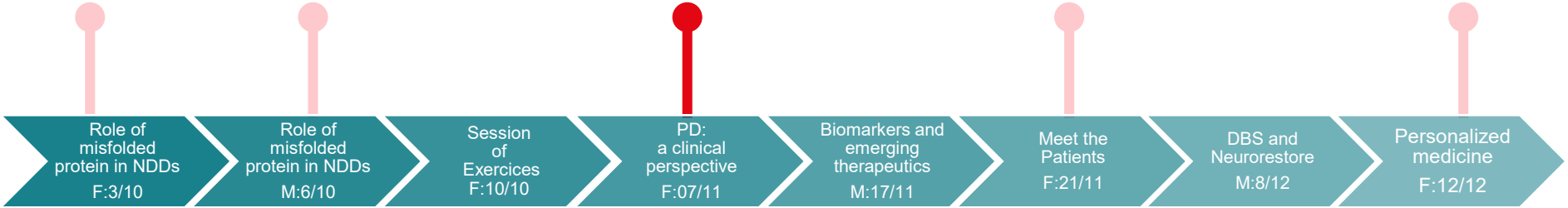
Course organisation:

From proteins misfolding, to aggregation pathways, through spreading in NDDs

Dr. Julien Bally, *Head of the Movement Disorders Unit*

PD patients Session

iPSCs, organoid and AI in advancing therapies



2-hour exercise session With Lukas ☺

Overview of the latest advances in drug design and therapies

Prof. Eduardo Moraud

Open positions (Master internship):

EPFL

Master project

In silico screening and AI-assisted discovery of small-molecule inhibitors targeting the ceramide transfer protein cert in CerTra syndrome

PIs : Giovanni D'Angelo and Matteo Dal Peraro
Starting date: as soon as possible

Background

The ceramide transfer protein (CERT, encoded by CERT1) mediates non-vesicular transfer of ceramide from the endoplasmic reticulum to the Golgi, a crucial step in sphingolipid metabolism. Mutations in CERT1 have been linked to **a rare neurodevelopmental disorder**, known as CerTra, which is caused by hyperactive forms of CERT that disrupt lipid homeostasis and lead to excess sphingomyelin production. Targeting CERT with small-molecule inhibitors offers a promising therapeutic strategy with both pharmacological and medical relevance.

Aim

This Master's project aims to conduct an in silico screen of a large compound library (over 100,000 molecules) to identify inhibitors of CERT. The focus will be on docking compounds to different functional domains of CERT, such as the START domain (which binds ceramide), the PH domain (which interacts with Golgi lipids), and regulatory regions. Special attention will also be given to how disease-associated mutations may alter binding sites and influence druggability.

Methods

The project will employ state-of-the-art molecular docking approaches in combination with modern AI and machine learning methods for compound scoring, clustering, and ADMET prediction. This will allow prioritization of structurally diverse compounds with favorable pharmacological properties. Computational modeling of mutant CERT proteins will also be performed to assess potential differences in compound binding compared to the wild-type protein.

Expected Outcomes

The study will generate a prioritized list of candidate inhibitors with high predicted binding affinity and promising drug-like properties. These compounds will form the basis for subsequent experimental validation in cellular assays and, eventually, in animal models of CerTra. Beyond identifying potential therapeutic leads, the project will also provide new insights into CERT structure-function relationships and the molecular basis of disease-causing mutations.

For more information:

https://www.epfl.ch/labs/dangelo-lab/
https://www.epfl.ch/labs/lbm/

USF Health
University of South Florida

The prospective student will deepen their understanding of biochemical, cell-biological and microscopy methods to study the synaptic biology of alpha-synuclein (αS). αS is an abundant presynaptic protein that regulates neurotransmission. αS orchestrates neurotransmitter release by synaptic vesicle cycling, SNARE assembly, clustering of synaptic vesicles, and dilation of the fusion pore during exocytosis.

αS is also a key protein implicated in a broad class of neurodegenerative disorders termed "*synucleinopathies*", which includes Parkinson's disease (PD), dementia with Lewy Bodies (DLB), and Multiple System Atrophy (MSA). The pathological αS deposits, Lewy Bodies (LBs), and Lewy Neurites (LNs) are also documented in certain forms of Alzheimer's disease and related forms of dementia, thus extending the list of dementias with LB pathology.

Remarkably, about 90% of αS in the LB and LN is acknowledged to be present in its serine-129 phosphorylated form (pS129). Therefore, pS129 is widely used as a surrogate marker for pathology. However, we have recently demonstrated that physiological pS129, triggered by neuronal activity, positively regulates synaptic transmission (PMID: 36646701; 38862330).

These unexpected and intriguing results raise the following critical questions:

1) How does pS129 influence synaptic transmission?

2) How to distinguish pS129 in physiological and pathological states?

The student will employ a combination of biochemical, cell biological, and microscopy techniques to address one of these questions.

Prof. Nagendran Ramalingam