

Producing, isolating and characterizing the human ABHD6 lipase for high-throughput screening and for structural analyses

Keywords: Bioproduction; protein purification; lipid nanodisc; enzymatic assays; automated HTS; neutron scattering

Duration: 5-6 months starting January or February 2027

Location: IMPReSs department of the PCBIS Drug Discovery platform, ESBS, Illkirch (www.pcbis.fr/departements/impress)

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Project description:

Global context

The alpha/beta hydrolase domain-containing protein 6 (ABHD6) is an integral membrane serine hydrolase that modulates the abundance of several bioactive lipid species in both central and peripheral tissues [1,2]. Recent evidence [3] identifies ABHD6 as a promising therapeutic target for the treatment of metabolic dysfunction-associated steatohepatitis (MASH) [4,5] and for preventing one of its more severe complication, namely hepatocellular carcinoma (HCC) [6].

In this context, we set a collaborative project establishing an integrated translational drug discovery pipeline dedicated to the identification and validation of novel ABHD6-targeting compounds for the treatment of MASH and the prevention of MASH-associated HCC. Specifically, the project seeks to (i) identify potent ligands capable of inhibiting or modulating ABHD6 activity through high-throughput screening (HTS), (ii) evaluate their therapeutic potential in advanced human cellular models of MASH, and (iii) structurally characterize their mechanisms of action.

Objectives of the internship

The main objective of the internship will be to contribute the production, preparation and biochemical characterization of the different samples required for the project, including ABHD6 purified in detergent micelles or reconstituted in lipid nanodiscs. The Master student will then directly participate to the screening of a 10,000 compounds library via an activity assay that has been miniaturized in an automated 384-wells HTS format on the PCBIS screening platform. He / she will be also associated to a structural study of the nanodiscs samples via the acquisition of neutron scattering data in a campaign expected in March-April 2027 at the ILL institute in Grenoble.

References

- [1] Thomas et al. *Cell Rep.* 2013, 5(2):508-20.
- [2] Prisbanig et al. *J Biol Chem.* 2015, 290(50): 29869-881.
- [3] Orabi et al. *bioRxiv* [Preprint]. 2025, 07.29.667509
- [4] Miller et al. *Endocrinol Diabetes Metab.* 2025, 8(6).
- [5] Younossi et al. *Clin Mol Hepatol.* 2025, 31(Suppl):S32-S50.
- [6] Singh et al. *J Clin Exp Hepatol.* 2025, 15(2):102446.