UFR de Chimie et de Biologie
UNIVERSITÉ Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2022-2023

Laboratory/Institute: Institut de Biologie Structurale **Director:** Winfried Weissenhorn
Team: Membrane transport team **Head of the team:** Hugues Nury

Name and status of the scientist in charge of the project: **HDR: yes** x **no** ☐
Address: Institut de Biologie Structurale, 71, avenue des Martyrs, 38044 Grenoble cedex 9

Phone: 0457428593 **e-mail:** Hugues.nury@ibs.fr

Program of the Master's degree in Biology:

☐ Microbiology, Infectious Diseases and Immunology x Structural Biology of Pathogens
☐ Physiology, Epigenetics, Differentiation, Cancer x Neurosciences and Neurobiology

Title of the project:

Toward the structure of an atypical insect $GABA_A$ receptor

Objectives (up to 3 lines):

The objective of the internship is to express and purify a heteropentameric insect receptor GRD/LCCH3. The structure of the receptor will then be obtained by cryo-electron microscopy (CryoEM), and will allow to better understand its role as an insecticide target.

Abstract (up to 10 lines):

Insecticides have been used for decades to control pests. However, their toxicity is now proven and there is a need to find new, more specific and less harmful molecules. One of the main targets of neurotoxic insecticides are the insect $GABA_A$ receptors, a class of ligand-gated pentameric ion channels. $GABA_A$ receptor subunits are encoded by several genes in insects, known as RDL, GRD and LCCH3. RDL subunits assemble to form a chloride-selective receptor. However, less is known about the GRD and LCCH3 subunits, except that they appear to assemble to form an atypical cation-selective receptor.
In our lab, we are trying to obtain structures of these pentameric channels, using cryo-electron microscopy. We study model species such as the honey bee and its parasite, the varroa mite. The goal of this project is to express and purify this cationic $GABA_A$ receptor from different species. This work will contribute to the development of biomolecules that specifically target pest species and protect pollinator populations.

Methods (up to 3 lines):

The project relies on a combination of molecular biology, cell biology and biochemistry. We use lentiviruses to generate stable HEK cell pools that over-express our receptors of interest. Those receptors are then solubilized, purified and reconstituted in nanodiscs for CryoEM imaging.

Up to 3 relevant publications of the team:

1-Zarkadas E, Pebay-Peyroula E, Thompson MJ, Schoehn G, Uchański T, Steyaert J, Chipot C, Dehez F, Baenziger JE, Nury H. Conformational transitions and ligand-binding to a muscle-type nicotinic acetylcholine receptor. Neuron 2022 20;110(8):1358-1370.e5. doi: 10.1016/j.neuron.2022.01.013. Epub 2022 Feb 8. PMID: 35139364.

2-Uchański T, Masiulis S, Fischer B, Kalichuk V, López-Sánchez U, Zarkadas E, Weckener M, Sente A, Ward P, Wohlkönig A, Zögg T, Remaut H, Naismith JH, Nury H, Vranken W, Aricescu AR, Pardon

E, Steyaert J. Megabodies expand the nanobody toolkit for protein structure determination by single-particle cryo-EM. Nat Methods. 2021 Jan;18(1):60-68. doi: 10.1038/s41592-020-01001-6. Epub 2021 Jan 6. PMID: 33408403; PMCID: PMC7611088.

3-Polovinkin L, Hassaine G, Perot J, Neumann E, Jensen AA, Lefebvre SN, Corringer PJ, Neyton J, Chipot C, Dehez F, Schoehn G, Nury H. Conformational transitions of the serotonin 5-HT_3 receptor. Nature. 2018 Nov;563(7730):275-279. doi: 10.1038/s41586-018-0672-3. Epub 2018 Oct 31. PMID: 30401839; PMCID: PMC6614044.

Requested domains of expertise (up to 5 keywords):

Biochemistry, molecular & cell biology, interest in structural techniques