Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2025-2026

Laboratory/Institute: DCM
Director: Didier Boturyn
Team: SITh
Head of the team: Anne Milet

Name and status of the scientist in charge of the project: Professeure Helene Jamet

HDR: yes x no ☐

Address: 301 rue de la chimie, 38058 Grenoble cedex 9
Phone: **e-mail:** helene.jamet@univ-grenoble-alpes.fr

Program of the Master's degree in Biology:

☐ Microbiology, Infectious Diseases and Immunology x Biochemistry & Structure
☐ Physiology, Epigenetics, Differentiation, Cancer ☐ Neurosciences and Neurobiology

Title of the project: Molecular Modeling of the Impact of Chaperone Stabilization on Selected Mutants of the Acid Alpha-Glucosidase (GAA), the Defectuous Enzyme in Pompe Disease

Objectives (up to 3 lines):

This project explores the potential of a lead compound, identified by Dr Sandrine Py from the SeRCO team in DCM for the treatment of specific forms of Pompe disease. The approach studies the structural stability of the most relevant genetic variants of the GAA protein using biocomputational tools and molecular dynamics (MD) simulations.

Abstract (up to 10 lines):

Recent advances in computational chemistry have significantly influenced the field of structural biology. On the results provided by a first database screening performed by Dr John Rendu from the CHU Grenoble Alpes, the most relevant genetic variants of the GAA protein will be studied using biocomputational tools and molecular dynamics to evaluate the energetic impact of mutations on the GAA protein with and without the lead compound called **PIPG-4** and investigate some selected mutants in depth. Starting from the crystallographic structures of the wild-type GAA (PDB 5NN3) and of GAA in complex with **PIPG-4** (PDB 9GSV), several analytical tools, such as average deviation values (RMSD), fluctuations (RSMF) radius of gyration (RG), will be used to study the structural stability of mutants compared to the native protein. The results of the proposed studies will constitute a first set of computational data interconnecting genetic mutations to structural features of the GAA treated by **PIPG-4**.

Methods (up to 3 lines):

Analysis of database, Molecular modeling software (evoEF2, AMBER), Bioinformatics tools

Up to 3 relevant publications of the team:

1- Vieira Da Cruz, A., Perraudin, V., Minopoli, N., Iacono, R., Roig-Zamboni, V., Bossio, A., Tangara, S., Fayolle, M., Kanazawa, A., Philouze, C., Tarallo, A., Heming, J.J.A., Artola, M., Behr, J.-B., Overkleeft, H.S., Moracci, M., Sulzenbacher, G., Parenti, G., **Py, S**., "*C*-Branched Iminosugars as Selective Pharmacological Chaperones of Lysosomal Alpha-Glucosidase for the Treatment of Pompe Disease". Accepted for publication with minor revisions in the *Journal of Medicinal Chemistry*.

2- Gentil, S., Che Mansor S. , **Jamet**, H., Cosnier, S., C. Cavazza, C. and Le Goff, A. "Oriented Immobilization of [NiFeSe] Hydrogenases on Covalently and Noncovalently Functionalized Carbon Nanotubes for H2/Air Enzymatic Fuel Cells" *ACS Catalysis*, **2018**, *8*, 3957.
3- Faure, C., Ng, Y., M., Belle, C., Soler-Lopez, M., Khettabi, L., Saidi, M., Berthet, N., Maresca, M., Philouze, C., Rachidi, W., Reglier, M., Du Moulinet d'Hardemare, A., **Jamet, H**. "Interactions of phenylalanine derivatives with human tyrosinase: Lessons from experimental and theoretical studies" *ChemBioChem* **2024**, *25*.

Requested domains of expertise (up to 5 keywords):

~~Biochemistry,~~ Structural biology, Protein folding and stability, Bioinformatic tools, Molecular modelling, interest in Drug Design and connected scientific fields.