UFR CHIMIE & BIOLOGIE Université Grenoble Alpes

Master's degree in Biology – Chemistry-Biology Department

Master 2 internship project
Year 2026-2027

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: Prof Hélène JAMET (DCM) / Drs John RENDU and Sabrina VERGNAUD (CHU Grenoble Alpes)

HDR: yes x no ☐

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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: 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 in the Department of Molecular Chemistry (DCM) for the treatment of specific forms of Pompe disease. It combines biocomputational tools and molecular dynamics (MD) simulations to investigate its interaction with relevant variants of GAA with functional validation in cells affected by the mutations of interest.

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 (**PIPG-4**). 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 interaction of **PIPG-4** with selected mutants. In parallel, cells carrying the selected mutations will be cultured in presence of **PIPG-4** to evaluate its potential to rescue their intrinsic deficiency in GAA activity. The results of the proposed studies will constitute computational data serving for interconnecting genetic mutations to structural features of the GAA impacting its sensitivity to a treatment with **PIPG-4**, with the aim to define which mutations are susceptible to respond such treatment in a personalized medicine approach.

Methods (up to 3 lines):

Analysis of database, Molecular modeling software (AMBER), Bioinformatics tools
Cell cultures, functional assays to measure GAA activity in cells carrying specific mutations

Up to 3 relevant publications of the team:

1- Vieira Da Cruz, A. *et al. C*-Branched Iminosugars as Selective Pharmacological Chaperones of Lysosomal Alpha-Glucosidase for the Treatment of Pompe Disease. *J. Med. Chem.* **2025**, *68* (18), 19269–19286. https://doi.org/10.1021/acs.jmedchem.5c01349.
2- Faure, C. *et al.* Interactions of phenylalanine derivatives with human tyrosinase: Lessons from experimental and theoretical studies. *ChemBioChem* **2024**, *25*, e202400235. https://doi.org/10.1002/cbic.202400235.
3- Donoghue, S. *et al.* The Expanding Clinical and Genetic Spectrum of Muscle Glycogen Storage Disease 0, (GSD0B). *American J of Med Genetics Pt A* **2025**, *197* (11), e64149. https://doi.org/10.1002/ajmg.a.64149.

Requested domains of expertise (up to 5 keywords):

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