Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: IBS/IRPAS group

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Research project title: Structural and functional implications of C1r protease mutations identified in patients with a rare disease.

5 Keywords to describe the project: Serine proteases, structure-function, mutations, gain of function

Description of the project (aims, experimental techniques, recommended background):
Rare mutations in the C1r and C1s proteases have been recently identified in peridontal Ehlers-Danlos patients. Whereas these two highly controlled proteases are known as innate immune triggers, these mutations are unexpectedly associated to periodontitis, leading for example to premature loss of teeth. To better understand the molecular mechanisms involved in these new pathophysiological conditions, we need to investigate how the mutations impact the structural integrity of the proteins and their function.

These dominant heterozygote missense or in-frame insertion/deletion mutations do not alter the catalytic serine protease domain, but likely impact the assembly of the proteases. These mutations might therefore induce a gain of a new function or perturb an essential physiological balance. One aim will be to check the impact of the pathogenic mutation ont the structure and assembly of the recombinant protease, as compared to the wild type. New potential targets of the C1r and C1s proteaseswill be investigated, according to their known enzymatic specificity profile. This work will be performed in collaboration with an Austrian medical research team (Medical University Innsbruck).The student should have a background in biochemistry and biophysics and ideally apply to the M2 specialty *Biochemistry and Structural Biology.*

Justification that the internship's subject fits with the general theme of GRAL:
The team addresses the question of the structural/functional impact of patient mutations in the proteases C1r and C1s and works in close collaboration with a medical research team analysing patient samples and cellular dysfunctions.

Relevant publications of the team:

Periodontal Ehlers-Danlos Syndrome Is Caused by Mutations in C1R and C1S, which Encode Subcomponents C1r and C1s of Complement. I. Kapferer-Seebacher, M. Pepin M, R. Werner, T. Aitman, A. Nordgren, H. Stoiber, N. Thielens, C. Gaboriaud, …, P. Byers, J. Zschocke. *Am J Hum Genet.* (**2016)**, 9:1005-1014.

Deciphering the fine details of C1 assembly and activation mechanisms: "mission impossible"? C. Gaboriaud, W.L. Ling, N.M. Thielens, I. Bally, V. Rossi *Front Immunol.* (**2014)** 5:565. doi: 10.3389/fimmu.2014.00565.

Crystal structure of the catalytic domain of human complement C1s: a serine protease with a handle. C. Gaboriaud, V. Rossi, I. Bally, G.J. Arlaud, J.C. Fontecilla-Camps. *EMBO J.* (**2000)** 19:1755-65.