Grenoble Alliance for Integrated Structural & Cell Biology

GRAL MASTER 2 RESEARCH SCHOLARSHIP - Program 2017 - 2018

INTERNSHIP PROPOSAL

Institute and Group: IBS, group IRPAS

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Research project title: Deciphering the molecular bases of a newly discovered autosomal dominant disorder: what is the gain in function induced by patient mutation in C1r/s?

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 likely correspond to a gain of a new function for these proteases, because their assembly, but not their catalytic site, seems to be impacted by the mutation(s).

One aim will be to produce recombinantly the protease domain including natural mutations in order to check their impact on the structure and assembly, as compared to the wild type. It will be also interesting to predict *in silico* new potential targets of the C1r and C1s proteases according to their known enzymatic specificity profile, and to check them *in vitro*. Finally, we will try to observe the impact of some mutations at the cellular level. This work is performed in collaboration with an austrian medical research team (Medical University Innsbruck) and is supported by an international research grant.

The student should have a background in biochemistry and biophysics and ideally apply to the *Specialty biochemistry and structural Biology.*

Relevant publications of the team:

1. 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.
2. 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.
3. 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.