Grenoble Alliance for Integrated Structural & Cell Biology

INTERNSHIP PROPOSAL

Institute and Group: IBS / IRPAS group

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Research project title:

Do C1s mutations identified in diseases affect the multiple functions of this immune protease?

5 Keywords to describe the project: Cancer, protease, mutation, complement system, innate immunity

Description of the project (aims, experimental techniques, recommended background):

C1s variants have been recently identified in rare diseases. The highly controlled C1s protease is known as an innate immune trigger. It associates with a homologous protease (C1r) and a defense collagen (C1q) to form C1, the initiation complex of the complement cascade. Triggering of the cascade by C1 will consequently produce different biological effects leading to the elimination of pathogens or self-debris. Due to its **modular structural organization**, C1s is **a highly specialized serine protease**, restricted to a few substrates, mainly C2 and C4 of the complement cascade. C1s homozygous variants have been observed in cases of systemic lupus Erythematosus (SLE), an autoimmune disease related mainly to complete C1s deficiency and to the impairment of its complement associated function. Lately, other different heterozygous variants have been identified in the context of a severe periodontal Ehlers-Danlos syndrome, or discovered within **renal tumors**. In these cases, a gain of new catalytic functions independent of complement involvement could be one hypothesis for their implication in the disease. The main goal of this M2 project will be to initiate the work on the molecular dissection of the effects of the mutations associated to renal cancer on C1s function. The student task will be to obtain the recombinant C1s variants using site-directed mutagenesis and to produce them in a mammalian expression system. C1s variants will then be tested for their impact on the structure and assembly of the C1 complex and for their enzymatic activity, as compared to the wild type C1s. The functional impact of the mutations on the cleavage of other new potential targets that could be linked to the disease will also be addressed.

The student should have a strong background in biochemistry and an interest in biophysics and apply to one of the ***Masters in biology:*** *Specialty biochemistry and structural Biology or Specialty immunology, microbiology, infectiology***.**

Justification that the internship's subject fits with the general theme of GRAL: The project addresses the question of the structural/functional impact of patient mutations in the C1s protease in relation to diseases.

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. boriaud, 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.