Friday, July 28, 2023

International PhD PPU-IMAGINE Proposal

Call 2023/2024

PhD PROPOSAL IDENTIFICATION

PhD Project title	Investigation of TLR and cytosolic nucleic acid signalling cross-talk through Mendelian disease
Project Acronym	TLRC-MD
Project Keywords	TLR; Cytosolic; Innate immunity; Mendelian

LABORATORY PRESENTATION

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PhD PROPOSAL

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Number of ongoing PhD students supervised by the Supervisor	1
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PhD Co-Supervisor position	Researcher (Inserm CRCN)
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Number of ongoing PhD students supervised by the Co-Supervisor 1

PhD Proposal abstract (1000 characters maximum)

As exemplified by the type I interferonopathies, Mendelian diseases associated with chronically enhanced type I interferon signalling, while essential in protection against infection, inappropriate activation of interferon signalling can be pathogenic. To date, characterisation of the type I interferonopathies has emphasised cytosolic nucleic acid sensing pathways in disease pathogenesis. However, we have recently implicated Toll-like receptor (TLR) endosomal signalling as central to the pathogenesis of three novel type I interferonopathies. Notably, our unpublished data indicate an unexpected degree of 'cross-talk' between the TLR and cytosolic nucleic acid sensing pathways. The current PhD proposal is designed to explore these observations in detail.

PhD Proposal (10 000 characters maximum)

While type I interferons (IFNs) play an essential role in the antiviral response, inappropriate activation of IFN signalling can be pathogenic, leading to tissue damage. This dichotomy is particularly well illustrated by the type I interferonopathies (T1Is), Mendelian diseases associated with chronically enhanced type I IFN signalling - first defined by our group in 2011 (Crow Y. Ann N Y Acad Sci 2011 PMID: 22129056). Systemic lupus erythematosus (SLE) and chilblain lupus (CBL), a subtype of cutaneous SLE, comprise a set of heterogeneous phenotypes also characterized by upregulation of type I IFN signalling, with the Crow laboratory playing an important role in the study of Mendelian causes of SLE and CBL (e.g. Briggs et al. Nat Genet 2011 PMID: 21217755).

To-date, characterisation of the T1Is has emphasised the involvement of ('inappropriate') cytosolic receptor-mediated sensing of self-derived DNA and RNA by the cGAS-STING and MDA5/RIGI-MAVS axes respectively (Crow, Stetson. Nat Rev Immunol 2022 PMID: 34671122). However, endosomal TLRs can also recognize self-RNA and self-DNA (Lind et al. Nat Rev Immunol 2022 PMID: 34272507). In homeostasis, TLR7 signalling is controlled through its sorting into intralumenal vesicles of multivesicular bodies and subsequent signal termination, an effect mediated by the TLR trafficking chaperone UNC93B1 (uncoordinated 93 homolog B1) (Majer et al. Nature 2019 PMID: 31546246). Recently, de novo and inherited heterozygous gain-of-function (GOF) mutations in TLR7 have been described to cause severe, childhood-onset lupus (Brown et al. Nature 2022 PMID: 35477763), and introduction of one of these mutations (p.Tyr264His) into mice resulted in a lupus phenotype which was rescued by deficiency of myeloid differentiation primary response gene 88 (MyD88), an adaptor protein downstream of TLR7 (and TLR9). Notably, while both TLR7 and TLR9 signal through the proinflammatory adaptor MyD88, studies from multiple groups, using *Tlr7*- and *Tlr9*-knockout (KO) lupus-prone MRL/lpr mice, show that TLR7 and TLR9 have opposing effects: thus, while loss of TLR7 is protective against the development of murine lupus, loss of TLR9 exacerbates disease (Christensen et al. Immunity 2006 PMID: 16973389; Nickerson et al. PLoS ONE. 2017 PMID: 28278279). The explanation for this so-called 'TLR9 paradox' is unresolved, but may relate to a negative regulatory effect of TLR9 on TLR7 function through UNC93B1 (Fukui et al. Immunity 2011 PMID: 2163627; Pelka et al. Immunity 2018 PMID: 29768176).

As part of an ongoing protocol involving the screening of patients with uncharacterized phenotypes for an upregulation of IFN signalling (elevated 'IFN score') in blood, we have identified multiple individuals manifesting overlapping features of the paradigm type I interferonopathy Aicardi-Goutières syndrome (AGS), early-onset SLE and CBL to carry pathogenic mutations in distinct components of the TLR signalling complex. Interestingly, our data, and that of others (Sharma et al. J Immunol 2015 PMID: 26432899; Deb et al. J Immunol 2020 PMID: 32471881), indicate an unexpected degree of cross-talk between the cytosolic and endosomal nucleic acid signalling pathways. Thus, the current PhD proposal is designed to explore these observations in detail. Under expert supervision, the candidate will leverage the power of Mendelian disease mutations to inform our understanding of the relationship between TLR and

cytosolic innate immune signalling pathways in the human context. This work will involve the use of patient-derived primary material in *ex vivo* studies, sophisticated *in vitro* cellular systems (including models of plasmacytoid dendritic cell function), and state-of the-art cell imaging technologies and bioinformatic approaches.

Laboratory's best 5 publications

1. Crow YJ, Stetson DB. The type I interferonopathies: 10 years on. Nature Reviews Immunology 22:471-483 (2022).
2. Lepelley A, Della Mina E, Van Nieuwenhove E, Waumans L, Fraitag S, Rice GI, Dhir A, Frémond ML, Rodero MP, Seabra L, Carter E, Bodemer C, Buhas D, Callewaert B, de Lonlay P, De Somer L, Dyment DA, Faes F, Grove L, Holden S, Hully M, Kurian MA, McMillan HJ, Suetens K, Tyynismaa H, Chhun S, Wai T, Wouters C, Bader-Meunier B, Crow YJ. Enhanced cGAS-STING dependent interferon signaling associated with mutations in ATAD3A. Journal of Experimental Medicine 218, e20201560 (2021).
3. Uggenti C, Lepelley, A, Depp M, Badrock AP, Rodero MP, El-Daher MT, Rice GI, Dhir S, Wheeler AP, Dhir A, Albawardi W, Frémond ML, Seabra L, Doig J, Blair N, Martin-Niclos MJ, Della Mina E, Rubio-Roldán A, Garcia-Pérez J, Sproul D, Rehwinkel J, Hertzog J, Boland-Auge A, Olaso R, Deleuze J-F, Baruteau J, Brochard K, Buckley J, Cavallera V, Cereda C, De Waele LMH, Dobbie A, Doummar D, Elmslie F, Koch-Hogrebe M, Kumar R, Lamb K, Livingston JH, Majumdar A, Marques Lorenço C, Orcesi S, Peudenier S, Rostasy K, Salmon CA, Scott C, Tonduti D, Touati G, Valente M, van der Linden H, Van Esch H, Vermelle M, Webb K, Jackson AP, Reijns MAM, Gilbert N, Crow YJ. cGAS-mediated induction of type I interferon due to inborn errors of histone pre-mRNA processing. Nature Genetics 52, 1364-1372 (2020).
4. Lepelley A, Martin-Niclós MJ, Le Bihan M, Marsh JA, Uggenti C, Rice GI, Bondet V, Duffy D, Hertzog J, Rehwinkel J, Amselem S, Boulisfane-El Khalifi S, Brennan M, Carter E, Chatenoud L, Chhun S, Coulomb l'Hermine A, Depp M, Legendre M, Mackenzie KJ, Marey J, McDougall C, McKenzie KJ, Molina TJ, Neven B, Seabra L, Thumerelle C, Wislez M, Nathan N, Manel N, Crow YJ, Frémond ML. Mutations in COPA lead to abnormal trafficking of STING to the Golgi and interferon signalling. Journal of Experimental Medicine 217, e20200600 (2020).
5. Rice GI, Meyzer C, Bouazza N, Hully M, Boddaert N, Semeraro M, Zeef LAH, Rozenberg F, Bondet V, Duffy D, Llibre A, Baek J, Sambe MN, Henry E, Jolaine V, Barnerias C, Barth M, Belot A, Cances C, Debray FG, Doummar D, Frémond ML, Kitabayashi N, Lepelley A, Levrat V, Melki I, Meyer P, Nougues MC, Renaldo F, Rodero MP, Rodriguez D, Roubertie A, Seabra L, Uggenti C, Abdoul H, Treluyer JM, Desguerre I, Blanche S, Crow YJ. Reverse transcriptase inhibitors in Aicardi-Goutières syndrome. New England Journal of Medicine 379, 2275-7 (2018).

Expected profile of the candidate

We wish to recruit an intelligent and hard-working student who is driven to explore new biology relating to innate immune signalling in the context of human disease. The student must be committed to their work, motivated, thoughtful and willing to learn. Previous experience in innate immunity, and type I interferon signalling in particular, would be a plus. Interested students are encouraged to contact us at: marie-louise.fremond@institutimagine.org and alice.lepelley@institutimagine.org.