PhD Research Proposal Form
China Scholarship Council (CSC)

BIOLOGY

Thesis subject title: Understanding host-pathogen interaction processes controlling acute vs. chronic infections of human hepatitis viruses and nairoviruses

Name of the French doctoral school/Ecole doctorale: BMIC

Name of the Research team/Equipe de recherche: Team EVIR – Enveloped viruses, Vectors and Immunotherapy

Website: http://ciri.inserm.fr/en/team/all-teams/enveloped-viruses-vectors-innate-responses/research-themes/

Name of the Supervisor/Directeur de thèse: COSSET François-Loïc

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Lab Language/ Langue de travail: English and French

Research Proposal Abstract/Présentation du sujet:
Viruses use and abuse their hosts to replicate, escape immune responses and invade new cells or organisms. By comparing different viral species and genera, we seek to understand how interactions with host pathways of certain viral pathogens can establish chronic infections versus acute infections, and how they are transmitted and transgress species specific barriers to infection. For this, we study very different viruses responsible for infectious diseases in humans: hepatitis B virus (hepadnavirus), C (hepacivirus) and D (deltavirus) as well as the Crimean-Congo hemorrhagic fever virus (CCHFV, orthonairovirus). We are interested in the mechanisms by which their nonstructural proteins facilitate the assembly of viral particles by interacting with cellular factors of the secretory pathway. We also study the processes by which their surface glycoproteins intervene in cell penetration by exploiting surface receptors and specific cell entry pathways. We have also initiated projects aimed at understanding the processes of interspecies transmission and the (re) emergence of zoonotic infectious diseases transmitted by bats and ticks. On the other hand, we seek to understand how certain immune mechanisms restrict infection or, conversely, are neutralized, subverted or perverted by pathogens; the understanding of such mechanisms to facilitate the development of antiviral strategies. Finally, capitalizing on our viral engineering technologies, we invent innovative biotherapies against chronic diseases, with specific applications in gene therapy, vaccinology or

immunotherapy, in particular, for this last aspect, the exploration of a concept of reprogramming of the immunological memory B that we invented and patented.
The technologies and methods that will be used in the proposed PhD thesis project are biochemistry, molecular biology, cell biology, imaging by confocal microscopy, and virology in P2 and P3 laboratories.

References (selection from ORCID: https://orcid.org/0000-0001-8842-3726):

1. Perez-Vargas, J., F. Amirache, C. Mialon, B. Boson, N. Freitas, C. Sureau., F. Fusil and F.-L. Cosset (2019). "Enveloped viruses distinct from HBV induce dissemination of hepatitis D virus in vivo." *Nature Communications*. (IF=12.5)
2. Denolly, S., C. Granier, N. Fontaine, B. Pozzetto, T. Bourlet, M. Guerin and F. L. Cosset (2019). "A serum protein factor mediates maturation and apoB-association of HCV particles in the extracellular milieu." *J Hepatol* 70(4): 626-638. (IF=15.1)
3. Douam, F., F. Fusil, M. Enguehard, L. Dib, F. Nadalin, L. Schwaller, G. Hrebikova, J. Mancip, L. Mailly, R. Montserret, Q. Ding, C. Maisse, E. Carlot, K. Xu, E. Verhoeyen, T. F. Baumert, A. Ploss, A. Carbone*, F. L. Cosset* and D. Lavillette* (2018). "A protein coevolution method uncovers critical features of the Hepatitis C Virus fusion mechanism." *PLoS Pathog* 14(3): e1006908. *co-senior authors. (IF=6.2)
4. Boson, B., S. Denolly, F. Turlure, C. Chamot, M. Dreux and F. L. Cosset (2017). "Daclatasvir Prevents Hepatitis C Virus Infectivity by Blocking Transfer of the Viral Genome to Assembly Sites." *Gastroenterology* 152(4): 895-907 e814. (IF=20.8)
5. Denolly, S., C. Mialon, T. Bourlet, F. Amirache, F. Penin, B. Lindenbach, B. Boson and F. L. Cosset (2017). "The amino-terminus of the hepatitis C virus (HCV) p7 viroporin and its cleavage from glycoprotein E2-p7 precursor determine specific infectivity and secretion levels of HCV particle types." PLoS Pathog 13(12): e1006774. (IF=6.2)

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