

EuReCa International PhD Program
PhD thesis project
2022 Call for application

Finding a viral needle in a nuclear haystack: molecular mechanism of HIV detection by NONO-cGAS in the nucleus

General information

Call	2022
Reference	2022-08-LAHAYE_MANEL
Keyword(s)	HIV; Innate immunity; Virus detection; Nuclear sensors; cGAS-STING pathway

Director(s) and team

Thesis director(s)	Xavier Lahaye & Nicolas Manel
Research team	Innate Immunity
Research department	U932 – Immunity and Cancer

Description of the PhD thesis project

The ability of cells to detect viruses is essential for their defense. The cGAS-STING pathway has emerged in the recent years as the main pathway for sensing viral DNA in the cytosol across the tree of life. In mammals, this detection activates a signaling cascade that culminates into the production of antiviral interferons and immune responses.

However, most DNA viruses and some RNA viruses enter the nucleus to replicate in cells. The viral sensors in the nucleus are largely unknown. The nucleus is so full of DNA and RNA already that finding a virus is like finding a needle in a haystack. Recent studies from our lab (Lahaye et al. Immunity 2013, Gentili et al. Science 2015, Silvin et al. Science Immunology 2017, Lahaye et al. Cell 2018, Gentili et al. Cell Reports 2019) have shown that human dendritic cells and macrophages can detect HIV in the nucleus. We discovered that HIV is detected by a duo of sensors: the NONO proteins first detects the viral capsid protein. Then, the cGAS protein detects the viral DNA. This activates cGAS in the nucleus, leading to activation of the cGAS-STING-interferon signaling pathway.

The PhD will use interdisciplinary approaches in immunology, virology, biochemistry and biophysics to ask the following questions: How do NONO and cGAS manage to detect locally HIV, as it enters the nucleus? What is the biochemical reaction taking place and how is it isolated from the rest of the nucleus? Can this reaction be modeled using a "HIV sensing in a test tube" assay? By addressing these questions, the PhD will provide a crucial understanding of how viral sensors detect viruses in the nucleus.



International, interdisciplinary & intersectoral aspects of the project

The project on HIV sensing by NONO is the result of a long-standing "International" collaboration with the lab of Charles Bond in Australia University (see Lahaye et al., Cell 2018). The Charles Bond lab has been developing novel biochemical tools. This expertise will greatly benefit the PhD student. For the "Industrial" dimension, the Manel lab collaborate with the start-up Stimunity. Sylvain Carlioz CEO, has a strong background in patents, technology transfer, licensing, business development, biotech financing and clinical applications. The PhD students will be exposed to interactions with Stimunity. For the "interdisciplinary" dimension, the project operates at the intersection of biology (virology of HIV and immunology for innate sensing) and some physical chemistry.

Recent publications

1. Anvita Bhargava, Alice Williard, Mathieu Maurin, Patricia M. Davidson, Mabel Jouve, Matthieu Piel, **Xavier Lahaye**, **Nicolas Manel**. Inhibition of HIV infection by structural proteins of the inner nuclear membrane is associated with reduced chromatin dynamics. Cell Reports. 2021. doi: 10.1016/j.celrep.2021.109763
2. Marius Döring, Kevin De Azevedo, Guillermo Blanco-Rodriguez, Francesca Nadalin, Takeshi Satoh, Matteo Gentili, **Xavier Lahaye**, Nilushi S. De Silva, Cécile Conrad, Mabel Jouve, Mireille Centlivre, Yves Lévy, and **Nicolas Manel**. Single-cell analysis reveals divergent responses of human dendritic cells to the MVA vaccine. Science Signaling. 2021. doi: 10.1126/scisignal.abd9720
3. Matteo Gentili, **Xavier Lahaye**, Francesca Nadalin, Guilherme F. P. Nader, Emilia Puig Lombardi, Solène Herve, Nilushi S. De Silva, Derek C Rookhuizen, Elina Zueva, Christel Goudot, Mathieu Maurin, Aurore Bochnakian, Sebastian Amigorena, Matthieu Piel, Daniele Fachinetti, Arturo Londoño-Vallejo, **Nicolas Manel**. The N-terminal domain of cGAS determines preferential association with centromeric DNA and innate immune activation in the nucleus. Cell Reports. 2019. doi: 10.1016/j.celrep.2019.01.105
4. Xavier Lahaye, Matteo Gentili, Aymeric Silvin, Cécile Conrad, Léa Picard, Mabel Jouve, Elina Zueva, Mathieu Maurin, Francesca Nadalin, Gavin J. Knott, Baoyu Zhao, Fenglei Du, Marlène Rio, Jeanne Amiel, Archa H. Fox, Pingwei Li, Lucie Etienne, Charles S. Bond, Laurence Colleaux, Nicolas Manel. NONO Detects the Nuclear HIV Capsid to Promote cGAS-Mediated Innate Immune Activation. Cell. 2018. doi: 10.1016/j.cell.2018.08.062
5. **Xavier Lahaye**, Takeshi Satoh, Matteo Gentili, Silvia Cerboni, Cécile Conrad, Ilse Hurbain, Ahmed El Marjou, Christine Lacabaratz, Jean-Daniel Lelièvre, **Nicolas Manel**. The capsids of HIV-1 and HIV-2 determine immune detection of the viral cDNA by the innate sensor cGAS in dendritic cells. Immunity. 2013. doi: 10.1016/j.immuni.2013.11.002

Expected profile of the candidate

The PhD candidate should be intensely motivated to study molecular mechanisms and to perform experiments in molecular virology, molecular innate immunity, biochemistry and biophysics. A strong background in biochemistry of proteins and DNA is recommended. A previous academic lab experience in molecular biology and biochemistry is highly desirable.

