INSTITUT DES MALADIES GÉNÉTIQUES

Proposal for the 2020 Imagine International PhD program

Laboratory: Human genetics of infectious diseases: monogenic predisposition
Head of laboratory: Jean-Laurent Casanova (PUPH)
Project and student supervisor: Béziat Vivien (CR, HDR)
Number of HDR in the lab: 7
Field of research: Genetics - Immunology
Number and names of PhD students currently in the lab in 2020: 7
1st y: Tom Le Voyer, Majistor MAGLORIUS, Anna-Lena NEEHUS, Quentin PHILIPPOT
2nd Y: Paul BASTARD, Jérémie ROSAIN
4th Y: Cecilia KOROL
Number and names of PhD students under the Imagine program: 2, Anna-Lena Neehus, Cécilia Korol
Project Title: Inborn errors of immunity to Human Papillmomaviruses

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Project:

Papillomaviruses (PVs) are small, non-enveloped viruses with double-stranded circular DNA genomes packaged into an icosahedral capsid, highly host-specific and with a strict tropism for cutaneous or mucosal stratifying epithelia. PV infections are widespread across animal species, usually asymptomatic or benign and self-healing, as a consequence of proper intrinsic, innate, and adaptive immunity. Human PVs (HPVs) are divided into five genera and over 200 genotypes have been recognized by the International Human Papillomavirus Reference Center. α-HPVs have mucosal and cutaneous tropism. They are responsible for common warts, condyloma, cervical and oropharyngeal mucosal lesions. In contrast, β-, γ-, μ- and ν-HPVs have a strict cutaneous tropism. γ-, μ- and ν-HPVs are responsible of benign cutaneous common and plantar warts, while infections with β-HPVs are usually asymptomatic but responsible for flat warts in rare patients with epidermodysplasia verruciformis (EV). Persistent infections can lead to benign tumors and sometime malignant transformation and progression toward invasive cancer. Both α- and β-HPVs comprise genotypes associated with low-risk and high-risk to develop cancers. High-risk α-HPV genotypes are mainly related to cervical cancers, while β-HPV can underlie non-melanoma skin cancer (NMSC) in patients with EV. Demonstrating an important role of adaptive immune system in the control of HPVs, severe HPV infections are frequent in patients with acquired immunodeficiencies or undergoing immunosuppressive treatment.

HPVs can also persist and spread in patients with inherited immunodeficiencies. Genetic disorders predisposing to severe HPV infections are either syndromic (associated with other symptoms and/or infections) or isolated. Autosomal dominant (AD) GATA2 and CXCR4 deficiencies lead to syndromic susceptibility to HPVs, with multiple cytopenias. Several T cell deficiencies were associated with broad infectious susceptibility including susceptibility to HPVs (e.g. autosomal recessive RHOH, DOCK8 or CARMIL2 deficiencies). Autosomal recessive (AR) EVER1, EVER2 and CIB1 deficiencies cause isolated EV due to impaired keratinocyte-intrinsic immunity to β -HPVs. More recently, our laboratory identified AR NLRP1 mutations probably impairing intrinsic mucosal immunity in patients with respiratory papillomatosis, and AR CD28 deficiency impairing T cell response in patients with isolated common wart and the "tree man" syndrome (submitted). Numerous patients without risk factors (e.g. AIDS,

immunosuppressive drugs…) but severe HPVs infections, remain without genetic diagnosis. The main objective of the project is to identify novel mutations and genes underlying susceptibility to common warts and mucosal HPVs using a cutting edge strategy combining comprehensive whole exome sequencing (WES) analysis with in-depth functional studies. We have exciting preliminary results of the WES analysis in some patients with promising candidate rare variants. Notably, we recently identified biallelic predicted loss of function mutations in *FLT3LG* in a kindred with lung bacterial infections and widespread common warts. The functional impact of this novel allele on the immune response has to be deciphered by in-depth immunological and genetic approaches. FLT3LG (FMS-like tyrosine kinase 3 ligand) is major cytokine involved in the generation and/or maintenance of lymphoid and myeloid precursors from $Flt3^+$ lymphoid and myeloid-committed progenitors. It is of course most surprising that patients with complete FLT3LG deficiency would reach adulthood with such narrow infectious phenotype. Their vulnerability to HPVs is also surprising. This project will provide new insights into the pathogenesis of infectious diseases and into the understanding of the intrinsic and extrinsic immunity against HPVs. It will also shed new light onto the essential and redundant features of FLT3LG. Moreover, the clinical implications will help the patients and their families in terms of molecular diagnosis, genetic counseling, treatment and clinical outcome.

Lab members

Vivien Béziat (CR, HDR), Natasha Vladikine (Technician), Marie Materna (Master 2) et Jean-Laurent Casanova (PU-PH)

Major Publications

1. Crequer A, Troeger A, Patin E, Ma CS, Picard C, Pedergnana V, Fieschi C, Lim A, Abhyankar A, Gineau L, Mueller-Fleckenstein I, Schmidt M, Taieb A, Krueger J, Abel L, Tangye SG, Orth G, Williams DA, Casanova JL, Jouanguy E. Human RHOH deficiency causes T cell defects and susceptibility to EV-HPV infections. J Clin Invest. 2012 Sep 4;122(9):3239–47.
2. de Jong SJ, Créquer A, Matos I, Hum D, Gunasekharan V, Lorenzo L, Jabot-Hanin F, Imahorn E, Arias AA, Vahidnezhad H, Youssefian L, Markle JG, Patin E, D'Amico A, Wang CQF, Full F, Ensser A, Leisner TM, Parise LV, Bouaziz M, Maya NP, Cadena XR, Saka B, Saeidian AH, Aghazadeh N, Zeinali S, Itin P, Krueger JG, Laimins L, Abel L, Fuchs E, Uitto J, Franco JL, Burger B, Orth G, Jouanguy E, Casanova J-L. The human CIB1–EVER1–EVER2 complex governs keratinocyte-intrinsic immunity to β-papillomaviruses. J Exp Med. 2018 Sep 3;215(9):2289–2310. PMID: 30068544
3. Drutman SB, Haerynck F, Zhong FL, Hum D, Hernandez NJ, Belkaya S, Rapaport F, Jong SJ de, Creytens D, Tavernier SJ, Bonte K, Schepper SD, Bosch J van der W ten, Lorenzo-Diaz L, Wullaert A, Bossuyt X, Orth G, Bonagura VR, Béziat V, Abel L, Jouanguy E, Reversade B, Casanova J-L. Homozygous NLRP1 gain-of-function mutation in siblings with a syndromic form of recurrent respiratory papillomatosis. Proc Natl Acad Sci. 2019 Sep 17;116(38):19055–19063. PMID: 31484767
4. Wang Y, Ma CS, Ling Y, Bousfiha A, Camcioglu Y, Jacquot S, Payne K, Crestani E, Roncagalli R, Belkadi A, Kerner G, Lorenzo L, Deswarte C, Chrabieh M, Patin E, Vincent QB, Müller-Fleckenstein I, Fleckenstein B, Ailal F, Quintana-Murci L, Fraitag S, Alyanakian M-A, Leruez-Ville M, Picard C, Puel A, Bustamante J, Boisson-Dupuis S, Malissen M, Malissen B, Abel L, Hovnanian A, Notarangelo LD, Jouanguy E, Tangye SG, Béziat V, Casanova J-L. Dual T cell– and B cell–intrinsic deficiency in humans with biallelic RLTPR mutations. J Exp Med. 2016 Oct 17;213(11):2413–2435. PMID: 27647349