Proposal for the 2020 Imagine International PhD program

Laboratory: Laboratory of Intestinal immunity
Head of laboratory: Nadine Cerf-Bensussan
Project and student supervisor: Nadine Cerf-Bensussan (HDR Y)
Number of HDR in the lab: 5
Field of research: Genetics- Mucosal Immunology
Number and names of PhD students currently in the lab in 2020: 3rd y (Sofia Berrabah), 4th Y (Roman Goguyer-Deschaumes)
Number and names of PhD students under the Imagine program: 0
Project Title: Single cell based characterization of inflammatory pathways and therapeutic targets in inflammatory bowel diseases

Project description (Max 2 pages including abstract and publications)

Considerable effort has been made over the past 20 years to dissect genetic factors predisposing to common polyfactorial forms of inflammatory bowel diseases (IBD). Genome-wide association studies in IBD have identified over 230 susceptible genetic polymorphisms (McGovern, 2015). Those variants have provided insight into IBD pathophysiology and pointed to genes controlling the epithelial barrier, innate immunity toward the microbiota as well as T-helper cells function among many others. Yet, individual variants have very limited contribution to IBD development and inheritability; many are located in intergenic regions and overall their contribution to the development of intestinal inflammation is still unclear. As a consequence, it has been difficult to define personalized anti-inflammatory therapies and treatment of IBD remains largely based on drugs with broad and unspecific effects. The genetic landscape of IBD has recently broadened with the discovery of an increasing number of monogenic diseases. Monogenic IBD are usually characterized by a very early onset (VEO-IBD). We have recently shown that systematic screening for genetic defects of VEO-IBD patients, using TNGS and WES, resulted in a significant number of genetic diagnoses (Charbit-Henrion F et al, J Crohns Colitis. 2018) and in the identification of novel genetic etiologies (Parlato M et al, EMBO Mol Med. 2018; Parlato M et al, bioRxiv 768028 2019), respectively. Preliminary results also indicate that monogenic disorders of late onset can be identified in a substantial fraction of adult patients with severe intestinal inflammation either complicating common variable immunodeficiency or associated with immune dysfunction without immunoglobulin deficiency. This project stems from our recent analysis suggesting an overlap between mono and polygenic IBD (Parlato M et al, bioRxiv 768028. 2019) and will take advantage of the power of single cell transcriptomics and to our access to biopsies and blood from patients with monogenic forms of IBD to establish a detailed single cell resolution analysis of known monogenic disorders and to construct models of disease gene-associated cell types, their expression profiles and putative interactions. So far, this approach has been used to dissect in depth cells and pathways differentially activated between homeostasis and pathological conditions. We expect that the establishment of a single cell-based atlas of cells and pathways dysregulated as a consequence of a defect in one single key gene in monogenic IBD will provide an important reference dataset to guide the stratification of patients with undiagnosed IBD and to potentially reveal subgroups of patients with similar signatures who could benefit from targeted treatments.

Lab members

Nadine Cerf-Bensussan, head of the lab (DR); Valérie Gaboriau-Routhiau (CR); Marie Cherrier (CR); Georgia Malamut (PUPH); Frank Ruemmele (PUPH); Fabienne Charbit-Henrion (CCA); Corinne Lebreton (IR); Nicolas Guegan (AI); Bernadette Begue (AI); Anis Khiat (AI); Benoit Clement (postdoc); Sascha Cording(postdoc); Marianna Parlato (postdoc); Anais Levescot (postdoc); Roman GOGUYER-DESCHAUMES (PhD student); Sofia Berrabah (PhD student); Manon Haas (Master 2 student); Alison Gilot (Master 2 student); Valentina Fraccascia (Master 2 student); Clara Lemoine (Master 2 student).–

Major Publications

1. Parlato M, Pazmandi J, Nian Q, Charbit-Henrion F, Bègue B, Martin E, Thian M, Müller F, Maggioni M, Duclaux-Loras R, Rieux-Laucat F, Molina TJ, Latour S, Ruemmele F, Menche J, Rodrigues-Lima F, Boztug K, Cerf-Bensussan N. Network Analysis of Inflammatory Bowel Disease Reveals PTPN2 As New Monogenic Cause of Intestinal Inflammation. bioRxiv 768028; doi: https://doi.org/10.1101/768028

2.Parlato M, Charbit-Henrion F, Elie AN, Begue B, Guegan N, Bruneau J, Khater S, Macintyre E, Picard C, Frédéric RL, Le Bourhis L, Allez M, Goulet O, Cellier C, Hermine O, Cerf-Bensussan N, Malamut G. Efficacy of Ruxolitinib Therapy in a Patient With Severe Enterocolitis Associated With a STAT3 Gain of-Function Mutation. Gastroenterology. 2019 Mar;156(4):1206-1210.

3. Charbit-Henrion F, Parlato M, Hanein S, Duclaux-Loras R, Nowak J, Begue B, Rakotobe S, Bruneau J, Fourrage C, Alibeu O, Rieux-Laucat F, Lévy E, Stolzenberg MC, Mazerolles F, Latour S, Lenoir C, Fischer A, Picard C, Aloi M, Amil Dias J, Ben Hariz M, Bourrier A, Breuer C, Breton A, Bronski J, Buderus S, Cananzi M, Coopman S, Crémilleux C, Dabadie A, Dumant-Forest C, Egritas Gurkan O, Fabre A, Fischer A, German Diaz M, Gonzalez-Lama Y, Goulet O, Guariso G, Gurcan N, Homan M, Hugot JP, Jeziorski E, Karanika E, Lachaux A, Lewindon P, Lima R, Magro F, Major J, Malamut G, Mas E, Mattyus I, Mearin LM, Melek J, Navas-Lopez VM, Paerregaard A, Pelatan C, Pigneur B, Pinto Pais I, Rebeuh J, Romano C, Siala N, Strisciuglio C, Tempia-Caliera M, Tounian P, Turner D, Urbonas V, Willot S, Ruemmele FM, Cerf-Bensussan N. Diagnostic Yield of Next-Generation Sequencing in Very Early-Onset Inflammatory Bowel Diseases: A Multicenter Study.J Crohns Colitis. 2018 May.

4. Parlato M, Charbit-Henrion F, Pan J, Romano C, Duclaux-Loras R, Le Du MH, Warner N, Francalanci P, Bruneau J, Bras M, Zarhrate M, Bègue B, Guegan N, Rakotobe S, Kapel N, De Angelis P, Griffiths AM, Fiedler K, Crowley E, Ruemmele F, Muise AM, Cerf-Bensussan N. Human ALPI deficiency causes inflammatory bowel disease and highlights a key mechanism of gut homeostasis. EMBO Mol Med. 2018 Apr.

5. Parlato M, Charbit-Henrion F, Hayes P, Tiberti A, Aloi M, Cucchiara S, Bègue B, Bras M, Pouliet A, Rakotobe S, Ruemmele F, Knaus UG, Cerf-Bensussan N. First Identification of Biallelic Inherited DUOX2 Inactivating Mutations as a Cause of Very Early Onset Inflammatory Bowel Disease.Gastroenterology. 2017 Aug;153(2):609-611

6. Ettersperger J, Montcuquet N, Malamut G, Guegan N, Lopez-Lastra S, Gayraud S, Reimann C, Vidal E, Cagnard N, Villarese P, Andre-Schmutz I, Gomes Domingues R, Godinho-Silva C, Veiga-Fernandes H, Lhermitte L, Asnafi V, Macintyre E, Cellier C, Beldjord K, Di Santo JP, Cerf-Bensussan N, Meresse B. Interleukin-15-Dependent T-Cell-like Innate Intraepithelial Lymphocytes Develop in the Intestine and Transform into Lymphomas in Celiac Disease. Immunity. 2016 Sep 20;45(3):610-625.

7. Charbit-Henrion F, Jeverica AK, Bègue B, Markelj G, Parlato M, Avčin SL, Callebaut I, Bras M, Parisot M, Jazbec J, Homan M, Ihan A, Rieux-Laucat F, Stolzenberg MC, Ruemmele FM, Avčin T, Cerf-Bensussan N; GENIUS Group. Deficiency in Mucosa-associated Lymphoid Tissue Lymphoma Translocation 1: A Novel Cause of IPEX-Like Syndrome. J Pediatr Gastroenterol Nutr. 2017 Mar;64(3):378-384.

8.Schnupf P, Gaboriau-Routhiau V, Gros M, Friedman R, Moya-Nilges M, Nigro G, Cerf-Bensussan N, Sansonetti PJ. Growth and host interaction of mouse segmented filamentous bacteria in vitro. Nature. 2015 Apr 2;520(7545):99-103.

9. Lécuyer E, Rakotobe S, Lengliné-Garnier H, Lebreton C, Picard M, Juste C, Fritzen R, Eberl G, McCoy KD, Macpherson AJ, Reynaud CA, Cerf-Bensussan N, Gaboriau-Routhiau V. Segmented filamentous bacterium uses secondary and tertiary lymphoid tissues to induce gut IgA and specific T helper 17 cell responses.Immunity. 2014 Apr 17;40(4):608-20.

10. Korneychuk N, Ramiro-Puig E, Ettersperger J, Schulthess J, Montcuquet N, Kiyono H, Meresse B, Cerf-Bensussan N. Interleukin 15 and $CD4^+$ T cells cooperate to promote small intestinal enteropathy in response to dietary antigen. Gastroenterology. 2014 Apr;146(4):1017-27.