Proposal for the 2020 Imagine International PhD program

Laboratory: Cellular and molecular mechanisms of hematological disorders and therapeutic implications
Head of laboratory: Olivier Hermine
Project and student supervisor: Pascal Amireault and Olivier Hermine (HDR)
Number of HDR in the lab: 6
Field of research: Hematology
Number and names of PhD students currently in the lab in 2020: 11, including 1st y (Bahia Bekhouche, Louise Condon, Héloise Halse, Madeleine Casimir), 3rd y (Elia Colin, Matthias Papo, Laura Polivka), 4th y (Marion Falabrègue, Sandra Mignot, Justine Siavellis, Alexandre Morel)
Number and names of PhD students under the Imagine program: 1, Matthias Papo
Project Title: Erythropoietin deactivation of red blood cell elimination: implications in ß-thalassemia and transfusion

Project description (Max 2 pages including abstract and publications)

State of the art

The laboratory of molecular mechanisms of hematologic disorders and therapeutic implications of the Imagine Institute covers several aspects of the physiopathology and treatment of malignant and benign hematologic disorders. The team belongs to INSERM U1163 research units and is associated to the Necker Hospital clinical hematological department of hematology as well as to national reference centers for mastocytosis (CEREMAST), immunodeficiencies (CEREDIH) and hemoglobinopathies.

The proposed project aims to better understand ß-thalassemia, the most common congenital anemia, caused by mutations that reduce or eliminate production of ß-globin. Intracellular accumulation of free α-globin chains and precipitation of α-globin-heme complexes on red blood cell (RBC) membranes inhibits late-stage erythroid differentiation, and is also thought to cause RBC hemolysis. A novel class of molecule is in clinical trials for the treatment of thalassemia: activin ligand traps (ALT). ALT are recombinant fusion molecules linking the extracellular domain of a human activin receptor with a human immunoglobulin Fc domain. ALT increases the efficiency of erythropoiesis in mice, but the exact mechanism(s) by which they alleviate or cure anemia are still under exploration. As such, **the impact of ALT on RBC clearance has never been directly explored** and recent results from our team suggest that, similarly to RBC production, RBC elimination is regulated by erythropoietin (EPO) and could be dysregulated in thalassemic individuals. Indeed, RBC elimination is downregulated during hypoxia and EPO is sufficient and necessary to mediate this physiological function. The cellular target of EPO remains to be identified, but a number of evidence suggest that macrophages could mediate this signalization.
Macrophages in the splenic red pulp and hepatic Kupffer cells, recognize, remove and recycle senescent RBC thereby regulating the biomass of circulating RBC. Macrophages express EPO receptors and its signaling could modify their activation state. A dysregulation of this mechanism could play a role in the pathophysiological context of *ß*-thalassemia. In addition, the dysregulation of macrophage activation by anemic signals may have strong implications in these chronically transfused patients by modifying the proportion of storage-damaged RBC rapidly removed from the circulation after transfusion. **We propose that a combination of reduced RBC lifespan and reduced transfusion efficacy contribute to the pathophysiology of ß-thalassemia**.

Hypothesis

In thalassemic individuals, a combination of reduced RBC lifespan and reduced transfusion efficacy contribute to the pathophysiology of ß-thalassemia. ALT would alleviate anemia in these patients by reversing the pathogenic activation of macrophages.

Objectives and experimental plan

Our general objectives are to identify and characterize signals regulating the macrophage recognition and phagocytosis of altered RBC (in thalassemia) or storage-damaged RBC (transfusion). Specifically, *in vitro* and *in vivo* mouse models of transfusion (including ß-thalassemic mice) will be used to explore the impact of ALT treatment on RBC lifespan/elimination and transfusion efficacy. Also, we will determine whether macrophage activation/deactivation (by GDF-11/ALT) impacts the phagocytosis of storage-damaged human RBC by cultured macrophages *in vitro*.

Perspectives

The mainstay of current treatment in severe ß-thalassemia consists of regular blood transfusions and iron chelation. This chronic transfusion regime exposes the patients to an important risk of iron overload. ALT treatment could improve both the RBC lifespan of thalassemic patients and the efficacy of their transfusions by decreasing pathophysiological RBC elimination. This is important in view of recent results from clinical trials, showing ALT to be effective, safe, and well tolerated in patients with non-transfusion-dependent and transfusion-dependent β-thalassemia.

Lab members

Director
Olivier Hermine
Tenured Researchers
Pascal Amireault, Amélie Bigorgne, Francine Côté, Geneviève Courtois, Leïla Maouche-Chrétien, Patrick Mayeux, Asma Smahi, Thiago Trovati Maciel
Rsearchers
Mirjana Weimerhaus
Research associates
Elisa Bayard, Marie Bouillié, Caroline Carvalho, Michael Dussiot, Yves Lepelletier, Rachel Rignault
Clinicians
Lucile Couronné, Coralie Bloch-Queyrat, Julie Bruneau, Morgane Cheminant, Laurent Frenzel, Felipe Suarez
PhD students
Bahia Bekhouche, Héloise Halse, Madeleine Casimir, Elia Colin, Matthias Papo, Laura Polivka, Marion Falabrègue, Sandra Mignot, Justine Siavellis, Alexandre Morel, Louise Condon

Major Publications

1. Cappellini MD, Porter J, Origa R, Forni GL, Voskaridou E, Galactéros F, Taher AT, Arlet JB, Ribeil JA, Garbowski M, Graziadei G, Brouzes C, Semeraro M, Laadem A, Miteva D, Zou J, Sung V, Zinger T, Attie KM, **Hermine O**. Sotatercept, a novel transforming growth factor β ligand trap, improves anemia in β-thalassemia: a phase II, open-label, dose-finding study. Haematologica (2019)
2. Lortholary O, Chandesris MO, Bulai Livideanu C, Paul C, Guillet G, Jassem E, Niedoszytko M, Barete S, Verstovsek S, Grattan C, Damaj G, Canioni D, Fraitag S, Lhermitte L, Georgin Lavialle S, Frenzel L, Afrin LB, Hanssens K, Agopian J, Gaillard R, Kinet JP, Auclair C, Mansfield C, Moussy A, Dubreuil P, Hermine O. Masitinib for treatment of severely symptomatic indolent systemic mastocytosis: a randomised, placebo-controlled, phase 3 study. Lancet (2017)
3. Le Gouill S, Thieblemont C, Oberic L, Moreau A, Bouabdallah K, Dartigeas C, Damaj G, Gastinne T, Ribrag V, Feugier P, Casasnovas O, Zerazhi H, Haioun C, Maisonneuve H, Houot R, Jardin F, Van Den Neste E, Tournilhac O, Le Dû K, Morschhauser F, Cartron G, Fornecker LM, Canioni D, Callanan M, Béné MC, Salles G, Tilly H, Lamy T, Gressin R, Hermine O; LYSA Group. Rituximab after Autologous Stem-Cell Transplantation in Mantle-Cell Lymphoma. N Engl J Med (2017)
4. Gautier EF, Ducamp S, Leduc M, Salnot V, Guillonneau F, Dussiot M, Hale J, Giarratana MC, Raimbault A, Douay L, Lacombe C, Mohandas N, Verdier F, Zermati Y, Mayeux P. Comprehensive Proteomic Analysis of Human Erythropoiesis. Cell Rep (2016)
5. Arlet JB, Ribeil JA, Guillem F, Negre O, Hazoume A, Marcion G, Beuzard Y, Dussiot M, Moura IC, Demarest S, de Beauchêne IC, Belaid-Choucair Z, Sevin M, Maciel TT, Auclair C, Leboulch P, Chretien S, Tchertanov L, Baudin-Creuza V, Seigneuric R, Fontenay M, Garrido C, Hermine O, Courtois G. HSP70 sequestration by free α-globin promotes ineffective erythropoiesis in β-thalassaemia. Nature (2014)
6. Dussiot M, Maciel TT, Fricot A, Chartier C, Negre O, Veiga J, Grapton D, Paubelle E, Payen E, Beuzard Y, Leboulch P, Ribeil JA, Arlet JB, Coté F, Courtois G, Ginzburg YZ, Daniel TO, Chopra R, Sung V, Hermine O, Moura IC. An activin receptor IIA ligand trap corrects ineffective erythropoiesis in β-thalassemia. Nat Med (2014)