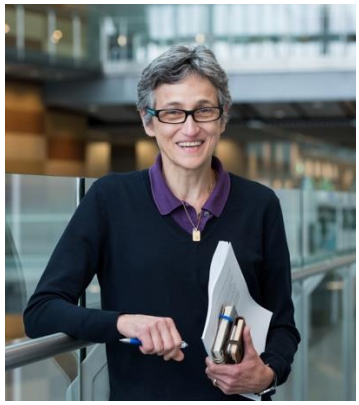
Name	DOMINIQUE BONNET
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2001



Career History

1992: PhD in Human Genetics
University Paris VII, Marie Currie, Paris, France
1993-1998: Research Fellow, Hospital of Sick Children, Toronto, Ontario, Canada
Mentor: Prof. John E. Dick.
1998-2001: Assistant Professor, Dept. of Hematology/Oncology, University of Medicine and Dentistry of New Jersey, USA
1998-2001: Head of the Molecular and Cellular Biology of Haematopoieisis Laboratory Assistant Professor, Corriell Institute for Medical Research
2001-2005: Honorary Assistant Professor, University of Pennsylvania, School of Medicine, Dept. Hemato/Oncology, Philadelphia, USA
2001-2015: Head of the Haematopoietic Stem Cell lab, London Research Institute (LRI) London, UK
2001-2006 Junior Group Leader, (Tenure position)
2006-2015 Senior Group Leader (Tenured track position)
2015-present: Head, Haematopoietic Stem Cell Laboratory, Senior Group Leader
The Francis Crick Institute (encompassing the former LRI)
2002-present: Honorary Professor, Dept of Bioscience, University College of London, London, UK
2002-present: Honorary Professor, Division of Hemato/Onocolgy, Dept of Medicine, Kings College of London, London, UK
2014- present: Honorary Professor, Imperial College of London, London UK

Major Awards, Honours and Prizes

1994-1997 Research fellowship from the Human Frontier Organization Program.
1993-1994 Research fellowship from the Cancer Research Association in France.
1989-1992 Research fellowship “CIFRE”: French Research Ministry/Beaufour Institute.
1989 Prize of the “Chancellerie des Universités de Paris”

Membership of external committees, editorial boards, review panels, SABs etc

2009- 2012 Scientific Advisory Board (SAB) member of European Hematology Association
2011- 2013 SAB of the Ludwig Boltzmann Cluster for Oncology and Translational Oncology
2011- 2013 SAB of Johnson & Johnson Pharmaceutical R&D
2011- 2015 Jury member for the Prize Léopold GRIFFUEL -ARC
2015- 2016 Danish Council for independent Research Expert Review Panel member

2016- 2017 ERC Consolidator Review panel (panel LS3- Cellular and Development Biology)
2016- 2017 CRUK Expert Panel member of Program grant review
2012- Now SAB member of DanStem – Faculty of Health Sciences in Copenhagen
2016- Now Member of the Scientific commission of the Fund for Scientific Research (FNRS) Belgium – Section: “Science de la vie”
2017- Now Scientific Board Committee member of LEUKA
2015- 2020 Italian AICR Study Section
2019- Now FWO – Research Fund Flanders- Chair of Expert review panel
2019- 2020 ANR (French NIH) review panel
2018-2021 Swedish Research Council Expert-Review Panel member
2007- Now Ad-Hoc reviewers for Bloodwise, Kay Kendall UK, BBSRC, British Heart Foundation, INSERM review panel, Welcome Trust, Italian Cancer Research, Medical Research council of Hong Kong, Medical Research council of Singapore
2008- Now Editorial Board of director, Experimental Hematology
2010- Now Editorial Board member, Stem Cells, Current Stem Cell Report, World Journal of Translational Medicine, Journal of Hematology
2016-Now Editorial Board member of Advance Blood and Cell Stress
2019-Now Editorial Board member of Blood and Haematologica

Lab Name	***Human Haematopoietic Stem Cell Laboratory***

Research programme and achievements

The Bonnet lab works in the fields of human normal and malignant hematopoietic stem cell, focusing on the nature of leukaemic stem cells and their relationship to undiseased human hematopoietic stem cells (HSCs). We were the first to identify and isolate cancer stem cells from human leukaemia.

Our most recent achievements involve:
- Combining next generation sequencing with functional assays, we reported on the evolution history of the genetic mutations present in low--risk myelodysplastic patients and described that in this sub--group of patients, the MDS--propagating cells arise from the haematopoietic stem cell (HSC) compartment (1).
- Using non- invasive intravital imaging techniques to visualise and track human normal and leukaemic hematopoietic development, we showed that AML cells induce vascular leakiness in a response to nitric oxide (NO) production by endothelial cells, which contributes to disease progression and normal HSC dysfunction after chemotherapy, suggesting potential new avenues for therapeutic intervention (3).
- In order to evaluate the role of human BM stroma cells, we developed a new and versatile 3D ossicle model allowing us to grow human AML in a humanized BM niche (2). And also revealed how AML cells impact on normal residual haematopoiesis (4).
- Using proteomic analysis (CYTof) we revealed that RET expression is enriched in human HSC and that human umbilical cord blood HSC treated with the key RET ligand/co-receptor complex, GDNF/GFRa1, show improved progenitor function at primary transplantation and improved long-term HSC function at secondary transplantation (5).

Future plans:
The goal on the lab is to continue evaluating the interactions between normal and leukaemic stem cells and their interactions with the bone marrow microenvironment. We

will use spatial transcriptomics, single cell RNAseq, proteomics and imaging of the BM niche to dissect the spatial and temporal organisation of the leukemic subclones in the bone marrow as well as study their response after chemotherapy. We want to provide an atlas of the molecular alterations of the BM microenvironment over time and after chemotherapy intervention. We also aim to validate using Crispr-Cas knock-down or overexpression, the potential micro-environmental "factors" critical for leukaemic stem cell survival and provide approaches to block niche supportive activity. In parallel to this work we aim at further investigating the heterogeneity of the normal HSC compartment and test whether different HSCs reside on distinctive BM niches.

Research outputs

Mian SA, Rouault-Pierre K, Smith AE, Seidl T, Pizzitola I, Kizilors A, Kulasekararaj AG, Bonnet D Mufti GJ. (2015) *SF3B1 mutant MDS-initiating cells may arise from the haematopoietic stem cell compartment*. Nat Commun 6:10004. DOI: 10.1038/ncomms10004
Using next generation sequencing and single cell assays, we report the order of mutations being acquired in human haematopoietic stem cells of patients with MDS which initiate the disease and report on the variegation of the mutations over time and during the transformation from MDS into AML.

Abarrategi A, Foster K, Hamilton A, Mian SA, Passaro D, Gribben J, Mufti G, Bonnet D. (2017) *Versatile humanized niche model enables study of normal and malignant human hematopoiesis*. J Clin Invest. 127(2):543-548. DOI: 10.1172/jci89364
We developed using a bioengineering scaffold a new versatile humanised bone marrow niche which support the engraftment of both normal and leukaemia stem cells *in vivo*.

Passaro D, Di Tullio A, Abarrategi A, Roualt-Pierre K, Foster K, Ariza-Mc Naughton L, Montaner B, Chakravarty P, Bhaw L, Diana G, Lassailly F, Gribben J, Bonnet D. (2017) *Increased vascular permeability in the bone marrow microenvironment contributes to disease progression and drug response in acute myeloid leukemia*. Cancer Cell, 32(3):324-341.e6. DOI: 10.1016/j.ccell.2017.08.001
Using non-invasive intravital imaging, we reported on the effect of primary AML cells on the bone marrow vasculature increasing the permeability and leakiness of the vessels via increase of nitric oxide synthase (NOS3) and in nitric oxide, demonstrating that AML can directly effect the bone marrow niche components.

Waclawiczek A, Hamilton A, Rouault-Pierre K, Abarrategi A, Albornoz MG, Miraki-Moud F, Bah N, Gribben J, Fitzgibbon J, Taussig D, Bonnet D. (2020) *Mesenchymal niche remodeling impairs hematopoiesis via stanniocalcin 1 in acute myeloid leukemia*. J Clin Invest 1,130(6):3038-3050. DOI: 10.1172/JCI133187
Following on the description by our group in 2013 of the effect of AML on residual normal haematopoietic stem cells, we reported here that AML forces normal HSC into quiescence by inducing the secretion by mesenchymal stroma cells of stanniocalcon.1.

Grey W, Chauhan R, Piganeau M, Huerga Encabo H, Garcia-Albornoz M, McDonald NQ, Bonnet D. (2020) *Activation of the receptor tyrosine kinase, RET, improves long-term hematopoietic stem cell outgrowth and potency.* Blood 136(22):2535-2547. DOI: 10.1182/blood.2020006302
Recent evidence has implicated the nervous system and glial family ligands (GFLs) as potential drivers of hematopoietic survival and self-renewal in the bone marrow niche, but

how to apply this to HSC maintenance and expansion had not been explored. We demonstrated a role for the GFL receptor, RET, at the cell surface of HSCs, in mediating sustained cellular growth, resistance to stress and improved cell survival throughout *in vitro* expansion. HSCs treated with the key RET ligand/co-receptor complex, GDNF/GFRa1, show improved progenitor function at primary transplantation and improved long-term HSC function at secondary transplantation.