THE FRANCIS CRICK INSTITUTE

Mathematical and in-silico modelisation of normal and malignant HSC in their niche and of their interactions with stromal cells

A joint Crick-Imperial College London funded PhD position for the 2019 programme between the labs of Dominique Bonnet and Pierre Degond.

Additional eligibility criteria

Dominique Bonnet

- Job title: Group Leader
- Lab: Haematopoietic Stem Cell Laboratory

(/research/find-a-researcher/dominique-bonnet)

Pierre Degond

Find out more about the work of Professor Pierre Degond (https://www.imperial.ac.uk/people/p.degond) at Imperial College London.

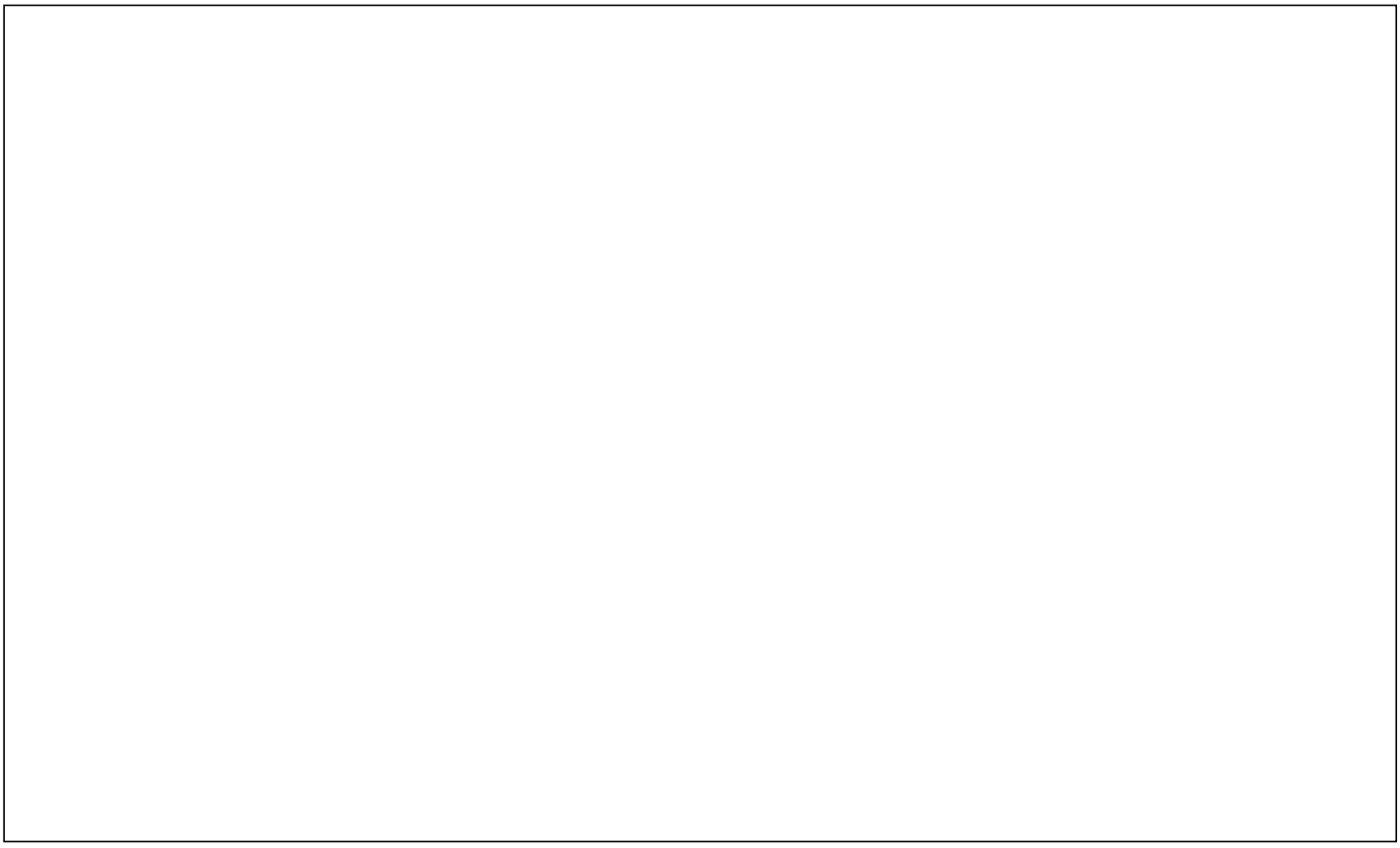
In addition to meeting the standard Crick academic eligibility criteria applicants to this position will be expected to hold either a 4-year integrated MSci degree with 1st class honours, or a Bachelor degree (in Maths, Physics or other related subject) at 2:1 or better plus a Masters with Distinction.

Non-EU candidates are not eligible for the funding for this project.

Project

Although it is widely accepted that the local microenvironment of haematopoetic stem cells (HSCs), i.e. the niche, plays a major role in controlling stem cell functions, and even though a number of important niche components are already known,

a complete picture of these regulatory elements, in particular, of their interactions with each other and with stem cells, is not yet available. The mechanisms controlling HSC function and behaviour within different bone marrow (BM) regions and cellular environments as well as the systemic interplay of the different niche types are far from being understood. The same holds true for the role of the niche in the development of haematological malignancies.



Objective and specific aims. It is our aim to establish a computational framework which can quantify, describe and predict stem cell function and behaviour in response to different niche-mediated signals. Specifically, we will investigate differences between non-malignant and malignant situations (characterized by experimental results), with the aim of establishing mathematical models which are able to predict cellular behaviour and regulatory mechanisms and, therefore, to contribute to the identification of therapeutic targets.

The objective of the project is to use mathematical / in silico modelling to quantitatively describe and predict mechanisms of HSC-niche interactions, considering processes at the intra-cellular and the cellular/tissue level. Of particular interest will be the relation of molecular regulations including different aberrations and changes in the functional properties of HSCs. To achieve a better mechanistic understanding of HSC-niche interactions, we will develop a new spatio-temporal dynamic model. To estimate model parameters, we will implement analysis pipelines for single cell tracking experiments and analyse different sets of in vivo imaging data, some being available, others will be acquired by Dr. Bonnet's group using non-invasive live haematopoietic stem/progenitor cell tracking using both calvaria imaging and 3D humanised scaffolds (see refs).

Mathematically, individual and collective HSC motion will be investigated. Individual HSC motion can be modelled by a stochastic process. The question to be investigated is whether the final cell position is correlated to spatial structures (stroma) present in the medium and what mechanisms best explain this bias. To answer this question, we will use experimental data to calibrate two types of models: either a stochastic differential equation at the individual cell level, or a Kolmogorov partial differential equation at the macroscopic probability density level. While the mathematical framework for solving these questions has been widely established for passive particles (such as electrons), similar concepts for active particles which produce their own motion, like cells, are still in their infancy. This project will develop novel concepts based on recent advances in data science and assess them within a precisely targeted application. Collective motion, which will occur when competition between normal and malignant HSC for their niche will be investigated, will lead to considerably larger and more nonlinear mathematical problems. This will greatly complicate their use in the interpretation of the corresponding data sets and will require deep new mathematical developments. Their solution will be of great use to a wide community of data scientists far beyond the strict application context of this proposal.

The project will involve:

A) Consolidation of data analysis strategy and of spatio-temporal HSC-niche model based on experimental data sets

B) Extension of the model to account for malignant alterations of cell and niche properties

C) Evaluation of the interaction and potential competition between normal and malignant HSC for their niche (see D Passaro *et al.*, *Cancer Cell*, 2017).

How to apply

How to apply: 2019 PhD students programme

Guidance on how to submit your application for the 2019 PhD programme.

(/careers-and-study/students/phd-students/phd-student-recruitment/how-to-apply-phd-students-programme)

References

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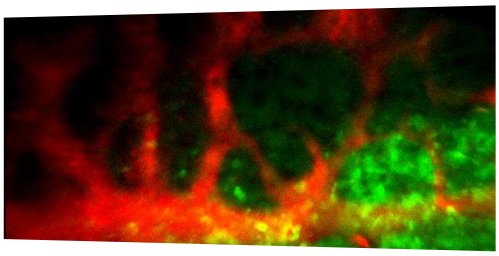

Dominique Bonnet

Haematopoietic Stem Cell Laboratory

Developmental dynamics of spinal cord formation

A Crick funded PhD position for the 2019 programme in the lab of James Briscoe.

Tissue growth control during development and regeneration

A Crick funded PhD position for the 2019 programme in the lab of Nic Tapon.

Understanding the structural and mechanistic basis of autophagosomal membrane formation

A Crick funded PhD position for the 2019 programme in the lab of Anne Schreiber.