How do Leukaemia Mutations Alter Tissue Dynamics of Blood Stem / Progenitor Cells?

Principal supervisor's name: Prof **Bertie Gottgens**
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Principal supervisor's CRUK CC theme: Haematological Malignancies Programme

Department for student registration: Haematology
Department or institute where research will take place: Cambridge Stem Cell Institute

Postgraduate scheme: **MRes + PhD (1 + 3-year non-clinical applicants only)**

MRes project outline:

In vitro Cell Competition between Normal and Leukaemia Stem Cells to Quantify Clonal Fitness and Differentiation Dynamics

The healthy blood system is continually replenished by blood stem cells, which divide and differentiate to (i) maintain stable numbers of blood and immune cells, and (ii) respond to external shocks such as blood loss or severe infection to rapidly produce the required cells on demand. This complex and finely tuned system depends on tight control of cell proliferation and differentiation. Leukaemia-causing mutations disrupt these control processes by blocking differentiation and/or enhancing proliferation, thus producing malignant clones that outcompete normal stem cells. The past 30 years have delivered deep insights into the molecular processes affected by leukaemogenic mutations. Much less however is known about (i) how mutations drive changes in cellular abundance by enhancing the fitness of mutant clones, and (ii) what therapeutic interventions may reset aberrant tissue dynamics back to normal.

For the MRes Rotation project offered in the Gottgens group, the student will use state-of-the-art in vitro models (haematopoiesis in a dish) combined with single cell genomics to quantify the aberrant behaviour of leukaemia stem cell clones mixed together in competition assays with normal cells. The student will be part of a multidisciplinary team ideally suited to provide training in the range of cutting-edge techniques required for this project. The results of this MRes project will directly lay foundations for the PhD project outlined below.

MRes experimental plan:

Blood stem cells not only maintain our blood and immune cells during steady-state, but also respond to external perturbations to rapidly produce the required cells on demand. Leukaemia-causing mutations alter the balance between cell proliferation and differentiation, thus producing hypercompetitive malignant clones. Our research group investigates how mutations enhance the fitness of mutant clones, to identify new mechanistically informed therapies.

This MRes project will combine sophisticated “haematopoiesis in a dish” in vitro models with single cell genomics and molecular barcoding, to simultaneously track the molecular properties and stem cell fitness of individual wild type and mutant clones.

Specific techniques include: Culture of primary mouse haematopoietic stem/progenitor cells in

so-called expansion cultures, which represent a powerful in vitro model of haematopoiesis. State-of-the-art analytical method will be employed to monitor long-term cultures including microscopy, flow cytometry (FACS) and single cell RNA-Seq, with full training in data analysis being provided in the group (including molecular barcode analysis). Genetic manipulation of stem cell clones will be achieved by lentiviral infection, to enable sophisticated gain and loss of function analysis for specific candidate genes.

PhD project outline:

The healthy blood system is continually replenished by blood stem cells, which divide and differentiate to (i) maintain stable numbers of blood and immune cells, and (ii) respond to external shocks such as blood loss or severe infection to rapidly produce the required cells on demand. This complex and finely tuned system depends on tight control of cell proliferation and differentiation. Leukaemia-causing mutations disrupt these control processes by blocking differentiation and/or enhancing proliferation, thus producing malignant clones that outcompete normal stem cells.

The past 30 years have delivered deep insights into the molecular processes affected by leukaemogenic mutations. Much less however is known about (i) how mutations drive changes in cellular abundance by enhancing the fitness of mutant clones, and (ii) what therapeutic interventions may reset aberrant tissue dynamics back to normal. This PhD project will combine sophisticated leukaemia models with single cell genomics and computational modelling to identify new candidate therapies that directly tackle the drivers of aberrant (leukaemic) tissue dynamics.

The student will be part of a multidisciplinary team ideally suited to provide training in the range of cutting-edge techniques required for this project. The training environment is enhanced further through close interactions with academic collaborators and pharma/biotech, as well as a strong track record in producing publications and promoting post-PhD career progression.
PhD experimental plan:
This PhD project will combine sophisticated leukaemia models with single cell genomics and computational modelling. Mouse models for acute myeloid leukaemia (AML) will be complemented with state-of-the-art “haematopoiesis in a dish” in vitro models. Single cell genomics combined with molecular barcoding will be used to simultaneously track the molecular properties and stem cell fitness of individual wild type and mutant clones. Computational modelling of clonal dynamics will pinpoint when and how new candidate therapies should be applied to directly tackle the drivers of aberrant (leukaemic) tissue dynamics. Subsequent experimental validation will establish the kind of preclinical data critical for possible translation into new leukaemia treatments.
The student will be part of a multidisciplinary team of biologists, clinician scientists and computer science graduates, thus providing an ideal training environment to learn all the cutting-edge techniques required for this project. The training environment is enhanced further through close interactions with academic collaborators and pharma/biotech, as well as a strong track record in producing publications and promoting post-PhD career progression.

Main techniques:

Specific techniques will include: Cell Culture, lentiviral infection, flow cytometry (FACS), single cell RNA-Seq, data analysis (including molecular barcode analysis), computational modelling, CrispR gene knock-outs, culture and analysis of primary cells (bone marrow; normal and leukaemic)

Key references:

Further Reading/Information:
https://www.stemcells.cam.ac.uk/people/pi/gottgens

Laurenti E. & Göttgens B. (2018) “From haematopoietic stem cells to complex differentiation landscapes” NATURE 553: 418–426

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Takahashi M, Barile M, Chapple RH, Tseng YJ, Nakada D, Busch K, Fanti AK, Säwén P, Bryder D, Höfer T, Göttgens B (2021) “Reconciling Flux Experiments for Quantitative Modeling of Normal and Malignant Hematopoietic Stem/Progenitor Dynamics” Stem Cell Reports: 16(4):741-753

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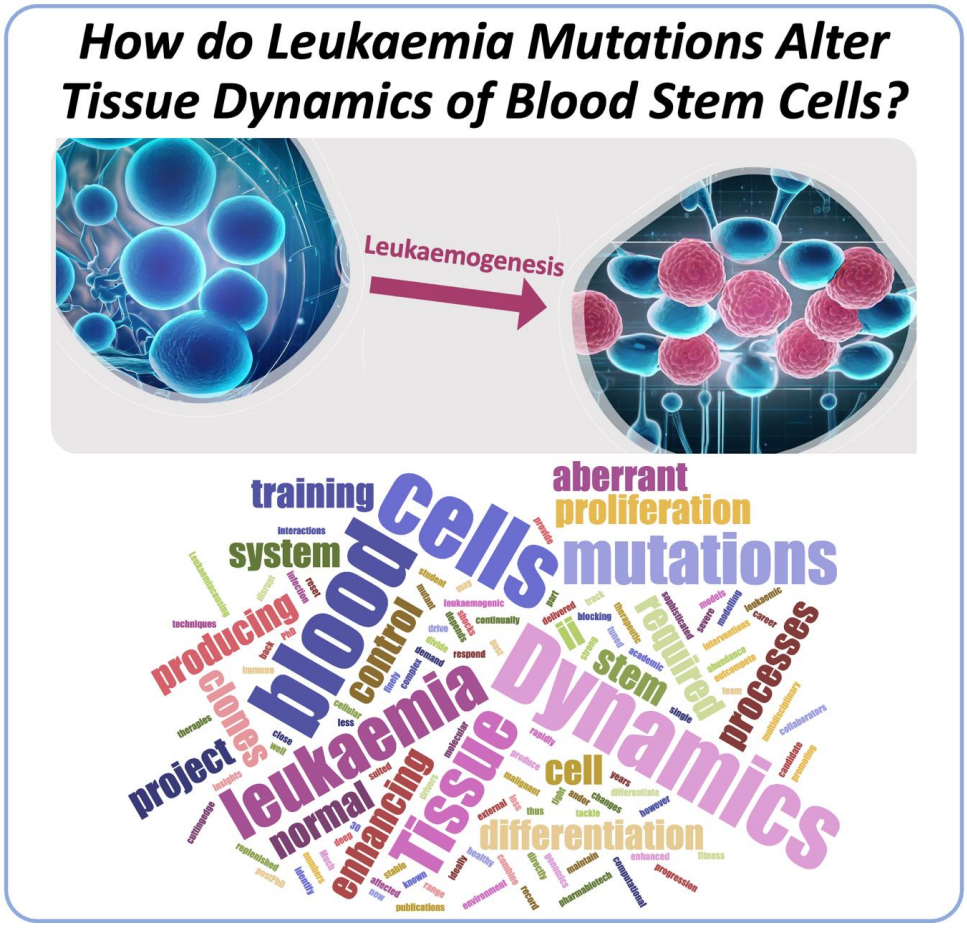

MRes Rotation Project 2024

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