Telomere maintenance, ageing and leukaemia prevention.

Principal supervisor's name: Prof **George Vassiliou**
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Principal supervisor's CRUK CC theme:

- Early Cancer Institute
- Haematological Malignancies Programme
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Department for student registration: Haematology
Department or institute where research will take place: Wellcome-MRC Cambridge Stem Cell Institute

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

MRes project outline:

Acute myeloid leukaemia (AML) and related myeloid cancers develop from the premalignant phenomenon of clonal haematopoiesis (CH), the clonal expansion of a haematopoietic stem cell (HSC) and its progeny driven by somatic mutations. Most cases of CH are driven by mutations affecting a specific set of genes, namely epigenetic regulators DNMT3A, TET2 & ASXL1, splicing factor genes SRSF2, SF3B1 & U2AF1, DNA damage response genes TP53 & PPM1D and signalling kinase gene JAK2. We have shown that individuals at high risk of progression from CH to myeloid cancer can be identified years in advance from the nature of the somatic mutations and the clonal size. Our team is working to improve our understanding of these mutations drive CH develops and how CH can be prevented from progressing to myeloid cancer.

Recently, we reported that people who inherit genetic variants associated with longer telomeres are at increased risk of developing CH. Our downstream investigations of these findings are revealing that telomere length and maintenance are critical modulators of CH development and progression. In fact, we found that some types of CH preferentially develop in people with longer and others in those with shorter telomeres. As telomeres shorten with age, ageing is a key determinant of the type of CH observed resulting in distinct age-distribution of CH depending on the driver gene. The successful applicant will investigate the interaction between telomere maintenance, ageing and CH, with the ultimate aim of developing new treatment to prevent the development of AML and related cancers.

MRes experimental plan:

The successful applicant will investigate the basis of the interaction between one of the types of CH, ageing and telomere maintenance. Our lab is interested in all types of CH and the precise focus of the project will be adjusted to suit the interests and skills of the successful candidate. There will be opportunity to use experimental studies in humans and mice, genetic screens, computational approaches, next generation sequencing (incl. long-read and single cell), analysis of data from large cohorts such as the UK Biobank and other omics approaches.

In the MRes phase the applicant will carry out experiments to establish key concepts pertaining

to the impact of the selected type of CH on telomere maintenance and vice-versa. For example they will measure telomere length in samples from patients or volunteers carrying the relevant mutations using Telomere Flow-FISH and/or qPCR and generate hematopoietic cell colonies form individuals with the selected mutations in order to examine the impact of the process of clonal expansion on telomere length.

PhD project outline:

The PhD project will be a continuation of the MRes, focusing on investigating the molecular mechanisms of the interaction between the selected type of CH mutation and telomere maintenance. For example, our data suggest that some CH mutations may have a direct impact on telomere maintenance, whilst other rely on long telomere to facilitate their ability to drive clonal expansion.

PhD experimental plan:

This will be determined according to the findings during the MRes.

Main techniques:

The experimental approach will be adapted to the expertise and interest of the candidate. There will be opportunity to carry out experimental studies using human samples and/or mice, measure telomere length using diverse approaches and use gene editing using CRISPR-Cas9, computational approaches, next generation sequencing (incl. long-read and single cell), analysis of data from large cohorts such as the UK Biobank and other omics approaches.

Key references:

Relevant publications from our lab
1. Vassiliou, G. Telomere Length and Clonal Hematopoiesis. N Engl J Med, doi: 10.1056/NEJMe2303022 (2023).
2. Gu, M. et al. Multiparameter prediction of myeloid neoplasia risk. Nat Genet - in press (2023).
3. Vassiliou, G. S. & Kar, S. New genetic loci associated with the risk of clonal hematopoiesis. Nat Genet 54, 1072-1073, doi:10.1038/s41588-022-01125-9 (2022).
4. Kar, S. P. et al. Genome-wide analyses of 200,453 individuals yield new insights into the causes and consequences of clonal hematopoiesis. Nat Genet 54, 1155-1166, doi:10.1038/s41588-022-01121-z (2022).
5. Fabre, M. A. et al. The longitudinal dynamics and natural history of clonal haematopoiesis. Nature 606, 335-342, doi:10.1038/s41586-022-04785-z (2022).
6. Fabre, M. A. et al. Concordance for clonal hematopoiesis is limited in elderly twins. Blood 135, 269-273, doi:10.1182/blood.2019001807 (2020).
7. Abelson, S. et al. Prediction of acute myeloid leukaemia risk in healthy individuals. Nature 559, 400-404, doi:10.1038/s41586-018-0317-6 (2018).
8. McKerrell, T. & Vassiliou, G. S. Aging as a driver of leukemogenesis. Sci Transl Med 7, 306fs338, doi:10.1126/scitranslmed.aac4428 (2015).
9. McKerrell, T. et al. Leukemia-associated somatic mutations drive distinct patterns of age-related clonal hemopoiesis. Cell Rep 10, 1239-1245, doi:10.1016/j.celrep.2015.02.005 (2015).