ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	ICR

Project details

Project title:	Role of the non-coding genome in the evolution of myeloma

Supervisory team

Primary Supervisors:	Martin Kaiser and Richard Houlston
Associate Supervisor(s):	
Secondary Supervisor:	

Divisional affiliation

Primary Division:	Genetics and Epidemiology/Cancer Genetics
Primary Team:	Myeloma Molecular Therapy
Site:	Sutton

Project background

Multiple myeloma (MM) results from the uncontrolled clonal expansion of plasma cells, usually in the bone marrow. Despite recent advances, MM is essentially an incurable malignancy, and most patients die from progressive disease caused by the emergence of drug resistant clones. Identifying the molecular changes which drive the evolution of MM is fundamental to developing new therapeutic strategies to overcome drug resistance. Our recent work has demonstrated that the evolution of MM is under Darwinian selection, however clonal expansion is primarily driven by non-coding mutations and epigenetic changes. The project is focused on identifying and deciphering the functional impact of these changes and how they influence clonal selection. The project will exploit state-of-the art molecular technologies and apply mathematical models of evolutionary dynamics to address this clinically important question.

Project aims

- Define the epigenetic profile of myeloma
- Identify sequence changes under evolutionary constraints within non-coding regions
- To perform functional screens, to establish the biological consequences of identified changes

• To examine the relationship between these changes and the evolutionary dynamics of myeloma

Research proposal

Understanding the evolution of multiple myeloma (MM) and how patient tumours respond/adapt to therapeutic interventions is central to addressing drug resistance in order to improve patient outcome. The overarching goal of this project is to identify non-coding changes in multiple myeloma genome which are under Darwinian selection and decipher their functional impact. The project will exploit longitudinal tumour sampling from over 100 patients enrolled in a phase 3 clinical trial being whole genome sequenced using short and long-read technologies and profiled using RNA-sequencing. Using information from analyses of these data the project will combine laboratory and experimental techniques with bioinformatics analysis to address study aims. The project will be based within laboratory with expertise in both bioinformatic and state of the art molecular technologies and offers the prospect of tailoring to the appointee's relative interests in these accordingly.

Stage 1 (0-12 months). Reducing the genomic space: Although regional excess of somatic mutations is suggestive of positive selection in tumours, the size of the non-coding genome places a high burden on robustly establishing statistical significance. Coding regions provide obvious, discrete intervals in which to search for mutations, and it would be highly propitious to define similar functional elements for non-coding regions. Cis-regulatory elements (CREs) modulating gene expression represent a highly enriched subset of the non-coding genome in which to search for driver mutations. These CREs are highly tissue-specific, are often dispersed over long ranges, and only a small fraction of distal enhancers target the nearest transcript. Hence to contextualize mutations, epigenetic and regulatory profiles of MM tumours will be defined using a combination of ATAC-seq and histone ChIP-seq. Micro-C profiles will be generated to resolve enhancer-promoter interactions allowing for the linking of CREs to target genes.

Stage 2 (-24 months) Data integration: A search for mutations under positive selection will be made with the restricted genomic space defined by Stage 1 profiling. An additional attribute of the Micro-C generated profiles is being able to define the topological associated domains within the MM genome, using these data and additionally searching for structural variants influencing gene expression by directly disrupting enhancer-promoter interactions. To provide supporting evidence for pathogeneticy the relationships with presumptive target genes will be examined.

Stage 3 (24-36 months) Functional analyses: While the above work will provide good evidence for any non-coding drivers identified, direct functional assessment is required to demonstrate the pathogenicity. Based on plausibility and tractability, complementary assessments tailored to the type(s) of mutation will be performed.

For example, (i) reporter assays (e.g. MPRA) to assess the effects of each mutation on transcription in vitro; (ii) use of CRISPR or Perturb-Seq to generate mutations in MM cell lines and directly examine the impact of mutations on gene expression and potentially effects on features of tumorigenesis (e.g. proliferation, viability, migration, clonal propagation); (iii) using predictions from wildtype and mutant consensus binding motifs assess TF binding in wildtypes and mutants; (v) perform bespoke functional assessments based on the likely TFs and target genes involved. These analyses will confirm functionality and demonstrate which mutations are likely to be deleterious and how they act.

Stage 4 (36-48 months) Write up and submission of papers.

Literature references

Kaiser MF, Hall A, Walker K, Sherborne A, De Tute RM, Newnham N, Roberts S, Ingleson E, Bowles K, Garg M, Lokare A, Messiou C, Houlston RS, Jackson G, Cook G, Pratt G, Owen RG, Drayson MT, Brown SR, Jenner MW. Daratumumab, Cyclophosphamide, Bortezomib, Lenalidomide, and Dexamethasone as Induction and Extended Consolidation Improves Outcome in Ultra-High-Risk Multiple Myeloma. J Clin Oncol. 2023 Aug 10;41(23):3945-3955. doi: 10.1200/JCO.22.02567.

Hoang PH, Cornish AJ, Sherborne AL, Chubb D, Kimber S, Jackson G, Morgan GJ, Cook G, Kinnersley B, Kaiser M, Houlston RS. An enhanced genetic model of relapsed IGH-translocated multiple myeloma evolutionary dynamics. Blood Cancer J. 2020 Oct 14;10(10):101.

Diamond B, Yellapantula V, Rustad EH, Maclachlan KH, Mayerhoefer M, Kaiser M, Morgan G, Landgren O, Maura F. Positive selection as the unifying force for clonal evolution in multiple myeloma. Leukemia. 2021 May;35(5):1511-1515. doi: 10.1038/s41375-021-01130-7.

Rasche L, Schinke C, Maura F, Bauer MA, Ashby C, Deshpande S, Poos AM, Zangari M, Thanendrarajan S, Davies FE, Walker BA, Barlogie B, Landgren O, Morgan GJ, van Rhee F, Weinhold N. The spatio-temporal evolution of multiple myeloma from baseline to relapse-refractory states. Nat Commun. 2022 Aug 3;13(1):4517. doi: 10.1038/s41467-022-32145-y.

Landau HJ, Yellapantula V, Diamond BT, Rustad EH, Maclachlan KH, Gundem G, Medina-Martinez J, Ossa JA, Levine MF, Zhou Y, Kappagantula R, Baez P, Attiyeh M, Makohon-Moore A, Zhang L, Boyle EM, Ashby C, Blaney P, Patel M, Zhang Y,

Dogan A, Chung DJ, Giralt S, Lahoud OB, Peled JU, Scordo M, Shah G, Hassoun H, Korde NS, Lesokhin AM, Lu S, Mailankody S, Shah U, Smith E, Hultcrantz ML, Ulaner GA, van Rhee F, Morgan GJ, Landgren O, Papaemmanuil E, Iacobuzio-Donahue

C, Maura F. Accelerated single cell seeding in relapsed multiple myeloma. Nat Commun. 2020 Jul 17;11(1):3617. doi: 10.1038/s41467-020-17459-z.

Hoang PH, Cornish AJ, Dobbins SE, Kaiser M, Houlston RS. Mutational processes contributing to the development of multiple myeloma. Blood Cancer J. 2019 Aug 6;9(8):60.

Ajore R, Niroula A, Pertesi M, Cafaro C, Thodberg M, Went M, Bao EL, Duran-Lozano L, Lopez de Lapuente Portilla A, Olafsdottir T, Ugidos-Damboriena N, Magnusson O, Samur M, Lareau CA, Halldorsson GH, Thorleifsson G, Norddahl GL, Gunnarsdottir K, Försti A, Goldschmidt H, Hemminki K, van Rhee F, Kimber S, Sperling AS, Kaiser M, Anderson K, Jonsdottir I, Munshi N, Rafnar T, Waage A, Weinhold N, Thorsteinsdottir U, Sankaran VG, Stefansson K, Houlston R, Nilsson B. Functional dissection of inherited non-coding variation influencing multiple myeloma risk. Nat Commun. 2022 Jan 10;13(1):151. doi: 10.1038/s41467-021-27666-x.

Candidate profile

Note: the ICR's standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1).

Pre-requisite qualifications of applicants:	Degree in a quantitative discipline (maths, physics, computer science, engineering, natural sciences)
Intended learning outcomes:	Skills in mathematical modelling of biological systems Skills in computational biology Skills in bioinformatics analysis of genomic data Skills in scientific writing and presentation skills

Advertising details

Project suitable for a student with a background in:

- [x] Biological Sciences
- [x] Physics or Engineering
- [ ] Chemistry
- [x] Maths, Statistics or Epidemiology
- [x] Computer Science