ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	ICR

Project details

Project title:	**Enhancer-Gene Networks as Therapeutic Targets in Multiple Myeloma**

Supervisory team

Primary Supervisor:	Professor Martin Kaiser (primary) and Professor Richard Houlston (co-primary)
Associate Supervisor(s):	
Secondary Supervisor:	

Divisional affiliation

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

Project background

Multiple myeloma (MM) affects over 5,500 people annually in the UK, with a 5-year survival rate below 50% in advanced stages. Resistance to therapies is driven by transcriptional addiction, where dysregulated enhancer-gene (E-G) networks, modulated by structural variants (SVs), sustain oncogenic gene expression via transcription factors (TFs) like IRF4 and MYC. Super-enhancers drive oncogene overexpression (e.g., MYC, CCND1), while SVs, such as IGH translocations, enable enhancer hijacking. Monoclonal gammopathy of undetermined significance (MGUS), a precursor to MM, shows early epigenetic changes, offering preventive potential. This project will map E-G networks in MM and MGUS using advanced technologies including single-cell multi-omics and CRISPR screens to identify novel therapeutic targets.

Project aims

- Map enhancer-gene interactions in MM.
- Identify key TFs and super-enhancers driving oncogenic expression.
- Validate functional dependencies using CRISPR screens.
- Develop a computational model to predict therapeutic vulnerabilities.
- Inform the design of transcriptional network-targeting therapies.

Research proposal

This PhD project, undertaken by the student, will aims to map enhancer-gene (E-G) networks in multiple myeloma (MM) and its precursor, monoclonal gammopathy of undetermined significance (MGUS), to develop novel therapeutic and preventive strategies. The student will employ single-cell multi-omics, CRISPR screens, and computational modelling to identify and validate therapeutic targets, contributing to precision medicine for MM and prevention of MGUS progression.

Work Package 1: Mapping Enhancer-Gene Interaction. The student will generate an E-G atlas using bone marrow patient samples from MM patients (hyperdiploid, t(11;14), t(4;14) subtypes), and cell lines (e.g., MM.1S, U266, RPMI-8226). The student will perform assays to profile chromatin accessibility and gene expression. Hi-C will be used to detect enhancer-promoter loops, with 4C-seq validating key targets (e.g., MYC, IRF4 enhancers). Structural variants (SVs) will be annotated using in house whole-genome sequencing data. The student will process data with Cell Ranger pipelines, integrate it using Seurat/Signac, and predict E-G linkages using Cicero. Non-MM cell lines (e.g., Jurkat) will serve as controls. **Expected Outcome**: A subtype-specific E-G atlas annotated with SVs, providing a foundation for identifying regulatory elements.

Work Package 2: Identifying Key Regulatory Elements. The student will identify transcription factors (TFs), such as IRF4 and MYC, and super-enhancers driving oncogenic expression. Using CAP-SELEX, the student will map TF–TF interactions for selected candidate TFs, while BioID will be employed to map protein–protein interactions in MM cell lines via mass spectrometry. ChIP-seq (H3K27ac, H3K4me1) will profile super-enhancers, with ROSE identifying high-intensity regions. The student will validate findings using siRNA knockdown and CRISPR interference (CRISPRi) in patient samples and cell lines, assessing proliferation (MTT assays) and apoptosis (Annexin V). AlphaFold2 will be used to predict TF interaction interfaces to inform PROTAC design in collaboration with the ICR. Controls will include scrambled siRNAs and non-targeting CRISPRi guides. **Expected Outcome**: A prioritised list of TFs and super-enhancers validated through direct mapping and functional assays.

Work Package 3: Functional Validation. The student will design and apply CRISPR interference (CRISPRi) and activation (CRISPRa) libraries targeting enhancers and TFs, delivered to MM cell lines and patient samples. Pooled CRISPR screens will assess proliferation (CellTiter-Glo) and apoptosis (Caspase-3/7). The student will validate significant hits with individual CRISPRi/a guides, analysed using MAGeCK. Single-cell RNA-seq will capture transcriptional changes, with analysis performed using Seurat. Controls will include non-targeting guides and non-MM cell lines. **Expected Outcome**: Validated E-G dependencies identifying high-priority therapeutic targets.

Work Package 4: Computational Modelling and Therapeutic Prediction. The student will integrate multi-omics data (ATAC-seq, RNA-seq, ChIP-seq, Hi-C, CAP-SELEX, BioID) using Graph Convolutional Networks, representing genes/enhancers as nodes and SVs as edges. A random forest classifier will predict therapeutic vulnerabilities. The student will conduct in vivo drug screens to test BET inhibitors (e.g., JQ1) and other compounds. **Expected Outcome**: A validated computational framework predicting therapeutic targets for clinical translation.

Literature references

[1] Cancer Research UK (2023) Multiple Myeloma Statistics. Available at: https://www.cancerresearchuk.org.

[2] Jolma A, et al. (2025) DNA-guided transcription factor interactions. *Nature*, doi:10.1038/s41586-025-08844-z.

[3] Stengel A, et al. (2022) Transcription factor interaction networks. *Nat Commun*, 13:765.

[4] Hanahan D (2022) Hallmarks of Cancer. *Cancer Discov*, 12(1):31–46.

[5] Hnisz D, et al. (2013) Super-enhancers in disease. *Cell*, 155(4):934–947.

[6] Walker BA, et al. (2014) Intraclonal heterogeneity in myeloma. *Leukemia*, 28(2):384–390.

[7] Bergsagel PL, Kuehl WM (2005) Molecular pathogenesis of multiple myeloma. *J Clin Oncol*, 23(26):6333–6338.

[8] Takeda DY, et al. (2018) Enhancer of the androgen receptor. *Cell*, 174(2):422–432.

[9] Northcott PA, et al. (2014) Enhancer hijacking in medulloblastoma. *Nature*, 511(7510):428–434.

[10] Morgan GJ, et al. (2012) Genetic architecture of multiple myeloma. *Nat Rev Cancer*, 12(5):335–348.

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:

BSc/BA or equivalent in molecular biology, bioinformatics, or related field.

Interest in cancer genomics and translational research.

Intended learning outcomes:

Skills in mathematical modelling of biological systems
Proficiency in advanced data analysis.

Expertise in CRISPR screens and other molecular techniques.

Skills in computational modelling for cancer research.

Strong scientific communication skills.

Advertising details

Project suitable for a student with a background in:

- [ ] xBiological Sciences
- [ ] Physics or Engineering
- [ ] Chemistry
- [ ] xMaths, Statistics or Epidemiology
- [ ] Computer Science