

## PhD Project Proposal

### Funder details

**Studentship funded by:** The Institute of Cancer Research

### Project details

**Project title:** Immunopeptidome landscape of multiple myeloma

### Supervisory team

**Primary Supervisor:** Richard Houlston, Jyoti Choudhary, Martin Kaiser

**Associate Supervisor(s):**

**Secondary Supervisor:**

### Divisional affiliation

**Primary Division:** Genetics and Epidemiology

**Primary Team:** Cancer Genomics

**Site:** Sutton

### Project background

Multiple myeloma (MM) is caused by the clonal expansion of plasma cells in the bone marrow. While survival from MM has improved significantly over the last decade with the introduction of immunomodulatory drugs, proteasome inhibitors and monoclonal antibodies, the disease essentially remains incurable, and many patients die following relapse.

Recently, T-cell based approaches that target plasma cell differentiation receptors, such as BCMA and GPR5D, equally expressed on healthy and tumour cells have shown high response. However, these treatments have profound side effects through targeting of healthy cells, prohibiting their use in areas such as early intervention. Most importantly, most MM tumours still relapse, in part due to dispensability of these non-specific differentiation markers for survival.

A key strategy to expand the effectiveness of immunotherapy, both in terms of vaccine and T-cell based therapies, is to promote the recognition of tumour cells by T-cells through the identification and targeting of tumour antigens. Tumour antigens, derived from endogenous and exogenous proteins, are processed into peptides and presented on the cell surface by human leukocyte antigen (HLA) molecules (HLA-I and HLA-II respectively). These antigens, which form the immunopeptidome, can be recognized by the immune system as nonself, triggering an immune response. Immunopeptidomics uses mass spectrometry to characterise peptides bound to HLA, representing an area of increasing focus of cancer research, since these peptides represent targets for therapeutic intervention.

While such specific T-cell based therapies have shown promise in the treatment of MM only a subset of patients respond and how tumour cells can escape the antigen presentation machinery (APM) and immunosurveillance through molecular mechanisms remain elusive.

To advance our understanding of the MM immunopeptidome and the genetics that shape its profile and to inform opportunities for therapeutic intervention the project will combine state of the art genomic and mass spectrometry-based analyses of MM models and primary patient material.

## Project aims

- To perform genomic and proteomic analyses to decipher the immunoproteomic profile of multiple myeloma both in terms of canonical and non-canonical transcripts
- To investigate importance of down-regulation of antigen presentation machinery as a means of immune escape in myeloma
- To investigate opportunities to diversity the antigenic landscape of myeloma through immunoproteasome activators for therapeutic benefit

## Research proposal

This project will be based around three inter-related workstreams.

### **Workstream 1: Genomic analysis of MM**

Whole genome sequencing (WGS) and RNAseq data on a large series of patients which have been generated in house will be used to derive predicted canonical neoantigens generated because of somatic mutation. Specifically, after deriving patient specific HLA-types a set of complementary *in silico* approaches will be implemented to estimate neoantigen binding strengths. This analysis will be complemented by exploiting additional publicly accessible datasets. WGS data will also be used to profile the genetic landscape of immune escape focusing on curated antigen presenting genes (APGs) spanning the genetic components of antigen presenting machinery, the IFN- $\gamma$  pathway, the PF-L1 receptor, the CD58 receptor, and epigenetic escape. To complement these analyses and inform downstream work a series of MM cell lines will also be profiled.

### **Workstream 2: Mass spectrometry analysis of the MM immunopeptidome**

Established methods for enrichment of the immunopeptidome will be used in combination with quantitative mass spectrometry to profile immunopeptidome landscape in MM cell lines and patient samples. Peptide spectra will be assigned using database searching using databases of the canonical protein coding genes and personalised sequences from Workstream 1. We will evaluate the intersection between the cell models and patient antigen landscapes. Bioinformatics will be used to characterise distinguishing antigen features, which will be associated with data from genomics and clinical attributes. We have captured diverse datasets from normal samples and medullary thymic epithelial cells that will be used as controls to distinguish tumour specific and immunogenic antigens, which represent the high value target for therapeutic use. These candidates can be followed up to evaluate immune escape and immune responses using TCR sequencing.

### **Workstream 3: Exploring immunopeptidome activation to unmask neoantigens**

The proteasome degrades intracellular proteins generating antigenic peptides recognized by the adaptive immune system. Since tumours can subvert the antigen processing and presenting machinery (APM) to escape immunosurveillance hence proteasome active has the potential to increase antigen abundance and diversity and hence offer an additional therapeutic strategy. This possibility will be explored by MS profiling of cells treated with proteasome and HAD inhibitors, as described in Workstream 2.

## Literature references

1. Ghorani E, Reading JL, Henry JY, Massy MR, Rosenthal R, Turati V, Joshi K, Furness AJS, Ben Aissa A, Saini SK, Ramсков S, Georgiou A, Sunderland MW, Wong YNS, Mucha MV, Day W, Galvez-Cancino F, Becker PD, Uddin I, Oakes T, Ismail M, Ronel T, Woolston A, Jamal-Hanjani M, Veeriah S, Birkbak NJ, Wilson GA, Litchfield K, Conde L, Guerra-Assunção JA, Blighe K, Biswas D, Salgado R, Lund T, Bakir MA, Moore DA, Hiley CT, Loi S, Sun Y, Yuan Y, AbdulJabbar K, Turajilic S, Herrero J, Enver T, Hadrup SR, Hackshaw A, Peggs KS, McGranahan N, Chain B; TRACERx Consortium; Swanton C, Quezada SA. The T cell differentiation landscape is shaped by tumour mutations in lung cancer. *Nat Cancer*. 2020 May;1(5):546-561. doi: 10.1038/s43018-020-0066-y. Epub 2020 May 22. PMID: 32803172; PMCID: PMC7115931.
2. Perumal D, Imai N, Laganà A, Finnigan J, Melnekoff D, Leshchenko VV, Solovyov A, Madduri D, Chari A, Cho HJ, Dudley JT, Brody JD, Jagannath S, Greenbaum B, Gnjjatic S, Bhardwaj N, Parekh S. Mutation-derived Neoantigen-specific T-cell Responses in Multiple Myeloma. *Clin Cancer Res*. 2020 Jan 15;26(2):450-464. doi: 10.1158/1078-0432.CCR-19-2309. Epub 2019 Dec 19. PMID: 31857430; PMCID: PMC6980765.
3. Ferguson ID, Patiño-Escobar B, Tuomivaara ST, Lin YT, Nix MA, Leung KK, Kasap C, Ramos E, Nieves Vasquez W, Talbot A, Hale M, Naik A, Kishishita A, Choudhry P, Lopez-Girona A, Miao W, Wong SW, Wolf JL, Martin TG 3rd, Shah N, Vandenberg S, Prakash S, Besse L, Driessen C, Posey AD Jr, Mullins RD, Eyquem J, Wells JA, Wiita AP. The surfaceome of multiple myeloma cells suggests potential immunotherapeutic strategies and protein markers of drug resistance. *Nat Commun*. 2022 Jul 15;13(1):4121. doi: 10.1038/s41467-022-31810-6. PMID: 35840578; PMCID: PMC9287322.

## 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 a quantitative discipline.

(MSc/MMath/MEng or equivalent preferred)

### Intended learning outcomes:

Skills in computational biology

Skills in genomic and mass spectrometry-based analyses

Skills in scientific writing

Skills in delivering scientific presentations

## Advertising details

Project suitable for a student with a background in:

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