Project title: Deciphering the Evolution of Bispecific Antibody Resistance in Multiple Myeloma

Project Summary:

Multiple myeloma (MM) remains a major haematologic malignancy despite advancements in targeted therapies, such as bispecific antibodies (BsAbs) that engage T-cells to eradicate myeloma cells. Resistance to BsAb therapy limits sustained responses and impacts patient outcomes. This PhD project will seek to decipher the mechanisms driving BsAb resistance in MM by exploiting samples and data from an ongoing clinical trial.

The research will analyse serial patient samples (e.g., bone marrow aspirates, peripheral blood) collected before and after BsAb treatment. Cutting-edge molecular techniques, including single-cell RNA sequencing (scRNA-seq), whole-exome sequencing (WES), and proteomics, will profile tumour cells, the immune microenvironment, and evolutionary dynamics. Advanced bioinformatic tools, incorporating machine learning for clonal evolution tracking and pathway analysis, will integrate multi-omics data to pinpoint resistance signatures, such as antigen loss, T-cell exhaustion, or microenvironmental adaptations.

The project's objectives include: (1) Identifying genomic and transcriptomic changes linked to resistance; (2) Modelling the temporal evolution of resistant clones through computational simulations; (3) Validating findings in preclinical models to propose strategies for overcoming resistance, such as combination therapies or novel BsAbs.

This interdisciplinary study integrates clinical haematology, immunology, and computational biology, offering translational insights to enhance BsAb efficacy. By elucidating resistance mechanisms, the project aims to inform personalized treatment strategies, improving survival for MM patients. The fellowship will support the applicant's development as a clinician-scientist, enabling impactful contributions to precision oncology.

Supervisory Team: Professors Kaiser and Houlston

Clinical Specialities: Haematology, Oncology, Immunology