ICR The Institute of Cancer Research

PhD Project Proposal

Funder details

Studentship funded by:	ICR

Project details

Project title:	Identifying molecular pathways of drug resistance in multiple myeloma

Supervisory team

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

Divisional affiliation

Primary Division:	Genetics & Epidemiology
Primary Team:	Myeloma Molecular Therapy Team
Site:	Sutton

Project background

Multiple myeloma, a cancer of bone marrow plasma cells, is characterised by non-oncogenic dependencies on protein and nucleic acid homeostasis regulators, including the nuclear membrane transporter Exportin 1 (XPO1). We and others have characterised XPO1's role in myeloma biology and resistance to therapy in patients. Recently, a first-in-class selective inhibitor of XPO1 (Selinexor) has been licensed by FDA and EMA for the treatment of relapsed-refractory myeloma. However, the specific molecular networks relating to XPO1 dependency are not well characterised. This project aims to explore molecular dependencies related to XPO1 in multiple myeloma by high-throughput CRISPR-Cas vulnerability screening and by generating and integrated molecular profiling of models of XPO1 resistance.

Project aims

- Molecular characterisation, including proteomic profiling, and selection of cell line models for XPO1 dependency testing
- Identification of mediators of resistance or sensitivity to small molecule XPO1 inhibition by CRISPR-Cas9 Resistance Screening
- Generation and integrated molecular characterisation of XPO1 inhibitor resistant cell lines compared to wildtype
- Validation of hits in cell lines, patient samples and data mining of myeloma clinical trial datasets

Research proposal

Introduction: Multiple myeloma (MM) is a malignancy caused by clonal expansion of plasma cells in the bone marrow. MM cells produce high amounts of monoclonal antibodies and are characterised by non-oncogenic vulnerability related to protein homeostasis mechanisms, including nuclear shuttling mediated by XPO1. Despite advances in the treatment of MM all forms of the disease are essentially incurable with patients inevitably succumbing to resistant clonal expansion.

Highly selective and orally bioavailable XPO1 inhibitors have recently been developed and licensed for the treatment of MM (refs). Although XPO1 inhibition is effective in relapsed/refractory MM, a proportion of patients does do not respond. We aim of this project is to identify the basis of XPO1-related vulnerability and resistance mechanisms in MM.

A number of MM cell line models representative of key molecular subtypes of MM, will be employed to identify unifying processes related to XPO1 inhibitor sensitivity (refs). Genome wide CRISPR-Cas9 vulnerability screens will be undertaken, comparing XPO1 inhibitor to carrier control, following depletion of essential genes, to identify co-dependencies of XPO1 inhibition in MM. In parallel, XPO1 resistant cell lines will be generated through repeat and/or long-term exposure, and molecular genomic and proteomic changes associated with development of resistance identified through integrated profiling.

Genes and associated pathways mediating resistance or sensitisation to XPO1 inhibitor treatment will be validated individually and in combination through genetic and small molecule manipulation in an independent set of MM cell lines. Dependencies that can be exploited by small molecules will be further in vitro validated in patient bone marrow tumour cells, accessible through a multi-centre MM tissue research protocol (London-Chelsea REC 19/LO/0599). Cross-referencing with mediators of resistance to other perturbations such as proteasome inhibitors will be used to identify XPO1 specific effects.

Validated hits will be further interrogated in context of clinical data from molecularly annotated clinical trial datasets (including MUKnine and MUKtwelve trials), to identify candidates with highest potential for further treatment optimisation in the clinic.

Findings of this project should inform strategies to overcome de novo or acquired resistance to XPO1 inhibition in MM.

Literature references

[1] Stewart AK. Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276. Leukemia. 2013 Dec;27(12):2357-65. doi: 10.1038/leu.2013.172. Epub 2013 Jun 11.

[2] Vogl DT, Dingli D, Cornell RF, Huff CA, Jagannath S, Bhutani D, Zonder J, Baz R, Nooka A, Richter J, Cole C, Vij R, Jakubowiak A, Abonour R, Schiller G, Parker TL, Costa LJ, Kaminetzky D, Hoffman JE, Yee AJ, Chari A, Siegel D, Fonseca R, Van Wier S, Ahmann G, Lopez I, Kauffman M, Shacham S, Saint-Martin JR, Picklesimer CD, Choe-Juliak C, Stewart AK. Selective Inhibition of Nuclear Export With Oral Selinexor for Treatment of Relapsed or Refractory Multiple Myeloma. J Clin Oncol. 2018 Mar 20;36(9):859-866. doi: 10.1200/JCO.2017.75.5207.

[3] Azmi AS, Uddin MH, Mohammad RM. The nuclear export protein XPO1 – from biology to targeted therapy. Nat Rev Clin Oncol. 2021 Mar;18(3):152-169. doi: 10.1038/s41571-020-00442-4.

[4] 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. doi: 10.1038/s41408-020-00367-2.

[5] 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. doi: 10.1038/s41408-019-0221-9.

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:	BA/BSc or equivalent in biochemistry, molecular biology or natural sciences

Intended learning outcomes:	• Knowledge of oncogenic basis of cancer • Strategies for identifying and exploiting cancer vulnerabilities • Experience of cutting-edge molecular tools and systems • Experience in state-of-the-art bioinformatics • Experience in bringing research to publication

Advertising details

Project suitable for a student with a background in:	☒ Biological Sciences ☐ Physics or Engineering ☐ Chemistry ☐ Maths, Statistics or Epidemiology ☐ Computer Science