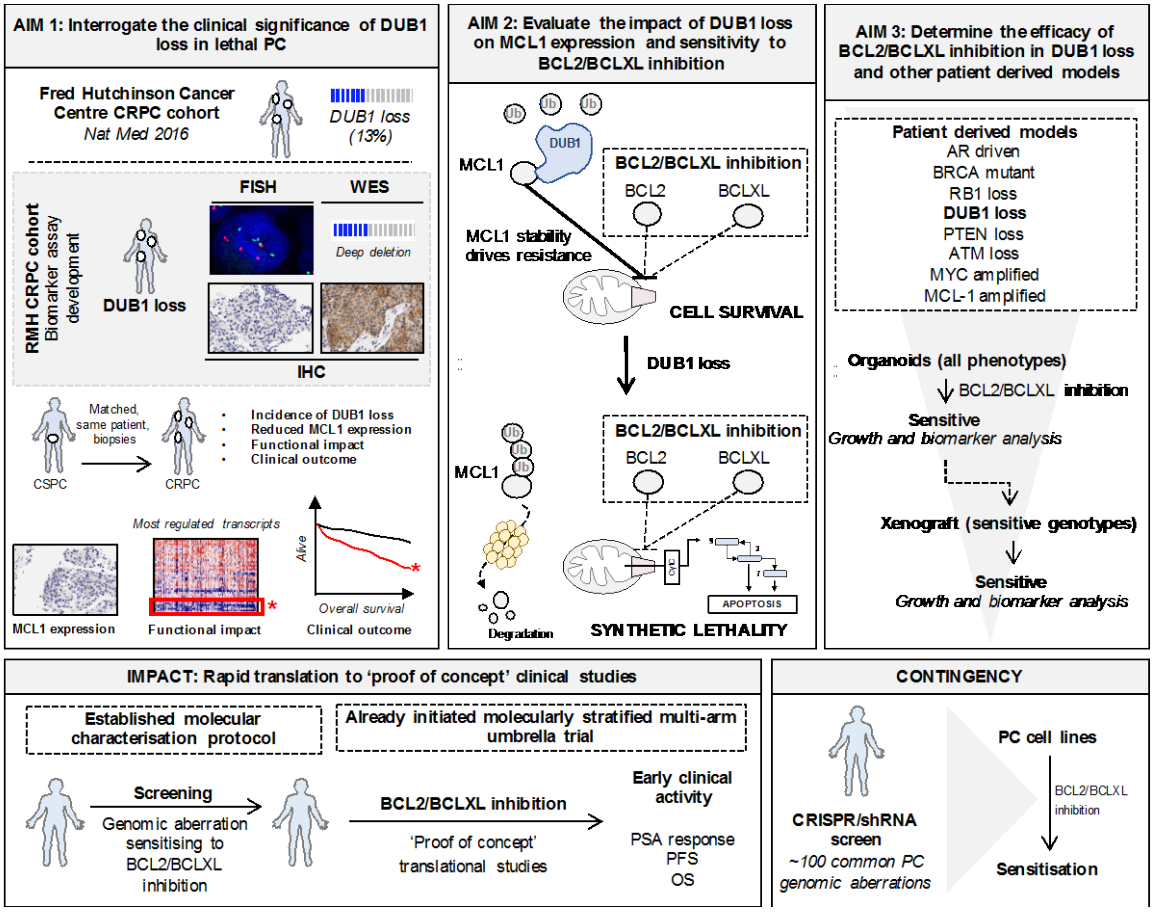
ICR and Imperial Clinical Academic Training Programme in Cancer Research
Expressions of Interest

1) A broad project title/area

Targeting BCL2 family proteins in deubiquitinating enzyme 1 (DUB1; pseudonym) loss lethal prostate cancer

2) A short paragraph outlining the project area, in general up 250-300 words is sufficient

Overview:



Background: Prostate cancer (PC) is the commonest male cancer. Advanced PC is invariably fatal. There is an urgent need to develop novel therapeutic strategies to improve outcomes, such as targeting the BCL2 family (including BCL2, BCLXL and MCL1) which enhance apoptosis. Navitoclax is a BH3-mimetic that targets BCL2/BCLXL, blocking their binding to pro-apoptotic BH3 proteins such as BIM and their ability to neutralize BAX/BAK. Targeting BCL2/BCLXL has limited anti-tumour activity in solid tumours due, in part, to high MCL1 protein expression.

Supporting data: We identified the deubiquitinating enzyme DUB1, located on chromosome 13, to be deleted in 13% of advanced PC. It is co-deleted with RB1 in many cancers, and lost in a subtype of poor prognosis PC for which effective therapeutic strategies are urgently required. We identified DUB1 to be a critical regulator of MCL1 stability, showing that DUB1 loss decreased MCL1 expression and sensitised PC cells to BCL2/BCLXL inhibition (unpublished).

Hypothesis: We now hypothesize that BCL2/BCLXL inhibition is a viable therapeutic strategy for DUB1 loss solid tumours, including lethal PC.

Aims: (1) Study the incidence of DUB1 loss in lethal PC, and determine the impact of DUB1 loss on (a) MCL1 protein expression; (b) PC transcriptome; (c) response to established therapies; and (d) outcome from lethal PC.

(2) Evaluate impact of DUB1 loss in PC models, pursuing mechanistic studies to determine how this reduces MCL1 expression and increases sensitivity to BCL2/BCLXL inhibition.

(3) Determine anti-tumour activity of BCL2/BCLXL inhibition, as a single agent and in combination with established anticancer drugs (androgen-deprivation, enzalutamide, docetaxel and olaparib), in patient-derived models (organoids and mouse xenografts) representing different subtypes of lethal PC resistant to available therapies, and demonstrating increased efficacy and apoptosis in DUB1 loss models.

Impact: This proposal will identify DUB1 loss as a predictive biomarker for BCL2/BCLXL blockade in PC and other solid tumours that can be rapidly translated to "proof of concept' clinical studies.

Contingency: PC relevant genomic aberrations (~100, majority loss of function) that sensitise to BCL2/BCLXL inhibition will be identified using a CRISPR/shRNA screen; and these will be validated as predictive biomarkers for BCL2/BCLXL blockade PC and other malignancies.

3) Details of the supervisory team and site

Adam Sharp (ICR, Sutton, UK)
Paul Workman (ICR, Sutton, UK)
Jessica Downs (ICR, Sutton, UK)
Bissan Al-Lazikani (ICR, Sutton, UK)
Johann de Bono (ICR, Sutton, UK)

Collaborators

Charlotte Bevan (Imperial, London, UK)
Steven Balk (Harvard, Boston, US)

4) Any clinical specialties particularly required

Medical Oncology (preferable)