ICR The Institute of Cancer Research

The Institute of Cancer Research **PHD STUDENTSHIP PROJECT PROPOSAL**	
FUNDER DETAILS	
Studentship funded by:	The Institute of Cancer Research
PROJECT DETAILS	
Project title:	Targeting RNA helicases to suppress aberrant androgen receptor expression and abrogate persistent androgen receptor signalling in lethal prostate cancer
SUPERVISORY TEAM	
Primary Supervisor	Dr Adam Sharp
Associate Supervisor(s)	Dr Paul Clarke, Dr Juan Jimenez Vacas, Dr Jon Welti
Secondary Supervisor	Professor Johann de Bono
DIVISIONAL AFFILIATION	
Primary Division	Clinical Studies
Primary Team	Translational Therapeutics
Site	Sutton

ABSTRACT

BACKGROUND: Despite robust responses to abiraterone and enzalutamide which target full length androgen receptor (AR-FL) signalling, patients with advanced prostate cancer inevitably progress to lethal, treatment-resistant, prostate cancer with persistent AR signalling. Mechanisms driving resistance to these treatments include AR gene amplification, AR-FL activating mutations, and AR splice variant-7 (AR-V7) expression, none of which are impacted by currently available therapies. Therefore, novel therapeutic strategies blocking mechanisms driving persistent AR signalling are urgently needed. **HYPOTHESIS**: We hypothesise that specific RNA helicases play a critical role in AR RNA metabolism and provide a druggable therapeutic target to suppress AR-FL/V7 expression and abrogate persistent AR signalling in lethal prostate cancer. **AIMS:** (1) Determine the role of RNA helicases in AR RNA metabolism; (2) Validate RNA helicases as a novel therapeutic target to inhibit AR RNA metabolism and overcome persistent AR signalling in lethal prostate cancer; (3) Evaluate the clinical significance of RNA helicases expression in lethal prostate cancer. **IMPACT:** This innovative research proposal has the potential to develop a novel treatment strategy that could improve the outcome and quality of life for men suffering from lethal prostate cancer.

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LITERATURE REFERENCES

Westaby D, Fenor de La Maza MLD, Paschalis A, Jimenez-Vacas JM, Welti J, de Bono J, et al. A New Old Target: Androgen Receptor Signaling and Advanced Prostate Cancer. Annu Rev Pharmacol Toxicol. 2022;62:131-53.

Armstrong AJ, Halabi S, Luo J, Nanus DM, Giannakakou P, Szmulewitz RZ, et al. Prospective Multicenter Validation of Androgen Receptor Splice Variant 7 and Hormone Therapy Resistance in High-Risk Castration-Resistant Prostate Cancer: The PROPHECY Study. J Clin Oncol. 2019;37(13):1120-9.

Sharp A, Coleman I, Yuan W, Sprenger C, Dolling D, Rodrigues DN, et al. Androgen receptor splice variant-7 expression emerges with castration resistance in prostate cancer. J Clin Invest. 2019;129(1):192-208.

Sharp A, Welti JC, Lambros MBK, Dolling D, Rodrigues DN, Pope L, et al. Clinical Utility of Circulating Tumour Cell Androgen Receptor Splice Variant-7 Status in Metastatic Castration-resistant Prostate Cancer. Eur Urol. 2019;76(5):676-85.

Ferraldeschi R, Welti J, Powers MV, Yuan W, Smyth T, Seed G, et al. Second-Generation HSP90 Inhibitor Onalespib Blocks mRNA Splicing of Androgen Receptor Variant 7 in Prostate Cancer Cells. Cancer Res. 2016;76(9):2731-42.

Welti J, Sharp A, Yuan W, Dolling D, Nava Rodrigues D, Figueiredo I, et al. Targeting Bromodomain and Extra-Terminal (BET) Family Proteins in Castration-Resistant Prostate Cancer (CRPC). Clin Cancer Res. 2018;24(13):3149-62.

Paschalis A, Welti J, Neeb AJ, Yuan W, Figueiredo I, Pereira R, et al. JMJD6 Is a Druggable Oxygenase That Regulates AR-V7 Expression in Prostate Cancer. Cancer Res. 2021;81(4):1087-100.

Bourgeois CF, Mortreux F, and Auboeuf D. The multiple functions of RNA helicases as drivers and regulators of gene expression. Nat Rev Mol Cell Biol. 2016;17(7):426-38.

Heerma van Voss MR, van Diest PJ, and Raman V. Targeting RNA helicases in cancer: The translation trap. Biochim Biophys Acta Rev Cancer. 2017;1868(2):510-20.

Mitsopoulos C, Di Micco P, Fernandez EV, Dolciami D, Holt E, Mica IL, et al. canSAR: update to the cancer translational research and drug discovery knowledgebase. Nucleic Acids Res. 2021;49(D1):D1074-D82.

Abida W, Cyrta J, Heller G, Prandi D, Armenia J, Coleman I, et al. Genomic correlates of clinical outcome in advanced prostate cancer. Proc Natl Acad Sci U S A. 2019;116(23):11428-36.

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:	Master's or BSc in Biomedical Sciences (or a related subject)

Intended learning outcomes:	• RNA analysis (RT-PCR, RNA-sequencing, RIP-sequencing) • Protein analysis (western blot, proteomics) • Molecular cloning (site directed mutagenesis) • Genomic manipulation (siRNA, shRNA, CRISPR) • Patient derived models (in vivo and in vitro) • Clinical biomarker validation, development and qualification (transcriptome and immunofluorescence) • Data analysis and Scientific writing
ADVERTISING DETAILS	
Project suitable for a student with a background in:	☒ Biological Sciences ☐ Physics or Engineering ☐ Chemistry ☐ Maths, Statistics or Epidemiology