Targeted Biodegradable Nanogels for Intracellular Delivery of Therapeutic RNAs in Prostate Cancer

Project Summary:

Prostate cancer (PC) affects 1-in-8 UK men. Despite major advances in precision oncology, metastatic PC (mPC) remains incurable. Standard-of-care chemotherapies confer only modest survival benefits and are associated with systemic toxicity and resistance development. There is an urgent need for efficacious, tumour-selective and resistance-resilient therapies.

This proposal uses prostate-targeted, biodegradable nanogels for intracellular delivery of therapeutic microRNAs (miRs). These act through novel mechanisms distinct from small-molecule therapies, and their combined use may prevent/delay resistance-onset and sensitise to DNA-repair/cell-cycle inhibitors:

- miR-X: causes potent, genome-wide DNA damage and apoptosis in advanced PC cells; synergises with ATM/ATR/PARP/DNA-PKc inhibitors, induces tumour regression *in vivo*
- miR-Y anti-sense-oligonucleotide (ASO-miR-Y, inhibitor of miR-Y): induces apoptosis, inhibits proliferation *in vitro/in vivo* in breast and PC
- miR-A/B: 'master regulators' of cell-cycle progression demonstrating potent synergy with clinical Wee-1/ATM/ATR/PARP inhibitors that target cell cycle and DNA repair.

The **nanogel platform** addresses key translational bottlenecks associated with conventional lipid nanoparticles and viral vectors: it is chemically-defined, modular, exhibits high cargo encapsulation-efficiency. Nanogels degrade selectively in cytosol in a glutathione-responsive manner and avoid endosomal retention, supporting precise release of therapeutic payloads whilst avoiding systemic off-target effects. Flexible chemistry enables integration of peptide/antibody-fragment ligands for precision delivery. We will target prostate-specific PSMA, using clinically-approved and in-lab validated ligand, PSMA-617. Crucially, this approach directly tackles therapeutic resistance and permits **precision management of the most common cancer in men.**

We will:

1) **Encapsulate therapeutic miRs in PSMA-617-liganded nanogels** using high-throughput Opentron-enabled nanogel library synthesis platform and perform comprehensive physicochemical characterisation.
2) **Evaluate nanogel-miR internalisation and therapeutic efficacy** by assessing PC-relevant phenotypes (proliferation/apoptosis/cell-cycle/DNA damage) in cells lines mimicking different PC stages
3) **Assess synergy of nanogel-miRs with standard-of-care therapeutics** (chemotherapy/DNA repair inhibitors/AR pathway inhibitors)
4) **Evaluate nanogel-miR efficacy in patient-derived tumour tissues and genetically-defined murine PC organoids.**

We hypothesise that 'programmable' prostate-targeted nanogels can deliver potent miR therapeutics to PC tissues at high efficiency, providing proof-of-principle for future pre-clinical efficacy studies and clinical trials.

Supervisory Team:

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Clinical Specialities: oncology, urology.