Project Details	
Project Code	MRCIIAR24Ba Pascu
Title	Theranostics and Multimodal Imaging with Near-Infrared Emitting Peptide Nucleic Acids
Research Theme	Infection, Immunity, Antimicrobial Resistance & Repair
Summary	The cancer incidence number is expected to double by 2035. This project will establish new theranostic medicines design with nucleic acids (PNAs) to unlock the potential of early cancer diagnostics and expedite advances in precision medicine. PNA constructs are synthetic DNA/RNA mimics with nucleobases connected via a peptide backbone: this interdisciplinary project will develop new radiolabelled and fluorescent PNAs to target cancer-specific mRNAs.
Description	This interdisciplinary project will develop multimodal radiolabelled/fluorescent imaging tracers to target tumour hypoxia-specific mRNA expression in vitro and in vivo. It involves a closely knit group of co-supervisors, who have worked together before and who currently supervise jointly a PhD student who is due to complete her PhD in 2024 (Miss Kexin Song). This is a challenging yet potentially highly rewarding project, supported by three different research groups across the GW4 and having full access to the PETIC Centre Cardiff along with their external contribution of the LSF CLF MRC Complex at Harwell collaboration with Professor Stan Botchway (where the PI is a researcher-in-residence since 2009). Knowledge from the chemistry and chemical biology fields will be translated to radiochemistry assays in the medical radioimaging facility. PETIC is unique in the UK to be producing 89-Zr and has developed strategies to radiolabel antibodies, cells and exosomes for in vivo imaging which will be accessed hereby. Tumour hypoxia is a poor prognostic factor due to resistance mechanisms initiated by cells in a hypoxic environment. With approximately 60% of all solid tumours containing regions of hypoxia, it is critical to stratify patients to ensure they receive personalized treatment. Research training will be achieved in cutting-edge imaging technologies based on Peptide Nucleic Acid (PNA) constructs which will be engineered to emit detectable fluorescence in the near-IR domain, allowing deep tissue imaging in vivo as well as by matching assays in living cancer cells and spheroids. PNAs are synthetic DNA/RNA mimics with nucleobases connected via a peptide backbone that bind extremely tightly to DNA/RNA and are not degraded by proteases or nucleases. Previous work in the team (Paisey) has shown that radiolabelled cells and antibodies (with 89-Zr, a long lived, T1/2 = 78.4 Hrs positron-emitting radioisotope) can be imaged in vivo for up to 15 days post injection. This could facilitate the probing of the hypothesis that labelling NIR-emitting PNA constructs will improve the image quality and sensitivity and allow the tracing of PNAs /biolocalisation monitoring over several days. Guided by the complementary expertise of the supervisory team, the student will take the novel PNA chimeric construct from initial design (Cardiff and Bath), to synthesis of candidate tracers (Bath), followed by in vitro testing in hypoxic tissue culture conditions (Cardiff and Bath), radiolabelling and a small scale pilot in vivo imaging study in a mouse model of xenograft hypoxic tumours (Cardiff). The student will be trained to prepare PNA on an automated synthesiser in

	the laboratory of Prof Sofia Pascu (Bath Chemistry) with additional guidance from our close collaborator, Dr James Redman (Cardiff Chemistry) who is experienced in chemical biology. PNAs will be conjugated to existing cell entry peptides and bimodal fluorescent/radiometal chelators from established collaborations between the Pascu labs and PETIC. The student will be trained in fluorescence spectroscopy/imaging and hypoxic tissue culture in the labs of Dr Charareh Pourzand (Bath) which will enable the screening and of candidate PNAs in vitro. The student will also be trained in radiolabelling techniques and PET/CT imaging by Stephen Paisey in PETIC to enable the assessment of lead candidates in vitro and in a small-scale in vivo PET/CT study. This boundary-crossing project will be a unique opportunity for a student to drive the development of a novel radiotracer from initial design to early proof of concept testing in vivo guided by the complementary expertise of the project supervisors. The student will develop skills in peptide nucleic acid synthesis and conjugation chemistry, hypoxic tissue culture and fluorescence imaging/spectroscopy, radiation handling and radiolabelling techniques, and PET/CT image acquisition and analysis.
Supervisory Team	
Lead Supervisor	
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