Project Details	
Project Code	MRC21IIRCa Paisey
Title	New Multimodal Peptide Nucleic Acid (PNA) constructs for the imaging of hypoxia-specific mRNA expression for the early diagnosis and therapy monitoring of cancers
Research Theme	Infection, Immunity & Repair
Summary	The mission of this project is to define the use of nucleic acids as synthetic platforms to unlock the potential of early cancer diagnostics and precision genetic medicines, to expedite clinical advances in cancer treatment. PNA constructs are synthetic DNA/RNA mimics with nucleobases connected via a peptide backbone. This multidisciplinary project will develop new multimodal radiolabelled/fluorescent PNA constructs to image hypoxia specific mRNA expression in vivo.
Description	This challenging and well supported interdisciplinary project, led by the PETIC Centre Cardiff along with their GW4 collaborators, aims to develop multimodal radiolabelled/fluorescent PNA based imaging tracers to target hypoxia specific mRNA expression in vivo. Research training will be achieved in cutting-edge imaging technologies based on Peptide Nucleic Acid (PNA) constructs. 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. Our preliminary research showed that antisense PNA constructs are ideal targeting vectors for imaging, and here we will probe their usefulness for imaging mRNA expression in vitro and vivo. Added value emerges from our long standing interest and track record in hypoxia tracers: this multidisciplinary project aims to design and develop new multimodal radiolabelled/fluorescent PNA based imaging tracers to target hypoxia specific mRNA expression in vivo. 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. Previous work (Tian et al., J. Nuc. Med. 2007, 48(10), 1699–1707) has shown that a chimeric construct containing a cell entry peptide, an antisense PNA and a radioactive isotope can detect tumours in vivo. 99m-Tc SPECT and 64-Cu PET imaging showed that accumulation was slow, with tumour to background intensity ratios still rising as the radioactive signal was fading at 24 Hrs post injection, suggesting that a construct with a longer lived radioisotope could be more sensitive and provide clearer images. We hypothesise that labelling PNA constructs with 89-Zr, a recently discovered long lived (T1/2 = 78.4 Hrs) PET isotope, will improve the image quality and sensitivity of this promising imaging methodology. 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. Previous work has shown radiolabelled cells and antibodies can be imaged in vivo for up to 15 days post injection. 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).

	Knowledge from the chemistry and chemical biology fields will be translated to the in vitro and in vivo radiochemistry assays in the medical radioimaging facility. The student will be trained to prepare PNA on an automated synthesiser in the laboratory of Sofia Pascu (Bath Chemistry) with additional guidance from James Redman (Cardiff Chemistry). 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 Rachel Errington to enable them to screen and characterise candidate PNA constructs in vitro. The student will also be trained in radiolabelling techniques, animal handling and PET/CT imaging by Stephen Paisey in PETIC to enable the assessment of lead candidates in vitro and in vivo in a PET/CT study. In these final stages, the imaging data will be analysed in collaboration with the University of Bath SAMBA Centre (http://www.bath.ac.uk/centres-for-doctoral-training/epsrc-centre-for-doctoral-training-in-statistical-applied-mathematics-samba/) using AI and mathematical tools to develop predictive models of hypoxia levels and disease progression.
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