Project Details	
Project Code	MRCNMH25Ca Newland
Title	Developing a new therapeutic strategy for brain cancers: getting therapeutics directly to the tumour
Research Theme	Neuroscience & Mental Health
Summary	Some brain cancers cannot be surgically removed, and many potent therapeutics cannot reach the tumour site. This project aims to overcome these hurdles by utilizing a recently developed multifunctional nanoparticle drug delivery system that can be injected directly into tumours. With state-of-the-art equipment and the supervision of a neurosurgeon, this project will explore how a range of promising drugs can be repurposed to attack brain tumours from within.
Description	**Background** The prognosis for many types of brain cancers remains poor, especially when surgical removal of the tumour is not possible due to its position within the brain. The cells within a brain tumour exhibit vast heterogeneity in their identity and function, so it is our view that a single drug is unlikely to yield a step change in therapeutic outcome that we hope for. Whilst many potent chemotherapeutics and other anti-cancer drugs exist, the majority cannot reach the brain tumour due to the selective barrier that protects our brain in normal function. This means that drugs which show great promise for many cancers cannot be repurposed for use in the brain. **Aim** Analyse whether a recently developed nanoparticle drug delivery system can be used to deliver repurposed therapeutics to brain tumours. Specific Objectives 1) Synthesise and characterise polyacrylic acid nanoparticles and analyse the loading and release characteristics of a range of therapeutics. 2) Analyse the antitumour efficacy of these nanoparticles on 3D in vitro tumour models (e.g., glioblastoma spheroids). 3) Use stereotactic surgery combined with convection enhanced delivery to administer chosen therapeutic candidates and combinations thereof, to rodent models of brain cancer. 4) Assess the biocompatibility of the nanoparticles, their spread throughout the tumour, and their effect on the median survival of the animals compared to untreated controls. **Methods and Training** This project is highly interdisciplinary in nature, spanning multiple research fields from nanoparticle synthesis, drug loading and release analysis, in vitro cell culture and in vivo neurosurgery. The composition of the supervisory team matches these individual research disciplines but also holds significant overlap in expertise across these fields. This will allow seamless progression through the PhD, with hands-on training required for each step of this project. This project therefore equips the student with a rare experience of taking a biomaterial drug delivery system from the lab bench, right through in vitro and pre-clinical analysis, yet steering and guiding the project as it progresses. A broad skill set will be acquired that will be

	highly applicable for the pharmaceutical industry or post-doctoral research in tissue engineering, regenerative medicine or oncology. Our labs have a vibrant, team-orientated, and friendly atmosphere with PhD students, post-docs, junior and senior members which will help guide the student in all aspects of PhD life. Finally, all levels of our teams formulate professional development plans to identify strong and weak points, and training is available from both Universities to encourage growth, confidence and expertise in self-identified weak areas. **Milestones and Outlook** The development of the nanoparticles and proof-of-efficacy has been well-established in the Newland lab (unpublished data). 3 Months – Student choses brain cancer, models and candidate therapeutics (all labs) 6 Months – Nanoparticle synthesis and characterization (Newland Lab) 12 Months – Drug loading/release analysis and initial cytotoxicity analysis (Newland lab) 30 Months – In vitro analysis including dose optimisation for required combinations (Siebzehnrubl and Kurian labs) 36 Months – Set up animal model and perform biodistribution/toxicity analysis (Singleton lab) 46 Months – In vivo efficacy analysis (Singleton lab) 48 Months – Completion of project write-up The student will be encouraged and assisted with writing up all parts of this work as the project progresses. We will assist the student to carry out a systematic review of the pre-clinical evidence for promising drug candidates for brain tumours. Furthermore, we expect to generate enough data for two primary research publications based on 1) synthesis, characterization and in vitro analysis and 2) in vivo analysis of biodistribution and efficacy. These will form the mainstay of their PhD thesis, though there will be several opportunities for contributing to related work in the group for the student to gain experience and co-author publications.
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