Department of Pathology fully-funded PhD studentships: project proposal form

Division	Cellular and Molecular Pathology
Supervisor	Nicholas Coleman
Second supervisor (If supervisor's contract ends before October 2024)	
Project title	MicroRNA dysregulation in malignant germ cell tumours: more than a biomarker?
Project abstract for advert (Max 100 words)	Malignant germ cell tumours (mGCTs) are the most common cause of cancer deaths in young adult males. Our group discovered that all mGCTs, despite being clinically and pathologically variable, are characterised by specific abnormalities in microRNA levels. This important finding has led to the development of widely-adopted blood tests for mGCT diagnosis and monitoring. The current project will investigate whether the microRNA changes can also be targeted as new biological therapies for mGCTs. Initial work will involve the generation of inducible lentivirus constructs for replenishment of tumour suppressor microRNAs and depletion of oncogenic microRNAs in established tumours. The effects of rectified microRNA expression will then be investigated using multiple in vivo model systems. The ultimate aim is to progress the work to first-in-man clinical trials.
Keywords Please provide up to five	Germ cell tumours, microRNAs, therapy,
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Malignant germ cell tumours (mGCTs) are clinico-pathologically heterogeneous tumours that are the most common cause of cancer deaths in young adult males. In 2010, we identified changes in microRNA expression levels that were seen in all malignant GCTs, regardless of patient age, tumour site or histologic subtype. The most significant were co-ordinate over-expression of the oncogenic miR-371~373 and miR-302/367 clusters and under-expression of the tumour suppressors miR-99a/100 and miR-125b (see Figure). Multiple international studies have confirmed our findings that quantification of serum levels of miR-371~373 and miR-302/367 microRNA improve mGCT diagnosis. It is widely predicted that this approach will enter routine clinical use world-wide in the next 2-3 years. The current project will test the hypothesis that the dysregulated microRNAs represent important therapeutic targets in mGCTs. Many of the microRNAs share the same functional 'seed' at nt 2-7, leading to deregulation of mRNA targets and recapitulation of a stem cell phenotype. The project will use inducible systems for in vivo manipulation of microRNA levels in a panel of luciferase-labelled mGCT cell lines representing all major histological types. We have generated tetracycline-inducible lentiviral vectors for increasing expression levels of miR-99a/100 and 125b, either singly or in combination, and will derive inducible shRNA vectors for reducing levels of miR-371~373/miR-302/367. After in vitro characterisation, the student will quantify the effects of inducing tumour suppressor microRNAs and/or depleting oncogenic microRNAs on

	established subcutaneous, testicular orthotopic and metastatic lung tumours in nude mice. Readouts will include tumour morphology and mRNA expression profiling, including measurement of direct miRNA effects using the Sylamer algorithm (Enright lab). In due course, the work will be extended using patient-derived xenografts and nanoparticle delivery, with the aim of progressing to first-in-man trials via our collaboration with the Cambridge Clinical Trials Unit.
Three of your most important publications in support of the proposed project	1. Murray MJ and Coleman N (2019) MicroRNA dysregulation in malignant germ cell tumours: more than a biomarker? Journal of Clinical Oncology (in press) 2. Kucia-Tran JA, Tulkki V, Scarpini CG, Smith S, Wallberg M, Paez-Ribes M, Araujo AM, Botthoff J, Feeney M, Hughes K, Caffarel MM, Coleman N. (2018) Anti-oncostatin M antibody inhibits the pro-malignant effects of oncostatin M receptor overexpression in squamous cell carcinoma. The Journal of Pathology 244: 283-295 3. Murray MJ, Watson HL, Ward D, Bailey S, Ferraresso M, Nicholson JC, Gnanapragasam VJ, Thomas B, Scarpini CG, Coleman N. (2017) 'Future-proofing' blood processing for measurement of circulating microRNAs in samples from biobanks and prospective clinical trials. Cancer Epidemiology, Biomarkers and Prevention 27:208-218