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

PIs to complete Parts A & B and to send to your Head of Division by 1 November 2020.
Heads of Division to complete Part C and to send to hod.sec@path.cam.ac.uk

PART A: PROJECT PROPOSAL	
Division	CMP
Supervisor	Dr Anton Enright
Second supervisor (If supervisor's contract ends before October 2025)	Dr Stephen Smith
Project title	Developing new treatments by targeting RNA splicing control in squamous cell carcinoma.
Project abstract for advert (Max 100 words)	Despite extensive work to understand squamous cell carcinoma biology there are few targeted therapies in this disease. Transcriptional programs are consistently dis-regulated in SCC across organ types and RNA splicing is consistently disrupted in cancers, particularly SCCs. There are extensive splicing changes in the shift from normal epithelium to SCC. We found splicing alterations implicated in the shift from normal to malignant epithelium in patient-derived RNA sequencing data which is recapitulated in cell line models. We will deploy sophisticated computational RNA modeling to identify specific targets in the splicing machinery which underpin SCC development and develop therapeutic molecules against them.
Keywords Please provide up to five	Cancer, Bioinformatics, Therapeutics, Splicing, RNA
Full details (Max 250 words) **Will be published on Departmental website; please do not include confidential information**	i. We will deploy sophisticated computational RNA modeling to identify specific targets for intervention in the splicing machinery which underpins SCC development. • We have generated high depth RNA sequencing data from patients with squamous cell carcinoma associated with high quality clinical information. We have access to extensive raw data from large scale cancer genomics projects (TCGA, GTEx, CCLE, TARGET).

	• We will use an existing tool which has been deployed extensively to analyse micro-RNA targets in cancer data (Sylamer) and re-purpose it to identify specific splicing motifs enriched in cutaneous SCC compared with control normal samples as well as non-cutaneous control SCC. • We will use network biology techniques (ARACNe/GCNA etc) to develop a network model of splicing factors, RNA binding proteins and splicing events specific to cutaneous SCC. This network will identify the splicing factors central to differential splicing and specific transcriptional control in cSCC. ii. We will use genetic interventions (siRNA, CRISPR-Cas9) to test the functional consequences of reversing critical splicing changes in vitro. iii. We will produce targeted molecules to splicing alterations critical in cancer as a first step towards targeted therapy in SCC. • We will use the SELEX technique to generate RNA aptamers which bind specifically and powerfully to those splicing factors or RNA binding motifs identified above and the resulting aptamer pool to demonstrate proof-of-principle phenotype alteration in vitro in representative SCC cell lines. • We will use Sylamer information to derive synthetic miRNA mimetics to precisely target whole pathways involved in SCC biogenesis.
Three of your most important publications in support of the proposed project	Vitsios DM, Davis MP, van Dongen S, Enright AJ. Large-scale analysis of microRNA expression, epi-transcriptomic features and biogenesis. Nucleic Acids Res. 2017 Feb 17;45(3):1079-1090 P Maziere, AJ Enright . Prediction of microRNA targets. Drug discovery today. 2007. 12 (11-12): 452-458 S Van Dongen, C Abreu-Goodger, AJ Enright . Detecting microRNA binding and siRNA off-target effects from expression data. Nature methods, 2008. 5 (12) 1023-1025