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

To be completed and returned to your Head of Division by Friday 21st September 2018

Division	Molecular and cellular pathology
Supervisor	Isaia Barbieri
Project title	Understanding the role of the Guanosine Trimethylase TGS1 in Acute myeloid leukaemia.
Project abstract for advert (Max 100 words)	RNA methylation is a reversible post-translational modification to RNA that epigenetically numerous biological processes. The biological and molecular functions of RNA methylation are generally very poorly understood, both in normal and pathological biological processes. Recently we identified the RNA Guanosine trimethylase TGS1 as a factor specifically required for the proliferation of Acute myeloid leukaemia cells (AML). Trimethylation of guanosine has been previously reported on Small nuclear non-coding RNAs and on a specific subset of mRNAs. The aim of the project will be to better understand the role of TGS1 and to characterise it as a potential therapeutic target in AML.
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Trimethylguanosine SInthase (TGS1) is an RNA methyltransferase that mediates 2 serial methylations for the conversion of the 7-monomethylguanosine (m(7)G) caps of snRNAs and snoRNAs to a 2,2,7-trimethylguanosine (m(2,2,7)G) cap structure. Hypermethylation of the m7G cap of U snRNAs leads to their concentration in nuclear foci and the formation of canonical Cajal bodies (CBs). The trimethylation of the Guanosine cap structure was also reported in specific mRNAs but its role is still not fully understood. We identified TGS1 as a factor required for the proliferation of in AML cells in a CRISPR-CAS9 dropout screen, specifically designed to target the catalytic activity or RNA modifying enzymes. Importantly TGS1 targeting does not affect the proliferation of untransformed cells such as mouse immortalised fibroblasts or normal haematopoietic precursors. The project will involve the characterisation og TGS1 role in AML. Particularly the effects of TGS1 depletion on the proliferation and clonogenic potential of AML cells will evaluated in vitro. The effects of TGS1 inactivation on Gene expression will be analysed through RNA-seq experiments. Successively the molecular mechanism involved will be studied, in particular the direct targets of TGS1 in AML will be identified through RNA immunoprecipitation experiments (RIP) using antibodies specifically recognising 2,2,7 trimethylguanosine. And the effect of the modification on these RNAs will be evaluated. The ultimate goal of the project is the characterisation of TGS1 as a therapeutic and the development of new therapeutic strategies for the treatment of AML.

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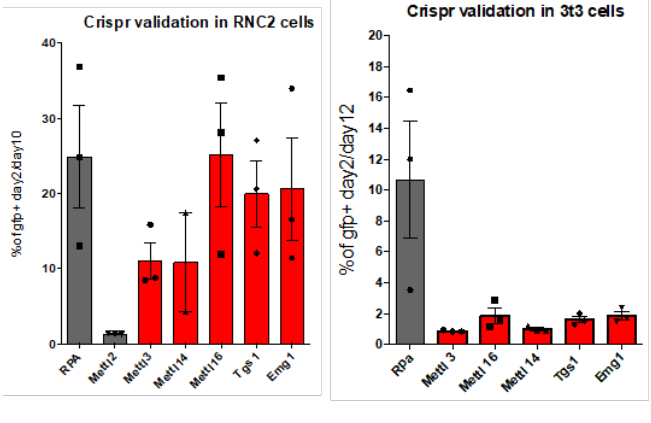
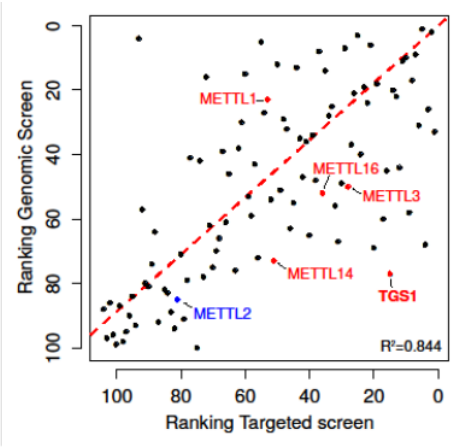
Image(s) related to project (For use in adverts and on Departmental website)	 
5 recent publications	Barbieri I, Tzelepis K, Pandolfini L, Shi J, Millán-zambrano G, Robson SC, Aspris D, Migliori V, Bannister AJ, Han N, De Braekeleer E, Ponstingl H, Hendrick A, Vakoc CR, Vassiliou GS & Kouzarides T 2017, 'Promoter-bound METTL3 maintains myeloid leukaemia by m6A-dependent translation control' Nature. DOI: 10.1038/nature24678 MicroRNAs-143 and -145 induce epithelial to mesenchymal transition and modulate the expression of junction proteins. Avalle L, Incarnato D, Savino A, Gai M, Marino F, Pensa S, Barbieri I, Stadler MB, Provero P, Oliviero S, Poli V. Cell Death Differ. 2017 Oct;24(10):1750-1760. doi: 10.1038/cdd.2017.103 The Breast Cancer Oncogene EMSY Represses Transcription of Antimetastatic microRNA miR31. Viré E, Curtis C, Davalos V, Git A, Robson S, Villanueva A, Vidal A, Barbieri I, Aparicio S, Esteller M, Caldas C, Kouzarides T. Mol Cell. 2014 Apr 10;54(1):203. doi: 10.1016/j.molcel.2014.03.041. BET protein inhibition shows efficacy against JAK2V617F-driven neoplasms. Wyspiańska BS*, Bannister AJ*, Barbieri I*, Nangalia J, Godfrey A, Calero-Nieto FJ, Robson S, Rioja I, Li J, Wiese M, Cannizzaro E, Dawson MA, Huntly B, Prinjha RK, Green AR, Gottgens B, Kouzarides T. Leukemia. 2014 Jan;28(1):88-97. doi: 10.1038/leu.2013.234 Bromodomains as therapeutic targets in cancer. Barbieri I, Cannizzaro E, Dawson MA. Brief Funct Genomics. 2013 May;12(3):219-30. doi: 10.1093/bfgp/elt007. Review.