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	Immunology
Supervisor	James Edgar
Project title	Tetherin exosomes
Project abstract for advert (Max 100 words)	Exosomes represent a subpopulation of extracellular vesicles that are released from cells upon fusion of specialised endosomes with the cell surface. These extracelluar vesicles have been implied in several physiological and pathological processes, including immune presentation, cell migration, cancer metastasis and in the spread of proteins associated with neurodegeneration. However, our understanding of how exosomes function at a fundamental level is still very much in its infancy. We have recently shown that exosomes can act locally, by tethering to the cell surface by a protein called tetherin, suggesting that exosomes act in local presentation in addition to long-range interactions.
ull details (Max 250 words. Will be published on Departmental website; do not include confidential information)	We have recently shown exosomes to undergo physical tethering to the outer surface of cells. Exosomes are formed as intralumenal vesicles (ILVs) within multivesicular bodies (MVBs), and only become termed 'exosomes' when the MVB fuses with the cell surface, liberating the ILVs/exosomes to the extracelluar environment. Exosome have been reported to transfer a huge variety of proteins, and they are reported to play a role in the spread of several disease-associated proteins, including beta amyloid and alpha synuclein. Our recent discovery that exosomes can undergo plasma membrane tethering raises the possibility that exosomes also act in local interactions in addition to more long-range roles. Within cells multiple populations of MVBs exist, and within these, different ILV sub populations exist which are generated using distinct molecular machineries. But which population of MVB or ILV traffics tetherin is unknown. Using a combination of biochemical, molecular and immuno-electron microscopy techniques, we will characterise how tetherin is trafficked, and to which population of MVBs/ILVs, in order to understand which cargos are likely to undergo exosome tethering, and better understand what roles tethered exosome play in cells. Which populations of exosome are tethered, and what happens to cells upon loss of tetherin? Using CRISPR/Cas9 we will generate tetherin knockout cell lines, and by cell surface and exosome-enriched preparation proteomics we will identify cargos which are found on tethered exosomes in different cell types. Exosomes are readily released from various immune cell types, including antigen presenting cells, and we will assess how tetherin contributes to the presentation of antigen and the presentation

	of co-stimulators molecules. Does loss of, or overexpression of tetherin alter the behaviour of these cells? Which molecules allows exosomes to exit cells, and which molecules allow exosome to enter a new ones? Numerous functions have been attributed to exosomes, yet how these vesicles exit the host cell, and what allows them to fuse with the recipient cell remain open questions. We will perform a screen to identify the molecules involved in exosome egress from cells, and uptake to other cells, and using a combination of biochemistry, flow cytometry and microscopy techniques identify where these molecules are acting within exosome transfer.
Image(s) related to project (For use in adverts and on Departmental website)	
5 recent publications	Tetherin is an exosomal tether. Edgar JR, Manna PT, Nishimura S, Banting G, Robinson MS. Elife. 2016 Sep 22;5. pii: e17180. doi: 10.7554/eLife.17180. Q&A: What are exosomes, exactly? Edgar JR. BMC Biol. 2016 Jun 13;14:46. doi: 10.1186/s12915-016-0268-z. ESCRTs regulate amyloid precursor protein sorting in multivesicular bodies and intracellular amyloid-β accumulation. Edgar JR, Willén K, Gouras GK, Futter CE. J Cell Sci. 2015 Jul 15;128(14):2520-8. doi: 10.1242/jcs.170233. Epub 2015 May 22. Hrs- and CD63-dependent competing mechanisms make different sized endosomal intraluminal vesicles. Edgar JR, Eden ER, Futter CE. Traffic. 2014 Feb;15(2):197-211. doi: 10.1111/tra.12139. Epub 2014 Jan 8. Aβ accumulation causes MVB enlargement and is modelled by dominant negative VPS4A. Willén K, Edgar JR, Hasegawa T, Tanaka N, Futter CE, Gouras GK. Mol Neurodegener. 2017 Aug 23;12(1):61. doi: 10.1186/s13024-017-0203-y.

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