Department of Pathology fully-funded PhD studentships

Division	CMP
Supervisor	Pier Paolo D'Avino
Second supervisor	Anton Enright
Project title	Regulation of midbody formation and function by phosphorylation
Project abstract	The midbody is an organelle that forms between the two daughter cells at the end of cell division and is crucial for their final separation. Recent studies have implicated the midbody in various post-mitotic processes, including cell fate, tissue organization, cell proliferation, brain development, cancer and microcephaly. Despite the evidence of the involvement of the midbody in these important processes, our understanding of the mechanisms that regulate its formation and functions are still very limited. The aim of this project is to characterise how phosphorylation controls the dynamics, stability, and interactions of key midbody components by using a multi-system approach involving a combination of advanced methodologies, including gene editing, affinity purification, quantitative proteomics, bioinformatics, and multi-dimensional imaging.
Keywords	cell division, cytokinesis, phosphorylation, proteomics, cancer
Full details	Cell division is regulated by reversible post-translational modifications, like phosphorylation. Although significant advances have been made in understanding how phosphorylation controls chromosome alignment and segregation, much less attention has been devoted to the regulation of cytokinesis. The aim of this project is to study how phosphorylation regulates the formation and functions of the midbody, an organelle that forms between the two dividing cells during cytokinesis. The midbody is crucial for the abscission of

	the daughter cells and has been implicated in various post-mitotic processes, including cell fate, proliferation, apical-basal polarity, cancer and microcephaly. Although initial studies have revealed that phosphorylation plays a key role in regulating the activity, function, and associations of midbody proteins in time and space, our understanding of the mechanisms that regulate midbody formation and functions are still very limited. We propose to employ a multi-system approach, involving a combination of affinity purification, quantitative proteomics, bioinformatics, and high resolution multi-dimensional imaging, to investigate how phosphorylation controls the dynamics, stability and interactions of key midbody proteins. We will identify the interactomes and analyse the dynamics of these proteins in normal conditions and after perturbing cytokinesis with inhibitors of mitotic kinases and phosphatases. Computational analysis of these results will lead us to design mechanistic hypotheses that we can then test using a combination of cell biology and biochemical experiments. Our findings will unravel the molecular mechanisms by which phosphorylation regulates midbody formation and functions, thus helping us understand how this organelle mediates so many important cellular and developmental functions.
Three of your most important publications in support of the proposed project	1) Bassi I.Z., Audusseau, M., Riparbelli, M.G., Callaini, G. and D'Avino P.P. (2013) Citron kinase controls a molecular network required for midbody formation in cytokinesis. *Proceedings of the National Academy of Sciences USA*, 110(24):9782-9787. 2) McKenzie C., Bassi I.Z., Debski, J., Gottardo M., Callaini, G., Dadlez, M. and D'Avino P.P. (2016) Cross-regulation between Aurora B and Citron kinase controls midbody architecture in cytokinesis. *Open Biology*, 6: 160019 (doi: 10.1098/rsob.160019). 3) Capalbo, L., Bassi, Z., Geymonat, M., Todesco, S., Copoiu, Enright, A., L., Callaini, G., Riparbelli, M.G., Yu, L., Choudhary, J., Ferrero, E, Wheatley, S., Douglas, M.E., Mishima, M. and D'Avino P.P. (2019). The midbody interactome reveals new unexpected roles role for PP1 phosphatases in cytokinesis. *Nature Communications*, 10(1):4513