

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	Cellular and Molecular Pathology
Supervisor	Professor Ming-Qing Du
Project title	Characterization of clonal evolution of T-cell lymphoma
Project abstract for advert (Max 100 words)	It has long been assumed that malignant T-cell lymphoma is a monoclonal disease. i.e. the tumour grows and expands from a single cell. In contrast to this traditional view, our ongoing investigations show for the first time evidence of bi- or oligo-clonal T-cell populations in angioimmunoblastic T-cell lymphoma and its related entities. It is imperative to investigate whether each of these different clonal T-cell populations in a T-cell lymphoma is neoplastic, derived from a common progenitor cell population, and how they impact on disease presentation and treatment responses.
Full details (Max 250 words. Will be published on Departmental website; do not include confidential information)	Angioimmunoblastic T-cell lymphoma (AITL) is a neoplastic proliferation of mature T follicular helper cells with clinical and histological presentations strongly suggesting a role of antigenic drive in its development. Genetically, the lymphoma development is characterized by a step-wise acquisition of somatic mutations. Early mutations involve epigenetic regulators (<i>TET2</i> , <i>DNMT3A</i>) and occur in haematopoietic stem cells, most likely causing “clonal haematopoiesis” and increasing risk of lymphomagenesis. Subsequent genetic changes involve cellular signaling molecules (<i>RHOA</i> , <i>VAV1</i> , <i>PLCG1</i> , and <i>CD28</i> , and the <i>CTLA4-CD28</i> , <i>ITK-SYK</i> and <i>VAV1-STAP2</i> fusion), and occur probably in committed T-cells, thus important for malignant transformation and clonal expansion. By investigating both somatic mutation and TCR gene rearrangement, we found bi- or oligo-clonal T-cell populations in AITL, particularly in cases with multiple <i>TET2</i> mutations. This raises the possibility of independent malignant transformation from the haematopoietic stem cells carrying <i>TET2</i> mutation. We propose to characterize further the clonal composition, their temporal and spatial evolution during AITL development, and examine the impact of bi- or oligo-clonality on disease presentation and progression.
Image(s) related to project (For use in adverts and on Departmental website)	

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5 recent publications	<p>Moody S, Thompson JS, Chuang SS, Liu H, Raderer M, Vassiliou G, Wlodarska I, Wu F, Cogliatti S, Robson A, Ashton-Key M, Bi Y, Goodlad J, Du MQ. Novel GPR34 and CCR6 mutation, and distinct genetic profiles in MALT lymphomas of different sites. Haematologica 2018; 103 (8): 1329-1336.</p> <p>Cucco F, Clipson A, Kennedy H, Thompson JS, Wang M, Barrans S, van Hoppe M, Ochoa Ruiz E, Caddy J, Hamid D, Cummin T, Burton C, Davies AJ, Johnson P, Du MQ. Mutation Screening Using Formalin-Fixed Paraffin-Embedded Tissues: A Stratified Approach According to DNA Quality. Laboratory Investigation 2018 98 :1084 - 1092.</p> <p>Moody S, Escudero-Ibarz L, Wang M, Clipson A, Ochoa Ruiz E, Dunn-Walters D, Xue X, Zeng N, Robson A, Chuang SS, Cogliatti S, Liu H, Goodlad J, Ashton-Key M, Raderer M, Bi Y, Du MQ. <i>TNFAIP3</i> inactivation is significantly associated with biased <i>IGHV</i> usage in MALT lymphoma, suggesting cooperation in chronic NF-κB activation. Journal of Pathology 2017; 243:3-8</p> <p>Wang M, Zhang S, Chuang SS, Ashton-Key M, Ochoa E, Bolli N, Vassiliou G, Gao Z, Du MQ. Angioimmunoblastic T cell lymphoma: novel molecular insights by mutation profiling. Oncotarget 2017; 8:17763-70.</p> <p>Du MQ. MALT lymphoma: a paradigm of NF-κB deregulation. Seminars in Cancer Biology. 2016;39:49-60.</p>
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