Deadline for application: 28 February 2019

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 (*TET2*, *DNMT3A*) and occur in haematopoietic stem cells, most likely causing "clonal haematopoeisis" and increasing risk of lymphomagenesis. Subsequent genetic changes involve cellular signaling molecules (*RHOA*, *VAV1*, *PLCG1,* and *CD28,* and the *CTLA4-CD28, ITK-SYK* and *VAV1-STAP2* 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 *TET2* mutations. This raises the possibility of independent malignant transformation from the haematopoietic stem cells carrying *TET2* 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)	

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

5 recent publications	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. 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. 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**. *TNFAIP3* inactivation is significantly associated with biased *IGHV* usage in MALT lymphoma, suggesting cooperation in chronic NF-kB activation. **Journal of Pathology** 2017; 243:3-8 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. **Oncotarge**t 2017; 8:17763-70. **Du MQ**. MALT lymphoma: a paradigm of NF-κB deregulation. **Seminars in Cancer Biology.** 2016;39:49-60.