

Prof C Pritchard - Investigation of the role of the ^{V600E}BRAF oncogene in colorectal cancer

Mutations in the BRAF gene are detected in ~7% of human cancer samples with a particularly high frequency of mutation in malignant melanomas (66%) and colorectal cancers (15%). The most common mutation is a valine-glutamic acid mutation at residue 600 (V600E) that converts BRAF to an oncogene expressing a protein with constitutive BRAF kinase activity. The increased kinase activity of V600EBRAF stimulates endogenous MEK and ERK1/2 phosphorylation and this influences many hallmarks of cancer. In colorectal cancers it is also known that BRAF mutation is directly associated with a CpG island methylation phenotype (CIMP) which can contribute to tumour progression through tumour suppressor gene inactivation, but the mechanisms by which BRAF induces DNA methylation is not currently known. In order to gain more insight into the in vivo role of V600EB-raf, we have generated a mouse model in which ^{V600E}BRAF expression is restricted to the the gastrointestinal tract and this project will focus on investigating: a) Whether V600EBRAF expression is associated with changes in proliferation, apoptosis, senescence. Staining for markers such as Ki67, M30 and p16INK4a will be performed. b) Whether ^{V600E}BRAF expression is linked with increased CpG island methylation and tumour suppressor gene inactivation. Staining for DNA methyltransferases and assays for promoter methylation will be performed. These studies will allow us to gain greater insight into how this important oncogene contributes to the development of human colorectal cancer.

The PhD student funded through this work will receive expert training in a range of modern molecular and cellular technologies and will be exposed to an exciting area at the forefront of international cancer research. The proposed work will also involve close interactions with research scientists at the Institute of Cancer Research.

The Department of Biochemistry is superbly equipped for all aspects of cell and molecular biology, including state-of-the-art tissue culture and microscopy suites in the purpose-built Henry Wellcome Building. The studentship stipend will be in line with UK Research Council studentships and will also pay full UK tuition fees.

For further information about the project please contact Professor Catrin Pritchard, Tel: 0116 229 7061, or E.mail: cap8@le.ac.uk. For further information about the Department visit our website at www.le.ac.uk/biochem.

To apply, please send a full curriculum vitae and covering letter to cap8@le.ac.uk

References

1. Mercer, K. E. and Pritchard C. A. (2003) Raf proteins and cancer: B-Raf is identified as a mutational target. *Biochim. Biophys. Acta.* 1653:25-40.
2. Pritchard, C. et al. (2007) Mouse models for BRAF-induced cancers. *Biochem Soc. Trans.* 35: 1329-1333.
3. Dhomen et al. (2009) Oncogenic Braf induces melanocyte senescence and melanoma in mice. *Cancer Cell* 15: 294-303.
4. Davies, H. et al. (2002) Mutations of the BRAF gene in human cancer. *Nature* 417: 949-954.