

**BELFAST CANCER RESEARCH UK CENTRE
CLINICAL FELLOWSHIP**

The Centre for Cancer Research and Cell Biology is currently offering a three-year PhD Clinical Research Training Fellowship funded by Cancer Research UK, in one of the following research projects.

Project 1: Targeting c-FLIP expression to enhance sensitivity of castrate-resistant prostate cancer to androgen-targeted therapeutics

**Supervisors: Professor Joe O'Sullivan (joe.osullivan@qub.ac.uk)
Dr David Waugh (d.waugh@qub.ac.uk)
Dr Dan Longley (d.longley@qub.ac.uk)**



Project Abstract

Androgen receptor (AR) signalling is a predominant stimulus in prostate cancer (CaP), the disruption of which has been a long-standing basis for therapeutic intervention in this disease, e.g. the widespread use of bicalutamide. A new generation of agents with improved affinity and true antagonist behaviour for targets within the AR pathway are now in advanced clinical development (e.g., abiraterone, MDV3100, or TAK700), heralding the prospect of improved targeting of this receptor, including successful treatment of castrate-resistant patients. However, despite the significant responses observed for a sub-population of patients, these agents show only modest but significant improvement in overall survival and a significant proportion of patients still derive no benefit from these drugs. The objective of this clinical study is to ascertain the importance of c-FLIP as an intrinsic mode of resistance to AR-targeted therapeutics. We have confirmed over-expression of this target protein in castrate-resistant prostate cancer tissue, while *in vitro* experiments exploiting both molecular and pharmacological approaches have demonstrated that knockdown of this protein increases the sensitivity of AR-targeted therapeutics. Applications are now sought from a Clinical Research Fellow to further undertake clinical and laboratory investigations addressing our hypothesis that expression of c-FLIP is an Achilles heel of AR-targeted therapeutics in the treatment of prostate cancer. The successful applicant will undertake phase I and phase II trials that evaluate the safety and ultimately the clinical response of patients treated

with bicalutamide in combination with additional therapeutic agents shown to regulate c-FLIP expression in prostate cancer cells. These clinical studies will be complemented by a retrospective analysis of clinically annotated prostate cancer tissue to evaluate the relevance of c-FLIP as a predictive biomarker to assess bicalutamide response. Furthermore, the successful applicant will undertake a multi-dimensional laboratory project that will evaluate the relevance of c-FLIP in modulating the sensitivity to the next generation of AR-targeted therapeutic agents.

Project 2: The functional characterisation of an immune signalling profile, which defines a DNA repair deficient group in breast cancer

**Supervisors: Professor Richard Kennedy (r.kennedy@qub.ac.uk)
Dr Paul Mullan (p.mullan@qub.ac.uk)**

Loss of a normal DNA-damage response (DDR) sensitizes tumours to DNA-damaging as well as targeted therapies. However, there is no reliable method to detect DDR-deficiency. Therefore, we characterized the biology of a BRCA1/2 mutant enriched, and thus DDR-deficient (DDR^D), breast tumour cohort, resulting in the identification of a molecular subgroup defined by immune signalling. Enhanced immune signalling was also identified in 10 breast cancer cell lines including the HCC1937 BRCA1-mutant cell-line. A 44 gene signature, developed to identify this subgroup, was a significant independent predictor of response to neoadjuvant anthracycline-based chemotherapy (relative risk = 4.13). We wish to assess if this signalling is representative of other defective DNA repair pathways than BER (HR, NHEJ, etc), what sensors/signalling pathways/ networks mediate this signalling, are the breast cancers within this subtype sensitive to novel DNA repair targeted therapies and finally does the immune signalling represent a therapeutic target in breast cancer?

Applications for this Fellowship are invited from talented and highly motivated Specialist Registrars in Medical Oncology, Clinical Oncology, Surgical Oncology or Pathology. Ideally, applicants will have completed a minimum of two years of their clinical specialty training in an accredited programme and demonstrate clear enthusiasm for and capability to undertake laboratory-based research. Evidence of prior research experience is desirable.

The successful candidate will receive full training in basic scientific, translational and clinical research as appropriate for their project as it develops as well as undertaking research that should lead to a PhD thesis, presentations at national and international meetings and research publications in high impact journals. They will also develop skills in critical appraisal and communication of scientific findings, all of which should strongly aid their career development. Limited clinical service during the

Fellowship in the appropriate specialty will be negotiated between the supervisors and the appropriate Regional Training Programme Director.

CLOSING DATE: Thursday, 1 March 2012 at 5.00 pm

The application consists of two different processes:

- (1) Candidates should apply via the Queen's on-line portal:
https://dap.qub.ac.uk/portal/user/u_login.php
- (2) A copy of your Curriculum Vitae including a synopsis of laboratory experience **must also** be submitted to pgoffice.smdb@qub.ac.uk by the relevant closing date.

Please ensure that you adhere to the closing dates above.

For more information, please consult our website www.qub.ac.uk/ccrcb.

Eligibility for both fees and maintenance depends on the applicant being either an ordinary UK resident or those EU residents who have lived permanently in the UK for the 3 years immediately preceding the start of the studentship. Non UK residents who hold EU residency may also apply but if successful may receive fees only.