



PostDoc Job Opportunity



DUBLIN CITY UNIVERSITY	First Name	Last Name	email	Institute	Address
PI name & contact details:	Norma	O'Donovan	norma.odonovan@dcu.ie	DUBLIN CITY UNIVERSITY	Glasnevin, Dublin 9, Ireland.
School:	Biotechnology				
Research Centre / group affiliation:	National Institute for Cellular Biotechnology Ireland				
Research group / centre website:	Molecular Therapeutics for Cancer Ireland				

Brief summary of research group / centre activity

Molecular Therapeutics for Cancer, Ireland (www.mtci.ie), a Science Foundation Ireland funded research cluster, comprises researchers from 4 Dublin universities. The research focus of MTCI is the development of novel therapeutic strategies for breast cancer. Through MTCI, we have access to a range of facilities and expertise across the four institutions.

Description of postdoctoral project on offer:

Title: Biomarker evaluation in locally advanced HER2 positive breast cancer patients treated with trastuzumab with or without lapatinib

Investigators: Dr Norma O'Donovan, Dr Denis Collins, Prof John Crown

Affiliation: Molecular Therapeutics for Cancer Ireland, National Institute for Cellular Biotechnology, Dublin City University

HER2 is over-expressed in approximately 20-25% of breast cancers and is associated with poor prognosis.

Trastuzumab has significantly improved prognosis for patients with HER2 positive breast cancer. Lapatinib is a small molecule tyrosine kinase dual inhibitor of both EGFR and HER2, and is approved for the treatment of trastuzumab-resistant metastatic HER2 positive breast cancer.

Combined targeting of both the extracellular domain and the kinase domain of HER2 may improve response in HER2 positive breast cancer. Trastuzumab also induces antibody-dependent cell-mediated cytotoxicity (ADCC), while lapatinib inhibits activity of the p95 form of HER2. We have shown that combined treatment with trastuzumab and lapatinib is synergistic in HER2 positive breast cancer cell lines and improves response to chemotherapy.

We have conducted a neo-adjuvant clinical trial (ICORG 10-05 - TCHL), to test the combination of trastuzumab and lapatinib with chemotherapy, with the All-Ireland Cooperative Oncology Research Group (ICORG, www.icorg.ie). The trial consisted of two treatment arms comparing chemotherapy and trastuzumab (TCH) to chemo with trastuzumab and lapatinib (TCHL) in HER2 positive breast cancer patients. The pathological complete response rates were 48% (16/33) for the TCH arm and 44% (7/16) for the TCHL arm.

Patient samples (blood, serum, plasma, tumour tissue (FFPE)) have been collected from consented TCHL patients before and after treatment. These samples will be used to investigate molecular and immune-related changes following treatment with TCH or TCHL and correlated with response to treatment.

A number of potential serum biomarkers of response to trastuzumab and/or lapatinib will be measured in the pre- and post-treatment samples, including the HER2 extracellular domain (ECD), and correlated with response. Specific populations of immune cells within peripheral blood mononuclear cells (PBMCs) that are implicated in the ADCC response to trastuzumab will be investigated by flow cytometry in the patient samples. ADCC will be assessed using isolated PBMCs pre and post-treatment, by measuring activity against trastuzumab treated SKBR3 cells in vitro. In addition, plasma will be profiled for immune-related biomarkers of response using a Luminex multiplex assay capable of examining up to 40 immune-related factors.

Additional markers identified in cell line models of trastuzumab/lapatinib resistance will be examined, to determine their association with response to the TCH and/or TCHL regimens and to assess their clinical utility as predictive biomarkers of response.

Please indicate the core skills or disciplines that are required for this position:

Cancer biology, immunology, cell culture, immunoblotting, flow cytometry.

