

Undergraduate Summer Research Internship Scheme 2015

Project Title: Preclinical Evaluation of an EGFR Inhibitor in Triple Negative Breast Cancer

Principal Investigator: Dr Norma O'Donovan

School/Research Centre: National Institute of Cellular Biotechnology

Project Description

Triple negative breast cancer (TNBC) is an aggressive subtype of breast cancer with limited therapeutic options. One of the potential targets of the TNBC therapies is EGFR. Our research group in the NICB, in collaboration with Prof John Crown, is engaged in a programme of research to identify novel therapeutic targets for TNBC. We are currently involved in a collaborative research project with Boehringer Ingelheim (BI) evaluating the potential anticancer activity of afatinib, an irreversible pan-HER tyrosine kinase inhibitor, in TNBC. The postdoctoral scientist Dr Alexandra Canonici, funded by an Irish Research Council Enterprise Partnership Fellowship, has shown that afatinib shows promising activity in TNBC and its activity may be enhanced by combining afatinib with other targeted therapies. This summer project aims to test a number of rationally selected targeted therapies in combination with afatinib to identify synergistic combination regimens that may be progressed to *in vivo* studies and ultimately to clinical trials in breast cancer patients.

This research project will be supervised by Dr Norma O'Donovan with Dr Alexandra Canonici providing day-to-day supervision and hands-on training. Bi-weekly meetings will be held to discuss results, troubleshoot problems and plan future experiments. Data generated from this project will be presented at weekly group meetings and at multi-disciplinary triple negative breast cancer monthly meetings in St Vincent's University Hospital chaired by Prof John Crown. Furthermore, monthly meetings will be held with our enterprise partner Boehringer Ingelheim. Dr Flavio Solca is the scientific leader for the development of afatinib at BI. Dr Solca will provide his expert advice on the design and interpretation of the afatinib experiments.

The laboratory skills that will be acquired during this project will include cell culture and measurement of drug response using a variety of endpoints. For interpretation of the data generated, the student will be trained on statistical analysis, graphical presentation of data using Excel and Powerpoint, and on specialist software (Calculusyn) for analysing drug combinations. The National Institute for Cellular Biotechnology has all the requisite facilities and resources to successfully complete this project. In addition, the student will gain knowledge of cancer cell biology and signal transduction pathways through participation in

project meetings and group meetings. We anticipate that this research project will contribute to a manuscript for submission to an international peer-reviewed cancer journal.

As our research group includes postdoctoral scientists, PhD students and research assistants, the student will also gain insight into the research environment and the day-to-day activities of the various researchers. This will help to inform the student's future career, in particular with respect to pursuing a postgraduate degree by research.

Principle Duties and Responsibilities

Triple negative breast cancer (TNBC) is a subtype of breast cancer negative for expression of oestrogen and progesterone receptors and lack of HER2 gene amplification. It is associated with poor prognosis and lack of targeted therapies. Therefore, there is a need for identification of new therapies. EGFR, a receptor tyrosine kinase from the HER family, is frequently overexpressed in TNBC. Other molecular targets, including FGFR, PDGFR, mTOR and c-Met hold promise as targets for TNBC.

Based on the evidence provided by these studies, suggesting a role for each of the identified targets, we propose to test combinations of an EGFR inhibitor, with a FGFR/PDGFR inhibitor, an mTOR inhibitor and a c-Met inhibitor in TNBC cell lines.

Dose response proliferation assays will be performed to determine IC₅₀ concentration that is the concentration which inhibits 50% of growth, for inhibitors using the acid phosphatase assay. Combinations of the inhibitors will be tested and combination index values will be calculated to identify synergistic combinations. The cell lines tested will include representative cell lines from the different subtypes of triple negative breast cancer.

The ultimate goal of this translational research is to identify a rational combination of therapies to improve outcome for patients with TNBC.

This research project will be conducted in the National Institute for Cellular Biotechnology under the supervision of Dr Norma O'Donovan and Dr Alexandra Canonici. The student will join a team of 7 researchers including postdoctoral scientists, PhD students and research assistants, and will gain experience in cell culture, drug sensitivity assays and data analysis. This project also involves collaboration with clinicians and with the pharmaceutical industry.