**STUDENTSHIP PROJECT PROPOSAL**

**PROJECT DETAILS**

<table>
<thead>
<tr>
<th>Project Title:</th>
<th>Functional assessment of kinase mutations in endometrial cancer subtypes.</th>
</tr>
</thead>
</table>

**SUPERVISORY TEAM**

<table>
<thead>
<tr>
<th>Primary Supervisor:</th>
<th>Dr. Paul Huang &amp; Dr. Rachael Natrajan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other supervisory team members:</td>
<td></td>
</tr>
</tbody>
</table>

**DIVISIONAL AFFILIATION**

<table>
<thead>
<tr>
<th>Primary Division:</th>
<th>Cancer Biology / Molecular Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Team:</td>
<td>Protein Networks / Functional Genomics</td>
</tr>
</tbody>
</table>

**SUMMARY OF PROPOSED PROJECT**

The advent of next generation sequencing technologies have revolutionised the cost and speed at which whole genome sequencing can be performed. Cancer genome sequencing projects have uncovered a large number of kinase mutations, deletions and translocations in endometrial cancer. While some of these aberrations are found in mutational ‘hotspots’ and are fairly well characterised, many of the identified mutations are novel and their functional contribution to kinase activity and signalling specificity is unknown. A number of low frequency kinase gene mutations have been identified in different subgroups of endometrial cancer.

We have previously shown that mass spectrometry is a promising tool for resolving signalling features that occur downstream of kinase mutants and has the potential to inform the selection of signalling candidates for targeted therapy. Recent studies have also proposed that protein kinases employ a common effector processing network including the ERK, JNK, PI3K, mTOR pathways to regulate cancer cell fate decisions and that these common pathways may act as fragile points for therapeutic targeting. While contextual information such as the acquisition of functional mutations may result in differences in kinase-mediated signalling networks, the fundamental components or oncogenic effectors of signalling are likely to be common in most cancer cells.

Our hypothesis is that kinases that are mutated at low frequency in endometrial cancer subgroups activate common downstream oncogenic pathways which can serve as candidate targets for disease. Identifying and targeting these common pathways may be an attractive alternative strategy to developing individual drugs to specific mutant kinases. In this application, we propose to employ both discovery and targeted mass spectrometry to identify the effects of kinase mutations on common oncogenic signalling pathways. Kinase mutations that have been identified through a meta-analysis of current exome and whole genome sequencing studies will be expressed in isogenic endometrial cancer cell line models and subjected to both quantitative proteomic and phosphoproteomic profiling. Clustering approaches will be used to identify shared and unique signalling pathways which are activated by distinct mutant kinases. In addition, computational tools will be used to identify downstream signalling proteins that are strong drivers for tumour growth and clonogenic potential. These proteins will be experimentally tested as potential candidate targets for therapy in mutant kinase-driven endometrial cancer.

The pipeline that will be generated by this project also has the potential to be extended to kinase mutations in other endometrial cancer subtypes or to monitor the evolution of signalling networks during endometrial cancer progression and metastatic development.
The project will be composed of the following aims.

1. Identify and prioritise candidate kinase mutants from endometrial cancer molecular profiling datasets.

2. Stable expression of mutant kinases in endometrial cancer cell lines of the appropriate subtypes and phenotypic characterisation.

3. Proteomic/phosphoproteomic profiling of mutant kinase signalling and bioinformatic mining of candidate therapeutic targets in endometrial cancer.

4. Experimental validation of the targets identified in Aim 3 for their effect on tumour growth and clonogenic potential in 3D matrigel assays with shRNA and/or chemical inhibitors.

The goal of the project is for the student to evaluate if targeting of common “vulnerable” signalling pathways is a valid approach for inhibiting multiple mutant kinases in endometrial cancer.

**LITERATURE REFERENCES**


CANDIDATE PROFILE

Note: the ICR’s standard minimum entry requirement is a relevant undergraduate Honours degree (First or 2:1)

Pre-requisite qualifications of applicants: BSc/MSc in Biology, Biochemistry, Cancer Biology, Cell Biology

e.g. BSc or equivalent in specific subject area(s)

Intended learning outcomes:

- Critical evaluation of data
- Summarise findings in the form of a manuscript and PhD thesis
- Molecular Pathology, Proteomics, Breast Cancer Biology, Signal Transduction, Cancer Therapeutics, Cell and Molecular Biology