2016/2017 Summer Studentship Project Application Form

Send to: Research Office, University of Otago Christchurch, PO Box 4345, Christchurch, by 5pm on **4 July 2016**

Supervisor Information (First named supervisor will be the contact):	
First Supervisor's Name and Title: Dr Simran Maggo	
Department - UOC &/or CDHB (if applicable): Pathology (UOC)	
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First Supervisors Mailing Address: GSFL, 4th Floor, UOC Building	
Co-Supervisors Name and Title(s): Prof Martin Kennedy	

Research Category (Choose one category only – to be used for judging the students' presentations):		
~~**Clinical**~~	**Laboratory**	~~**Community**~~

Project Title (20 words MAXIMUM):

Analysis of *POR* gene mutations in patients with atypical drug responses

Project Description:

Introduction:

Our laboratory is interested in understanding the impact of genetic variation on response to drugs, and in particular on liability to severe adverse drug reactions. We have an ongoing project called UDRUGS (Understanding adverse Drug Reactions and Unusual responses through Genome Sequencing), in which we are seeking to identify genetic factors that may predispose to rare serious adverse drug reactions. We now have over 80 subjects in UDRUGS, and have applied many genetic analyses for specific pharmacogenes, as well as broader genome-based approaches such as whole exome sequencing [1-3], to selected participants. One important candidate pharmacogene we have yet to study directly is *POR*, a gene that encodes the enzyme cytochrome P450 oxidoreductase. This flavoprotein donates electrons to all microsomal cytochrome P450 enzymes, a process which is vitally important for effective drug metabolism [4-7]. We have several patients in UDRUGS who have experienced adverse outcomes or unusual responses to a wide range of drugs. One possible genetic explanation for this phenomenon is variation in their *POR* genes, which impacts on the electron donor function [4]. We propose to seek loss-of-function genetic variants in POR of these selected patients as a possible contributor to their adverse drug outcomes.

Aim:

The goal of this project is to analyse the *POR* gene in several UDRUGS patients who have extensive histories of poor or adverse responses to drug treatment. This will require establishing the appropriate analytical strategies, then carrying out the analysis and interpreting the results. The hypothesis we wish to test is that patients with these unusual drug responses will show rare, damaging variants in their POR genes, which might lead to reduced cytochrome P450 oxidoreductase activity. The specific aims of this project are:

- Design assays to amplify all coding regions and the promoter, of the *POR* gene.
- Apply these assays to several UDRUGS participants.
- Interpret the sequence data obtained and if necessary, validate any novel gene variants.

Possible impact (in lay terms):

This project focuses on a gene known to play a key role in metabolism of drugs, but which has been relatively under studied thus far. This gene, called *POR*, will be examined in depth in several patients who have displayed adverse drug reactions or other unusual drug responses. The outcomes of this project will help in understanding the genetic basis of adverse effects to prescribed medication.

Methods:

The methods to be used will be predominantly polymerase chain reaction (PCR) and Sanger sequencing. However, most of the exons of this gene (13 of 16) are contained within an 8.5kb region of DNA, a size which may also be amenable to long range PCR. Amplification of this product will be attempted, and if successful, the products may be indexed and then sequenced on the MinION (Oxford Nanopore Technologies) nanopore sequencer which is capable of reading large fragments, and is now fairly in routine use in our laboratory. This may be a more effective strategy than amplification and Sanger sequencing of multiple products. We have consented DNA samples from several UDRUGS patients that would be appropriate for this work. The precise number to be studied will be dictated by how well the assay development proceeds, and how much time remains for these analyses to be completed.