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: Prof Martin Kennedy	
Department - UOC &/or CDHB (if applicable): Pathology (UOC)	
First Supervisors Phone: 0212930056 or ext 81222	First Supervisors Email: martin.kennedy@otago.ac.nz
First Supervisors Mailing Address: GSFL, 4th Floor, UOC Building	
Co-Supervisors Name and Title(s): Dr Tony Walls, Paediatrics, CDHB. A/Prof John Horwood, CHDS, UOC.	

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

Project Title (20 words MAXIMUM):

Rare variants in the *IFIH1* gene and severe viral respiratory infections in early childhood

Project Description:

Introduction:

Most children who experience respiratory virus infections at an early age recover well, but perhaps 1-2% will be hospitalized with more severe infections, and of those, about 10% will require treatment in a paediatric intensive care unit. In a recent study of such severe cases, whole exome sequencing (a focused form of human genome sequencing) was used to seek potential underlying genetic risk factors [1]. In that analysis, several cases were found to have loss of function mutations in a gene called IFIH1 (also known as MDA5) [2]. This gene encodes an RNA-binding protein that is upregulated in response to treatment with beta-interferon, and is believed to play a role in sensing cellular infections by viruses [3-5]. The three mutations found in this study occur with a population frequency of about 2% (ExAc database), but are highly enriched amongst children hospitalised with respiratory virus infections [1].

Aim:

The hypothesis we seek to test is that rare genetic variants of *IFIH1* will be enriched in people who experienced severe respiratory infections in early life. This project will involve establishing and validating the analytical methods, and carrying out a pilot study using these methods. For the pilot study, the student will examine *IFIH1* variants of selected participants from the Christchurch Health and Development Study (CHDS), for whom we have consented DNA as well as detailed records of early life hospital admissions [6, 7]. Initial analysis of CHDS records suggests we will have some 15 CHDS participants who were hospitalised in early life with respiratory infections, and we will be able to examine these cases and individuals with little or no history of such infections as controls. Specific aims are:

- Develop laboratory assays (PCR and Sanger sequencing) for analysis of the three *IFIH1* variants (rs35732034, rs35744605, rs35337543) recently implicated in susceptibility to viral respiratory infections.

- Develop a similar assay for examining variation in the promoter region of this gene, which has not yet been studied in this context.
- Apply these assays to analysis of selected participants from the Christchurch Health and Development Study to determine the distribution of *IFIH1* variants amongst those with early life respiratory illness versus those with no such history.

Possible impact (in lay terms):

A connection between variation in a gene called *IFIH1* and severe early life virus infections has very recently been described, and much work needs to be done to confirm these findings in different settings. If the findings prove to be robust, then analysis of variation in this gene could ultimately be useful to identify at-risk children or families, and may also be useful in managing patients with severe infections.

Method:

Polymerase chain reaction (PCR) will be used to amplify selected regions of *IFIH1*, followed by Sanger sequencing to identify genetic variation in PCR products. The student will be trained in these and associated methods, including primer design, agarose gel electrophoresis, and use of the relevant bioinformatics software.