2017/2018 Summer Studentship Project Application Form

Send to: Research Office, University of Otago Christchurch, PO Box 4345, Christchurch, by 5pm on 3 July 2017

Supervisor Information (First named supervisor will be the contact):	
First Supervisor's Name and Title: Dr Jacqui Keenan	
Department - UOC &/or CDHB (if applicable): Surgery, UOC	
First Supervisors Phone: (03) 3640 570	Email: jacqui.keenan@otago.ac.nz
First Supervisors Mailing Address: Dept Surgery, UOC, PO Box 4345, Christchurc	
Co-Supervisors Name and Title(s): Professor Frank Frizelle	

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

Project Title (20 words MAXIMUM):

Does diet switch a bacterial commensal to a colon carcinogen?

Project Description:

Introduction: Throughout our life diet has a major influence on our health. Diet at the time of weaning influences an individual's gut microbiota, and determines the relative abundance of these bacterial species at any one time. In addition, diet may also have an underappreciated role in influencing whether health or disease-associated properties of individual species are expressed and this gains significance as diets in developing countries become increasingly westernized.

Bacteroides spp. have colonised the human gut for >50,000 years. These bacteria degrade dietary carbohydrates and limit inflammatory responses, thereby contributing to their own fitness and to that of their host. However, within the genus, one species has evolved into a potential pathogen. Specifically, a subset of *B. fragilis* strains possess a 6-kb DNA region that codes for two zinc metalloproteinase (*bft* and *mpII*) genes with high structural similarity to mammalian matrix metalloproteinases. Horizontal gene transfer of host genetic information to bacteria is extremely rare and acquisition of this insert may have originally provided these bacteria with an advantage unavailable to those lacking the insert. However, our research shows that strains carrying the insert are associated with early stage colorectal neoplasia via expression of one of the proteinases (known as *B. fragilis* toxin or BFT) that cleaves E-cadherin, a key protein that plays an important role in preventing neoplasia.

Currently little is known about the MPII other than it is poorly expressed in vitro under growth conditions that favour BFT expression and that it binds to, rather than cleaves E-cadherin. MPII may prove to be a second virulence factor. However, our finding of BFT toxin expression that parallels *B. fragilis* growth in the presence of heme iron leads us to speculate that MPII expression may instead contribute to bacterial persistence when this and/or other dietary factors are low. We are particularly interested in short-chain fatty acids (SCFA), which are dietary fermentation end products that reportedly act as a signal for virulence gene regulation in enteric pathogens. Our hypothesis is that high levels of a beneficial SCFA such as butyrate may act to limit *B. fragilis* toxin production, thereby helping to transition these bacteria from a potential toxigenic gut pathogen to a non-toxin-producing commensal.

Aim: To determine if heme iron and/or butyrate favours individual protease expression.

Possible impact: The incidence of CRC in NZ continues to increase, most notably in under 50 year olds. Our novel hypothesis links diet to risk of CRC via modification of a bacterial phenotype that either increases or reduces toxin production. If proven, this research would help provide insight into the potential impact of diet on CRC that may in time inform the development of new prevention strategies.

Method: Growth kinetic studies will be used to determine the rate of growth of an enterotoxigenic strain of *B. fragilis* in the presence of increasing concentrations of heme iron and/or butyrate in broth culture, with bacteria harvested after 48 hours for molecular analysis of bacterial proteinase expression, protein analysis of outer membrane phenotype and investigation of the ability to form biofilms. Bacteria will also be added to colonic epithelial cell lines, with molecular and protein analyses used to ascertain if a heme iron and/or butyrate effect on bacterial proteinase expression also influences cellular pathology.

Student Prerequisites (eg. Medical Student) if applicable:

Administration Details

1. Is ethical approval required? No

   If Yes: please circle or tick one of the following:

   a) Applied for (provide application #)

   b) Approved (attach a copy of the letter of approval from the ethics committee or application #)

   c) To be done

2. Are you able to provide the funding for this project (ie. $5,000 for the student, incidental expenses should be met from departmental or research funds) No

   If Yes: Please provide name of the funder _____

   If No: Please provide ideas of possible funding sources, including past funding agents and topics often associated with this research area, for the Research Office to contact.

   Possible funders would be Canterbury Westland Cancer Society or CMRF_____

3. Medical Records or Decision Support accessed No

4. Health Connect South or other DHB records No

5. Signatures:

   - I have read the 2017/2018 Summer Studentship programme handbook.
   - I am prepared to supervise the project and will be available to the student during the studentship (including Christmas/New Year break if the student is working during this time).
   - I agree to assume responsibility for the submission of the student's reports to the Research Office by the due date 29 January 2018.
   - I agree that the project lay report may be available to local media for publicity purposes.

Signature of Project Supervisor(s):	Date:

- I understand that I am responsible for hosting the Summer Student chosen for this project and will meet any costs incurred. I agree that incidental expenses will be met from departmental or research funds.

Signature of Head of Department: (Print Name)	Date:
Signature of Clinical Director: (if applicable) (Print Name)	Date: