2015/2016 Summer Studentship Project Application Form

Send to: Research Office, University of Otago Christchurch, PO Box 4345, Christchurch, by 5pm on **3 July 2015**

Supervisor Information (First named supervisor will be the contact):	
Supervisor's Name and Title(s): Prof Vicky Cameron, Dr Anna Pilbrow	
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Research Category (Choose one category only – to be used for judging the students' presentations):		
Clinical	**Laboratory**	**Community**

Project Title (20 words MAXIMUM):

The Dawn of Long Noncoding RNAs as Circulating Cardiac Biomarkers

Project Description:

Aim:

To investigate if plasma levels of three candidate long noncoding RNAs (lncRNAs) are predictors of incident cardiac events in a prospective cohort of healthy volunteers who were asymptomatic at recruitment.

Introduction:

The recent discovery that the vast majority of our genome generates non protein-coding RNA transcripts with biological functions [1], has rewritten our understanding of the inheritance of disease. Remarkably, genome-wide association studies have identified that at least 90% of the genetic variants associated with complex diseases and traits lie within these non protein-coding regions [2], including the genetic variant most strongly associated with inherited risk of coronary heart disease (CHD) [3, 4].

Coronary heart disease is a leading cause of morbidity and mortality in Aoteoroa/New Zealand and is especially prevalent among Māori and Pacific peoples [5]. In the general population, traditional risk factor profiling using the New Zealand 5-year Cardiovascular Disease (CVD) Risk Score [6] fails to identify many at-risk individuals [7], and does not effectively account for differences in risk for certain population groups, especially Māori and Pacific peoples [8, 9]. This highlights the need for new strategies, including accurate diagnostic biomarkers, for screening in the general population to identify people who are at risk of an impending acute cardiac event. To address this, this project will investigate long non-coding RNAs (lncRNAs) as circulating heart disease biomarkers to help identify individuals predisposed to heart disease, prior to the onset of symptoms.

Long noncoding RNAs (lncRNAs) are defined as noncoding RNAs greater than 200 base pairs [10]. Recently, lncRNAs have been detected in the circulation, indicating they may be useful as disease biomarkers [11, 12]. Five lncRNAs detected in circulating white cells of CHD patients predicted left ventricular dysfunction after a cardiac event [11]. Stable levels of a further seven lncRNAs were detected in plasma from CHD patients, and the lncRNA *LIPCAR-MT* was associated with prognosis [12]. Here we will investigate if three lncRNA candidates selected from these previous reports of lncRNAs in patients with existing CHD are also predictors of first CHD events.

Method:

The research will use existing samples from our plasma bank prospectively collected from Canterbury Healthy Volunteers cohort (HVOLs) at various time points prior to an unexpected CHD event. Although all HVOLs were asymptomatic and had no history of CVD at screening, 23% have since experienced an acute CVD event (n=783; 112 within 1 year of recruitment). By the time the student starts, RNA will already be extracted from cell-free plasma and converted to cDNA from HVOLs who have experienced a cardiovascular event 1) within 12 months of recruitment, 2) between 1 year and 5 years, and 3) who have remained event free for at least 5 years from recruitment (n=50 per group). The student will measure levels of candidate lncRNAs previously reported to have altered expression in CHD, including *LIPCAR-MT* [11, 12], by real-time quantitative PCR (RT-qPCR) using published primer sets and SYBR green assays. We have already shown we can robustly detect *LIPCAR-MT* in plasma from heart patients and HVOLs and human heart tissue by RT-qPCR. The student will establish RTqPCR assays for two additional candidate lncRNAs for this project (for example, *KCNQ10T1* and *MALAT1*). The student will perform statistical analyses of the data, under guidance from the Supervisors and Prof Chris Frampton, using SPSS software. Associations between normalised lncRNA levels, CVD Risk Score and clinical measures will be tested with ANOVA or

Pearson correlation, and with subsequent CVD events using log-rank tests and Cox proportional hazard models. A level of $p<0.05$ taken to indicate statistical significance.

Significance:

The discovery of novel circulating biomarkers among these long non-coding RNAs may help identify individuals predisposed to heart disease, prior to the onset of symptoms.

References

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6. New Zealand Guidelines Group. New Zealand Cardiovascular Guidelines Handbook: A Summary Resource for Primary Care Practitioners. 2nd Edition ed. Wellington: Ministry of Health; 2009.
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10. Uchida S, Dimmeler S. Long Noncoding RNAs in Cardiovascular Diseases. Circ Res. 2015;116:737-50.
11. Vausort M, Wagner D, Devaux Y. Long Noncoding RNAs in Patients with Acute Myocardial Infarction. Circ Res. 2014;115:668-77.
12. Kumarswamy R, Bauters C, Volkmann I, Maury F, Fetisch J, Holzmann A, Lemesle G, de Groote P, Pinet F, Thum T. Circulating Long Noncoding RNA, LIPCAR, Predicts Survival in Patients with Heart Failure. Circ Res. 2014;114:1569-75.

Student Prerequisites (eg. Medical Student) if applicable:
Some experience in molecular biology/genetics laboratory work would be advantageous