THE UNIVERSITY OF AUCKLAND

APPLICATION TO THE FACULTY RESEARCH DEVELOPMENT FUND

If sending your application by internal mail please allow at least three working days to ensure meeting the closing deadline.

Application Closing Date (*please insert*): 31st March 2010

Type of Application (*please insert; see Faculty Guidelines*): New Staff

1. APPLICANT IDENTIFICATION

Principal Applicant:
Last Name: Bartlett
First Name: Adam
Title: Dr
Department: Department of Surgery, Faculty of Medical and Health Sciences
ID Number: 9119454

2. PROJECT SUMMARY INFORMATION

a) Brief Title of Project *(No more than 150 characters)***:**

Bioenergetic Profiling in Non-alcoholic Fatty Liver Disease

b) Total amount sought in this Application *(GST Exclusive)***:** NZ$ **29,260.56**

c) Abstract *(Describe in up to 300 words the nature of your proposed research)***:**

Hepatic steatosis or non-alcoholic fatty liver disease (NAFLD) is the most common cause of liver disease in the Western world, with an estimated incidence of 20-30%. NAFLD is associated with obesity, type II diabetes and the metabolic syndrome.

Increased morbidity and mortality in patients with NAFLD undergoing liver surgery, resection or transplantation, is well-documented. However, the fundamental pathophysiological processes underpinning this relationship are poorly understood. It is hypothesized that the increased vulnerability of steatotic livers to ischemia and reperfusion at the time of surgery is due to a combination of microcirculatory changes within the hepatic sinusoids and aberrances in mitochondrial function resulting in critical depletion of cellular ATP. This manifests clinically as poor liver function post-operatively.

The aim of this project is to further elucidate the mechanisms by which steatosis affects liver function after surgery, in order to optimize patient selection and better predict outcome. We hypothesize that the degree of steatosis and the nature of the ischaemic insult contribute to micro-vascular and bioenergetic changes in the liver after surgery, and are related to post-operative organ recovery and outcome.

To investigate this hypothesis a rat model of NAFLD will be developed. Routine histology and vascular resistance will be examined. Mitochondrial respiration flux and cell substrate utilization will be determined using high resolution respirometry oxygraphs coupled with flourospectrometric analysis of free radical production and mitochondrial calcium buffering capacity. Cellular antioxidant status will also be determined along with measures of cellular energetic status. Once optimized, the assays will be performed in parallel on human tissue obtained from patients undergoing liver surgery for which I have ethical approval.

This project represents a unique collaborative opportunity at the interface of surgery and biological science. It combines both experimental models and human tissue samples, to examine the effect of steatosis on cellular and organ function and patient outcome after liver surgery.

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3. PROJECT DETAILS *(use no more than three pages excluding references)*

a) Specific Aim(s) of the Research *(state the general goals and specific objectives of the research proposal)*:

The primary goal of this research project is to establish a new basic science and clinical collaboration in order to better understand the mechanisms by which hepatic steatosis impacts hepatic function at the time of liver surgery. This project will contribute to building the foundations for a newly formed Liver Research Group, and foster future investigations into different aspects of liver surgery and transplantation. A suitable animal model will be developed to mirror human steatosis and tissue samples from this model and patients undergoing liver surgery will be compared in parallel. This will build a foundation on which novel clinically relevant interventions can be tested.

Specific aims of experimental model

1) To establish a validated animal model of hepatic steatosis that mimics the disease process in humans.
2) To develop a rapid non-invasive method to quantify hepatic steatosis
3) Characterize the relationship between hepatic steatosis and vascular resistance
4) Evaluate the relationship between steatosis and mitochondrial function

Specific aims of human tissue samples

1) Describe the effect of steatosis on the three dimensional architecture of the liver
2) Measure mitochondrial respiratory flux in various degrees of hepatic steatosis during liver surgery
3) Correlate the above with histological and biochemical markers of organ function.

b) Proposed Research Project *(the structure and detail of this section may vary with the nature of the award but overall should cover the research question, the methods to be used, and the significance of the expected results)*:

Background

Hepatic steatosis or non-alcoholic fatty liver disease (NAFLD) is gaining increasing recognition as a major heath issue in the 21st century. In the United States of America it is estimated that 20-30% of adults have excessive fat in the liver. NAFLD can be considered a hepatic manifestation of the metabolic syndrome, which also encompasses type II diabetes mellitus, obesity, hypertension and hypercholesterolemia. With an increased prevalence of metabolic syndrome in Western society there has been a dramatic rise in the number of patients with NAFLD, and it is now the most common form of chronic liver disease. In its infancy NAFLD presents as simple intracellular accumulation of lipid. Simple steatosis was traditionally considered to be a benign condition. However it has recently been shown that steatotic livers are more susceptible to ischemic injury and capable of evolving into a potentially harmful inflammatory form, “non-alcoholic steatohepatitis” (NASH) and eventually end-stage liver disease. It is the increased vulnerability of livers with simple steatosis to ischaemic injury which is the primary interest of this project.

The adverse effects of steatosis in liver surgery were first demonstrated in liver transplantation. Transplantation of livers with severe (>60%) steatosis is associated with a high risk of primary non-function (PNF), and it is generally accepted that these livers should not be used for transplantation. In contrast, the transplantation of livers with mild (<30%) steatosis yields similar results as in non-fatty livers. The outcome of livers with moderate steatosis (30-60%) is poorly predictive using the current histological means to assess steatosis. A similar relationship is seen in patients undergoing liver resection. Patients with moderate to severe steatosis have an increased peri-operative mortality compared to normal livers (14% compared to 3%) and intra-operatively they are more likely to require blood transfusion (Behrns KE, 1997).

Despite well defined associations between the extent of significant steatosis on histology and patient outcome, our knowledge of the pathogenic mechanisms of hepatic steatosis is lacking. Currently the selection of patients for liver resection, or donor organs for transplantation, is dependent upon hepatic morphology rather than functional consequences of steatosis. In order to further improve patient outcome a better means of identifying those organs at risk for failure is

necessary. To achieve this a better understanding of the mechanisms by which steatosis affects hepatic function is required. One of the goals of this project is to identify and measure functional consequences of hepatic steatosis in order to improve future patient and/or organ selection or tailor interventions to improve the outcome of this pathogenic state.

Steatosis can be divided morphologically into macro- or micro-vesicular. Microvesicular steatosis is characterised by the accumulation of numerous small fat vacuoles, and is usually the consequence of drug induced impairment of ß-oxidation and is not associated with an increased susceptibility to ischemic injury. In contrast, macrovesicular steatosis is associated with metabolic syndrome and leads to the accumulation of a single large fat vacuole that disrupts cellular architecture, displacing the nucleus to the periphery and narrowing the extracellular sinusoidal space. It is postulated by us and others that this cellular displacement impairs hepatic perfusion leading to a chronic state of cellular hypoxia. This is further exacerbated in the face of ischaemia, hypovolemia and fluid shifts at the time of surgery.

In addition to mechanical impediment of blood flow and tissue oxygenation, cellular utilisation of oxygen at the level of the mitochondria is also impaired in steatotic livers. The synthesis of ATP, the energy currency of the cell, is decreased in fatty hepatocytes, while the production of harmful reactive oxygen species is increased, due to an intrinsic derangement in mitochondrial oxidative phosphorylation processes (Chavin et al. 1999). During the ischaemia and reperfusion process that occurs with surgery, mitochondria in the steatotic liver are subjected to further cellular stresses. The aerobic pathway of ATP generation is suspended in the face of oxygen depletion and resumption of normal ATP production after reperfusion appears to be impaired. This results in insufficient ATP to meet metabolic demands, which triggers necrotic cell death, and dysfunctional mitochondria can also trigger apoptosis, both of which present clinically as organ dysfunction or failure.

To date, the relationship between the degree of steatosis and recovery of mitochondrial oxidative capacity following ischaemia and reperfusion has not been well documented. One of the goals of this project is to identify the threshold level of steatosis above which recovery of ATP synthesis is insufficient to meet cellular and organ demands, rendering the liver unsuitable for safe resection or transplantation using current methods.

Histopathology remains the gold-standard by which steatosis is assessed, however it is not without difficulties. Several studies have shown a difference in histological findings based on which lobe the biopsy was taken from, the size of the biopsy and the number of samples analyzed. In a study of 51 patients with NAFLD Ratziu *et al* (2005) performed bilateral liver biopsies and demonstrated significant discordance in measurements of steatosis, inflammation and fibrosis in 18%, 41% and 43% of patients, respectively. Other limitations include cost, inter-observer variability in reporting and its small but not inconsequential risk of complications including major bleeding (0.1%) and death (0.01%). For these reasons a non-invasive method of quantifying the degree of steatosis is required.

Potential attempts to evaluate steatosis have employed peripheral blood biomarkers, novel imaging techniques, such as transient elastography, magnetic resonance spectroscopy, and high throughput technologies including proteomics and transcriptomics. Such methods are generally, inaccurate, labour intensive, time consuming and often costly. We have preliminary data using near-infrared reflectance spectroscopy (NIRS) to quantify the lipid content in liver. Spectra of liver samples from normal and steatotic livers were significantly different in the visible and near-infrared wavelengths (figure 1). The use of NIRS to quantify differences in steatotic livers has not previously been performed and is part of this proposal. An alternative technique, known as bioelectrical impedance (BEI), also holds promise as a non-invasive objective means to assess hepatic steatosis. In experimental model using rats with varying degrees of steatosis Hessheimer *et al*, 2009, demonstrated that BEI correlated with the degree of macrovesicular steatosis. This is the only reported use of BEI in assessing hepatic steatosis and it has yet to be used on human tissue. We are in the process of collaborating with the authors of this paper to use BEI in both animal and human tissue, and will combine this with NIRS.

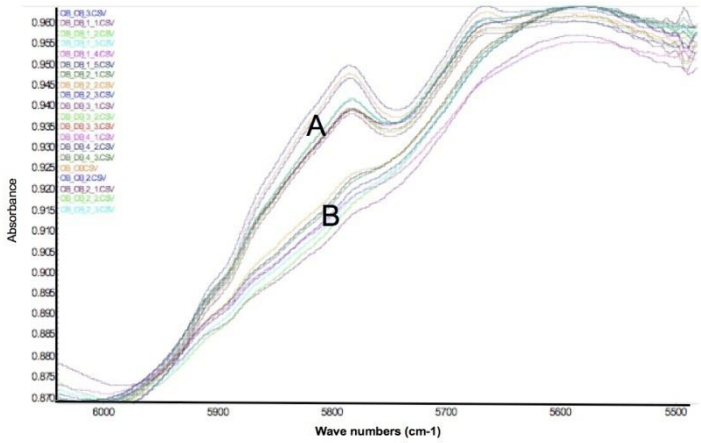

Figure 1. Spectra determined using near-infrared reflectance spectroscopy (NIRS) of normal (B) and steatotic (A) murine liver. Clear spectral demarcations are apparent between samples of solid tissue samples.

While much focus has been placed on severe steatotic and steatohepatitis liver pathology, the fundamental pathophysiology of less fatty NAFLD livers remains poorly characterized. Yet it is organs with this degree of steatosis that are most commonly encountered during liver surgery. Understanding the structural and functional changes that occur in NAFLD is necessary to further improve outcome in patients undergoing liver resection or transplantation. The current method of assessing surgical candidacy relies upon morphogical changes in the liver. The primary aim of this project is to understand the functional consequences of hepatic steatosis to enable us to better predict patient outcome in patients undergoing liver surgery and ultimately develop therapeutic modalities targeted at the hepatic microvasculature and mitochondria to enhance hepatic function in the presence of steatosis.

Experimental Design

A) Establishment of experimental model of NAFLD

Male Sprague-Dawley rats (n=60) will be fed a high-fat pellet diet to induce hepatic steatosis (Svegliati-Baroni et al. 2006). Ten animals will be euthanised at monthly intervals out to 6 months to obtain the time course of development of different grades of steatosis and compared to age matched controls (n=10) that will be fed a standard diet.

<u>Assessment of steatosis</u>

1. Histology
The current gold-standard by which steatosis is assessed in clinical practice. Liver biopsies taken at the time of euthanasia will be bisected, frozen and formalin-fixed, respectively, stained (Oil red-O, H & E) and graded both qualitatively and quantitatively by two individuals.

2. Near Infra-red Reflectance Spectroscopy (NIRS)
Samples will be analysed for fat content using a technique that we have adapted from the food industry (Molette et al 2001). NIRS will be carried out using wavelengths from 400 to 1098nm. Triplicate scans of each sample will be examined for repeatability and then averaged. See above.

3. Biochemical
Lipid will be extracted using standard chloroform and methanol methods (Folch et al. 1957), and total lipids and triglycerides determined enzymatically.

4. Bioimpedance
Bioimpedance has recently been used to measure fat content in liver (Hessheimer et al. 2009). Low frequency bioelectrical impedance will be measured at 1 kHz using custom-made tetrapolar electrodes applied to the liver surface *in vivo*.

Determination of vascular resistance

Under isoflurane inhalation anaesthesia the portal vein (PV) will be isolated and cannulated. At the time of exsanquination the PV will be flushed with University of Wisconsin preservation solution to maintain a PV perfusion pressure of 12mmHg. Perfusion flow (mL/min/g of liver) will be measured continuously. Vascular resistance (mmHg min g of liver/mL) will be defined as the ratio of PV perfusion pressure to the flow rate. Vascular reactivity of the capillary bed to acute vasodilators (e.g. acetylcholine) will also be undertaken to determine if there is steric hindrance to maximum dilatation to this process by fat. This will manifest as a lesser fall in vascular resistance.

Analysis of mitochondrial function

Mitochondrial respiration flux will be determined using proven methods of high resolution respirometry oxygraphs (OROBOROS® Oxygraph 2K) with a substrate inhibitor protocol that allows rapid analysis of respiratory chain function and integrity in tissue homogenates obtained from liver obtained at the time of euthanasia (Jullig et al. 2008). We will be measuring Complex I function, outer mitochondrial membrane integrity, complex II function, inner mitochondrial membrane stability, electron transport flux (ETS flux) and Cytochrome c oxidase flux (Complex IV). The Oxygraph system has additional features which allow the incorporation of in-house-built fluorospectrometers that permit the detection of free radical production, reduction/oxidation state, adenosine triphosphate (ATP) production and calcium uptake. We will measure these additional parameters simultaneously with respiration to provide a more global perspective of mitochondrial function. Antioxidant status, as it pertains to mitochondrial function, will be determined using thiobarbiturate reactive substances (TBARS) as an index of lipid peroxidation and oxidative stress in tissue samples by measurement of reduced glutathione. No other laboratory has such capacity to routinely measure multiple parameters simultaneously.

B) Analysis of human liver tissue

We have obtained ethics approval for the collection of liver samples from organ donors and patients undergoing liver resection (NTY/09/12/117). It is estimated that we will obtain liver tissue from 150 patients over the next three years. In the case of resected liver, a portion not required for clinical analysis will be obtained for this project whereas in the case of liver transplantation, a liver biopsy will be obtained from the donor liver at the time of procurement. Part of the tissue will be immediately stored in preservation buffer or formaldehyde and the rest will be frozen for later biochemical analysis.

Assessment of steatosis

1. *Histology:* See *Establishment of experimental model of NAFLD.*
   This is the current gold-standard by which steatosis is assessed in clinical practice and will be performed as part of the patients normal clinical care and read by a histopathologist.

2. *Near Infra-red Reflectance Spectroscopy (NIRS):* As per *Establishment of experimental model of NAFLD.*

3. *Biochemical:* As per *Establishment of experimental model of NAFLD.*

Analysis of mitochondrial function

Mitochondrial respiration flux will be determined as described in *Establishment of experimental model of NAFLD* above using a high resolution respirometry oxygraphs (OROBOROS® Oxygraph 2K).

Determination of vascular resistance

Changes in vascular resistance will be measured indirectly through describing the anatomical changes that occur in the hepatic architecture with varying degrees of steatosis.

1. Electron microscopy:

The intracellular relationship of organelles will be characterised using the electron microscope housed at the School of Biological Sciences.

2. Three-dimensional confocal laser scanning microscopy

Confocal laser microscopy will be performed using a Zeiss LSM410 laser scanning confocal microscope on formalin fixed tissue according to the method described by Chen-Izu et al (2006). Stacks of confocal sections at 0.2-0.3um intervals will be acquired for offline three dimensional data processing.

Future Directions

This proposal is the first collaborative project of the newly formed Liver Research Group combining basic science and clinical research. Understanding the structural and functional changes that occur in NAFLD will be critical if we are going to improve upon our current method of patient selection. It is hoped that the results of this project will allow for the development of treatment options to ameliorate the physiological consequences of hepatic steatosis prior to surgery.

References

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4. RESEARCHER CAREER DEVELOPMENT

a) Researcher Roles and Commitments

i) Principal and Associate Investigators *(specify the role and commitment to this project of each named investigator)***:**

Name	**FTE for this project**	**Total FTE for other research projects**	**Role in Project** *(specify activities for which the investigator will carry particular responsibility)*
Dr Adam Bartlett	0.1	0.12	Principal Investigator, involved in research design, supervision, data analysis and dissemination

ii) Other Staff Members Involved *(name and specify the role and commitment to this project of other staff e.g. research assistants)***:**

Name	**ID Number**	**FTE**	**Role in Project** *(specify activities for which the staff member will carry particular responsibility)*
Dr Anthony Phillips	6212717	0.1	Associate Investigator, contributing to overall research design, student supervision, animal work and laboratory expertise and analysis
Dr Anthony Hickey	8821209	0.1	Associate Investigator, contributing to research design, student supervision, mitochondrial analysis supervision and laboratory expertise and analysis

iii) Postgraduate Students *(refer to the Guidelines and specify details of any research students who will be working on this project)***:**

Name	**ID Number**	**Qualification**	**Support (Type & Origin)**
Dr Michael Chu	1608958	MBChB	Lectureship, Department of Surgery, University of Auckland

b) Researcher Achievements, Aims and Objectives

i) Principal Investigator *(use no more than one page in total)***:** Dr Adam Bartlett

Achievements to date *(provide a summary and attach a copy of the UoA standard format CV (maximum of two pages); publication details may be extracted from RIMS and appended)***:**

I completed my medical training (BHB, MB ChB) at The University of Auckland in 1996 and took three years out from clinical practice to undertake full-time research looking at the role of the co-stimulatory pathways in liver transplant rejection and was awarded a PhD in 2004. I completed my vocational training in General Surgery in 2005, and obtained post-fellowship training in abdominal transplantation in 2007-8. During my clinical training I remained actively involved in research and recently was appointed as a Senior Lecturer at the Department of Surgery.

Aims *(specify how the proposed project will advance the applicant's research career)***:**

This project represents the start of my research career at the University of Auckland, having been appointed as a Senior Lecturer in the Department of Surgery in March 2010. As a specialist liver transplant and hepatopancreaticobiliary (HPB) surgeon at Auckland City Hospital, this research is closely aligned with my clinical interests. Through close collaboration with Drs Anthony Phillips and Anthony Hickey, at the School of Biological Sciences we have set up the Liver Research Group. It is hoped that this project represents the foundation for other collaborative projects looking at clinical issues involving patients undergoing liver resection or transplantation. The current project forms the basis of a PhD for Dr Michael Chu. As the collaboration grows it is anticipated that the Liver Research Group will generate further research opportunities for postgraduate students in the coming years.

Objectives *(list specific output targets e.g. research publication, creative work; timing for achieving each target; and the external funding source(s) that will be targeted for future applications)*

Output Targets	Timeline
Several publications in peer reviewed journals, and presentations at national and international meetings	Over next 3-years
Submission of PhD thesis (Michael Chu)	Over next 3-years
External Funding Source(s) for Future Applications	**Timeline**
Maurice and Phyllis Paykel Trust	Decision pending May 2010
Health Research Council	Dec 2010

ii) Associate Investigator *(use no more than one page in total)*: **Dr Anthony Phillips**

Achievements to date *(provide a summary and attach a copy of the UoA standard format CV (maximum of two pages); publication details may be extracted from RIMS and appended)***:**

I have a background in surgery, basic research, biotechnology and share joint appointments as SBS and the Dept of Surgery.

Key research advances a) With Prof Cooper I undertook and managed the physiological studies of a novel copper chelator compound. Several key publications and patents resulted from this work as well as establishment of a Biotech Company (Protemix). b) I was directly involved with the isolation and characterization of a new pancreatic hormone (Preptin). c) More recently I have become co-director of the Pancreas Research Group (PRG) and along the way we have produced several novel fundamental surgical research findings that have made good journals related to lymphatic fluid and most recently the role of mitochondria in surgical disease states.

Dedicated research space: during the course of my research I worked very hard to establish a surgical/metabolic small animal integrated physiology laboratory. I have expanded this and equipment over the last few years to where it now services the requirements of over 30 students/post docs including the Surgery Department students under my supervision. I continue as its overall scientific research manager working at the moment to increase its staff and research capacity.

Grants and publications: There have been many smaller grant and publication successes but the most cherished is our first major HRC grant for a surgical research topic based on our work on surgical mitochondrial disease. We have a good publication record.

Supporting surgical research: With others (especially Prof Windsor and recently Dr Hickey) we have developed the most rapidly growing surgical research group in Australasia (3 yrs ago just 1x PhD in PRG & now 5xPhDs, 1x MSc, 2xpost docs, 1xTech). I have strong collaborations with Dr Hickey at SBS. My plan is to now work with Adam (PI) and Tony Hickey (AI) to develop together a new transplant research group in the UoA.

Aims *(specify how the proposed project will advance the applicant's research career)***:**

My personal goal is the continued development of a defined research group directed at supporting surgical basic research endeavors in the Department of Surgery. I share joint appointments to surgery and SBS that enable me to direct this type of specialized basic research group spanning the resources of both sites. I work closely with Prof Windsor, Dr Hickey and now Dr Bartlett (PI).

I plan to increase university FTEs by providing a premier research experience attractive for surgeons who want to do a PhD that involves laboratory work.

Through my collaboration with the PI (Dr Bartlett) I plan to increase my PBRF standing by expanding my research group endeavors to cover other aspects of surgery. The recently formed liver transplant group between myself and Dr Bartlett is a new initiative to broaden the base of the surgical research platform of the Dept.

Objectives *(list specific output targets e.g. research publication, creative work; timing for achieving each target; and the external funding source(s) that will be targeted for future applications)*

Output Targets	Timeline
Co-supervise the PhD thesis (Michael Chu)	Over next 3-years
Increase students in liver transplant group	
External Funding Source(s) for Future Applications	Timeline
Maurice and Phyllis Paykel Trust	Decision pending May 2010
Health Research Council	Dec 2010

iii) Associate Investigator *(use no more than one page in total)***: Dr Anthony Hickey**

Achievements to date *(provide a summary and attach a copy of the UoA standard format CV (maximum of two pages); publication details may be extracted from RIMS and appended)***:**

Dr Anthony Hickey was recently appointed to Senior lecturer, at the School of Biological Sciences. He currently holds two Marsdens (one as Principal Investigator and the other as Associate Investigator), a Health Research Council Grant (as Associate investigator held jointly with Professor John Windsor and Dr Anthony Phillips) and a FoRST grant (AI).
The Marsden and HRC grants are all investigating metabolism in pathological or stressed states.
Dr Hickey worked within Professor Garth Cooper's group as a Post Doctoral Fellow studying diabetes and has an established background in proteomics and mitochondriology. He is currently the only researcher in New Zealand conducting functional assays on mitochondrial respiration.
Dr Hickey has comparative physiology background and understanding of population genetics genomics. He has researched fish and invertebrate physiology in the context of thermal stress and more recently he has commenced research into warm hypoxia tolerance in sharks and ischemia tolerance in aestivating frogs. These studies are of direct relevance to conditions such as ischemia reperfusion and organ preservation, given that the sharks studied repeatedly endure in bouts of severe hypoxia lasting up to 10 hours at 30^{o}C, and the aestivating frogs survive metabolic depression for up to five years at 25-30^{o}C.
Dr Hickey's collaborative HRC funded work focuses on mitochondrial function in multiple organ failure using acute pancreatitis as a model, and this work aims to determine the role of mitochondria in organ failure and to test mitochondrial targeted therapies for acute pancreatitis. This work also involves the development of assays aimed to explore mitochondrial function in white blood cells, and this has been progressed to clinical evaluation in patients presenting with acute pancreatitis.

Aims *(specify how the proposed project will advance the applicant's research career)***:**

Success of this grant proposal will continue to fuel productive research into metabolism in extreme settings, such as invasive surgery and organ transplant. Importantly, it will also help develop momentum for this group led by Drs Bartlett and Phillips to establish a platform for Surgical Research scientists and aid the development of a high caliber research centre for surgeons. Dr Hickey has a keen interest in metabolism in extreme circumstances. Development of this group will bring together unique expertise and access to surgical expertise, knowledge and clinical samples and research conducted in this group will have direct relevance to surgery.

Objectives *(list specific output targets e.g. research publication, creative work; timing for achieving each target; and the external funding source(s) that will be targeted for future applications)*

Output Targets	Timeline
Peer Reviewed Publications	2011
External Funding Source(s) for Future Applications	Timeline
Health Research Council	2010
AMRF	2010

c) Details of Other Existing Grants/Contracts

i) Research grants *relevant to this proposal* previously awarded to Applicant(s)

Granting Agency	Purpose of Award *eg research assistant salary, lab costs, travel*	Amount	Term of Grant	
			Start date	End date
Lotteries Health Equipment	Oroboros mitochondrial Equipment	$75,000	2010	2010
Maurice Phyllis Paykel Trust	Oroboros mitochondrial Equipment	$25,000	2009	2010

ii) All other research grants awarded to Applicant(s) in last *five* years

Granting Agency	Purpose of Award *e.g. research assistant salary, lab costs, travel*	Amount	Term of Grant	
			Start date	End date
Royal Society of New Zealand Marsden Grant	Research project	$850,000	2010	2013
Health Research Council	Research project	$650,000	2010	2013
Foundation for Research Science and Technology	Research project	$250,000	2009	2010
Royal Society of New Zealand Marsden Grant	Research project	$300,000	2009	2012
Auckland Medical Research Foundation	Research project	$64,000	2009	2010
Staff Development Fund	Research project	$30,000	2009	2010
National Heart Foundation	Research project	$14,700	2009	2010
Health Research Council of New Zealand	Research project	$679,651	2009	2010
Maurice Wilkins Center	Research project	$17,000	2009	2010
Auckland Medical Research Fund	Research project	$84,700	2008	2010
Cross Faculty Research Initiatives Fund	Research project	$24,000	2008	2009
Maurice and Phyllis Paykel Trust	Equipment	$15,000	2008	2010
School of Biological Sciences PBRF fund	Research project	$3,000	2008	
Health Research Council of New Zealand	Research project	$4,500,000	2008	2011
School of Biological Sciences PBRF fund	Research project	$3,000	2008	
School of Biological Sciences PBRF fund	Research project	$3,000	2008	
Auckland Medical Research Foundation	Research project	$84,000	2008	2010
Auckland University Research Committee	Equipment	$15,000	2007	
Maurice & Phyllis Paykel Trust	Equipment	$12,000	2006	
Health Research Council of New Zealand	Research project	$3,402,018	2006	2009
Auckland University Research Committee	Research project	$16,000	2006	

Auckland Medical Research Foundation	Research project	$87,000	2006	
Maurice & Phyllis Paykel Trust	Research project	$16,000	2006	2008
Health Research Council of New Zealand	Research project	$2,988,691	2005	2008

iii) Have all reporting obligations been met for all research grants? If not, please state when these reports will be submitted.

Yes

5. RESOURCES REQUESTED

Note: **Refer to Faculty Guidelines for maximum per application**

a) Budget for Project *(additional rows may be entered as required)***:**

Budget Category	Item Description	Amount Requested
People costs *State position for each salary requested e.g. research assistant*		
	Total Salary	0.00
Working Expenses *e.g. Travel Costs, Consumables*	**Animal related costs**	
	Sprague-Dawley (70)	3,150.00
	Caging and diet	2,100.00
	Tissue collection	1,400.00
	Electronic identification tags	840.00
	UW buffer (2 litres)	1,200.00
	Histology	
	Sectioning	1,400.00
	Slides	560.00
	Histological staining	2,100.00
	NIRS	
	Processing & analysis	1,800.00
	Biochemical analysis	
	Processing & analysis	1,814.25
	Bioelectrical impedance	
	Set up and analysis	No cost for reagents
	Mitochondrial function	
	Reagents for measuring free radical production	2,628.05
	Oligomycin (5mg)	370.80
	Antimycin A (50mg)	133.90
	FCCP (10mg)	229.18
	ADP (1g)	149.35
	NADH (100mg)	125.15
	Lactobionate (400g)	1,849.88
	Confocal microscopy	
	Reagents/antibodies	2,875.00
	Signal enhancer	135.00
	Microscopy (50hrs)	2,500.00
	Electron microscopy (15 samples)	
	Processing	900.00
	TEM time (50 hours) – CM12	1,000.00
	Total Working Expenses	29,260.56
Equipment *(items costing more than $5,000)*		
	Total Equipment	0.00
	Overall Total	**29,260.56**

b) Justification of Budget *(State the importance of the requested budget items to this particular research project and to the applicant's overall research strategy)***:**

A total of 70 Sprague-Dawley rats, at a cost of $45 each, will need to be purchased to complete the proposed project. The cost of caging and feeding is estimated to be $30/animal and obtaining tissue for analysis under isoflurane anaesthesia is estimated at $20/animal. Electronic identification tags are priced at $12/animal. Tissue will be stored in University of Wisconsin solution, the standard buffer used for organ preservation in transplantation costs $600 per litre. Histology will be performed by a technician at the School of Biological Sciences at a cost of $20/animal for sectioning, $2/slide (4 slides per animal) and $30/animal for performing routine H and E staining. The cost of performing histology on the human samples is not included in this budget as it will be part of the patient's clinical care. NIRS will

be performed at University of Auckland, Department of Chemistry at a cost of $50/hr. Provisional analysis has shown that it takes 6 hours to analyze 50 samples and it is estimated that we will analyze 300 samples including both animal and human tissue. Biochemical analysis of hepatic steatosis will be performed by the research fellow. Cost of reagents to extract lipid from the parallel samples analyzed by histology, NIRS and bioimpedance, is estimated to be $1,814.25. Mitochondrial function will be analyzed on previously purchased oxygraphs. Cost of reagents and buffers to analyze the various steps in the respiratory chain and free radical production is estimated to be $5,486.31 to analyze 300 samples. Confocal microscopy will be performed at the Imaging unit, The University of Auckland at a cost of $50/hr with an estimated time of analysis of 2 samples/hr and purchase of 6 fluorescent antibodies at a cost of $2,875.00. The purchase of a signal enhancer improves signal-to-noise ratio allowing clearer visualization of cellular targets. Electron microscopy will be performed on 15 human liver samples at School of Biological Sciences at a total cost of $1,900 which includes processing samples and use of electron microscope.

Note: Please append current written quotations.

6. FACULTY SPECIFIC INFORMATION IF REQUIRED.

See Faculty guidelines for details

Please refer to the attached letter of support from the Head of the School of Medicine.

7. ADMINISTRATIVE DECLARATION

RESEARCH ETHICS & BIOLOGICAL SAFETY COMMITTEE APPROVAL (Animal Ethics Committee, Ministry of Health Regional or Multicentre Ethics Committee, UoA Human Participants Ethics Committee, UoA Biological Safety Committee etc):

	Animal Subjects	Human Participants	Biological Safety
Is approval required?	Yes	Yes	No
Has approval been sought?	Yes	Yes	No
Has approval been obtained?	Yes	Yes	No

(Attach a copy of approval letters)

☞ SIGNATURE(S) OF APPLICANT(S):

I have read the Guidelines for Applicants - Faculty Research Development Fund and confirm that this application has been completed in accordance with University and faculty policy as laid down therein. Should this application result in the awarding of a grant, I understand that:

1. The authorization of expenditure will be the responsibility of me and my department, and that any over-expenditure of the grant will be a charge against my department's budget.

2. I must submit a written report on the research project within three months of the end date of the grant, and failure to furnish this report will rule me ineligible to apply for funding in future rounds.

3. I agree to ensure that the research will have been approved, where necessary, by the appropriate institutional review committee and/or all other regulatory agencies before research is commenced.

Principal Researcher _____ Date _____

Associate Researcher _____ Date _____

Associate Researcher  _____ Date 25/03/2010 ___

☞ SIGNATURE OF HEAD OF DEPARTMENT/SCHOOL:

Should this application result in the awarding of funding, I agree that:

1. The research as proposed will support the development of the applicant's research career.

2. The department will host and support the work described in the proposal by making available the basic facilities and services for research that are normally found in a department for these purposes.

Head of Department/School _____ Date _____

Name *(please print)* _____

University of Auckland
Standard
ACADEMIC CV

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

NAME: **ADAM BARTLETT**
CURRENT POSITION: **SENIOR LECTURER**
DEPARTMENT: **SURGERY**
FACULTY: **MEDICAL AND HEALTH SCIENCE**

EDUCATIONAL QUALIFICATIONS:

2005 Fellowship of Royal Australasian College of Surgeons
2003 Doctor of Philosophy (Surgery), University of Auckland
1997 MB ChB Medicine, University of Auckland

CURRENT ACADEMIC APPOINTMENTS:

2009 - Present Senior Lecturer, Department of Surgery, UoA

CURRENT OTHER POSITIONS:

2009- Present Specialist liver transplant and hepatopancreaticobiliary (HPB) surgeon, ADHB

PREVIOUS APPOINTMENTS

2006-2009	Senior Surgical Fellow, King's College Hospital, London
2005-2006	NZ Liver Transplant Unit Fellow, Auckland Hospital, New Zealand
1998-2001	Lecturer in Surgery, University of Auckland, New Zealand
1998-2001	PhD Student, Department of Surgery, University of Auckland, New Zealand
1997, 2001-2005	various registrar and hospital house surgeon positions

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SIGNIFICANT DISTINCTIONS / AWARDS:

2003	Louis Barnett Research Prize, Royal Australasian College of Surgeons Annual Scientific Meeting of New Zealand Fellows, Wellington, New Zealand
2003	Young Investigator Award, Transplantation Society of Australia and New Zealand (TSANZ), 21st Annual Scientific Meeting, Canberra, Australia
2001	Young Investigator Award, Transplantation Society of Australia and New Zealand (TSANZ), 19th Annual scientific meeting, Canberra
2000	Tyco Young Investigators Award, Surgical Research Society of Australasia annual scientific meeting, Adelaide, South Australia, 10 – 11 August 2000.
1996	Sir Carrick Robertson Prize in Surgery, University of Auckland

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PROFESSIONAL SOCIETIES / SERVICE / OTHER ACTIVITIES:

2005 - Present Fellow of Royal Australasian College of Surgeons

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TEACHING:

- Student supervision: Currently supervising 1x PhD candidate
- Teaching – 4th to 6th year Medical students (Surgery, liver transplantation)

RESEARCH SPECIALTIES / CAREER: Surgery, Liver transplantation

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RESEARCH PUBLICATIONS:

Faraj W, **Bartlett A**, Vilca-Melendez H, Mukherji D, Dhawan A, Heaton N, Rela M. Auxiliary Liver Transplantation for acute liver failure in children. Accepted Annals of Surgery August 2009.

Bartlett A, Vara R, Mariott P, Dhawan A, Rela M, Heaton N. A single centre experience of donation after cardiac death (DCD) liver transplantation in paediatric recipients. Published in advance online: July 2009. Paediatric Transplantation, July 2009.

Dar F, Faraj W, Zaman MB, **Bartlett A**, Bomford A, O'Sullivan A, O'Grady J, Heneghan M, Rela M, Heaton N. Outcome of liver transplantation in hereditary hemochromatosis. Transplant International 2009; 22(7):717-24.

Faraj W, Dar F, Marangoni G, **Bartlett A**, Vilca-Melendez H, Hadzic D, Dhawan A, Mieli-Vergani G, Rela M, Heaton N. Liver transplantation for hepatoblastoma. Liver Transplantation 2008; 14(11):1614-19

Bartlett A and Heaton N. The evidence base for treatment of hepatocellular carcinoma between 2-8 cm. Accepted for publication May 2008 in Key Advances in Medical Management.

Bartlett A and Heaton N. Hepatocellular carcinoma: Defining the place of surgery in an era of organ shortage. World J Gastroenterol 2008; 14(28):4445-53.

Davila D, **Bartlett A**, Heaton N. Temporary porto-caval shunt in orthotopic liver transplantation: Need for a standardized approach? Liver Transplantation 2008; 14:1414-19.

Thomas H, Madanur M, **Bartlett A**, Marangoni G, Heaton N, Rela M. Pancreatic trauma: Twelve year experience from a tertiary centre in the United Kingdom. Pancreas 2009; 38(2):113-6.

Bartlett A and Rela M. Progress in surgical techniques in pediatric liver transplantation. Published in advance online: Jul 29 2009, Paediatric Liver Transplantation.

Bartlett A, Rela M, Heaton N. Reperfusion of the liver with blue blood. Is it still the royal perfusate? Am J Transplantation 2009; 7:1689-91

Fong E, **Bartlett A**, Alak S, Anderson I. Tensile strength of surgical sutures and knotting techniques. Aust NZ J Surg 2008; 78:164-66.

Bartlett A, McCall, Koea J, Holden A, Yeong M-L, Gurusinghe N, Gane, E. Hepatocellular carcinoma in a hepatitis B endemic area. World J Surg 2007; 31:1175-81

Bartlett A and Heaton N. Current challenges and controversies in liver transplantation. European Gastroenterology Review 2007 – Volume 3, Issue 1, December 2007. Touch Gastroenterology

Lo A, Oehley M, **Bartlett A**, Adams D, Blyth P, Al-Ali S. Anatomical variations of the common carotid artery bifurcation. Aust NZ J Surg 2006; 76:970-72.

Mathur S, **Bartlett A**, Gilkison W, Krishna G. Quality of Life Assessment of Patients with Inguinal Hernias. Aust NZ J Surg. 2006; 76: 491-3.

Sammour T, Poole G, **Bartlett A**, Blacklock H. Laparoscopic splenectomy at Middlemore Hospital, New Zealand: A safe procedure with heterogeneous indications. NZ Med J 2006; 119 (1230): 1-8.

Bartlett A, Deo S, Oosthuysen W, Krishna G. Oncocytic mucinous cystadenoma of the pancreas. Pathology. 2005; 36(3):286-8.

University of Auckland
Standard
ACADEMIC CV

THE UNIVERSITY OF AUCKLAND
NEW ZEALAND

NAME: **ANTHONY RONALD JOHN PHILLIPS**
CURRENT POSITION: **SENIOR LECTURER**
DEPARTMENT: **SCHOOL OF BIOLOGICAL SCIENCES**
FACULTY: **SCIENCE**

EDUCATIONAL QUALIFICATIONS:

2006 PhD Surgery/Biochemistry, University of Auckland
1993 Part I Royal Australasian College of Surgeons Examination
1991 MB ChB (with distinction) Medicine, University of Otago
1986 BSc Chemistry/Biochemistry, Victoria University Wellington

CURRENT ACADEMIC APPOINTMENTS:

2007 - present Senior Lecturer, School of Biological Sciences, UoA
2007 - present Senior Research Fellow Department of Surgery, UoA

CURRENT OTHER POSITIONS:

2004 - Present Organ Transplant Surgical Fellow, (Part time) Auckland Hospital, NZ.
2006 - Present Associate Investigator Maurice Wilkins Centre
2008 - Present Medical Director, CoDa Therapeutics, (Part time), Auckland, NZ
2008 - Present Co-Director Pancreas Research Group, Dept of Surgery, UoA

PREVIOUS APPOINTMENTS

2003-2007	Group Leader, Physiology Research Group, Protemix Corp, Auckland
2003-2007	PhD student and Honorary Research Fellow, School of Biological Sciences, University of Auckland
1997-2003	Liver Transplant assistant (Part time), Auckland Hospital, NZ.
1992 1997	various registrar and hospital house surgeon positions

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SIGNIFICANT DISTINCTIONS / AWARDS:

2008	Spark Entrepreneurial Business competition (first runner-up prize with Nerian idea with Drs Loomes and Aitken)
2008	Best Oral presentation Award at International Hepato-Pancreatico-Biliary Association 8th World Congress, Mumbai, India,
2001	R.E.F. Mathews Prize in Cellular & Molecular Biology (co-author on winning paper)
1999	Louis Barnett Research Prize, Royal Australasian College of Surgeons
1998	Health Research Council Training Fellowship
1997	Royal Australasian College of Surgeon's Research Fellowship
1991	Medical Degree awarded with Distinction (Otago University)
1991	Boyd Memorial Prize for Excellence in Clinical Medicine (Otago University)
1988	University of Otago Academic Award (Otago University)
1986	Daniel O'Sullivan Scholarship (Otago University)
1986	New Zealand University Senior Scholar Award (Victoria University)

PROFESSIONAL SOCIETIES / SERVICE / OTHER ACTIVITIES:

2008 - present Reviewer for Australian and New Zealand Surgical Journal
2006 - present Animal Ethics Committee Deputy Chairperson
2003 - present Liver Transplant Fellow Auckland Hospital (part time).

TEACHING:

- Bioscience 358 – Nutritional Science Lecturer
- Student supervision: currently co-primary supervisor: 3 x PhD students, 1 x MSc student
- Previous co-primary supervision: 3 x PhD Students; 1 x BHB (hons); 2 x BTech
- Summer students: x 3
- Public Continuing education: "Origins of Life" lecture series for public (with Dr Paul Kilmartin)

RESEARCH SPECIALTIES / CAREER: Diabetes, Lymph, Pancreatitis, Metabolic syndrome, Surgery Liver transplantation

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RESEARCH PUBLICATIONS:

1. Loveday BPT[5], Rossaak JI3, Mittal A[5], **Phillips ARJ**, Windsor JA .High quantity and variable quality of guidelines for acute pancreatitis: A systematic review. Am J Gastro 2010 (IN PRESS)
2. Mittal A[5], Middleditch MJ, Ruggiero K, Loveday BPT[5], Delahunt B[3], Jullig MCC, Cooper GJS, Windsor JA, **Phillips ARJ**. Changes in the mesenteric lymph proteome induced by haemorrhagic shock. *Shock*, 2010 (IN PRESS)
3. Loveday BPT[5], Rossaak JI[3], Mittal A[5], **Phillips ARJ**, Windsor JA. Trends in minimally invasive intervention for necrotizing pancreatitis: a survey of Australian and New Zealand surgeons. *ANZ Journal of Surgery* 2010 (IN PRESS)
4. Mittal A[5], Goke FJM[4], Loveday BPT[5], Thompson NM, Delahunt B[3], Kilmartin PA, Cooper GJS, Macdonald JR, Hickey AJR, Windsor JA, **Phillips ARJ**. The redox status of experimental haemorrhage shock as measured by cyclic voltammetry. *Shock* 2010 (IN PRESS)
5. Lu, J. Gong D[5], Choong S, Xu YH, Chan Y-K, Chen X,. Fitzpatrick S, Glyn-Jones S, Zhang S. Nakamura T, Ruggiero K, Obolonkin V, Poppitt S. D, **Phillips ARJ**. Cooper GJS. Copper(II)-selective chelation improves function and antioxidant defences in cardiovascular tissues of rats as a model of diabetes: comparisons between triethylenetetramine and three less copper-selective transition-metal-targeted treatments *Diabetologia* 2010 (IN PRESS)
6. Petrov MS[5], Loverday BPT[5], Pylypchuk R, McIlroy K, **Phillips ARJ**, Windsor JA. Systematic review and meta-analysis of enteral nutrition formulations in acute pancreatitis *British Journal of Surgery 2009;*96(11):1243-1252
7. Gong D, Chen XN, Middleditch MJ, Huang L, Amarsingh GV, Reddy S, Lu J, Zhang S, Ruggiero K, **Phillips ARJ**, Cooper GJS. Quantitative proteomic profiling identifies new renal targets of copper(II)-selective chelation in the reversal of diabetic nephropathy in rats', *Proteomics* 2009;*9:*4309-4320
8. Cooper GJS, Gamble GD, Young AA, Occleshaw CJ, Dissanayake A, Cowan BR, Brunton DH, Baker J, **Phillips ARJ**, Frampton CM[3], Poppitt SD, Doughty R. A copper(II)-selective chelator ameliorates left-ventricular hypertrophy in type 2 diabetic patients: a randomised placebo-controlled study. *Diabetologia* 2009;*52(4):*715-722
9. Aitken JF, Loomes KM, Scott DW[5], Reddy SG[4], **Phillips ARJ,** Virijevic G, Fernando C, Zhang S, Broadhurst R, L'huillier PJ[3], Cooper GJS. Tetracycline treatment retards the onset and slows the progression of diabetes in human amylin transgenic mice. Diabetes, 2009 59:161-171
10. Hickey AJR, Chai CC[5], Choong SY, Costa S, Skea GL[5], **Phillips ARJ**, Cooper GJS. Impaired ATP turnover and ADP supply depresses cardiac mitochondria respiration and elevates superoxide in falling spontaneously hypertensive rats. *American Journal of Physiology: Cell Physiology* 2009;*297:*766-774
11. Hickey AJR, Bradley JW, Middleditch MJ, Buchanan CM[1], **Phillips ARJ,** Cooper GJS. Proteomic analysis of immunopurified granules from a model pancreatic islet B-cell system: snapshot of an endocrine secretory granule. *Journal of Proteome Research* 2009;*8(1):*178-186
12. Mittal A[5], **Phillips ARJ**, Middleditch MJ, Ruggiero K, Loveday BPT[5], Windsor JA. The proteome of mesenteric lymph during acute pancreatitis and implications for treatment. *Journal of Pancreas* 2009;*10(2):*130-142
13. Sammour T[5], Mittal A[5], Loveday BPT[5], Kahokehr A[5], **Phillips ARJ**, Windsor JA, Hill AG. Systematic review of oxidative stress associated with pneumoperitoneum. *British Journal of Surgery* 2009;*96:*836-850
14. Dare A[1], **Phillips ARJ**, Hickey AJR, Mittal A, Loveday BPT[5], Thompson NM, Windsor JA. A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. *Free Radical Biology and Medicine* 2009;*47(11):*1517-1525
15. Mittal A[5], Middleditch M, Ruggiero K, Buchanan CM, Jullig MCC, Loveday BPT[5], Cooper GJS, Windsor JA, **Phillips ARJ**. The proteome of rodent mesenteric lymph. *AJP - Gastrointestinal and Liver Physiology* 2008;*295:*895-903
16. Flint RS[5], **Phillips ARJ**, Power SE[1], Dunbar R, Brown CE, Delahunt B[3], Cooper GJS, Winsor JA. Acute pancreatitis severity is exacerbated by intestinal ischemia-reperfusion conditioned mesenteric lymph. *Surgery* 2008;*143(3):*404-413
17. Zhang L[5], Cannell MB, **Phillips ARJ**, Cooper GJS, Ward ML. Altered calcium homeostasis does not explain the contractile deficit of diabetic cardiomyopathy. *Diabetes* 2008;*57(8):*2158-2166
18. Gong D, Lu J, Chen X[1], Reddy SG[1], Crossman DJ[1], Glyn-Jones S[5], Choong YS, Kennedy J, Barry B, Zhang S, Chan YK, Ruggiero K, **Phillips ARJ**, Cooper GJS. A copper(II)-selective chelator ameliorates diabetes-evoked renal fibrosis and albuminuria, and suppresses pathogenic TGF-beta activation in the kidneys of rats used as a model of diabetes. *Diabetologia* 2008;*51(9):*1741-1751
19. Cooper GJS, Barnett MPG[5], **Phillips ARJ**, Harris P[3]. Impaired insulin secretion in perfused pancreases isolated from offspring of protein malnourished rats. *Journal of Pancreas* 2008;*9(4):*477-488

20. Mittal A[5], Flint R[5], Famous M, Delahunt B, Kilmartin PA, Cooper GJS, Windsor JA, **Phillips ARJ**. Redox status of acute pancreatitis as measured by cyclic voltammetry: initial rodent studies to assess disease severity. *Critical Care Medicine* 2008;*36:*866-872

21. Danaher RN[5], Loomes KM, Leonard BL[1], Whiting L, Hay DL, Xu LY, Kraegen EW[3], **Phillips ARJ**, Cooper GJS. Evidence that ±-calcitonin gene-related peptide is a neurohormone that controls systemic lipid availability and utilisation. *Endocrinology* 2008;*149 (1):*154-160

22. Loveday BPT[5], Mittal A[5], **Phillips ARJ**, Windsor JA. Minimally Invasive Management of Pancreatic Abscess, Pseudocyst, and Necrosis: A Systematic Review of Current Guidelines. *World Journal of Surgery* 2008;*32:*2383-2394

23. Barnett MPG[5], **Phillips ARJ,** Harris P[3], Cooper GJS. Impaired insulin secretion in perfused pancreases isolated from offspring of protein malnourished rats. *Journal of Pancreas* 2008;*9(4):*447-488

24. Lloyd CM[5], **Phillips ARJ,** Cooper GJS, Dunbar PR. Three colour fluorescence immunohistochemistry reveals the diversity of cells staining for macrophage markers in murine spleen and liver. *Journal of Immunological Methods* 2008;*334:*70-81

25. Jullig MCC, Hickey AJR, Chai CC[1], Skea GL[1], Middleditch MJ, Costa SADF[1], Choong YS, **Phillips ARJ**, Cooper GJS. Is the failing heart out of fuel or a worn engine running rich? A study of mitochondria in old spontaneously hypertensive rats. *Proteomics* 2008;*8(12):*2556-2572

26. Mittal A[5], **Phillips ARJ**, Loveday BPT[5], Windsor JA. An emerging role for xanthine oxidase inhibition in major intra-abdominal surgical operations - A review of two decades of animal studies. *World Journal of Surgery* 2007;*32(2):*288-295

27. Jullig MCC, Cheng X[1], Hickey AJR, Crossman DJ, Xu A[1], Wang Y[1], Greenwood DR, Choong YS, Schonberger SJ[1], Middleditch MJ, **Phillips ARJ**, Cooper GJS. Reversal of diabetes-evoked changes in mitochondrial protein expression of cardiac left ventricle by treatment with copper(II)-selective chelator. *Proteomics Clinical Applications* 2007;*1(4):*387-399

28. Fanous MY[1], **Phillips ARJ**, Windsor JA. Mesenteric lymph: the bridge to future management of critical illness. *Journal of Pancreas* 2007;*8(4):*374-399

29. Glyn-Jones S[5], Song S, Black M, **Phillips ARJ,** Choong YS, Cooper GJS. Transcriptomic Analysis of the Cardiac Left Ventricle in a Rodent Model of Diabetic Cardiomyopathy-Molecular Snapshot of a Severe Myocardial Disease. *Physiological Genomics* 2007;*28:*284-293

30. Wichmann KA, Boyd PDW, Söhnel T, Allen GR[1], **Phillips ARJ,** Cooper GJ. Characterisation of Dicarboxylic salts of H4TETA4+ Useful for the Treatment of Copper-related Pathologies. *Crystal Growth and Design* 2007;*7*:1844-1850

31. Flint RS[5], **Phillips ARJ**, Farrant G[1], Mckay D[1], Buchanan CM[1], Cooper GJS, Windsor JA. Probing the urinary proteome of severe acute pancreatitis. *Journal of the International Hepato Pancreato Bilary Association Oxford* 2007;*9(6):*447-455

32. Gong D, Lu J, Chen X[1], Choong YS, Zhang S, Chan YK, Glyn-Jones S[5], Gamble GD, **Phillips ARJ**, Cooper GJS. Molecular changes evoked by triethylenetetramine treatment in the extracellular matrix of the heart and aorta in diabetic rats. *Molecular Pharmacology* 2006;*70(6):*2045-2051

33. Leonard BL[1], Watson RN[5], Loomes KM, **Phillips ARJ**, Cooper GJS. Insulin resistance in the Zucker Diabetic Fatty rat: a metabolic characterisation of obese and lean phenotypes', *Acta Diabetologia* 2005;*42(4):*162-170

34. Poppitt SD, Keogh G[5], Mulvey T, **Phillips ARJ**, Mcardle BH[1], Macgibbon AKH, Cooper GJS. Effect of moderate changes in dietary fatty acid profile on postprandial lipaemia, haemostatic and related CVD risk factors in healthy men', *European Journal of Clinical Nutrition* 2004;*58*:819-827

35. Cooper GJS, **Phillips,ARJ**, Choong YS, Leonard BL[1], Crossman DJ, [1] Brunton DH[1], Saafi EL[5], Dissanayake A, Cowan BR, Young AA, Occleshaw C.J, Chan Y, Leahy FE[1], Keogh G[1], Gamble GD, Allen GR[1], Pope A, Boyd PDW, Poppitt SD, Borg T, Doughty RN, Baker JR. Regeneration of the heart in diabetes mellitus by selective copper chelation', *Diabetes* 2004;*53:*2501-2508

36. Koea JB, **Phillips ARJ**, Rodgers MS, Windsor JA, McCall, JL. Gallbladder cancer, extra-hepatic bile duct cancer and ampullary carcinoma in New Zealand: demographics, pathology and survival. *ANZ Journal of Surgery* 2002;*72*:857-861

37. **Phillips, A.R.J.,** Lawes, C.M., Cooper, G.J.S., Windsor, J.A. 'Ethnic disparity of pancreatic cancer in New Zealand', *International Journal of Gastrointestinal Surgery*, *231*, p137-145, 2002

38. **Phillips ARJ,** Farrant G[5], Abu-Zidan F[1], Cooper GJS, Windsor JA. A method using laser Doppler flowmetry to study intestinal and pancreatic perfusion during an acute intestinal ischaemic injury in rats with pancreatitis. *European Surgical Research* 2001;*33:*361-369

39. Buchanan CM[1], **Phillips ARJ,** Cooper GJS. Preptin derived from proinsulin-like growth factor II (proIGF-II) is secreted from pancreatic islet beta-cells and enhances insulin secretion', *Biochemical Journal* 2001;*360*:431-439

40. **Phillips ARJ,** Abu-Zidan F[1], Farrant G[5], Zwi JL, Cooper GJS, Windsor JA. Plasma amylin concentration is related to the severity of intestinal ischemic injury in rats. *Surgery* 2001;1*29*:730-735

41. **Phillips ARJ**, Abu-Zidan F[1], Bonham MJD[5], Cooper GJS, Windsor JA. Amylin and severe acute pancreatitis. *Pancreas* 2000;*20*:105-106

42. **Phillips ARJ**, Abu-Zidan F[1], Bonham MJD[5], Simovic MO[1], Cooper GJS, Windsor JA. Intestinal ischaemia-reperfusion increases plasma amylin concentration in rats. *European Surgical Research* 1999;*31*:457-464

43. **Phillips ARJ**, Fleischl J[3]. Videoscopic Subfascial Incompetent Perforator Vein Ablation. *British Journal of Surgery* 1996;*83*:1552-1552

NAME: Dr Anthony J. R. Hickey
CURRENT POSITION: Lecturer (L7)
DEPARTMENT: School of Biological Sciences
FACULTY: Science

EDUCATIONAL QUALIFICATIONS:

2004 PhD in Biological Sciences, University of Auckland, New Zealand

1999 MSc (1st Class Honours) in Biological Sciences, University of Auckland

1997 BSc in Biological Sciences, University of Auckland

PREVIOUS APPOINTMENTS:

2009	University of Auckland Senior Lecturer
2007-2009	University of Auckland Lecturer/Research Fellow Proteomics and Biomedicine
2005-2006	Project Leader Protemix Ltd
2004	Research Scientist Protemix Ltd
2003	Research Fellow Invasive UoA
2003	Larval fish recruitment to reefs (collaboration with Victoria University),
2000	Lipid metabolism of New Zealand lobster larvae (*Jasus erdwardsii*) (NIWA)

SIGNIFICANT DISTINCTIONS / AWARDS:

2009 University of Auckland Early Career Excellence Award.

RESEARCH SPECIALTIES / CAREER:

Research Publications:

Total number of refereed publications: 20

HILTON, Z., CLEMENTS, K.D. AND **HICKEY AJR** (in Press) Temperature sensitivity of cardiac mitochondria in intertidal and subtidal triplefin fishes. Journal of Comparative Physiology and Biochemistry

MITTAL, A., **HICKEY, A. J. R.,** CHAI, C. C., LOVEDAY, B. P. T., THOMPSON, N., DARE, A., DELAHUNT, B., COOPER, G. J. S., WINDSOR, J. A., AND PHILLIPS, A. (In Press) Early organ specific mitochondrial dysfunction of jejunum and lung found in rats with experimental acute pancreatitis. *Journal of Surgical Research*.

MITTAL, A., GOKE, F.J.M., LOVEDAY, B.P.T., THOMPSON, N.M., DELAHUNT, B.,KILMARTIN, P.A., COOPER, G.J.S., MACDONALD, J.R., **HICKEY, A.J.R.,** WINDSOR,J.A., PHILLIPS, A.R.J. (2009)The redox status of experimental haemorrhage shock as measured by cyclic voltammetry', Shock, Sep 25., pEpub-

DARE, A., PHILLIPS, A.R.J., **HICKEY, A.J.R.,** MITTAL, A., LOVEDAY, B.P.T., THOMPSON, N.M., WINDSOR, J.A. (2009) 'A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome', Free Radical Biology and Medicine, 47, (11), p1517-1525,

HICKEY, A.J.R., CHAI, C.C., CHOONG, S.Y., COSTA, S.D.F., SKEA, G.L., PHILLIPS, A.R.J., COOPER, G.J.S. (in press). Impaired ATP turnover and ADP supply depresses Cardiac mitochondria respiration and elevates superoxide in non-failing spontaneously hypertensive rat hearts. American Journal of Physiology - Cell Physiology.

MITTAL A, GÖKE F, FLINT R, LOVEDAY B, THOMPSON N, DELAHUNT B, KILMARTIN PA, COOPER GJS, MACDONALD J, **HICKEY AJR,** WINDSOR JA, AND PHILLIPS ARJ (in press). The redox status of experimental haemorrhagic shock as measured by cyclic voltammetry. *Shock*.

HICKEY A.J.R., LAVERY S., HANNAN D.A., BAKER C.S., CLEMENTS K.D. (2009) New Zealand triplefin fishes (Family Tripterygiidae): contrasting population structure and mtDNA diversity within a marine species flock, Molecular Ecology. 18(4) 680 - 696

HICKEY A.J.R., BRADLEY J.W.I., MIDDLEDITCH M.J., GREENWOOD D.G., BUCHANAN C.M., COOPER G.J.S. (2009). Proteins associated with immunopurified granules from a model pancreatic islet b-cell system: proteomic snapshot of an endocrine secretory granule, Journal of. Proteome Research.8 (1):178-186

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JULLIG, M., **HICKEY, A.J.R.***, CHAI, C.C., SKEA, G.L., MIDDLEDITCH, M.J., Y.S., C., COSTA, S., PHILIPS, A.J.C., COOPER, G.J.S. (2008) Is the failing heart out of fuel or a worn engine running rich? A study of mitochondria in old spontaneously hypertensive rats. *Proteomics*; 8(12):2556-2776

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* Denotes shared first authorship

Research Grants / Funding

2010 Royal Society of New Zealand Marsden Grant ($850,000, AI)
2010 Lotteries Health Equipment ($75,000, PI)
2009 Maurice Phyllis Paykel Trust ($25,000, PI)
2009 Health Research Council (HRC, $650,000, AI)
2009 Foundation for Research Science and Technology (FoRST, $250,000, AI)
2009 Royal Society of New Zealand Marsden Grant ($300,000, PI)
2008 Maurice and Phyllis Paykel Trust Project Grant-in-aid ($28,000, PI)
2008 Royal Society of New Zealand ISAT ($7,500, PI)
2008 Maurice and Phyllis Paykel Trust Project Travel Grant ($2,500)
2007 Auckland Medical Research Foundation Travel Grant ($3,000)
2007 Auckland Medical Research Foundation Grant ($110,000, AI)
2007 Maurice and Phyllis Paykel Trust Project Grant-in-aid ($22,000, PI)
2005 Auckland University Vice Chancellors Contestable Research Fund ($7,000)
2002 Auckland University Research Fund ($3,000)
2001 Auckland University Research Fund ($3,000)

CHECKLIST

IMPORTANT: This checklist is not intended to replace a thorough reading of the guidelines and application form. The responsibility ultimately rests with the applicant to ensure that his or her application is sound and complete.

Please check:

Details of Applicant(s) completed in full?		☐
Have you attached:	Budget details?	☐
	Current quotations?	
	equipment	☐
	travel ☐	
	accommodation	☐
	Ethics approval (*if applicable)*?	☐
	CVs for each named applicant?	☐
	Supervisor Comment *(if a student)*	☐
	Report on previous/current FRDF grant	☐
Application signed by:	Applicant(s)?	☐
	Head of Department?	☐
Coversheet signed by:	Principal Applicant?	☐
	Head of Department?	☐

Please attach this page for submission with the application. The application is to be paper-clipped (not stapled) and single-sided.