

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Alicia Wright –Concordia University

POSTER #30

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
3	Student	Clinical	Respiratory Health

ABSTRACT:

Effects of Aerobic Exercise on Asthma Morbidity: a Pilot Project

Introduction: Asthma is a growing problem in Canada. In 2005 more than 2.2 million Canadians had this respiratory disease. Currently, more than half of all asthmatics are poorly controlled, meaning that their asthma symptoms severely disrupt their daily activities. Some studies in children have shown that aerobic exercise, such as swimming, running, and playing basketball, have helped reduce their symptoms. However, we do not know if this is the same in adults. The aim of this study was to look at the effect of an 8-week aerobic exercise program on asthma control in adults. We will present preliminary data for this on-going project. We expect that after 8 weeks of aerobic exercise asthma patients will have improved asthma control.

Method: Before starting the exercise program a total of 4 adults from the HSCM asthma outpatient clinic underwent a brief sociodemographic and medical history interview. Patients also completed the Asthma Control Questionnaire (ACQ) and the Asthma Control Test (ACT), which they also completed at the end of the exercise program. The exercise program consisted of supervised 1-hour exercise sessions, 3 times per week. The exercise included cycling, running, and using an elliptical trainer.

Results: Statistical analysis of the data found that there was a significant change in both ACT ($F=106.8$, $p=.002$) and ACQ ($F=81.0$, $p=.003$) following the exercise program. There was an average change of ACQ of -1.29 and an average ACT change of 6.75, both of which show that asthma control improved. Based on previous data, the change in the ACQ was 'clinically' significant, meaning that the improvement in asthma control reduced the amount of disruption in patients' daily activities.

Conclusion: Although this is preliminary data, the results suggest that 8 weeks of aerobic exercise can cause a significant improvement in asthma control in adult patients with asthma.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Amanda Marcella –University of Toronto

POSTER #31

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
4		Health Services/Systems	Stroke

ABSTRACT:

Transitioning Home: Family caregivers' experiences with stroke survivors' weekend passes

BACKGROUND/PURPOSE: With up to 80% of stroke survivors returning home to continue their recovery in the care of a family caregiver, one of the most important steps in stroke rehabilitation becomes community reintegration. However, the transition from hospital to home is described as one of the most stressful and burdensome transitions in the care continuum. Both patients and caregivers express feelings of significant anxiety due to the lack of preparedness for such a transition. To make it possible for patients to return home after a stroke without risking the physical or psychological health of the caregiver, or the rehabilitation process of the stroke survivor, it is essential to support caregivers in transition. The weekend home pass portion of in-patient rehabilitation was developed to ease stroke survivors' transition from inpatient rehabilitation, to the home environment. Such passes afford stroke survivors and their family caregivers the opportunity to practice living in the home environment prior to being fully discharged. Weekend home passes have been recommended since the early 1970s, yet no formal research has been conducted on their use, or the experiences of those involved. As a result, weekend home visits lack evidence to support their practice.

OBJECTIVE: To examine family caregivers' perceptions of, and experiences with, weekend home passes during inpatient rehabilitation, and to determine the educational and support needs of family caregivers in order to optimize the potential benefits weekend home passes have to offer.

METHODS: We are conducting a qualitative study using a Husserlian phenomenological perspective. Family caregivers of stroke survivors will participate in two interviews: 1) within one-week following the first scheduled home pass, and 2) two-weeks following discharge home. **RESULTS:** After interviewing a total of 15 family caregivers, our preliminary results have revealed caregivers experience mixed reactions to weekend passes, ranging from positive to extremely negative views of the process.

IMPACT: Results from this study will directly inform the weekend home pass program offered at Toronto Rehab, as well as other health care organizations offering a weekend pass program. Results will provide program administrators and clinicians with feedback regarding the experiences of family caregivers, informing them of the supports and education required to facilitate a successful weekend pass.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Andrea Mitchell –Lawson Health Research Institute

POSTER #32

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
7	Student / MSc candidate	Biomedical	Cardiovascular Health

ABSTRACT:

Cardiac Cell Therapy: Optimizing Injection Strategies to Maximize Transplanted Cell Survival

With the increasing prevalence of heart disease, therapies to improve cardiac function following a heart attack (infarction) have great potential. We have been exploring ways to follow transplanted cells by labeling them with a radioactive material, ¹¹¹Indium, and imaging them with Single Positron Emission Computed Tomography (SPECT) [1]. SPECT gives a three dimensional image of the body showing the location of the radioactivity attached to the transplanted cells. The purpose of this study is to determine the optimal time for cell transplantation after infarction by comparing the cell clearance rate immediately following infarction, one week and four weeks following infarction. It is hypothesized that cell clearance will be slowest when cells are transplanted four weeks after infarction. Blood was harvested from five adult canines to culture endothelial progenitor cells. Canines underwent an open thoracotomy and infarction was induced by blocking the left anterior descending coronary artery. Thirty million cells were labeled with a small amount of ¹¹¹Indium and transplanted into the border of the damaged region in the heart by either: injection into the outer muscle of the heart wall four hours after the onset of infarction (n=2), or injection into the inner muscle of the heart wall one week after infarction (n=3). All canines had a second injection of thirty million cells into the inner muscle of the heart wall, four weeks following infarction. Imaging by SPECT followed each injection on days 0,4,10 and 15. Imaging the radioactively labeled cells allowed us to calculate a half life of cell clearance. In the first injection, no significant difference was found in the cell clearance between the injections into the inner (41.4±0.8 hrs) and outer (44.5±5.6 hrs) wall of the heart (p=NS). The cell clearance was significantly slower (70.8±10.4 hrs) in the second injection (p=0.001). The two injection strategies were comparable in the rate of cell clearance at the first injection. As hypothesized, cell clearance was slower four weeks after infarction. This slower cell clearance likely reflects increased cell survival, due to a less hostile environment for the transplanted cells, as initial inflammation from the heart attack has subsided.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Annegret Ulke-Lemee –University of Calgary

POSTER #33

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
8	Student / PhD	Biomedical	Blood and Blood Vessels

ABSTRACT:

The tropomyosin-binding properties of the smooth muscle protein SMTNL1 may be important in high blood pressure.

Purpose: Blood vessels can contract to increase blood pressure. This is due to the contraction of smooth muscle cells lining these vessels. Smooth muscle contraction is very dynamic, but not very well understood and incorrect contraction can lead to high blood pressure and its associated problems. We discovered a protein called SMTNL1 that increases contraction of blood vessels. SMTNL1 can bind to tropomyosin, a protein needed for muscle contraction. We studied how SMTNL1 binds to tropomyosin. Additionally, SMTNL1 is labeled (phosphorylated) following signals that cause muscle relaxation in blood vessels. We studied the link of this phosphorylation to SMTNL1's function.

Methods: We combined SMTNL1 and tropomyosin to see if they could bind to each other. Further, we cut SMTNL1 into shorter pieces and studied their ability to bind to tropomyosin. The same experiment was done after phosphorylating SMTNL1. Furthermore, we used biophysical methods to visualize the structure of SMTNL1 to compare it to related proteins and study which part of it is important for its function.

Results: SMTNL1 can bind to tropomyosin and this binding is dependent on a specific region of the protein. This specific region of SMTNL1 is structured like related proteins, but it has very different functions. Further, when SMTNL1 is phosphorylated, it binds less to tropomyosin.

Conclusion and impact: We found that the region of SMTNL1 that binds to tropomyosin behaves differently than originally predicted according to its structure, which resembles other proteins. Thus, we found a new function for this region. In the future, we will measure the effects of SMTNL1 (and its shorter pieces) on smooth muscle contraction by measuring contraction directly. Using our information of its structure, we can modify SMTNL1's function specifically. Tropomyosin is necessary for muscle contraction. Its properties may be changed through the binding of SMTNL1. Signals that lead to muscle relaxation cause phosphorylation of SMTNL1 which in turn changes its binding to tropomyosin. This whole process may lead to changes in the blood vessels. Thus, the protein we discovered may play a key role in the development of high blood pressure.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Brooke-Hogarth –University of Calgary

POSTER #34

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
12	Masters Student	Clinical	Cardiovascular Health

ABSTRACT:

Characterization of the cardiotoxic effects of chemotherapies by contrast-enhanced cardiac magnetic resonance imaging (CMR)

Purpose: To identify Cardiac MRI (CMR) findings in patients with a clinically suspected cardiotoxic reaction (toxic side effects on the heart) after treatment with potentially cardiotoxic chemotherapies.

Methods: Thirty-four chemotherapy patients (mean age 51yrs, range 20yrs-77yrs) with clinical indications for cardiac imaging underwent a comprehensive CMR Tissue Characterization (TC) protocol consisting of T1 early enhancement ratio (T1 EE ratio: measuring cardiac inflammation), T2 ratio (measuring fluid accumulation in the heart), late Gadolinium enhancement (LGE: measuring cardiac scarring) and cardiac pumping function (known as the ejection fraction or EF). Fifteen of the 34 patients had breast cancer, including 7 with tumors positive for the HER-2 gene, which when expressed at high levels, can cause cancer.

Results: All patients tolerated the scans well and had good image quality. Mean EF was mildly reduced at 45% (normal range 55-75%), mean left ventricle size was normal at 98 ml/m (normal range 55-103 ml/m), mean T1 EE ratio was elevated at 4.20 +/- 2.31 (normal range < 4.0), mean T2 ratio normal was 1.57 +/- 0.48 (normal range < 2.0), and abnormal LGE was present in 44% of patients.

Conclusion: Image findings in our pilot study suggest that early cardiotoxicity can be safely assessed using a comprehensive TC protocol. The pumping function of the heart in these patients was below the normal range. This parameter may be used as an early marker for cardiovascular disease. The abnormal LGE, which represents scarring in the heart, was present in a large percent of the subject group. This scarring is likely a result of irreversible damage to the heart (fibrosis). This CMR protocol may be used in the future to identify patients at risk for development of cardiotoxicity and for the clinical follow-up of those patients.

Impact: Prediction and assessment of cardiotoxic reactions is difficult using standard imaging methods, which can only detect severe and late forms of cardiotoxicity. CMR may be the ideal, non-invasive test to predict and to follow-up cardiotoxicity. This hypothesis will be tested in an ongoing trial in our centre with patients with first-time diagnosis of HER-2 positive breast cancer undergoing chemotherapy with the drug Herceptin.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Christopher d'Estherre –Robarts Research Institute

POSTER #35

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
17		Biomedical	Stroke

ABSTRACT:

Predicting Cerebral Hemorrhage with Computed Tomography Perfusion

Purpose Intracerebral hemorrhage is a dreaded complication of stroke, as it is associated with a worse outcome in surviving patients. We investigated whether measurement of blood-brain-barrier (BBB) permeability surface product (PS), derived from a CT perfusion (CTP) study, has the potential to identify stroke patients at risk of hemorrhagic transformation (HT).

Method and Materials All stroke patients had CTP and CTA scans upon admission at our institution, then a non-contrast CT (NCCT) scan 1-15 days later to confirm intracerebral hemorrhage. The CTP scan was modified to allow measurement of BBB PS product. 45-50 ml of contrast was injected via an antecubital vein, and at 5-6 s into the injection, five mm thick slices (4 or 8 tissue slices per patient) were acquired using 80 kVp and 190 mA every 1-2 s for 45 s, then at 15 s intervals for an additional 90 s using either a GE Lightspeed or VCT scanner. The BBB PS map, which measures the leakage rate of contrast from the blood into the interstitial space of the brain, was calculated using GE CT Perfusion 4 software. Over a 6 month period, there were 10 patients with intracerebral hemorrhage confirmed by late NCCT. A region of interest was drawn using the NCCT images to encompass the hemorrhagic area in the PS map for each patient; a homologous region in the contralateral hemisphere was also obtained. Mean BBB PS was determined for the hemorrhagic and homologous contralateral regions. Data from 5 patients without HT were also analyzed.

Results A paired t-test revealed a significant increase ($p < 0.01$) in the mean BBB PS of the hemorrhagic regions compared to the homologous contralateral regions at admission in patients with confirmed intracerebral hemorrhage. The mean (95% confidence interval) BBB PS for the hemorrhagic and homologous contralateral regions were 0.2648 (0.0766 - 0.4530) and 0.0458 (-0.0444 - 0.1368) (ml/min/100g) respectively. Mean PS of ischemic regions without HT was different from that with HT ($p < 0.05$).

Conclusion Early BBB leakage detected by CTP is a potential predictor for HT in acute ischemic stroke.

Clinical Relevance/Application CTP derived BBB PS is a potential marker for identifying stroke patients at risk of HT prior to the use of thrombolytic therapy.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Claudia Blais –Institut national de santé public du Québec

POSTER #36

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
19	New Investigator	Social, cultural, environmental and Population Health	Cardiovascular Health

ABSTRACT:

Is the decline in coronary heart diseases mortality in Quebec attributed to effective secondary prevention?

Purpose: Person dying suddenly outside of a hospital from coronary heart diseases (mostly myocardial infarction) can be named sudden cardiac death, which is a major public health problem. On top of that, if the person did not know about his/her cardiac condition, this represents unexpected sudden cardiac death and can be related to a lack of primary prevention. Since the mortality from coronary heart diseases in Quebec has substantially decreased since 1982, we investigated if these trends were different between people dying in-hospital compared to persons dying out-of-hospital (sudden cardiac death).

Methods: We used provincial linked hospital and mortality databases to first determine patients who died at the hospital (group 1: in-hospital mortality) or outside (group 2: out-of-hospital mortality). We further divided each group into patients who were hospitalized or not for any cardiovascular causes (using the 9th international classification of diseases codes: 390-459) in the year before their coronary death. We compared the two extremes group: group 1a (in-hospital mortality + cardiac hospit) with group 2b (out-of-hospital mortality - cardiac hospit). This last group is the unexpected sudden cardiac death. Poisson regression models were conducted to assess temporal trend rates adjusted for age, sex and socioeconomic status to see which group has displayed the biggest decline in mortality.

Results: Among all coronary deaths (84 337), 86% were in group 1 (in-hospital mortality). This group is further divided, 47% were in the group 1a (in-hospital mortality + cardiac hospit) while 84% of the patient in the group 2 (out-of-hospital mortality) were unexpected sudden cardiac death (group 2b). This means that among the small proportion of patients dying outside of hospital, the majority of them did not know about their cardiac condition. The yearly aged and sex-adjusted decline in coronary heart diseases mortality in group 1a was significantly greater (27%) compared to patients in group 2b (18%). This decline in both groups was greater for men (28%) compared to women (19%).

Conclusion and impact: In Quebec, unexpected sudden cardiac death is decreasing less compared to patients that known about their cardiac condition which means that have been hospitalized for any cardiovascular diseases in the year before their death. Moreover, the decline was always better for men compared to women. This might be explained by effective secondary prevention.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Dominique Yelle –Ottawa Health Research Institute

POSTER #37

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
24	Student	Biomedical	Cardiovascular Health

ABSTRACT:

Investigating the role of endothelial cell loss in pulmonary arterial hypertension using a BMPR2 mutant mouse model

Pulmonary arterial hypertension (PAH) is a rare, fatal disease characterized by increased pressure in the vessels carrying blood from the heart to the lungs (pulmonary arteries). This disease is caused by excessive narrowing and blockage of small pulmonary arteries (arterioles). Death (apoptosis) of the cells lining the inside of arterioles (endothelial cells, ECs) is believed to initiate PAH by leading to degeneration of these fragile vessels, causing increased pressure in those that remain. As PAH worsens, progressive thickening of the muscular walls and narrowing of arteries also contributes to increasing pressure. Unfortunately, there is currently no cure for this disease. The recent identification of the 'PAH gene' has advanced our understanding of the mechanism leading to the development of PAH. Loss-of-function mutations in the bone morphogenetic protein receptor 2 (BMPR2) have been identified in 70% of patients with a family history of PAH. However, exactly how this leads to PAH is still unclear. The purpose of our study is to elucidate the early events leading to the initiation and progression of the disease. We hypothesize that loss-of-function mutations in BMPR2 lead to PAH by making ECs more susceptible to apoptosis. To test this, we generated a mouse model expressing a mutation in BMPR2 originally identified in individuals with a family history of PAH. Our objectives are 1) to characterize this mouse model and determine whether it mimics the course of human PAH and 2) to examine the role of EC apoptosis and loss of arterioles in the initiation of PAH. Pressure is measured by inserting a catheter in the heart, and lung tissue is collected and stained to observe vessel structure and search for evidence of EC apoptosis in small arteries and arterioles. Fluorescent microbeads are also injected in the lung vessels to visualize where blood circulates and identify blockages. We found that BMPR2 mutant mice exhibit increased lung arterial pressures, associated with thickening of the muscle wall and decreased blood flow in these vessels. These preliminary results suggest that our model appears to reproduce human PAH and could be useful in elucidating the underlying mechanisms, ultimately enabling us to develop new potential treatments for this disease.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Drew Kuraitis –University of Ottawa Heart Institute

POSTER #38

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
25		Biomedical	Blood and Blood Vessels

ABSTRACT:

Controlled Release of Stromal Cell Derived Factor-1 to Enhance Progenitor Cell Recruitment

Purpose: Stromal cell derived factor-1 (SDF-1) is a signaling molecule important for mobilization, trafficking, and homing of stem/progenitor cells by interacting through the receptor CXCR4. Circulating progenitor cells (CPCs) are commonly positive for markers CXCR4, flk & c-kit. Following ischemic injury, SDF-1 is briefly over-expressed in the myocardium. This study aims to develop a biomaterial system for the controlled release of SDF-1 to ultimately enhance the mobilization and homing of CPCs to target sites, such as ischemic muscle.

Methods: SDF-1 containing alginate microspheres were generated using a coaxial air stream apparatus. CPCs were isolated from peripheral blood and cultured for 4 days. Migration was observed by placing 4-day adherent cells in a Boyden chamber with SDF-1 microspheres in the lower compartment for 24 hours. SDF-1 microsphere biomatrices consisting of type I collagen and chondroitin sulfate-C were created and crosslinked with EDC/NHS. Suspensions of microspheres, embedded within matrix or without, were prepared and suspension aliquots were taken for SDF-1 analysis using ELISA. For evaluation in vivo, hindlimb ischemia was induced by femoral artery ligation in mice with bone marrow reconstituted with GFP+ cells, and animals received an intramuscular injection of SDF-1 microsphere-containing matrix or controls. On days 0, 1, 4, 7, and 14, circulating mononuclear cells were isolated and analyzed by flow cytometry for the cell surface markers c-kit, flk, and CXCR4.

Results: Microspheres containing total SDF-1 concentrations of 10 and 25 ng/mL induced greater CPC migration (45.3+/-2.8% and 70.2+/-9.6%) than controls of 50ng/mL VEGF or PBS (28.4+/-6.0% and 24.2+/-5.3%; p<0.05). Microspheres embedded in biomatrix released all their SDF-1 by 10.5 days; and without the matrix, SDF-1 was depleted by 6 days in suspension. Animals receiving SDF-1 treatment had greater flk expression at all stages post-op (by >47%; p<0.05), and greater CXCR4 expression at the early stages post-op (>54%; p<0.05).

Conclusions: A dose-response relationship exists between CPCs and SDF-1. SDF-1 release from alginate microspheres can be prolonged by biomatrix incorporation, and intramuscular treatment can increase circulating CPC numbers. This system of controlled SDF-1 release is a promising strategy to enhance the homing of stem/progenitor cells to target tissue.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Emilie Boudreau - University of Ottawa Heart Institute

POSTER #39

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
26		Biomedical	Cardiovascular Health

ABSTRACT:

Mutant lamin A/C disrupts sumo1 localization and sumoylation

A-type lamins A and C are major components of the nuclear lamina and are involved in many cellular functions including transcriptional regulation and providing structural support by anchoring and spacing nuclear pore complexes. Lamin A/C is encoded by the alternatively spliced LMNA gene. Mutations in LMNA are implicated in over ten tissue-specific disease phenotypes, collectively termed laminopathies, which include neuropathies, myopathies, lipodystrophies and premature aging. Studies of lamin A/C expression have shown that certain mutations result in the abnormal aggregation and distribution of lamins, and affect the localization of other nuclear proteins. We hypothesized that disease-associated LMNA mutations affect the localization of sumo1 and subsequently perturb the regulation of the sumoylation process. Sumoylation is the covalent post-translational attachment of the Small Ubiquitin-like Modifier 1 (sumo1) protein to target lysine residues on the substrate protein. Expression of mutant lamin A/C in C2C12 murine myoblasts has a mutation-dependent effect on the mislocalization of sumo1 to be trapped in, or localize with the mutant lamin A/C. Western blot analysis reveals an increase in the steady-state level of sumoylation, as well as non-conjugated sumo1. This indicates deficient de-sumoylation or degradation of the sumo protein which in turn implies a misregulation of the sumo1 process in these mutant systems. As sumoylation is a transient and reversible process, misregulation of sumoylation may have many downstream consequences that could account for a portion of the diversity of phenotypes associated with laminopathies.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Emilie Chan-Thim –Concordia University

POSTER #40

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
27	Student	Clinical	Respiratory Health

ABSTRACT:

Pulmonary Rehabilitation as an Aid to Smoking Cessation: A Preliminary Study

Purpose: Smoking cessation is the most successful intervention to slow down the progression of airflow obstruction in individuals with chronic obstructive pulmonary disease (COPD). Unfortunately, very few smokers achieve and maintain cessation even in a population with a smoking-related condition. Pulmonary rehabilitation (PR) has become widely accepted as a vital component in the management of COPD. The inclusion of smokers in PR is often debated. However, the role of PR as a potential aid to smoking cessation has been much less considered. The main objective of this preliminary retrospective study was to compare smoking cessation rates between COPD patients who completed a structured PR program and those who received usual care.

Methods: Data were obtained from a computerized database provided by the pulmonary function testing lab at Hôpital du Sacré-Coeur de Montréal. Inclusion criteria were: 1) evidence of COPD according to accepted standards (FEV1/FVC < 0.7); 2) two or more pulmonary function test results with carboxyhemoglobin (HbCO) measurements; and 3) an initial HbCO >= 2% suggesting an active smoking status. The sample was divided into two subgroups: those who completed a PR program (PR group) and those who did not (non-PR group). The evolution of smoking status was compared between the two subgroups.

Results: A total of 413 patients were included in the present study; 27 patients were in the PR group and 386 in the non-PR group. The average length of time for follow-up visits was 31 ± 24 months. At the last available follow-up, 81.5% of subjects from the PR group and 46.1% of subjects from the non-PR group had an HbCO value < 2%, suggesting smoking cessation. In addition, 37% of subjects in the PR group, compared to 8% in the non-PR group, had 2 or more consecutive final HbCO measurements <= 2%, suggesting sustained quitting.

Conclusions and Impact: Results from this preliminary study suggest that PR may play a role as an aid to smoking cessation in COPD patients. These results highlight the need for future well-designed intervention studies addressing this question.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Farshid S. Garmaroudi –University of British Columbia

POSTER #41

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
29	Student	Biomedical	Cardiovascular Health

ABSTRACT:

Global Properties of Signaling Networks in Virus-infected Cardiomyocytes

Purpose: Viruses must extensively manipulate host cell machinery to support viral replication. Meanwhile, infected cells mobilize an array of defence mechanisms to battle the invader. We and others have already shown the role of distinct signaling pathways (local properties) to support coxsackievirus B3 (CVB3) replication. We propose that cell signaling pathways are not autonomous units, but conjoined networks (global properties). Despite the key roles already shown for signaling networks in determining cellular function during infectious encounters, their global structure remains elusive.

Methods: To study the global properties of signaling networks, we generated a 3-dimensional data set: 1) signaling and viral components: nine signaling molecules and two virus replication indicators; 2) timepoints: sham-infected cells [0 h post-infection (p.i.)], virus-receptor interaction [0.17 h p.i.], internalization [1 h p.i.], viral RNA synthesis [8 h p.i.], viral protein synthesis [16 h pi] and virion progeny release [24 h pi], and 3) 23 different experimental conditions. We utilized graphical Gaussian modeling (GGM), Bayesian model averaging (BMA), and clustering to verify crosstalk between and among signaling pathways.

Results: We show that: 1) p38 MAPK (p38 mitogen-activated protein kinase) provokes crosstalk with other pathways at 8 h p.i.; 2) I κ B α (inhibitor of NF κ B alpha protein) plays a hub signaling role in assembling this network structure, and 3) CVB3 protein synthesis (VP1 expression) is negatively correlated with phosphorylated ATF-2 (activating transcription factor).

Conclusion: Constructing a systems-level and data-driven model allows us to generate new knowledge of how CVB3 evolved multiple strategies to regulate intracellular signaling networks in order to sustain its replication. Understanding the mechanisms that explain functional properties of signaling networks throughout infection will provide breakthroughs in the exploring of the master regulators that can be used as therapeutic targets for pharmacological interventions in the treatment of viral myocarditis and its major sequela, dilated cardiomyopathy.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Gaspard Montandon –University of Toronto

POSTER #42

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
31	Student	Biomedical	Respiratory Health

ABSTRACT:

Mechanisms underlying the generation of breathing in the adult rat in vivo

Objectives: Breathing is a fundamental function regulating gas exchange in the lung to support metabolism. In mammals, gas exchange requires continuous respiratory rhythmic activity to alternately absorb oxygen and reject carbon dioxide. In vitro studies using neonatal rat brains have discovered the existence of a brainstem structure called the pre-Botzinger Complex (pBC) responsible for the generation of respiratory rhythm, but these seminal studies have been limited to in vitro neonatal models where the complex behaviours present in the intact organism (e.g. sleep and wakefulness) are not present. Here, we determined the role of the pBC in regulating rhythmic respiratory activity in intact adult rats in vivo.

Methods: We developed a new animal model to locally manipulate neurotransmission of pBC neurons in the adult rat in vivo by perfusing drugs with miniature probes. We measured simultaneously breathing via recording of respiratory muscles such as the diaphragm muscle (which generates inspiration) and the genioglossus muscle (important for upper airway patency and obstruction), and sleep via electroencephalography and neck muscle activity.

Results: In anaesthetized adult rats, perfusion of the mu-opioid receptor agonist DAMGO, a well-known inhibitory neuromodulator, into the pBC decreased significantly breathing rate (by 54%, n=6) and decreased genioglossus muscle activity (by 71%), an effect reversed by a blocker of mu-opioid receptors. Similarly, somatostatin, an other neuronal inhibitor, decreased significantly breathing rate (by 48%, n=5), also reversed by a blocker for somatostatin 2 receptor. Post-mortem histology and immunohistochemistry of brainstem sections showed that the probes were properly implanted into the pBC anatomically defined by expressions of neurokinin 1 and somatostatin receptors. Similar approach was used in freely-behaving rats and showed that DAMGO decreased breathing rate during sleep (by ~30%, n=3) whereas no effect was observed during wakefulness.

Conclusion: Revealing the sites and understanding the mechanisms involved in the generation of breathing in mammals is of fundamental importance. Here, we demonstrated that pBC neurons are critically involved in the generation of breathing in naturally-sleeping rats. The fact that inhibition of these neurons leads to slowing of breathing rate as well as diminution of upper airway muscle tone is important to understand the underlying causes of sleep-disordered breathing such as central and obstructive sleep apneas.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Harjot K. Saini-Chohan –University of Manitoba

POSTER #43

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
34	Student	Biomedical	Cardiovascular Health

ABSTRACT:

Modification of the gene expression of myocardial cardiolipin biosynthesis and remodeling enzymes in a model of persistent pulmonary hypertension of the newborn

Purpose: Persistent pulmonary hypertension of the newborn (PPHN) is characterized by high pulmonary vascular resistance due to the failure of normal pulmonary vascular relaxation at or shortly after birth. Right-to-left shunting of blood across the ductus arteriosus and foramen ovale in PPHN causes the disturbances in cardiac performance by compromising the systemic and pulmonary circulation with right heart after-loading. Cardiolipin (CL), a mitochondrial polyglycerophospholipid, plays an important role in maintaining the heart function via modulating the activities of various enzymes involved in oxidative phosphorylation; however, the regulation of CL in PPHN is not known.

Methods: In the present study, new born piglets (<24 hrs old) were exposed to normoxic (21% oxygen) or hypoxic (10% oxygen) environment for three days. By using real-time PCR, the gene expression of different CL biosynthetic enzymes [cytidinediphosphate1,2-diacyl-sn-glycerol synthetase (CDS), phosphatidylglycerolphosphate synthase (PGPS) and cardiolipin synthase (CLS)] as well as CL remodeling enzymes [acyl-Coenzyme A: lysocardiolipin acyltransferase-1 (ALCAT1), an endoplasmic reticulum form of monolysocardiolipin acyltransferase, and tafazzin] were investigated both in the left ventricle (LV) and the right ventricle (RV) of control and PPHN piglets.

Results: Cardiac CDS-2 mRNA was increased, whereas CDS-1 mRNA was decreased in the RV of 3 day old hypoxic piglets. On the other hand, both CDS-1 and CDS-2 mRNA were increased in the LV of the hypoxic piglets. PGPS mRNA was decreased in the LV and RV of hypoxic piglets. An increase in the RV CLS mRNA was observed in the hypoxic piglets. CL remodeling enzymes ALCAT1 and tafazzin showed variable changes in hypoxic piglets. Tafazzin mRNA was decreased in the RV of hypoxic piglets without any significant change in the LV. In contrast, mRNA of ALCAT1 remained unaltered in both the LV and RV of the hypoxic piglets.

Conclusions and Impact: These results suggest that CL biosynthetic and remodeling enzymes are discordantly altered in the hearts of PPHN animals and defects in the expression of these enzymes may play an important role in cardiac dysfunction during PPHN.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

James Thackeray –University of Ottawa Heart Institute

POSTER #44

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
36	Student	Biomedical	Cardiovascular Health

ABSTRACT:

Dysfunctional Sympathetic Nervous System Signaling in a Rat Model of Type II Diabetes

Purpose: Patients with diabetes, insulin resistance, and high blood glucose have increased risk of heart disease. Part of this risk may relate to elevation of norepinephrine, which damages the ability of the heart to adapt to stressful situations, during which norepinephrine can signal the heart to increase contraction, rate, and energy consumption. This study assesses the effect of chronically high blood glucose on cardiac norepinephrine signaling in the progression of disease in an animal model that mimics human type II diabetes.

Methods: Sprague Dawley rats were rendered diabetic after 14 day high fat feeding by intraperitoneal injection of 45 mg/kg streptozotocin (STZ, n=89) or vehicle (n=48). Treated rats were stratified to hyperglycaemic (>11 mM n=45) or euglycaemic (<11 mM, n=44) subgroups. Radiolabeled compounds are used to quantify three distinct levels of norepinephrine signaling, where the presence of radioactivity is proportional to protein levels. Specifically, [11C]meta-hydroxyephedrine (HED) measures innervation; [3H]CGP12177 (CGP) measures beta-adrenoceptors on the heart muscle cells; and (R)-[11C]rolipram (ROL) measures phosphodiesterase-4 inside the cell as an indirect index of the downstream cAMP signaling. Response of ROL to acute elevations of norepinephrine was assessed by pre-treatment with the norepinephrine reuptake inhibitor desipramine. Cardiac health was evaluated using echocardiography and histopathology.

Results: High fat-fed rats treated with STZ or vehicle display insulin resistance. There was no change in tracer retention at 2 weeks post-STZ. At 8 weeks post-STZ, left ventricle retention of HED was reduced in hyperglycaemic rats (0.42 ± 0.05 percent ID/g x body weight) compared to euglycaemic (0.53 ± 0.08 , $p < 0.05$) and control rats (0.56 ± 0.11 , $p < 0.05$). Similarly, CGP binding to beta-AR in hyperglycaemic rats (3.73 ± 0.96) was significantly decreased compared to controls (5.60 ± 1.60 , $p < 0.05$). ROL specific binding to PDE4 was similar in all groups, despite the apparent reduction in beta-AR in hyperglycaemics. All groups showed normal response to acute elevation of NE by desipramine. Systolic echocardiography parameters were unchanged and histopathology was normal.

Conclusion: These data indicate reduced SNS innervation and beta-AR with normal systolic left ventricular function and preserved response of PDE4 to NE stimulation, suggesting compensatory maintenance of cAMP signaling in diabetes. Application of cardiac neurohormonal PET shows potential for monitoring progression of cardiac disease in type II diabetes.

YOUNG INV Poster Presentation Day 2

Jason Haley –University of Western Ontario
POSTER #45

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
37	Student	Biomedical	Cardiovascular Health

ABSTRACT:

Bioactive Scaffolds for Tissue Engineering Applications

Tissue engineering is recognized as a promising alternative to conventional reconstructive materials and donor tissues, which are in short supply. The effective use of nanofibers as tissue scaffolds relies on the localized delivery of signaling proteins, capable of providing biochemical cues for tissue regeneration. Inert scaffolds are deficient of these biological signals, demonstrating the need for a novel delivery of cell-signaling molecules within the scaffold environment. This study aims at fabricating bioactive nanofibrous scaffolds via incorporating bioactive proteins for controlled protein release through a coaxial electrospinning process. Coaxial electrospinning is capable of producing core-shell structured nanofibers by electrically charging a suspended droplet of two concentric biopolymer solutions. It was used to fabricate poly(ϵ -caprolactone) (PCL) fibers within which bovine serum albumin (BSA) was encapsulated. PCL imparts structural integrity while providing a cytocompatible surface for cells. BSA was chosen as a model protein due to its biochemical stability as well as its molecular weight of 66 kDa, similar to that of many growth factors. The intrinsic properties of naturally derived growth factors make them an attractive selection as they are known to improve communication at the cell-scaffold interface. Scaffolds were characterized using scanning electron microscopy and laser scanning confocal microscopy to verify uniformity and continuity of the core-shell structure. Protein loading efficiency and release kinetics of BSA was evaluated using a Bradford protein assay. Measurements of the fiber diameters indicate that fiber size has a narrow distribution with an average fiber diameter of 251 ± 34 nm. The protein release experiments show a slight burst release during the first day, followed by a relatively steady release profile, sustained over a seven-day period. The release rate can be mediated by varying the feed rates of the core and shell electrospinning solutions. Finally, cell culture studies were performed on scaffolds containing either EGF, TGF- β 1; or PDGF at 10ng/ml. Scaffolds were seeded with porcine radial artery cells and cell viability was evaluated using an MTT assay. The present results provide a basis for further optimization of processing parameters to control the core-shell nanostructure and protein encapsulation. The ability to incorporate potent growth factors during fiber formation offers extensive benefits for controlled delivery during tissue-specific formation.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Jennifer Shea –Memorial University of Newfoundland

POSTER #46

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
39	Student	Biomedical	Cardiovascular Health

ABSTRACT:

The prevalence of metabolic syndrome in obese subjects defined by BMI and dual energy x-ray absorptiometry

Purpose: Although BMI is the most widely used measure of obesity, dual energy x-ray absorptiometry (DXA) is considered a superior method for estimating adiposity. As BMI and DXA likely represent different physiological entities, their relationship with obesity-related disease may differ. We tested this hypothesis by analyzing differences in the prevalence of metabolic syndrome (MetS), a disease associated with obesity, among adiposity groups classified using BMI versus DXA criteria.

Methods: A total of 1692 adult volunteers from Newfoundland and Labrador (NL) participated in the study. BMI and body fat percentage (%BF; measured using DXA) were measured for all subjects following a 12 hour fasting period. Subjects were categorized as normal weight (NW), overweight (OW), or obese (OB) based on BMI and %BF criteria. Subjects were classified as metabolically abnormal according to standard ATP-III metabolic syndrome criteria or as metabolically healthy if they did not fulfill these criteria.

Results: In our cohort, 292 subjects had MetS. We found low agreement in the prevalence of MetS between BMI and %BF adiposity groupings (Kappa 0.4177). When subjects were classified using BMI criteria, 2.42% (95% CI, 1.50 - 3.84) of NW and 17.32% (14.59 - 20.44) of OW individuals were metabolically abnormal. However, when subjects were classified using %BF criteria, 5.25% (3.66 - 7.48) of NW and 14.53% (11.77 - 17.81) of OW individuals were metabolically abnormal. The difference was more pronounced among OB individuals as 44.09% (39.13 - 49.17) were metabolically abnormal using BMI-defined obesity while only 29.55% (26.14 - 33.22) were considered metabolically abnormal according to %BF criteria. There was also a significant difference in the prevalence of the metabolically healthy phenotype among OB subjects classified using BMI (55.91%) compared to %BF (70.05%) criteria.

Conclusions: The agreement between the prevalence of MetS among subjects defined by BMI compared to %BF was low. BMI is more accurate at defining MetS among obese subjects. Caution should be taken when making inferences about the metabolic health of an obese population depending on the method used to measure adiposity.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Jessie Lavoie –Ottawa Health Research Institute

POSTER #47

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
40	Student	Biomedical	Cardiovascular Health

ABSTRACT:

Proteomic signature of impaired progenitor cell regenerative function in a mouse model of metabolic syndrome

Blockage of the coronary artery supplying blood to the heart results in heart muscle injury, or myocardial infarction (MI) due to lack of oxygen. Clinical trials suggest that administration of precursor cells capable of stimulating blood vessel formation (endothelial progenitor cells, EPCs), represents a promising new treatment to enhance cardiac repair after MI. However, EPCs isolated from the same individual (autologous cell therapy) are affected by the same risk factors which initially cause heart disease, notably type 2 diabetes, reducing their ability to repair the heart. Therefore, we urgently need strategies to enhance the efficacy of autologous cell therapy to improve cardiac repair post-MI.

We have previously shown reduced expression and release of specific growth factors and inflammatory mediators in EPCs from patients with heart disease and its attendant risk factors. However, other changes in the cellular protein pathways likely contribute to the loss of regenerative activity of patient-derived EPCs. Therefore, we want to identify the 'proteomic signature' (large-scale study of proteins) of EPCs from a type 2 diabetes mouse model to identify the major differences in proteins involved in cell signaling processes.

EPCs were isolated from the bone marrow of normal or diabetic mice (Leprdb/db) and a proteomic analysis was performed using isotope-coded affinity tag to analyze changes in protein expression. A total of 89 proteins showed significant differential expression with up-regulation of proteins involved in glucose metabolism, and a significant down-regulation of proteins involved in the production of new proteins (translation) and the breakdown of complex molecules into simpler ones (catabolism). We also found a significant change in expression of proteins involved in cell movement (migration) and assembly of the cellular skeleton.

Collectively, these preliminary results validate the diabetic model and suggest that reduced regenerative activity of EPCs from this model is related to perturbations in processes that control cell movement and migration, which are necessary steps for the engraftment of progenitor cells. Once detailed studies confirm the expression and activity of component proteins, it may be possible to devise novel strategies using gene transfer to overcome these defects and restore the activity of autologous EPCs for the treatment of MI patients.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Jill Cameron –University of Toronto

POSTER #48

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
41	New Investigator	Health Services/Systems	Stroke

ABSTRACT:

Examining the Changing Needs of Stoke Family Caregivers

Background and Purpose: Family caregivers provide essential support to individuals who have experienced a stroke. As stroke survivors move across the care continuum, their interaction with health care professionals (HCPs), treatment focus, and functional abilities change. As a result, the needs of family caregivers will also change. We developed the Timing it Right (TIR) framework to facilitate a systematic approach to examining family caregivers' needs and, ultimately, creating and evaluating interventions aimed at supporting family caregivers across care environments. The objective of this research was to delineate family caregivers' support needs over time using the TIR framework as a conceptual guide.

Methods: A qualitative study using in-depth interviews with stroke family caregivers and health care professionals (HCPs) identified family caregivers' changing support needs over time and their experiences with having their support needs met. Family caregivers (n=24) were recruited from in- and out-patient rehabilitation, a rural community care organization, and a community-based aphasia program. HCPs (n=14) were recruited from an acute care hospital, a rehabilitation facility, and community-based health care organizations. Interviews examined family caregivers' needs for informational, instrumental, and emotional support. Interviews lasted approximately 60 minutes, were audio taped, transcribed, and analyzed using Framework Analysis.

Results: We identified four key themes: 1) The type and intensity of support needed by family caregivers change across the care continuum; 2) There is variability within and across care environments in the receipt of support by family caregivers; 3) Patient versus family-centered approaches to care affect families receipt of support; and 4) The availability of health care professionals affect the support provided to family caregivers. We also discuss how the themes change over time.

Conclusions: Stroke family caregivers' needs across the care continuum are complex. Needs change over time and are influenced aspects of service delivery including a lack of standardized approach to providing families with support, whether the focus of care is the patient or family, and the availability of health care professionals. **Significance:** This information can inform programs and modify health care delivery to better meet the needs of family caregivers.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Jonathon Beland –Montreal Heart Institute

POSTER #49

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
42	Student / M.Sc trainee	Biomedical	Cardiovascular Health

ABSTRACT:

Exploration of plasma biomarkers in coronary artery disease combining complementary proteomic methodologies. Preliminary results in a French-Canadian case-control cohort.

Purpose. Coronary artery disease (CAD) is the leading cause of mortality in Canada. Plasma biomarkers are precious tools for diagnosis and risk stratification, and the identification of new candidates may substantially impact on public health and health economics. Due to its complexity, the human plasma proteome remains challenging to explore. Our study aims at combining complementary approaches to determine the plasma proteome signature of patients with different manifestations of CAD. The results of the pilot studies that optimized the key steps of our working plan are herewith presented.

Method. The total cohort included 1006 individuals, 500 controls with normal coronary angiography, 235 with stable angina and 271 with a previous Myocardial infarction (MI). All were enrolled at the Montreal Heart Institute with a longitudinal follow-up of 5 years. At this phase, two pools of plasma were constituted selecting the extreme populations of control subjects with no MI during the follow-up (n=18) and CAD patients with an MI during the follow-up (n=18). The plasmas were depleted of highly abundant proteins (IgY14TM column) and subsequently analyzed in triplicates by three proteomic methods: 1. Protein fractionation using a PF2D system (ProteomeLabT) followed by a liquid chromatography tandem mass spectrometry analysis (LC-MS/MS); 2. Protein fractionation by 1D-SDS-PAGE followed by LC-MS/MS; 3. Further depletion of moderately abundant proteins (SupermixTM column) followed by 1D-SDS-PAGE fractionation and LC-MS/MS with analyses of both flow through (3a) and retained fractions (3b) of the SuperMixT.

Results. 108, 125 and 91 proteins were identified using methods 2, 3a and 3b, respectively, with partial overlap (23, 44 and 3 proteins between 2 and 3a, 2 and 3b and 3a and 3b, respectively). A total of 12 proteins, were identified with statistically different (p<0.05) peptide amounts between the two plasma pools, with no overlap. Preliminary analyses of PF2D elution spectra identified multiple differential protein fraction profiles between the two pools.

Conclusion and impact. Combining various methodologies for the analysis of plasma proteome signatures maximize the detection of differentially expressed proteins in various clinical situations what may lead to the identification of more performing biomarkers.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Joseph Gordon –York University

POSTER #50

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
44		Biomedical	Cardiovascular Health

ABSTRACT:

PKA REGULATED ASSEMBLY OF A MEF2/HDAC4 REPRESSOR COMPLEX CONTROLS C-JUN EXPRESSION IN VASCULAR SMOOTH MUSCLE CELLS

PURPOSE: Vascular smooth muscle cells (VSMCs) are specialized for regulating blood flow to tissues; however, these cells also maintain the ability to increase their numbers in order to heal an injured vessel. This modulation of cell 'programming' also plays a critical role in development, and in most vascular diseases. Previous studies have shown that mice with a genetic mutation in the myocyte enhancer factor 2C (MEF2C) gene fail to form a proper vasculature and have decreased expression of smooth muscle proteins. Therefore, we hypothesized that MEF2 proteins would have a critical role regulating VSMC division and specialization. **METHODS:** To evaluate the signals that regulate VSMC division and specialization, we utilized a cell culture model, and induced VSMC division by arterial injury in an animal model that makes a blue indicator when MEF2 proteins are activated. **RESULTS:** Stimulation of cultured VSMCs with platelet-derived growth factor (PDGF), an agent known to induce cell division, resulted in an increased expression of the MEF2-target gene called c-Jun. This increased production of c-Jun was inhibited by pharmacological agents that block the protein kinase C delta (PKC δ), and calcium/calmodulin kinase (CaMK) pathways. Given that these signaling pathways have been shown to relieve the repressive effects of histone deacetylases (HDACs) on MEF2 proteins, we performed gain and loss of function experiments on HDAC4 to reveal its involvement in c-Jun regulation. Using animal models of vascular injury we observed an increased MEF2 activation, and increased production of c-Jun. Furthermore, we demonstrate that protein kinase A (PKA) inhibits c-Jun production by promoting the formation of a MEF2/HDAC4 repressor complex. We also demonstrate that c-Jun production is inhibited when VSMC specialize. Finally, we document a physical interaction between c-Jun and myocardin, and we demonstrate that c-Jun represses myocardin's ability to promote VSMC specialization. **CONCLUSION AND IMPACT:** These studies demonstrate that MEF2 and HDAC4 act to repress c-Jun production in specialized VSMCs. PKA enhances this repression, and PDGF inhibits this repression. Regulation of this molecular 'switch' may prove critical for toggling between the cellular programs that regulate cell division and specialization during vascular disease.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Junfeng Zhang –Laurentian University

POSTER #51

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
45	New Investigator	Biomedical	Blood and Blood Vessels

ABSTRACT:

How Blood Flows in Microvessels - A Computational Study

Red blood cells (RBCs) are the major component of blood, which constantly traveling through our bodies to deliver oxygen and remove waste. In addition, RBCs are also an important determinant on how blood flows in vessels due to their large numbers (~ 5 millions/ml) and particular mechanical properties (biconcave shape, easily deformable membrane, highly viscous interior cytoplasm, aggregation interaction among RBCs, etc). People have observed experimentally that such RBC properties can change dramatically in many pathologic situations, including heart diseases, hypertension, diabetes, cancers, and malaria. Such abnormal properties certainly influence blood flow behaviors in our bodies and therefore negatively affect the crucial functions of blood.

This study aims to investigate the relationship between the dynamic blood flow behaviors and the RBC properties, especially in microvessels. Valuable information obtained could provide us a better understanding of the complex hemodynamics in microcirculation. In this work, an immersed-boundary lattice Boltzmann model has been developed and computer simulations have been conducted to examine the flow behaviors with different RBC properties in various flow situations. Several hemodynamic and hemorheological characteristics observed in experiments have been well reproduced, such as the cell free layers, blunt velocity profiles, increased flow resistance, and the Fahraeus effect of blood flows in microvessels. Moreover, the simulated dynamics process of cell free layer development demonstrates how RBCs are migrating toward the vessel center and how plasma is displaced toward the vessel wall. Such information is helpful to understand the accumulation of small particles (e.g., platelets) near vessel walls in microcirculation. Currently a diverging bifurcation model is also being employed to study the effects of cell properties and suspending plasma viscosity on the RBC partitioning and plasma skimming. Representative simulation video clips will also be shown on computer during the poster session.

Our simulation results show that this numerical model provides helpful information in understanding the effects of various factors involved in microcirculation. This model is especially valuable in those situations where direct experimental measurements are not practicable. Potential applications include leukocyte/platelet transport, nanoparticles dynamics for drug and gene delivery, blood substitutes, mechanotransduction via glycocalyx layers, etc.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Ken Stark –University of Waterloo

POSTER #52

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
46	New Investigator	Social, Cultural, Environmental and Population Health	Cardiovascular Health

ABSTRACT:

Omega-3 Fatty Acid Profiling to Assess Cardiovascular Disease Risk

Eating omega-3 fatty acids found in fish, namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) can reduce the risk of death from a heart attack (1). The amount of EPA and DHA in a person's blood may indicate a person's risk for death from a heart attack (2, 3). The measurement of omega-3 fatty acids in blood however, requires multiple analytical steps, is time consuming and can be very costly. Progress towards a simple, cost effective technique to measure fatty acids includes rapid analysis by gas chromatography (4) and simplified chemical sample preparation (5). Presently, we examine a method of determining fatty acid concentrations from drops of blood that could be collected from a fingertip prick rather than from a vein with a needle and syringe. Ten mL of blood was collected from one adult male. A portion of blood was applied to four strips of chromatography paper to mimic a fingertip prick blood sampling. The blood on the paper was allowed to dry briefly and then a paper die (similar to a single whole punch) was used cut a paper circle with an area of 195 mm². This circle was weighed and the mass of the blood was determined. The blood soaked paper was then chemically processed with rapid techniques and the fatty acids were determined by gas chromatography. The fatty acid concentrations were also determined using traditional techniques that require greater volumes of blood and more time. Both methods resulted in similar levels of omega-3 fatty acids in the blood, but there were differences between each of the four analyses done with the new method. This is believed to be due to the blood drying on the paper and follow-up experiments are in progress. However, the results are good enough to determine if a person is eating low and high levels of EPA and DHA. A rapid and cost effective fatty acid analytical method that can be used for routine "omega-3 fatty acid screening" is possible.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Kim Lavoie – University of Quebec at Montreal

POSTER #53

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
47	New Investigator	Clinical	Respiratory Health

ABSTRACT:

Psychological distress and maladaptive coping styles in patients with severe, asthma

Objective: Severe refractory asthma affects 5-10% of asthmatics, yet accounts for ~ 80% of the total costs associated with asthma.^{1,2} Though several biological factors have been suggested to play a role in the development and persistence of TR asthma, those associated with psychological factors remain poorly understood. This study assessed levels of psychological distress and a range of disease-relevant emotional and behavioral coping styles in patients with severe refractory asthma, relative to a comparison group of moderate asthmatics of similar age and sex.

Methods: 84 patients (50% female, M age 46 yrs) with severe (n=42) and moderate (n=42) asthma were referred to a study investigating the clinical characteristics of severe asthma by their physicians. Severe refractory asthma was defined according to the ATS criteria. Patients underwent demographic and medical history interviews, pulmonary function and allergy testing. Patients also completed a series of questionnaires measuring asthma symptoms as well as the Millon Behavioral Medicine Diagnostic Inventory, which assesses psychological factors that influence disease progression and treatment. It measures levels of psychological distress (e.g., depression, anxiety) and how patients cope emotionally (e.g., are they excessively afraid of being ill) and behaviorally (e.g., do they take their medication as prescribed) with their illness.

Results: Statistical analyses showed that patients with severe vs. moderate asthma reported experiencing more psychological distress (shown by having higher scores on anxiety-tension [F=4.02, p<.05] and cognitive dysfunction [F=6.72, p<.01] subscales), worse emotional coping with their disease (shown by having higher scores on fear of illness [F=9.57, p<.01], pain sensitivity [F=10.65, p<.01], pessimism about the future [F=8.53, P<.01], and fear of undergoing medical procedures subscales [F=7.18, p<.01]), and worse behavioral coping with their disease (shown by having higher scores on daily functioning difficulties [F=5.48, p<.05] and medication non-adherence [F=4.32, p<.05] subscales). These results could not be explained by whether or not patients smoked, were overweight, how long they had asthma, or by the number the asthma attacks in the past year.

Conclusions: To our knowledge, this is the first study to assess levels of psychological distress and coping styles in patients with severe vs. moderate asthma. Results showed that patients with severe refractory asthma have higher levels of psychological distress and more difficulty coping with their disease both emotionally and behaviorally than moderate asthmatics. Future treatment studies should focus on helping patients with severe asthma cope more effectively with their illness, which may improve treatment outcomes in these high-risk patients.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Kong Eric You-Ten –Mount Sinai Hospital UHN

POSTER #54

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
48	New Investigator	Clinical	Cardiovascular Health

ABSTRACT:

Role of Noninvasive Computer Tomography Coronary Angiogram In Predicting Perioperative Cardiac Complications Following Major Noncardiac Surgery

BACKGROUND: Perioperative cardiac complications are among the most feared complications after surgery and are responsible for the major cause of postoperative adverse outcomes and death. An accurate prediction of the cardiac risk is important because this allows for treatments before surgery that will lead to favourable postoperative outcome and survival. Currently, there lacks a noninvasive test that accurately predicts the cardiac risk. Only conventional coronary angiogram has been shown to accurately predict the cardiac risk. However, this cardiac test is invasive and is reserved for only a selected group of patients. On the other hand, computer tomography coronary angiogram (CTCA) has emerged as the noninvasive safer alternative.

PURPOSE: Our study seeks to determine whether or not noninvasive CTCA before surgery will improve the prediction of which patients will suffer cardiac complication(s) during and/or following surgery.

METHODS: A pilot study consisting of a prospective non-randomized clinical trial. After ethics board approval at Toronto General and Mount Sinai Hospitals, stable patients identified as intermediate-high cardiac risk by clinical characteristics and undergoing a major surgical procedure are selected. Cardiac risk is further assessed using standard of practice noninvasive cardiac tests (electrocardiogram/cardiac stress test/ echocardiography), as well as, with noninvasive CTCA using a newly developed 320-row CT scan. The occurrence of fatal and nonfatal cardiac complications are then assessed on day 0-3 and 30 after surgery.

RESULTS: During the early recruitment period, 5 patients completed the study. CTCA findings of patient #1, 3 and 5 showed nonsignificant coronary stenosis, but, were nondiagnostic for patient #2 due to high calcification. Patient #1-3 and 5 did not experience any cardiac complications. Despite an inconclusive cardiac stress test, CTCA of patient #4 displayed significant 3-vessel disease, subsequently confirmed by invasive coronary angiogram. Patient #4 surgery was cancelled and bare metal stents were inserted in the occluded coronary arteries.

IMPACT: Our preliminary data demonstrated that noninvasive CTCA has the potential to change clinical practice of cardiac risk assessment that may lead to improved postoperative patient outcome and survival.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Majid Yousif –University of Western Ontario

POSTER #55

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
51	Student	Biomedical	Blood and Blood Vessels

ABSTRACT:

A novel blood mimicking fluid for particle image velocimetry in vascular flow models

A new blood mimicking fluid (BMF) has been developed which enables to the study of flow in vascular models using particle image velocimetry (PIV).

PIV is a valuable engineering technique used to obtain accurate flow-related information, such as velocity and shear stress, in order to gain a better understanding of the hemodynamics related to the initiation and progression of vascular disease. In PIV, flow models are perfused with a fluid seeded with tiny particles. The distance travelled by particles over a specific time is measured, by correlating consecutive images from high resolution cameras, and used to determine fluid velocity. A major difficulty in PIV that affects the measurements accuracy is the deflection and distortion of light passing through the model and the fluid, due to the difference in the refractive index (n) between the two materials. The problem can be eliminated by using a fluid with a refractive index matching that of the model. Such fluids are not commonly available, especially for vascular research where the fluid should also have a viscosity similar to human blood (4.4 ± 0.6 cP).

In this work, a new blood mimicking fluid (BMF), composed of varying relative concentrations of water, glycerol, and sodium iodide, has been developed to accommodate commonly used modeling materials such as silicone elastomers. The fluid exhibits a refractive index ranging between, but not limited to, 1.40 and 1.43 and a viscosity ranging between 4.0 - 5.0 cP. A mixture suitable for use with our silicone (Sylgard 184; n=1.414) vascular models was produced by using relative concentrations (% by wt) of 47.4% water, 36.9% glycerol and 15.7% sodium iodide, with resulting viscosity of 4.3 ± 0.1 cP.

This BMF enables PIV studies in vascular models of materials with various refractive indices while maintaining a suitable viscosity with respect to blood. Results demonstrating the possible range of refractive index and viscosity will be presented, as well as demonstrative digital particle images from flow in a carotid artery bifurcation flow model.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Maria-Graciela Hollm-Delgado –University of Montréal

POSTER #56

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
53	PhD Student	Clinical	Respiratory Health

ABSTRACT:

AIDS and outbreaks of multi-drug resistant tuberculosis: Examining the link using DNA fingerprinting

PURPOSE: We studied the causes of an outbreak of multi-drug resistant tuberculosis (MDR-TB) among AIDS patients receiving directly observed treatment for pulmonary tuberculosis in Lima, Peru between 1999 and 2005.

METHODS: We identified two groups of patients receiving tuberculosis treatment based on population prevalence of AIDS [n=205 in AIDS group; n=386 in non-AIDS group]. All patients had physical exams and were interviewed before starting treatment. Sputum samples were collected from patients at study entry, week 1, month 1, month 2, and month 4 and once at the end of tuberculosis treatment. We obtained DNA fingerprints for patients with MDR-TB sputum samples using spoligotype and IS6110 RFLP techniques.

RESULTS: Patients in the AIDS group were at increased risk of presenting MDR-TB at the start of treatment [Crude Odds Ratio (OR): 2.97, 95% Confidence Interval (CI): 1.5 to 6.0], and at increased risk of acquiring multi-drug resistance during treatment [Crude Rate Ratio: 2.14, 90% CI: 1.0 to 4.5], as compared to those in the non-AIDS group. 92% (11/12) of patients in the AIDS group who developed multi-drug resistance during treatment were infected by a different drug resistant strain. 55% (6/11) of these patients were infected by the Lam9 strain of Mycobacterium tuberculosis. Although Lam9 was more common among patients in the AIDS group (χ2=5.00, p-value=0.02), we found no difference in the risk of infection with Lam9 between AIDS and non-AIDS groups, after adjusting for patients' baseline risk of exposure to circulating MDR-TB strains [Standardized Incidence Ratio for AIDS group: 1.63, 95% CI: 0.5 to 3.8 and for non-AIDS group 1.75, 95% CI: 0.4 to 5.1]. Conversely, all patients (i.e., both AIDS and non-AIDS groups) infected with Lam9 MDR-TB at the start of DOTS were more likely to present with diarrhea as compared to patients infected with other clones of MDR-TB [OR: 3.73, 95% CI: 1.1 to 12].

CONCLUSION AND IMPACT: The outbreak of MDR-TB among AIDS patients receiving tuberculosis treatment was due to infection with a particular strain of MDR-TB and not because of genetic mutations in the original strain of M. tuberculosis. These observations suggest that immunosuppressed patients may be at increased risk of infection with certain MDR-TB strains. However, further analysis revealed that the risk of infection with the outbreak strain did not differ between patients in the AIDS and non-AIDS groups. More research is needed to study the link between outbreaks of MDR-TB and diarrhea.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Mahammad Ali –University of Alberta

POSTER #57

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
58	PhD Student	Biomedical	Cardiovascular Health

ABSTRACT:

The giant protein titin is degraded by matrix metalloproteinase-2 in hearts

Heart attack is a medical condition that occurs when the blood supply to a part of the heart is interrupted, a term called ischemia. Restoring blood flow to the heart is the first logical option in its treatment. However, restoration of the blood supply after a critical period of ischemia results in further tissue damage. This latter condition is called ischemia-reperfusion (I-R) injury and represents a major clinical problem for the treatment of many heart diseases. Titin, the largest known protein in mammalian cells, plays a central role as a molecular spring of heart muscle cells and helps the heart to properly contract. Although loss of titin has been reported in ischemic hearts, the mechanism of this is unclear. Matrix metalloproteinase-2 (MMP-2) is an enzyme which can cut other proteins into smaller pieces and is abundant in heart muscle cells. We have shown that MMP-2 is localized inside heart muscle cells. In I-R injury MMP-2 becomes a problem as it destroys specific proteins that allow the heart to contract. Hypothesis: Titin is a target for MMP-2 and its degradation by MMP-2 during I-R contributes to poor heart contractile function. Methods & Results: We labeled both MMP-2 and titin in the rat heart with specific antibodies and using a microscope we showed that both MMP-2 and titin are found together at a certain region of the heart muscle called the Z disc. In the test tube MMP-2 was able to cut titin into pieces and this was prevented by drugs which inhibit MMP-2 activity. Hearts isolated from rats were subjected to I-R injury with or without ONO-4817 (a selective MMP inhibitor) and the amount of titin in these heart samples was analyzed. We found that I-R caused a loss of titin in the heart. ONO-4817 prevented titin degradation and improved heart function following I-R injury. Conclusions: MMP-2 localizes to titin at the Z disc region of heart muscle cells and contributes to titin degradation in I-R injury. Inhibiting MMP-2 activity may be a future therapeutic strategy for treating heart attacks.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Muhammad Nabeel Ghayur –McMaster University

POSTER #58

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
59	Post Doctoral Fellow	Biomedical	Cardiovascular Health

ABSTRACT:

Effect of betel nut and its constituents on platelet clump formation

Betel nut is a popular natural health product (NHP) used by millions of people all over the world. It is used medicinally for lowering blood pressure. This study shows the effect of betel nut extract (Ac.Cr), and its constituents, on platelet clumping in human blood. Venous blood was taken from human volunteers. These volunteers were known to be free of medications for one week. Platelet clumping was monitored at 37°C in an aggregometer. Results showed that Ac.Cr was able to stop the clumping of platelets. The agents used for stimulating platelet clumping were arachidonic acid, adenosine diphosphate (ADP), platelet activating factor and epinephrine. Ac.Cr also blocked platelet clumping started by calcium ionophore. This showed the ability of Ac.Cr in blocking Ca²⁺ signaling. Ac.Cr was stronger in stopping ADP and calcium ionophore than the other stimulants. Different constituents of betel nut were also tested. Except for catechin, none of the tested compounds showed any effect. Catechin was most strong in blocking epinephrine. Catechin was found to be less active than Ac.Cr. This indicates presence of additional compounds in betel nut with this activity. The study shows the potential of this popular NHP in stopping platelet clumping. It also justifies the known benefit of betel nut in cardiovascular health.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Myra Cocker –Stephenson CMR Centre at the Libin Cardiovascular Institute of Alberta

POSTER #59

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
60	Doctoral Student	Clinical	Cardiovascular Health

ABSTRACT:

Reduced Cardiac Function with Cardiac Edema and Hyperemia in Elite High-Endurance Athletes with Common Colds: A Cardiovascular Magnetic Resonance Study

Background: Basic research has shown that cardiac inflammation may be present during systemic viral infections, such as influenza. Moreover, performing physical activity while exposed to systemic viral infections increases the risk for serious cardiac complications in mice models. As such, current athletic training guidelines deter athletes from participating in sport during common colds, despite a lack of direct evidence of colds in athletes leading to cardiac inflammation. Cardiac inflammation is characterized by increased water content in the heart (reflecting edema), as well as increased blood flow to the heart (hyperemia). In addition, contractile function of the left ventricle (LV), may also decrease. Cardiovascular Magnetic Resonance (CMR) allows for non-invasive imaging of edema, hyperemia, and LV function. Using CMR-based imaging, we hypothesized that common colds in elite high-endurance athletes lead to cardiac edema, hyperemia, and reduced LV function.

Methods: 62 (32 male, 31±13 years) elite high-endurance athletes were prospectively recruited from training and development teams of Team Canada. CMR scans were performed at baseline, with an acute common cold, and 4 weeks after. Pre-defined symptoms were used to rule in an acute cold. LV function, edema, and hyperemia were imaged using standard imaging methods on a 1.5T MRI scanner. Standard approaches were used to quantify LV function, edema and hyperemia.

Results: During an 11-month period of recruitment, 21 athletes completed all 3 scans. With an acute cold, a decrease in LV function was observed: LV end-systolic volume indexed-to-height was increased, while LV stroke volume indexed-to-height and LV ejection fraction were reduced ($p<0.05$). At the 4-week follow-up, no differences in LV function were observed when compared to baseline or acute cold. Furthermore, at the baseline visit, 19% of athletes presented with evidence for cardiac edema, and 33% presented with hyperemia. With an acute cold, 19% of athletes had edema, and this increased to 24% at follow-up. Similarly, 38% of athletes had hyperemia during the acute cold; and this proportion increased to 48% at follow-up.

Conclusion: We provide first evidence of cardiac involvement with common colds in elite high-endurance athletes. Using CMR imaging, colds were associated with a small yet significant decrease in cardiac contractile function, with persisting cardiac edema and hyperemia. Further research is required to assess the impact of these findings.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Myriam Tellier –Montreal University

POSTER #60

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
61	Student	Services et systèmes de santé	Accident vasculaire cérébral

ABSTRACT:

L'accident vasculaire cérébral léger sans séquelle : mythe ou réalité? Recension des écrits.

Introduction et objectif : Avec l'avancement technologique médical et les changements démographiques, la prévalence des accidents vasculaires cérébraux légers (AVCL) est appelée à augmenter. L'objectif visé par cette étude est de réviser la littérature en lien avec ce sous-groupe d'AVC en ce concentrant sur les conséquences de cette pathologie pour le patient et sa famille, ainsi que les services de réadaptation leur étant offerts.

Méthodologie : Une revue de littérature a été effectuée sur Ovid («Embbase» et «Medline») de 1950 à 2008. Des articles ont aussi été cherchés sur « Pubmed », « CINHAL » et « Cochrane ». Le terme AVCL a été combiné à une variété de mots clés. Les critères d'inclusion étaient disponibilité en anglais ou en français. Critère d'exclusion : Représentation inférieure à 50% d'AVCL dans l'échantillon. Résultats : Treize articles répondant aux critères d'inclusion et d'exclusion ont été recensés. Les personnes ayant eu un AVCL peuvent présenter des déficiences. Ces dernières n'interfèrent pas avec l'accomplissement des activités de la vie quotidienne mais viennent contraindre les tâches plus complexes. Aucun article n'a été répertorié pour les proches. Plusieurs interventions à domicile ont prouvé leur efficacité. Toutefois, la réalité démontre que la majorité de ces personnes réintègrent leur milieu de vie sans suivi ni référence à des ressources externes. Conclusion : Les personnes ayant eu un AVCL présentent effectivement des séquelles qui lorsque non adressées, peuvent engendrer un déconditionnement ou un besoin accru de soins et services. D'autres études sont nécessaires pour développer des programmes qui aideront à gérer cette population en croissance constante et, dans une perspective d'équité, documenter l'impact de l'AVCL sur le quotidien et la qualité de vie des proches.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Neelam Khaper –Northern Ontario School of Medicine, Lakehead University

POSTER #61

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
63	New Investigator	Biomedical	Cardiovascular Health

ABSTRACT:

Role of Beta-3 Integrin In Cardiomyocyte Apoptosis

Integrin receptors are essential in the regulation of vital cardiac function. Impaired integrin function is detected in cardiac remodeling. Oxidative stress is known to be involved in apoptosis and cardiac remodeling and have emerged as important mediator with modulating integrin function thus suggesting that oxidative stress could have a profound effect on integrin regulation. The aim of this study was to determine the expression pattern and functional role of integrins in HL-1 cardiomyocytes under oxidative stress condition. Using RT-PCR, the mRNA expression for several integrin subunits (alpha-v, 5, 6, and beta-1, 3, 4, 5) was detected under normal conditions. Protein surface expression was also detected for integrins alpha-v, 5, beta-1, 3 using flow cytometry. Among the various subunits under study, the expression of the beta-3 integrin subunit was significantly increased at both the mRNA and protein level in cardiomyocytes exposed to hydrogen peroxide for three hours. Changes in beta-3 integrin expression correlated with increased oxidative stress and a decrease in cell viability. Gene silencing of beta-3 integrin using short interfering RNA resulted in a 2-fold increase in cardiomyocyte apoptosis upon hydrogen peroxide treatment. This increase in apoptosis measured by Annexin-V staining correlated with an increase in caspase 3, 7 activation. We conclude that under oxidative stress condition, beta-3 integrin plays a vital role in cardiomyocyte apoptosis (Supported by FedNor and NOSM).

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Pingchuan Zhang –University of Ottawa Heart Institute

POSTER #62

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
64	Fellow	Biomedical	Cardiovascular Health

ABSTRACT:

A Tissue-Engineered Biomatrix Enhances the Therapeutic Effects Of Circulating Progenitor Cells In A Model Of Ischemia

Purpose: Circulating progenitor cells home and engraft to sites of ischemia, mediated in part by the adhesion molecule L-selectin; however, accumulation in tissues such as the heart is low. In this study, a collagen-based matrix containing sialyl LewisX (sLeX), which binds L-selectin, was developed in order to enhance the endogenous progenitor cell therapeutic response.

Methods: The effect of the sLeX-collagen matrix on progenitor cells and angiogenesis were assessed in vitro and using a rat hindlimb ischemia model. Ischemic hindlimbs were injected with: (1) sLeX-collagen matrix; (2) collagen matrix alone; or (3) PBS; and a subset received systemic injection of human peripheral blood CXCR4+L-selectin+ cells, one day after ischemia. Rats underwent laser Doppler perfusion analysis immediately prior to injection and 2 weeks after. Blood samples were analyzed for circulating progenitor cell numbers. Two-week tissue was analyzed by immunohistochemistry and by cytokine antibody arrays.

Results: Increased angiogenic/chemotactic cytokine production and improved resistance to apoptosis were seen in cells cultured on sLeX-collagen matrix. In vivo, mobilization of endogenous circulating c-kit+, CXCR4+, VEGFR2+ and CD45+ progenitor cells was increased at 7 and 14 days, compared to the collagen-only and PBS groups. Greater recruitment of these and systemically injected human CXCR4+L-selectin+ cells to sLeX-collagen treated limbs was observed (by between 1.6- and 6.2-fold vs. other treatments; P<0.05). This was associated with differences in angiogenic/chemotactic cytokine levels, including the mobilizing agent GM-CSF, the chemoattractants MCP-1 and MIP-3α and the anti-apoptotic factor TIMP-1. Arteriole density was greater in hindlimbs treated with the sLeX-collagen matrix (12.2±1.2/mm²) than with collagen-only (3.8±0.4/mm²) or PBS (2.2±0.4/mm²) treatment (P<0.001); and perfusion was increased in sLeX-collagen treated hindlimbs by ≥58% (P≤0.04) ver sus the other treatments.

Conclusions: This study mechanistically supported that this experimental approach may address at least 3 obstacles (mobilization, recruitment and survival) to the efficacy of progenitor cells in restoring tissue vascularity and function. The sLeX-collagen matrix serves as an example of how tissue-engineered materials can be developed in order to enhance the response and effects of endogenous progenitor cells and improve cell-based regenerative therapies.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Robin MacLaren –University of Ottawa Heart Institute

POSTER #63

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
65	Post Doctoral Fellow	Biomedical	Cardiovascular Health

ABSTRACT:

UBR2, a novel E3^{ubiquitin} ligase, binds the cytosolic tail of scavenger receptor A.

Atherosclerosis is an inflammatory disease that involves many types of cells from the immune system, most notably the macrophage. Macrophage cells are involved in the clearing of excess cholesterol from within the artery wall. The excess cholesterol can be in the form of LDL-C (low density lipoprotein cholesterol) or modified LDL-C. It is the modified LDL-C that is the dangerous type for atherosclerosis. When cholesterol levels become too high within the macrophages, they become harmful 'foam cells' as a result. This can cascade into a fatty streak. The clearing of the modified LDL-C by the macrophage is via the SRA (scavenger receptor type A) receptor. Since the fatty streak is the beginning of atherosclerosis, the understanding of how SRA is regulated is crucial. If we can slow down or prevent the first step of fatty streak formation, we may be able to slow down or prevent the development of atherosclerosis. However, very little is known about the factors that regulate SRA. Our lab has recently discovered a novel interaction of a protein (E3^{ubiquitin} ligase aka UBR2) with SRA. Preliminary data demonstrate that UBR2 from the cytosol of macrophage cells binds to the immobilized cytosolic tail of SRA. The objective of my project is to determine the role of this unique interaction. On going studies include the regulation of UBR2 mRNA and protein levels during foam cell development; the effect of knocking down UBR2 using siRNA technology on foam cell formation; and visualizing the interaction of SRA with UBR2 within a live cell (co-localization) using confocal microscopy. Since SRA is needed for excess modified LDL-C to enter the cell and UBR2 may be a novel regulator of SRA, this project may help us understand the very beginning of heart disease. We hypothesise that UBR2 binds to SRA under normal conditions in the cell, is in charge of the internalization of SRA into the cell, and will signal for SRA to be destroyed rather than recycled.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Sarah Gilpin –UHN University of Toronto

POSTER #64

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
69	Student	Biomedical	Respiratory Health

ABSTRACT:

Lung Progenitor Cells As Biomarkers In Human Lung Disease And Repair.

HYPOTHESIS: Progenitor cells in bone marrow (BM) and peripheral blood (PB) can participate in disease pathology and also in tissue repair. In the context of lung disease, a novel cell expressing Clara Cell Secretory Protein (CCSP), a marker of mature lung epithelial Clara Cells, has been recently identified in both mice and humans. In mice, CCSP+ cells are increased following lung injury. A second circulating cell, the Fibrocyte (Fc+), is the progenitor for mature fibroblasts. Fc+ are increased in pulmonary fibrosis patients, and are mobilized in acute exacerbations of IPF. We hypothesize that progenitor cell numbers in patients with chronic lung disease may correlate with lung function and clinical disease. The cells may also response to acute lung injury, including reperfusion injury following transplantation.

PURPOSE: This study intends to quantify lung progenitors in the BM and PB of pre-operative lung transplant patients, and in the 48 hours following transplantation, to determine if cellular levels can predict clinical status or outcome, and to further determine the role of these cells in lung biology and tissue repair.

METHODS: Cell were assessed by flow cytometry for CCSP and CD45/Collagen-1 expression for epithelial and fibroblast progenitors respectively. Serum protein levels were measured by ELISA.

RESULTS: BM and PB samples were analyzed from 74 lung transplant recipients and 19 donors. CCSP+ cells ranged from 0-4%, with higher and more variable levels in the PB. Fibrocytes were increased in both IPF and BOS patients, compared to donors. A significant increase in PB CCSP+ cells was measured 24hrs post-op, followed by a decrease at 48hrs (n=15). A similar increase in Fc+ was observed in IPF patients but not in other diseases. Cell levels did not predict post-op oxygenation, but a trend suggested greater CCSP+ cell mobilization predicts shorter post-operative ICU stays. A subset of mobilized CCSP+ cells also express CXCR4, while serum SDF-1 protein was inversely related to PB CCSP+ cell levels. Soluble serum CCSP protein levels did not rise following injury, but was measured at significantly higher levels in IPF patients.

CONCLUSIONS: Both epithelial and fibroblast progenitors are found in patients with end-stage lung disease and can be mobilized following acute lung injury. Mobilization may be achieved via the SDF-1/CXCR4 axis and may predict outcome following lung transplant.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Selma Greffou –Université de Montréal

POSTER #65

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
70	Student / PhD	Biomedical	Critical / Intensive Care

ABSTRACT:

Development of visually driven postural reactivity: A fully immersive virtual reality study

The objective of this study was to investigate the development of visually driven postural regulation in typically developing children of different ages. Thirty-two typically developing participants from 5 age groups (5-7 years, 8-11 years, 12-15 years, 16-19 years, or 20-25 years) were asked to stand within a virtual tunnel that oscillated in an anterior-posterior fashion at three different frequencies (0.125, 0.25, and 0.5 Hz). Body sway (BS) and postural perturbations (as measured by velocity root mean squared or vRMS) were measured. Most of the 5- to 7-year-old participants (67%) were unable to remain standing during the dynamic conditions. For older participants, BS decreased significantly with age for all frequencies. Moreover, vRMS decreased significantly from the 8- to 11- through 16- to 19-years age groups (greatest decreases for 0.5 Hz, followed by 0.25-Hz and 0.125-Hz conditions). No difference of frequency or instability was found between the 16- to 19- and 20- to 25-year-old groups for most conditions. Results suggest an over-reliance on visual input relative to proprioceptive and vestibular inputs on postural regulation at young ages (5-7 years). The finding that vRMS decreased significantly with age before stabilizing between 16 and 19 years suggests an important transitory period for sensorimotor development within this age range. Keywords: posture, sensorimotor development, virtual environment, body sway, instability index.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Shannan Ho Sui

POSTER #66

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
72	Postdoctoral Fellow	Biomedical	Respiratory Health

ABSTRACT:

Computational approaches to aid identification of novel anti-infective drug targets in *Pseudomonas aeruginosa*

Chronic *Pseudomonas aeruginosa* infection of the lungs is a major cause of morbidity and mortality in cystic fibrosis (CF) patients, but treatment is complicated by its intrinsic resistance to commonly used antibiotics. Thus researchers are aggressively seeking novel drug and vaccine targets to combat *P. aeruginosa* infections. There is growing interest in disrupting bacterial virulence mechanisms, thereby 'disarming' pathogens as opposed to targeting essential cellular functions. This approach will be more likely specific to pathogenic bacteria and may be subject to less selection for drug resistance. The Bioinformatics for Combating Infectious Diseases (BCID) Project is developing a computational pipeline to aid identification of anti-infective drug targets in *P. aeruginosa*. A major focus is the identification of genes predominantly found in pathogens as these are likely to play more virulence-specific roles in infection.

By comparing the *P. aeruginosa* PAO1 proteome against the deduced proteomes of 298 pathogenic and 333 non-pathogenic genomes, we identified pathogen-associated genes that encode known virulence factors, as well as several novel hypothetical proteins that are absent from non-pathogenic bacteria but are found in diverse pathogens, diverse pathogenic *Pseudomonads*, or are specific to *P. aeruginosa*. Selected proteins have been prioritized for further study by considering such criteria as (i) the absence of human homologs to avoid unwanted cross-reactivity; (ii) existing functional annotations; (iii) location in genomic islands (horizontally acquired regions that frequently encode virulence factors); and (iv) subcellular localization predictions that place their protein products in the extracellular space or on the bacterial cell surface, making them most accessible to drugs. A number of candidates with known 3D structure are being subjected to computational docking to identify small molecule interactions, while those lacking a structure have been prioritized for structure determination by collaborators. We will evaluate some of the most interesting candidates and compounds in virulence assays using infection models. We are also integrating patent and drug target information into the *Pseudomonas* Genome Database to expand the resource to include CF-relevant information. Our prioritization of key targets and integration of drug target data has the potential to lead to genuinely novel insights regarding the pathogenesis of *P. aeruginosa* and new targets for therapy.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Shereen Hamza –University of Alberta

POSTER #67

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
73	Student / PhD candidate	Biomedical	Cardiovascular Health

ABSTRACT:

Splenic reflex neurohormonal control of mesenteric arterial tone

Portal hypertension (PH) is a syndrome associated with chronic liver disease and is known to increase splenic venous pressure and alter blood flow dynamics in the splanchnic circulation (i.e. liver, spleen & intestines). This contributes to the fatal cardiovascular complications of liver disease. In elucidating the underlying mechanism of this phenomenon, we have shown that elevated splenic venous pressure results in a reflex increase in splenic afferent and mesenteric efferent nerve activity. We hypothesized that this nerve reflex increases mesenteric arterial tone (constriction). In anesthetized male rats, splenic venous pressure was selectively elevated by partial splenic vein occlusion (SVO). Mean arterial pressure and superior mesenteric arterial blood flow were simultaneously measured; these values were subsequently used to calculate mesenteric arterial conductance (inverse of resistance and a measure of vascular tone). SVO caused a significant drop in mesenteric conductance ($-0.012 \pm 0.003 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, $p < 0.05$, RM ANOVA; $n=10$), which was abolished by splenic denervation ($-0.006 \pm 0.002 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$; $n=8$). Interestingly, this drop in conductance was not abolished by mesenteric denervation ($-0.015 \pm 0.004 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$, $p < 0.05$; $n=6$). As the spleen modulates renal function via the splenorenal neural reflex, we further hypothesized that renal release of angiotensin II (ANG II) mediates splenic control of mesenteric tone. In animals treated with the ANG II AT1 receptor blocker Losartan (3mg/kg i.v.), the SVO mediated drop in mesenteric conductance was abolished ($-0.005 \pm 0.004 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$; $n=6$); SVO also failed to produce a drop in mesenteric conductance after bilateral renal denervation ($-0.007 \pm 0.003 \text{ mL} \cdot \text{min}^{-1} \cdot \text{mmHg}^{-1}$; $n=5$). The response of mesenteric conductance to SVO in Losartan or bilateral renal denervated groups was not statistically different from that observed in splenic denervated animals ($p > 0.05$, RM ANOVA). In separate animals, mesenteric resistance arteries (40-70 μm) were directly visualized with intravital microscopy. Immediately following SVO, mesenteric arterial diameter fell ($-3.1 \pm 1.1 \mu\text{m}$, $n=13$); this was abolished by splenic denervation ($+0.3 \pm 0.5 \mu\text{m}$, $n=10$, $p < 0.05$), bilateral renal denervation ($+1.4 \pm 0.6 \mu\text{m}$, $n=4$, $p < 0.05$) and the angiotensin II AT1 receptor blocker Losartan ($+0.45 \pm 0.2 \mu\text{m}$, $n=6$, $p < 0.05$). Interestingly, mesenteric denervation only attenuated this effect ($-0.2 \pm 0.4 \mu\text{m}$, $n=7$, $p=0.048$). We propose that mesenteric arterial tone is modulated primarily by splenorenal reflex mediated release of angiotensin II, with possible contribution from mesenteric angiotensinergic nerves. This initial mesenteric arterial vasoconstriction has implications for initiation of hemodynamic complications of PH, namely the hyperdynamic circulation.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Simon Bacon –Concordia University

POSTER #68

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
74	New Investigator	Clinical	Cardiovascular Health

ABSTRACT:

The impact of psychiatric disorders on high blood pressure development

Purpose of the study: Psychiatric problems, for example, depression and anxiety, have been associated with the development of cardiovascular disease, though, how this occurs is not well understood. The development of hypertension or high blood pressure may be one to explain this link. However, little is known about the specific link between depression, anxiety and the development of high blood pressure.

Method: A total of 174 patients who had a standard clinical exercise treadmill test and had normal blood pressure levels were contacted 1 year after their test. At the time of their treadmill test they underwent a structured psychiatric interview (Primary Care Evaluation of Mental Disorders) to see if they had any depressive or anxiety disorders. At 1 year the patients were asked to report if they had been diagnosed with high blood pressure or if they were give medications to reduce their blood pressure.

Results: At the time of the exercise test, 21% of patients had a psychiatric disorder, 13% had a mood disorder, and 14% had an anxiety disorder. In total 6% of patients developed high blood pressure 1 year after the exercise test. Statistical analyses revealed that patients with an anxiety disorder were 6 times more likely to develop high blood pressure than those without an anxiety disorder (OR=6.39, 95%CI=1.18-34.48). There was no statistically significant effect of having a mood disorder (OR=0.71, 95%CI=0.08-6.66) or any psychiatric disorder (OR=2.14, 95%CI=0.46-9.92). All these analyses controlled for age, sex, BMI, and smoking.

Conclusion: Having an anxiety disorders, but not mood disorders, is associated with a higher risk of developing high blood pressure. It may be that the physical effects of anxiety disorders may lead to changes in blood vessels and the heart, that might account for this increase in high blood pressure. Of greater clinical importance, future studies should see if treating anxiety disorders helps to reduce the development of high blood pressure.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Soroush Samadian –UBC iCapture Centre

POSTER #69

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
76	Student	Biomedical	Cardiovascular Health

ABSTRACT:

Data and Knowledge Modeling in Support of Clinical Research

Recently standards have emerged that allow the explicit expression of knowledge as ontologies and sharing these over the Web; however, outside of very specific cases, there is a dearth of examples of how such knowledge can be used practically. The CardioSHARE project proposes a novel semantic framework for data and knowledge representation and the sharing of results in significantly more flexible and resilient knowledge exploration systems for the health sciences. In this framework, interpretation of raw data is delayed until a query is posed over it, and the query itself contains the information required to interpret the data. As such, data can be re-interpreted dynamically as the universe of biomedical knowledge expands. Achieving this behavior required the invention of two novel technologies: a database structure encouraging the submission of pure data (i.e., raw measurements); and a mechanism for utilizing the knowledge in ontologies that enabled the ontological representation of complex analytical pipelines rather than pure DL-logic. Here we present the prototype CardioSHARE framework. At the core of CardioSHARE is a data model amenable to ontological interpretation/re-interpretation. Overlain on this are several interpretation layers, which iteratively 'raise' the data into increasingly complex interpretations. Our vision allows complex models of patient phenotypes to be swapped in-and-out of the research analysis such that the data can be viewed from different perspectives without manipulating the database. To date, we have been focusing on a core set of ontologies describing fundamental health research concepts such as blood pressure, and are now extending these into less clearly-defined concepts such as hypertension and increasingly sophisticated concepts such as ischemic heart disease. We evaluate our framework by reproducing experimental analysis already completed using data in the BC Cardiac Registry; this provides a 'gold standard', objectively held by a third-party, with which to compare our output. Later, we will collaborate with clinical researchers to define new categories of patient that should exist within the BC Cardiac Registry, and attempt to automatically identify these categories using our software tools. The CardioSHARE initiative demonstrates the power of formalized knowledge sharing, and shows how to efficiently automate many analytical tasks that currently require extensive human intervention and expertise.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Surinder Janda –University of British Columbia

POSTER #70

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
77	Resident	Clinical	Respiratory Health

ABSTRACT:

Statins and COPD: A Systematic Review

Background HMG-CoA reductase inhibitors (statins) are widely used in patients with hypercholesterolemia and cardiovascular disease. There is emerging evidence suggesting a beneficial effect of statins on morbidity and mortality in patients with chronic obstructive pulmonary disease (COPD).

The objective of this study was to perform a systematic review of the literature evaluating the effect of statin therapy on outcomes in patients suffering from COPD. Methods MEDLINE, EMBASE, PapersFirst, and the Cochrane collaboration and the Cochrane Register of controlled trials were searched. Randomized controlled trials, observational cohort studies, case-control studies, and population-based analyses were considered for inclusion.

Results Nine studies were identified for review (4 retrospective cohorts, 1 nested case-control study of a retrospective cohort, 1 retrospective cohort and case-series, 2 population-based analyses, 1 randomized controlled trial). All studies showed a benefit from statin therapy for various COPD outcomes. These outcomes included number of COPD exacerbations (3 studies), number of and time to COPD related intubations (1 study), pulmonary function (e.g FEV1 and FVC) (1 study), exercise capacity (1 study), mortality from COPD (2 studies), and all-cause mortality (3 studies). No studies describing a negative or neutral effect from statin therapy on COPD outcomes were identified.

Conclusions The current literature collectively suggests statins may have a beneficial role in the treatment of COPD. However, the majority of published studies have inherent methodological limitations of retrospective studies and population-based analyses. There is a need for prospective interventional trials designed specifically to assess the impact of statins on clinically relevant outcomes in COPD.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Thomas Lagace –University of Ottawa Heart Institute

POSTER #71

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
78	New Investigator	Biomedical	Cardiovascular Health

ABSTRACT:

Enhanced binding of a mutant LDL receptor to secreted PCSK9: a novel molecular basis of familial hypercholesterolemia

The secreted protease PCSK9 mediates degradation of the low-density lipoprotein receptor (LDLR) in liver. It is unknown whether this event occurs within the secretory pathway or following PCSK9 secretion and reuptake.

Here, we show that a familial hypercholesterolemia (FH)-associated H306Y mutation in the epidermal growth factor-like repeat A (EGF-A) domain of the LDLR results in a mutant receptor with increased sensitivity to exogenous PCSK9-mediated cellular degradation owing to enhanced PCSK9 binding affinity.

Crystallographic structural analysis showed that His306Tyr in the EGF-A domain mimics a low pH conformational change undergone in wild-type EGF-A-His306, resulting in an improved hydrogen bond with PCSK9-Asp374. LDLR sub-fragments containing the H306Y mutation potently inhibited binding of secreted PCSK9 to cell surface LDLRs, resulting in recovery of LDLR levels in HepG2 cells stably overexpressing wild-type PCSK9 or gain-of-function PCSK9 mutants associated with hypercholesterolemia (S127R or D374Y).

We conclude that PCSK9 acts primarily as a secreted factor to cause LDLR degradation. Consequently, the molecular characterization of the FH-associated H306Y LDLR mutation supports a role for secreted PCSK9 in regulating LDL-cholesterol clearance in humans.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Yan (Mary) Zhang - University of Ottawa Heart Institute

POSTER #72

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
79	Student / PhD	Biomedical	Cardiovascular Health

ABSTRACT:

Development of Non-invasive PET Imaging for the Long-term Assessment of Progenitor Cells Transplanted with Collagen Matrices

Background: We have reported that collagen delivery matrices can improve the results of cell therapy by enhancing the early retention of transplanted circulating progenitor cells (CPCs), but their subsequent mechanisms of action remain unknown. To evaluate the long-term effects of a collagen matrix on cell engraftment after transplantation, a lentiviral vector was used to transduce human CPCs with a reporter gene in order to track cells in vivo using positron emission tomography (PET).

Methods: The bicistronic lentiviral vector, Lox-GFP-ires-TK expressing both the PET reporter gene, herpes simplex virus type 1-thymidine kinase (HSV1-tk), and the enhanced green fluorescence protein (EGFP) gene, was produced by co-transfection into 293T cells with pCMVR8.2, pMD2.G, and pLoxGFP-iresTK plasmids. Lentivirus supernatant was collected and concentrated. Afterwards, the prepared lentiviral vector was titrated on 293T cells. Human CPCs were transduced at different multiplicities of infection (MOI). The transduction efficiency was determined by flow cytometry analysis of GFP expression. The expression of HSV1-tk enzyme was examined by Western blot. The viability of transduced CPCs was measured. The transduced CPCs within or without collagen matrices (1×10⁵/0.5ml) were incubated and observed under the fluorescence microscope every week for 4 weeks.

Results: The transduction efficiency obtained was 15.1±5.6% at a MOI of 10. The transduced cells were isolated by fluorescence Activated Cell Sorting (FACS). Western blot analysis confirmed the expression of HSV1-tk enzyme in the transduced CPCs. There was no difference in the cell viability between transduced cells (87.9±9.2%) and untreated control (91.8±7.0%). After 4 weeks, the transduced CPCs were still visualized by fluorescence microscope. There was no significant difference in the GFP signal between cells in the matrix and cells alone.

Conclusions: These results provide a promising platform for the development of non-invasive PET imaging with reporter gene techniques to monitor over the long-term, the fate of transplanted cells in vivo and better understand the role of delivery matrices in cell-based therapies.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Sheryn Kirkpatrick - University of Ottawa Heart Institute

POSTER #73

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
80	M.Sc. Candidate	Biomedical	Cardiovascular Health

ABSTRACT:

[11C]Methyl-Candesartan Displays Binding Specificity for Angiotensin II AT1 Receptors

Purpose: Angiotensin II AT1 receptors play a role in the pathogenesis of cardiovascular and renal diseases. The aim of this study was to assess the potential of [11C]methyl-candesartan to study renal AT1 receptors in rats in vivo using small animal positron emission tomography (PET).

Methods: Male Sprague-Dawley rats (200-275g, n=10) intravenously injected with 0.5-2 mCi of [11C]methyl-candesartan underwent 60-minute dynamic PET scans (Inveon, Siemens). Four rats were scanned with co-injected AT1 receptor blocker candesartan (5 mg/kg). For each scan, regions of interest were drawn on the left atrial region and left kidney. Data for each scan were normalized to the scan peak blood activity. Mean normalized activity was compared using Student's T-test.

Results: High contrast images of the kidneys and liver were obtained using [11C]methyl-candesartan. The left kidney time-activity curves of co-injection scans showed similar peak activities but increased washout compared to control scans. No differences were observed in the blood time-activity curves. At 10-20 min, the mean normalized activity in the left kidney of co-injected rats (0.054 ± 0.006) was significantly reduced (70% decrease; $p < 0.0001$) compared to controls (0.179 ± 0.017), indicating binding specificity to AT1 receptors.

Conclusions: The high-contrast images obtained at baseline and increased washout following AT1 receptor blockade suggest potential for [11C]methyl-candesartan to image renal AT1 receptors.

YOUNG INVESTIGATORS FORUM 2009

Poster Presentation Day 2

Adam Thomas - University of Ottawa Heart Institute

POSTER #74

ABSTRACT ID #	CAREER STAGE	TRACK	RESEARCH AREA
81		Biomedical	Cardiovascular Health

ABSTRACT:

Imaging phosphodiesterase-4 in rat heart using (R)-[11C]rolipram and small animal PET

Purpose: The sympathetic nervous system controls the strength and frequency of cardiac contraction via norepinephrine and the downstream signaling molecule cyclic-AMP (cAMP). Alterations in this signaling axis have been observed in several cardiac pathologies. Regulation of cAMP levels in the heart is primarily controlled by the phosphodiesterase-4 (PDE4) enzyme which breaks down cAMP. (R)-Rolipram is a selective PDE4 inhibitor that can be labeled with the radioactive isotope carbon-11 to provide a direct index of PDE4 and an indirect measure of cAMP. Positron emission tomography (PET) imaging technology facilitates tracking of the distribution of (R)-[11C]rolipram within a living animal. This study aims to evaluate PDE4-specific binding of (R)-[11C]rolipram in the rat heart using small animal PET imaging to establish background data for future studies in cardiac disease.

Methods: Male Sprague-Dawley rats (n=3) were injected via tail vein with (R)-[11C]rolipram (0.45-2.65 mCi) and were scanned for 60 minutes using a small animal PET camera (Siemens Inveon). A second group of rats (n=3) received a blocking dose of (R)-rolipram (1 mg/kg iv 2 minutes prior) and were scanned for 60 minutes; blocking scans were followed by a 10 minute [13N]ammonia (2-3 mCi, iv) scan to delineate the heart for subsequent analysis. Regions-of-interest were defined as the left ventricle myocardium (LV), cavity (blood) and background (area adjacent to heart) and were used to measure tracer uptake and retention at 30 minutes. Data are expressed as a ratio of LV activity to blood or background activity and the Student's T-Test was used to determine statistical significance.

Results: (R)-[11C]rolipram uptake was detected in the heart, brain and liver. Retention was decreased in PDE4-rich regions (brain, heart) following (R)-rolipram, demonstrating the presence of PDE4-specific binding. At 30 minutes, LV-to-blood ratio was significantly higher in controls compared to blocked rats (1.45±0.27 vs. 1.03±0.02, p=0.04). A trend towards decreased activity in blocked rats was observed in the LV-to-background ratio (1.62±0.23 in controls vs. 1.33±0.02 in blocked rats, p=0.1).

Conclusions: These results support further work with (R)-[11C]rolipram for cardiac PDE4 measurements in rats. Small animal PET imaging allows for in vivo, high throughput, serial kinetic evaluation of radiotracer distribution and retention that can provide insight into small animal models of disease.