MED 602 Principles of Translational Medicine: Chronic Diseases

The aim of this course is to explore the translational aspects of important chronic diseases and emerging pharmacological and non-pharmacological approaches for treatment. This course is designed to align graduate students and medical residents with the current trends in preclinical and clinical research and modern medical training in order to become effective "translators of discovery and knowledge".

Prerequisite: *Mandatory for graduate students enrolled in MSc in Medicine –Translational Medicine; consent of Department.*

Objectives

I: Preclinical models: understand the principles of selecting optimal preclinical models of human disease and conducting preclinical research in a manner that promotes translation to early phase clinical trials. Understand the strengths and limitations of animal models of chronic diseases

II. Early phase clinical trials: understand the challenges in the conduction of early phase clinical trials and the requirements for successful translation of preclinical research: trial designs, endpoints, statistical challenges of small sample sizes, regulatory and funding challenges, structure of translational teams.

III. Biomarkers: recognize the importance of established biomarkers for the conduction of clinical research, particularly early phase trials or clinical care at the population levels, as well as principles for the discovery of novel biomarkers at the preclinical and clinical level.

IV. Populations and Health Services: Understand the importance of research at the population and health services level and the importance of conducting molecular and preclinical research with the future population/health services research in mind, in order to promote translational research and integration of the "molecule-animal-human-population-healthservices" continuum.

SESSION	CASE STUDIES
Multiple Sclerosis	**Preclinical Models -3** A 21 yr woman, triathlon athlete, presents with double vision and a tingling sensation in her hands. Facilitator: Discuss the case (5 min); What is the predominant theory for the pathogenesis of MS? (5 min)? What are the biggest challenges of translating animal research in patients with MS? (5 min) Student: Provocative observations have suggested that chronic cerebrospinal venous insufficiency may cause Multiple Sclerosis in patients: How would you design animal studies to study this hypothesis? Readings: *Multiple Sclerosis: John H. Noseworthy et al. N Engl J Med (2000); 343, 938-952 *Multiple Sclerosis – The Plaque and Its Pathogenesis: E. Frohman, et al. N Engl J Med (2006);354:942-55
Arthritis	**Preclinical Models -2** 30 yr old fit woman presents with swollen, red and painful joints. Facilitator: Discuss the case (5 min). Molecular Basis of Disease Modifying Drugs in patients with RA (5 min). Challenges of clinical research in RA (5 min). Student: Based on your understanding of the clinical disease, describe the features of an ideal animal model for RA and the evidence required in animals before an experimental therapy can be considered "ready" for translation in clinical trials. Readings: * The Pathogenesis of Rheumatoid Arthritis: I McInnes at al. NEJM (2011);365:2205-19 * Therapeutic Strategies for Rheumatoid Arthritis: J. O'DellNEJM (2004);350:2591-602

Heart Failure	**Preclinical Models -1** A 37 yr old man was discovered to have a "cardiomyopathy" on routine transthoracic echocardiography ordered because of "palpitations" Facilitator: Discuss the case (5 min); Challenges in the classification of cardiomyopathies: clinical vs genetic phenotypes (5 min). Challenges in the preclinical research of heart failure models (5 min) Student: What are the challenges in the genetic testing/family screening in patients with cardiomyopathies? What are the challenges of developing animal models of genetic cardiomyopathies in a manner that would allow the translation of findings to humans? Readings: * Contemporary Definitions and Classification of the Cardiomyopathies: Circulation. 2006;113:1807-1816 * Animal models of heart failure; a scientific statement from the AHA. Hauser S. et al. Circulation Research (2012); 11: 131-150
Dementia	**Biomarkers -1** 65 yr old woman with a history of ischemic stroke presents with accelerated memory loss. Facilitator: Discuss the case (5 min). A summary of the most promising AD therapies and their molecular basis (including the promise for a vaccine) (5min). What are the challenges of preclinical research for AD? (5 min) Student: Reliably separating vascular dementia from AD is important in the conduction of clinical studies (inclusion criteria, etc). Describe the properties of an ideal (hypothetical) biomarker that could separate the two. How would you design preclinical and clinical studies to validate it? Readings: * Alzheimer's Disease: H. Querfurth et al.N Engl J Med 2010;362:329-44 * Regulatory Innovation and Drug Development for Early-Stage Alzheimer's Disease: N. Kozauer et al. NEJM (2013); 368: 1169-1171
Heart Failure	**Early Phase Clinical Trials -2** A 55 yr old fit man with heart failure, following a large myocardial infarct, is sent for cardiac rehabilitation, but is skeptical: "if the damage is done and the heart muscle cannot grow back why do I have to drive 3 hours to get to the rehab sessions?" Facilitator: Discuss the case (5 min); What are the challenges and benefits of cardiac rehabilitation and what are the challenges of clinical research in this field in the modern era (10min)? Student: How would you conduct a "trial" in a rat model of myocardial infarction in order to study the mechanism of the benefit of rehabilitation? What would be the biggest challenges? Readings: *Cardiac Rehabilitation and Secondary Prevention of Coronary Heart Disease: P. Ades; N Engl J Med, Vol. 345, No. 12
Heart Failure	**Early Phase Clinical Trials -3** A 65 yr old previously healthy woman presents to the emergency room with acute dyspnea and fluid retention Facilitator: Discuss the case (5 min); What are the challenges in deciphering the triggers of acute heart failure in large populations (5 min)? What the challenges in the clinical research of acute heart failure therapies? (5 min) Student: Discuss the data that you would like to see in a candidate therapy for acute heart failure in animals, , before you can be convinced that it is appropriate for early phase clinical trials in humans. Readings: Acute Pulmonary Edema: L. Ware et al. N Engl J Med 2005;353:2788-96 * Clinical Trials of Pharmacological Therapies in Acute Heart Failure Syndromes. M Felker et al. Circulation (Heart Failure). (2010); 3: 314-325 * Clinical Trials of Pharmacological Therapies in Acute Heart Failure Syndromes. M Felker et al. Circulation (Heart

	Failure). (2010); 3: 314-325
Stroke-neuroprotection	**Early Phase Clinical Trials -1** A 60 yr old woman with atrial fibrillation presents to the ER 6 hours after the onset of right-sided weakness Facilitator: Discuss the case (5 min). Discuss the current gaps in knowledge in the management of stroke and how they are addressed by clinical research protocols (5 min). What are the challenges of clinical research in acute stroke? (5 min) Student: Despite promise in preclinical research, neuroprotective drugs aiming to limit the damage in the brain after the onset of stroke, have mostly failed in clinical trials. Discuss potential reasons for this apparent discrepancy. Readings: * Acute Ischemic Stroke: B. van der Worp et al NEJM (2007);357:572-9 * Intravenous Thrombolytic Therapy for Acute Ischemic Stroke: L. Wechsler NEJM 2011;364:2138-46
Arrhythmias	**Biomarkers -2** A 22 yr NHL player suddenly arrests while playing hockey. His brother has an abnormal ECG showing a long QT interval. Facilitator: Discuss the case (5 min); The molecular basis of the different types of exercise-induced arrhythmias and the challenges of preclinical research (10min) Student: Should all athletes be screened for lethal arrhythmias? What kind of preclinical, clinical or outcomes data would you like to see before you can argue one way or the other? Readings: Sudden Death in Young Athletes: Barry J. Maron N Engl J Med 2003;349:1064-75
Neurodegenerative diseases	**Populations and Health Services -1** A 40 y old man presents with difficulty swallowing, hallucinations and jerky movements in his extremities Facilitator: Discuss the case (5 min). What is the molecular basis of the disease and what are the challenges in translating animal research to humans (10min)? Student: How will you design population studies to prove that an outbreak of prion disease has an infectious basis? What would the biggest challenges be? Readings: *Neurodegenerative Diseases and Prions: S. Prusiner NEJM (2001) 344: 1516-26
Neuromuscular Diseases	**Populations and Health Services -2** A 15 yr old boy presents with muscle weakness and difficulty standing up from a sitting position Facilitator: Discuss the case (5 min). Discuss the progress on the genetic basis of these diseases and the potential for therapy (5 min). Discuss the regulatory challenges of the end-of-life care of these patients (5min). Student: A study showed that patients with NMD have cardiac arrhythmias that at times cause sudden death. A trial is proposed to test the usefulness of a defibrillator in patients, including patients on a ventilator (because of respiratory muscle failure) who have a life expectancy of more than a year. Is it ethical? Is it appropriate? Readings: * Electrocardiographic Abnormalities and Sudden Death in Myotonic Dystrophy Type 1: W. Groh, at al. N Engl J Med 2008;358:2688-97

	* Cell Therapies for Muscular Dystrophy: H. Blau N Engl J Med (2008) 359; 1403-1405
Heart Failure	**Populations and Health Services -3** A 60 yr old man is referred to a specialized heart function clinic following 3 admissions and readmissions for dyspnea and fluid retention over the past 6 weeks Facilitator: Discuss the case (3 min); Challenges in the management of CHF care and its cost at the health services level. Student: In 2012 the U.S. Centers of Medicare and Medicaid services introduced a readmission reduction program for heart failure and has suggested that 30-day readmission rates should be bundled to reimbursement for the index hospitalization. A national working group has been set up to examine whether Canada should institute a similar policy and has asked you to provide your justified opinion on whether an effective way to decrease 30 day readmissions for CHF is to deny payment to hospitals/physicians that cross an agreed upon threshold of readmission rates in their center. Readings: *Systolic Heart Failure: John J.V. McMurray; N Engl J Med 2010;362:228-38 Zubin J Eapen, Shelby D Reed, Yanhong Li, et al. *Do Countries or Hospitals With Longer Hospital Stays for Acute Heart Failure Have Lower Readmission Rates? Findings From ASCEND-HF. Circ *Heart Fail.* 2013;6:727-732. Finlay A. McAlister. *Decreasing readmissions: it can be done but one size does not fit all. BMJ Quality and Safety. 2013;22:975–976.
Debate	Debate session
Grant Review	Grant review session
Review and FINAL EXAM	

MED 604: Vascular Medicine

Co-ordinator: Dr E. Michelakis

The aim of this course is to explore the translational aspects of important chronic diseases and emerging pharmacological and non-pharmacological approaches for treatment. This course is designed to align graduate students and medical residents with the current trends in preclinical and clinical research and modern medical training in order to become effective "translators of discovery and knowledge".

Prerequisite: *Mandatory for graduate students enrolled in MSc in Medicine –Translational Medicine; consent of Department.*

Objectives

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SESSION	CASE STUDY
Peripheral Vascular Disease	A 60 yr old woman (history of smoking and hypertension) presents with calf pain during walking and found to have extensive peripheral vascular disease. On further work up he is also found to have extensive aortic, carotid and coronary disease. Facilitator: Discuss the case (5 min). What is the magnitude of this clinical problem (5 min)? What are the challenges in discovering therapies for PVD in preclinical research? (5 min) Student: Describe your approach in trying to pursue the hypothesis that the presence of PVD is an independent predictor of mortality in patents with established cardiovascular disease. What kind of resources or tools would you need? Readings: * Claudication: White C. NEJM (2007; 356:1241-1250* Peripheral Arterial Disease: Morbidity and Mortality Implications B. Golomb, et al. Circulation (2006);114:688-699
Erectile Dysfunction	A 35 yr old man with hypertension and hyperlipidemia presents with erectile dysfunction and depression. Facilitator: Discuss the case (5 min). The magnitude of the clinical problem and its vascular basis (5 min). The challenges in the preclinical and clinical research of this important multi-factorial clinical problem (5 min). Student: Describe a research protocol in which to study the hypothesis that ED is an independent risk factor for morbidity and mortality form cardiovascular disease Readings: Erectile dysfunction. McVary KT. NEJM. (2007); 13;357:2472-81
Acute Myocardial Infarction	A 40 yr old man presents with chest pain and a large anterior wall MI in his GP office 4 hrs away from the closest hospital. Facilitator: Discuss the case (5 min). What are the challenges in the conduction of clinical research in acute MI in a country like Canada? (10min) Student: Some evidence suggests that a provincial program in which paramedics can use thrombolytics in acute MI is feasible and may improve the outcome of the treated patients. Describe the kind of evidence required in order to convince the government that funding of such a provincial program is cost effective. Readings: * Current Concepts: Time to Treatment in Primary Percutaneous Coronary Intervention: Nallamothu B.K., et al. N Engl J Med (2007); 357:1631-1638 * Contemporary therapy of acute ST-elevation myocardial infarction. P Armstrong. Tex Heart Inst J. (2009);36:273-81. * Feasibility and applicability of paramedic-based prehospital fibrinolysis in a large North American center. Welsh RC et al. Am Heart J(2006);152:1007-14
Chronic Angina	An 84 yr old woman presents with worsening chest pain with minimal activity. She has documented diffuse coronary artery disease. She is already on 14 different medications, she is fully ambulatory and lives independently Facilitator: Discuss the case (5 min). The health care system challenges in the Treatment of heart disease in the elderly (5 min). The challenges in conducting clinical research in the elderly (5 min).

	Student: While the biology of the old myocardium is quite different than that of the young myocardium, the elderly patients (i.e. the majority) with heart disease receive treatments that have been tested in much younger patients and very young animals. Describe an animal model that could best model the patient in your case. What kind of endpoints would you use is such a model, when developing therapies for angina that could target the elderly? Readings: Can J Cardiol. 2004; Suppl A:7A-16A. Canadian Cardiovascular Society Consensus Conference 2002: Management of heart disease in the elderly patient
Hypertension	A 35 yr old fit man presents with moderate hypertension and a family history of premature death due to cardiovascular disease. He is a scientist and asks for the probability that he will die prematurely from cardiovascular disease. Facilitator: Discuss the case and the magnitude of the clinical problem (5 min). The challenges in the outcomes research of hypertension and the clinical trials with novel anti-hypertensive drugs in the modern era. (10 min) Student: Describe the principles of a clinical study in which a hemodynamic biomarker is used to study whether the improved outcomes of cardiovascular disease in response to an antihypertensive drug (for example an ACE inhibitor) are due to the decrease of the arterial pressure or to other effects of the drug Readings: * Is it the blood pressure or the blood vessel? Cohn, J.N., Journal of the American Society of Hypertension (2007); 1: 5-16. * Ventricular Arterial Stiffening: Integrating the Pathophysiology. Kass, D.A., Hypertension (2005); 46: 185-193. * Prediction of cardiovascular events and all-cause mortality with central hemodynamics: a systematic review and meta-analysis. Vlachopoulos, C. et al., European Heart Journal (2010); 31: 1865-1871.
Endothelial Dysfunction	A 33 yr "healthy volunteer" participates in a clinical study developing a method to measure brachial artery blood flow, and is found to have very abnormal values. He has no known risk factor for vascular disease and no symptoms. Facilitator: Discuss the case (5 min). Non-standard risk factors for vascular disease (5 min). Challenges in the studies of endothelial function in patients (5 min). Student: Describe the principles of a translational research program (animal and human studies) for the discovery of a blood-based biomarker of endothelial dysfunction. Readings: * Endothelial Function. J Vita. Circulation (2011); 124: e906-912 * Brachial flow-mediated dilation predicts incident cardiovascular events in older adults: the Cardiovascular Health Study. L. Yeboah J, et al. Circulation. (2007);115:2390–2397.
Pulmonary Hypertension	A 28 yr old woman presents with shortness of breath, lower extremity edema and syncope upon exertion. She is diagnosed with idiopathic pulmonary arterial hypertension Facilitator: Discuss the case (5 min). The molecular basis of PAH. Challenges in translational research in PAH, limiting the development of effective therapies. Student: Speculate on the reason(s) for which this disease affects the pulmonary arteries (causing proliferative vascular remodeling resembling in-stent restenosis) but spares all the other blood vessels in the body. Describe preclinical research approaches in the development of pulmonary circulation – specific therapies.

	Readings: * An evidence-based approach to the management of pulmonary arterial hypertension. Archer SL, et al Current Opinion in Cardiology (2006); 21(4): 385-392. * Translational Challenges in Pulmonary Arterial Hypertension Research and A Vision for change , Sutendra et al. Science Translational Medicine (2013) in press.
Debate	A 28 year old patient refugee in Canada with PAH cannot afford therapy with an endothelin antagonist which costs $85K/year/patient, since the government does not cover this for refugees. Student #1: Medical therapies need to be expensive because the cost of the trials to bring them to approval is huge and the cost needs to be absorbed by the consumers; otherwise the drug companies would not invest in drug development….better to have an expensive drug than no drug. No change in current drug approval policy is needed Student #2: The huge profitability of drug companies is unethical particularly since drugs that do not improve survival or significantly impact the course of the disease are still approved and given to patients that believe are getting treated well – better to have no drug than a very expensive drug that does not do much . A change in current drug approval policy is needed
Debate	In a federal competition for major grant funding (for example, granting one grant of 30$ million dollars over 5 years), there are two finalists that have to present their case in front of a panel. Scientifically both proposals received an excellent score and should be funded. Since only one can be funded, this special hearing is designed to compare the relative importance and impact to the health of Canadians of these two proposals, in order to facilitate the decision. Defend your case in 15 minutes: Student #1: A global "life intervention" approach to improve diet and exercise in ALL Canadians, in order to prevent cardiovascular disease. Student #2: A tissue engineering and regeneration program in order to build the first in the world center for "personalized vascular medicine", in which "custom-made" and patient-specific new blood vessels will be developed ex vivo based on patient-derived stem cell, and placed back to the patients with vascular disease.
Hypertension	A 55 year old man presents to the clinic with elevated blood pressure readings taken in a pharmacy. His reading in the pharmacy was 155/95 mmHg. You take his blood pressure twice in the clinic using a manual sphygmomanometer and get a similar reading. The patient is not convinced he has high blood pressure and is reticent to start medications. Is he right or should he be treated? Facilitator: Discuss the case (5 min). Describe how the continuous nature of BP as a physiologic parameter affects our ability to confidently make a diagnosis of hypertension. Discuss current guideline recommendations regarding blood pressure diagnosis. Student: Wearable technology is a huge emerging field in the biomedical space. Companies like Apple have developed sophisticated health care applications within their smartphone and smartwatch platforms. However, blood pressure measurement is conspicuously absent within these devices. Why? What are the biomedical challenges to measuring blood pressure using a cuffless device such as a wristwatch? How could you design a device to overcome these challenges? Readings: *Hypetension Poulter NR, Prabhakaran D, Caulfield M Lancet. 2015 Aug 22;386(9995):801-12. doi: 10.1016/S0140-6736(14)61468-9. Epub 2015 Mar 29. * Review A New Algorithm for the Diagnosis of Hypertension in Canada

	Lyne Cloutier, RN, PhD,a Stella S. Daskalopoulou, MD, PhD,b Raj S. Padwal, MD, MSc,c Maxime Lamarre-Cliche, MD,d Peter Bolli, MD,e Donna McLean, RN, NP, PhD,f Alain Milot, MD, MSc,g Sheldon W. Tobe, MD, MSc(HPTE),h Guy Tremblay, MD,i Donald W. McKay, PhD,j Raymond Townsend, MD,k Norm Campbell, MD,l and Mark Gelfer, MDm Canadian Journal of Cardiology 31 (2015) 620e630
Aortic Disease	A 50 yr old man presents with a pulsatile mass in a routine exam and is diagnosed with a 5.5cm abdominal aorta aneurysm. Facilitator: Describe the molecular basis of aneurysm formation in humans (5 min). What are the challenges of translational research on animal models and human tissues in discovering the mechanism of aneurysm formation and rupture? Student: Describe the nature of a hypothetical ideal biomarker predicting the presence and the probability of rupture of aortic aneurysms and the translational approach (preclinical and clinical research) to study its validity. Readings: Abdominal Aortic Aneurysm: Al-Omran M. and Aljabri B. NEJM (2009); 360:2004
Grant Review Session – 1	
Grant Review Session – 2	
	Review and FINAL EXAM

MODULE III: Immunity, Inflammation, Infection

(companion book: Principles of Translational Science in Medicine: From Bench to Bedside. Edited by Martin Wehling (Second Edition) ISBN: 978-0-12-800687-0

SESSION	CASE STUDY
Asthma 1 **Molecules to Animals**	25 year old female with long-standing asthma and frequent exacerbations despite preventive measures. Facilitator: Discuss the case (5 min). How can murine models of allergic airway inflammation be used to develop therapies for allergic asthma (10min) Student: A new signaling inhibitor UOA123 has been shown to inhibit the release of mast cell mediators (histamine, leukotrienes, prostaglandins and cytokines) from mast cell lines and also from mast cells in human tissue explants. All these mast cells products are important for the development of allergic diseases including allergic asthma. Design animal preclinical studies to identify the efficacy of UOA123 in asthma. Explain the choice of animals used, the characteristics that your animal model should have to be appropriate for this study and the outcomes you will follow. Reading: 1.Holmes Am et al, Animal Models of asthma: value, limitations and opportunities for alternative approaches. *Drug Discov Today*. 2011; 16(15-16):659-70. 2.Perrin S. Preclinical research: Make mouse studies work. Nature 2014; 507:423-425 3.Book Chapter 2.1.6
Asthma 2 **Animals to Humans**	Facilitator: The challenges of developing biomarkers to predict exacerbations in asthma (and other complex diseases that develop on predisposing genetic background and require multiple triggers and environmental interactions) Student: You have identified a new blood-based biomarker in asthma that your data in a small study indicate that it may be a marker to predict asthma exacerbations, but it appears that it may also be associated with severity of the disease. Design a study to separate the two first in animal models and then in a prospective human study Reading: Book Chapter 3.1, 3.2, 3.3, 3.4
Asthma 3 **Humans to**	Facilitator: Briefly discuss asthma treatment, and give an overview of the findings of Reading 1: *How to measure survival in clinical trials* Student: Give a framework for assessing causality (the causal relationship between a drug and a harmful

Populations	outcome). Discuss the Bradford Hill criteria. Based on this discussion, give your opinion as to whether beta-agonists increase the risk of death. Reading: 1. Nelson et al. The Salmeterol Multicenter Asthma Research Trial. A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. Chest 2006;129:15-26. 2. Drug Therapy: Asthma; Fanta C.H. NEJM (2009); 360:1002-1014 3. Book Chapter 6
Virology 1 **Molecules to Animals**	49 year old female post-kidney transplant presents with fever, elevated liver function tests, and diarrhea and is diagnosed with CMV disease. Facilitator: Discuss the case (5 min). The challenges of developing effective vaccines for diseases that affect immunocompromised individuals (10 min); optimizing preclinical studies Student: A new strategy for CMV vaccination has been developed using DNA vaccines combining proteins from different targets and has been tested in two animal models with very good results. You want to develop such vaccines for study in humans. Before you can get approval to use the vaccine in human studies you are asked by regulatory authorities to obtain data from a primate model. Describe the approach you will take for the primate studies you will do. Are there ethical considerations for this approach? Reading: 1.Cytomegalovirus in solid organ transplantation. Razonable R et al. Am J Transplant. 2013 Mar;13 Suppl 4:93-106. 2.Rieder F and Steininger C. Cytomegalovirus vaccine: phase II clinical trial results. Clin Microbiol Infect. 2014, Suppl 5:95-102. 3.McVoy MA et al, A cytomegalovirus DNA vaccine induces antibodies that block viral entry into fibroblasts and epithelial cells. Vaccine. 2015, 33:7328-36.
Virology 2 **Animals to Humans**	A 39 year old male with chronic undetected hepatitis C infection presents with liver failure. Facilitator: Discuss the case (5 min). The challenges and creative approaches in developing animal models of HCV (10 min) Student: You are sitting in a Health Canada committee when a company provides their data that suggest that an early phase clinical study (first in human) trial of their new HCV drug is feasible and safe. Describe the information you would expect to see before you give permission for this first in human trial. Reading: Chronic Hepatitis C Infection. Rosen H.R. NEJM (2011); 364:2429-2438
Virology 3 **Humans to Populations**	Case: A 50 year old male who is otherwise well presents to his physician for an insurance-related physical. At the end of the visit, the patient asks if he should be getting the flu vaccine this year. Facilitator: Brief background on influenza, vaccine efficacy and current expert consensus indications for vaccination. Explain the concepts of relative risk and absolute risk. Student: The target population for flu vaccination has evolved from administration to high-risk individuals only to administration to most of the population. Does the evidence support this? What factors should be weighted when deciding on mass vaccination? Discuss Rose's 'Prevention Paradox'. Discuss the costs of vaccination weighted against the expected benefit in the patient described above (cost-effectiveness). Reading: 1. Glezen WP. Prevention and treatment of seasonal influenza. N Engl J Med 2008;359:579-85. 2. Rose B. Strategies of prevention: lessons from cardiovascular disease. BMJ;1981:282:1847-1851. 3. Book Chapter 8
Inflammation 1 **Molecules to Animals**	64 year old female with acute sepsis due to an abscess in the foot, develops bilateral lung infiltrates and requires intubation. She is diagnosed with ARDS. Facilitator: Discuss the case (5 min). Challenges of understanding the pathogenesis and diagnosis of ARDS (5min). Challenges in the usage of animal models of ARDS (5 min). Student: A new molecule has shown promise in terms of decreasing vascular permeability (due to endothelial cell injury by a cytokine that is increased in sepsis) in an isolated perfused lung preparation. Describe the types of experiments needed and the type of data required before this drug is considered as a potential therapy for ARDS at the preclinical level. Reading: 1. The acute respiratory distress syndrome. Matthay MA, Ware LB, Zimmerman GA. J Clin Invest. 2012 Aug 1;122(8):2731-40. 2. Book Chapter: 2.1.3, 2.1.7, 2.2
Inflammation 2 ***A*nimals to humans**	A 34 year female presents with jaundice and pruritus. She is diagnosed with Primary Biliary Cirrhosis. Facilitator: Discuss the case (5 min). The molecular basis of PBC (5 min). The challenges in proving a viral etiology of autoimmune liver disease (5 min). Student: An investigator has linked the presence of retrovirus with the pathogenesis of PBC and proposes an early phase non randomized clinical trial with an anti-retroviral drug in 10 patients with PBC to Health Canada. What kind of data should this trial generate before a permission can be granted for a randomized

	large clinical trial? Reading: Linking human beta retrovirus infection with primary biliary cirrhosis. Mason AL, Zhang G. Gastroenterol Clin Biol. 2010 Aug-Sep;34(6-7):359-66
Inflammation 3 **Humans to Populations**	43 year female who develops severe diarrhea following recent antibiotic therapy. Stool is positive for C. difficile toxin and symptoms persist despite standard anti- C difficile therapy. Stool transplantation is being considered. Facilitator: Discuss the case and the findings of Reading 1. Cover the basic fundamentals of interpretation of meta-analyses. Student: Discuss the risk of bias associated with using observational studies to examine the benefits of a treatment. What are the potential sources of bias (list)? How can this bias be mitigated? Reading: Kassam et al. Fecal microbiota transplantation for clostridium difficile infection: a systematic review and meta-analysis. Am J Gastroent 2013;108:500-508.
Ethics committee review (animal and human) **Regulatory Process**	Each student will present a protocol within less than 10 minutes which is usually what happens in ethics board meetings. The student needs to be well aware of the details within the application, particularly around the important points discussed in the appendix A, B attached. The presentation should focus on and summarized potential points of concern that the committee needs to discuss. The role of the committee is, of course, to minimize the potential of harm to the patients while allowing research to unfold. Slides are not required (slides are not shown in the committee presentations) but could be used if the student feels it would help him to remain focused. After each presentation there will be 20 minutes discussion for each and all the students should participate asking relevant questions. The objective of this session is to give you an introduction of the main points raised during approvals of your future protocols, the process followed and the details of the paperwork and documents required. Reading: 1. Submitted Clinical Ethics Application with "Investigator's Brochure" – Michelakis, Evangelos 2. Submitted Animal Ethics Application – Vliagoftis, Harissios 3. Research Ethics Boards – General Ethics Applications Information
Grant review panel **Regulatory Process**	Simulating a grant review panel proceedings. Facilitator: Briefly describe the CIHR review panel process Two submitted grants (CIHR format) on subjects relevant to this cluster (written by our faculty members) will be distributed to all. As it happens in grant review panels, each of the two students will take 10 minutes to review the grant (present the summary of the proposal and identify the strengths and weaknesses) and propose a score (1-10 scale). The rest of the committee will ask questions after each grant and, following a discussion, the scores will be finalized and the grants will be ranked. More details on the process will be offered along with the grant proposals.
Practical and to-the-point brief lectures	**HV:** Statistical principles of small homogenous samples analysis (cells, rodents); the 5 things you need to know (20min) **EM:** Precision medicine trials and novel trial designs: the 5 things you need to know (20 min) **RP:** Statistical principles of large inhomogeneous samples analysis (human populations): the 5 things you need to know (20 min)
Debate	Group debate: To be determined
	FINAL EXAM

MODULE III: Metabolism, Obesity, Nutrition

The aim of this course is to explore the translational aspects of important diseases that relate to metabolism, ranging from obesity and diabetes to lipid metabolism. This course is designed to align graduate students and medical residents with the current trends in preclinical and clinical research and modern medical training in order to become effective "translators of discovery and knowledge".

Prerequisite: Mandatory for graduate students enrolled in MSc in Medicine –Translational Medicine; consent of Department.

SESSION	CASE STUDY
DM - 1	An 18 year old man presents in a coma and is found to have previously undiagnosed type I diabetes mellitus. Facilitator: Discuss the case (5 min). The immunologic basis of diabetes (5 min). What are the challenges in translating current knowledge of islet cell function and immunity into useful immune-based therapies? (5 min) Student: Propose a hypothetical framework in which a diabetes vaccine is developed: describe the key components of the preclinical studies and the key points of early phase clinical trial design. Readings: * Diabetes Mellitus and the beta cell: the last 10 years. Aschroft et al. Cell (2012); 148: 1160-70 * Type 1 diabetes: translating mechanistic observations into effective clinical outcomes. KC Herold et al. Nat Rev Immunol. (2013);13(4):243-56
DM -2	A 45-year-old man with uncontrolled diabetes, despite standard therapy, and obesity requires dietary counseling but skips several appointments with the dietician because "he needs more medicine and he knows he needs to lose weight already – he just cannot do it" Facilitator: Discuss the case (5 min). Discuss the impact of diet, exercise, and behavioural modification on the treatment of diabetes (5 min). What are the challenges in conducting clinical trials of health behavior modification in diabetes (5 min). Student: You are sitting in a hospital committee to decide on the funding of one of these two applications: $1million to buy a sequencing machine to study the genetics of all Edmontonians with diabetes referred to the diabetes clinics (goal is to provide personalized medicine to all diabetics in the city in 10 years) versus $1milion to establish and run a multidisciplinary behavioral modification clinic for all patients with DM type II referred to diabetes specialty clinics. What are the arguments that would convince you to fund one versus the other? Readings: * Genomics, Type 2 Diabetes and Obesity. M McCarthy. NEJM (2010) 363:2339-2350 * The LOOK AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. NEJM 2013: DOI: 10.1056/NEJMoa1212914
DM -3	A 65 year old woman has renal failure secondary to long standing undiagnosed diabetes and is considering dialysis. She lives in a remote northern area and has limited access to primary care. Facilitator: Discuss the case (5 min). What is the economic impact of type 2 diabetes in Canada? (5 min). What are the challenges of performing global population-based screening and surveillance for diabetes? (5 min) Student: Propose a hypothetical research framework by which the cost effectiveness of global screening for diabetes can be studied in a country like Canada. What would be its most essential components? Readings: Health care use and costs in the decade after identification of type 1 and type 2 diabetes: a population-based study. Johnson J et al, Diabetes Care 2006;29:2403-2408.

SESSION	CASE STUDY
	Global and societal implications of the diabetes epidemic. P Zimmet et al. Nature (2001);414:782-787
Obesity – 2	A 35-year-old female with recurrent weight cycling despite diet and exercise counseling and contraindications for bariatric surgery is interested in trying an investigational "diet pill". Facilitator: Discuss the case (5 min). The relative importance of pharmacotherapy in the treatment of obesity (5min). Challenges in clinical research on the role of pharmacotherapy in obesity (5 min) Student: You are sitting in a Health Canada Committee where a drug company presents evidence that a new drug can cause a 20% decrease in weight in a mouse model of obesity and a 10% weight loss (after 4 months of therapy) in 300 patients with obesity. Another group has shown animal evidence that this drug may also cause lethal pulmonary hypertension in animal models. The company argues that the benefits of weight loss far outweigh the risk of lethal pulmonary hypertension in some patients. What kind of evidence will be important for you to decide to offer approval of this drug or not? Readings: * Padwal R and Majumdar SR. Drug treatments for obesity: orlistat, sibutramine and rimonabant. Lancet 2007;369:71-7. * WP James et al. Effect of sibutramine on cardiovascular outcomes in overweight and obese subjects. NEJM (1010);363:905-17. * Appetite-Suppressant Drugs and the Risk of Primary Pulmonary Hypertension. Abenhaim L et al. NEJM (1996); 335:609-616
Obesity -3	A 45-year-old male with severe, refractory obesity, the metabolic syndrome, diabetes, treatment resistant hypertension and cerebrovascular disease is referred for bariatric surgery Facilitator: Discuss the case (5 min). Discuss the health policy ramifications of constrained resources for treating severe obesity (5min). Discuss the challenges of clinical research on the role of bariatric surgery for obesity (ethics of randomization, placebo effects, end-points, duration of follow up etc) (5 min). Student: Describe What parameters should be used in the enrollment of patients for research trials in bariatric surgery (inclusion criteria) and what are the most important end points to show efficacy and cost effectiveness of bariatric surgery? Readings: Padwal et al. A simple prediction rule for all-cause mortality in a bariatric surgery eligible cohort. JAMA Surg 2013. Bariatric Surgery for Morbid Obesity. Eric J. DeMaria. N Engl J Med 2007;356:2176-83
Obesity – 1	A 16 year old with severe obesity since the age of 8 (both parents are severely obese and have very low income) is referred for bariatric surgery. Facilitator: Discuss the case (5 min). The societal impact of childhood obesity (5 min). What are the challenges on the identification of the basis of obesity in children (genetic-societal-behavioral)? (5 min). What are the public health / regulatory challenges to establish global obesity prevention strategies in children? (5 min) Student: Describe a hypothetical research framework (preclinical and clinical) in which you can address the hypothesis that obesity has a significant genetic basis. You have an unlimited budget for animal work in your laboratory and a population of 300 morbidly obese children followed in a provincial children obesity clinic. Readings: Farooqi IS. The severely obese patient—a genetic work-up. *Nature Clinical Practice Endocrinology and Metabolism*. 2006;2:172-177. Han JC, Lawlor DA, Kimm SYS. Childhood obesity. *Lancet*. 2010;375:1737-1748.
Topic: Debate	Student 1: "The evidence that exercise interventions are not effective for weight loss is weak, as previous research has not comprehensively examined this in specific (i.e. children) vs the whole populations; effectively used

SESSION	CASE STUDY
	modern technologies to quantify activity; or use novel "motivational" techniques for population studies. Thus, more research on the effectiveness of exercise interventions at the population level is needed and government support is warranted." Student 2: "Enough evidence exists to suggest that exercise programs are not effective for long term lifestyle modification for obesity patients. This is particularly true at the population level. Thus, instead of government sponsored initiatives to promote exercise programs, the emphasis should be on the support of research for and implementation of medical and surgical therapies for obesity patients."
Nutrition -1	A 67-year-old woman with a small lung mass (1x2 cm non small cell lung cancer) presents with rapid decrease in muscle mass and weight loss despite adequate calorie intake Facilitator: Discuss the case (5 min). What is the molecular basis and the clinical impact of cancer-cachexia? (5 min). What are the challenges in conducting clinical research for the pharmacotherapy of cancer-cachexia, in patients that have untreatable cancer? (5 min) Student: Describe an ideal (hypothetical) model for cancer cachexia and the kind of parameters that would be important to follow in order to prove that a candidate drug for its treatment should be ready for translation into clinical research. Readings: * Mechanisms of cancer cachexia. M Trisdale. Physiological Reviews (2009); 89: 381-410 * Dodson S, Baracos VE, Jatoi A, et al. Muscle Wasting in Cancer Cachexia: Clinical Implications, Diagnosis, and Emerging Treatment Strategies. *Ann Rev Med*. 2011;62:265-279.
Nutrition -2	45-year-old aboriginal lady with obesity and metabolic syndrome lives in Northern Canada but refuses drugs and nutritional advice unless her elders agree Facilitator: Discuss the case (5 min). The social and health policy challenges involved in nutrition related issues for aboriginals and residents of remote regions (5 min). The challenges in conducting clinical research on nutrition in aboriginal patients (5 min) Student: You are sitting in a CIHR review committee. An investigator proposes an ambitious program ($2 million over 5 years) for a community intervention to improve the nutritional status in a remote community of 200 Inuit peoples that suffer from increased mortality due to cardiovascular disease and diabetes. What do you think you need to see in order to consider this a good investment of federal resources and fund the project? Readings: *Sharma S. Assessing diet and lifestyle in the Canadian Arctic Inuit and Inuvialuit to inform a nutrition and physical activity intervention programme. *J Hum Nutr Diet*. 2010;23 Suppl 1:5-17. *Ley SH, Hamdy O, Mohan V, Hu FB. Prevention and management of type 2 diabetes: dietary components and nutritional strategies. *Lancet*. 2014;383:1999-2007.
Lipids -1	A 40-year-old man (very fit and nonsmoker) presents with high LDL cholesterol levels in a routine test and a family history of premature death because of cardiovascular disease Facilitator: Discuss the case (5 min). The relative importance of genetics versus environmental factors in the pathogenesis of hyperlipidemia (5 min). The challenges or preclinical research and animal models for the pathogenesis and treatment of human hyperlipidemia (5 min) Student: A recent report describes that in mice, knockout of a lipid metabolism enzyme leads to severe hyperlipidemia and atherosclerosis. Another report shows that a mutation (loss of function) in the gene for this enzyme can be found in 10% of patients with hyperlipidemia. A drug company has produced a novel therapy that enhances the function of the affected enzyme and wants to test it in humans. Propose the structure of a clinical research program (early and late phase clinical trials) that would lead to approval of this medication.

SESSION	CASE STUDY
	Readings: * Rethinking Primary Prevention of Atherosclerosis-Related Disease: C. Napoli, et al, Circulation. (2006);114:2517-2527 * Inflammation, atherosclerosis, and coronary artery disease. GK Hansson. NEJM. (2005); 352: 1685– 1695. * Pharmacologic Treatment of Hyperlipidemia. A Last et al, American Family Physician 2011 Sep 1;84(5):551-558 * The CCS guidelines for the diagnosis and treatment of dyslipidemia for the prevention of cardiovascular disease in the adult. T Anderson et al. Can J of Cardiology (2013); 29:151-167 * Statistical Challenges in the Evaluation of Treatments for Small Patient Populations. E. Korn, et al. Sci Transl Med 27 March (2013) 5:178sr3
Lipid -2	A 55-year-old male with metabolic syndrome (obesity, hyperlipidemia, hypertension, type II Diabetes) and a recent stroke. Facilitator: Discuss the case (5 min). Challenges in the preclinical studies on the interaction of environmental to molecular and genetic factors and the role of animal models in the treatment of metabolic syndrome (10 min) Student: You are asked to be an expert consultant in the governments in the discussions to introduce a heavy tax on junk food along with increased premiums for the medical insurance of obese patients. The funds will be used to establish new research programs for the metabolic syndrome. What kind of evidence will you need to see before you argue for one way or the other? Readings: * Metabolic syndrome: from epidemiology to systems biology. A. Lusis et al Nature Reviews Genetics. 9, 819-830 * Metabolic Syndrome: A Clinical and Molecular Perspective, D Moller et al, Annual Review of Medicine (2005); 56: 45-62 * Definition of Metabolic Syndrome. S Gundy et al. Circulation (2004); 109:433-438
Osteoporosis	A 68-year-old woman with recent hip and wrist fracture following minor trauma and evidence of severe and previously undiagnosed osteoporosis Facilitator: Discuss the case (5 min). The challenges of outcomes research for osteoporosis and the current approach to the design of clinical trials on the efficacy and safety of osteoporosis therapeutics (10 min) Student: Discuss the profile of a hypothetical ideal biomarker for osteoporosis (either imaging or blood/serum based) and an overall approach for its validation from preclinical research to clinical outcomes studies. Readings: * SR Majumdar, et al. Promotion and prescribing of hormone therapy after report of harm by the Women's Health Initiative. JAMA (2004). 292:1983-1988. * Bisphosphonates for Osteoporosis — Where Do We Go from Here? M Whitaker, et al. NEJM (2012); 366:2048-2051
	Grant Review
Debate	Observational studies have shown that obesity is associated with improved survival in patients with chronic diseases including heart failure. That is, in patients with chronic heart failure, those that are overweight or mildly obese survive longer than normal weight individuals. In contrast, data from obese rodent models demonstrate that increased adiposity has a detrimental effect on cardiometabolic physiology even after heart failure is induced in these animals. Human randomized controlled trials in this area are not available and difficult to do. For this debate, Student #1: should argue that the observational data in humans are stronger than the animal data and that we should not be suggesting that obese humans with heart failure lose weight because it may reduce their lifespan.

SESSION	CASE STUDY
	Student #2: should argue that the human observational data cannot be trusted and that we should place higher value on the rodent studies. This debater needs to make a case for why these studies should be translatable to humans.
FINAL EXAM	