MED 602 Principles of Translational Medicine: Chronic Diseases (Preclinical Research)

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 of the whole course (MED 602-604-606-608)

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.

Objectives of MED 602 (translational PRECLINICAL RESEARCH)

- Features of good animal models
- Features of effective preclinical research (human tissues)
- Common flaws and challenges of preclinical and animal research and ways to address them
- Principles of statistical analysis in low sample size data
- Principles and approaches to intellectual property protection (patents)
- Effective abstract writing for papers and grants
- Effective grant writing

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<td>Multiple Sclerosis</td>
<td>A 21 yr woman, triathlon athlete, presents with double vision and a tingling sensation in her hands.</td>
<td>Facilitator: Discuss the case. What are the biggest challenges of translating animal research in patients with MS (5 min)? What are the principles of developing animal models in order to answer specific clinical questions (10 min).</td>
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<td>Student: Provocative observations have suggested that chronic cerebrospinal venous insufficiency may cause Multiple Sclerosis in patients: (<a href="https://mssociety.ca/hot-topics/chronic-cerebrospinal-venous-insufficiency-ccsvi">https://mssociety.ca/hot-topics/chronic-cerebrospinal-venous-insufficiency-ccsvi</a>). How would you design an animal study to investigate this hypothesis?</td>
<td>Objective: To understand the principles of “bedside-to-bench” translational research.</td>
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| Cancer | A 55 yr overweight man, who regularly consumes alcohol is diagnosed with Barrett’s Esophagus, a potential precursor of esophageal adenocarcinoma.  
**Facilitator:** Discuss the case. Discuss the challenges of predicting which patients will go on to develop cancer from a "precancerous" condition (5 min). Can you model the natural history of a disease with preclinical models (10 min)?  
**Students:** Based on a large tissue biobank (>3000 specimens) containing serial biopsies (based on up to 15 years follow up) from patients with Barrett’s esophagus (a potential pre-cancerous condition), including subset of these patients that went on to develop adenocarcinoma, researchers developed 5 molecular characteristics that predict "high risk" patients. These include 2 mutations in the esophageal epithelium, 2 polymorphisms that affect the whole genome and one upregulated growth factor receptor in the esophageal epithelium.  
**Student 1:** How would you use preclinical models to decide whether or not some (or all) of these abnormalities are "causal" for cancer (10 min)?  
**Student 2:** How would you use preclinical models to determine which of these is the most attractive to be developed as a potential therapeutic target (10 min)?  
**Objective:** Principles and challenges of modeling the natural history of a disease using preclinical models  
**Readings:**  
* Residual Embryonic Cells as Precursors of a Barrett’s-Like Metaplasia: Xia Wang et al. Cell (2011); 145(7), 1023-1035 |
|---|---|
| Heart Failure | A 20 yr old man was discovered to have a “cardiomyopathy” on routine transthoracic echocardiography, ordered because of "palpitations" and some skeletal muscle weakness. Genetic analysis revealed a mutation in a protein of the nuclear envelope of the cell that causes an 80% decrease in the protein levels in the cardiac and skeletal muscle.  
**Facilitator:** Discuss the case; Challenges in the classification of cardiomyopathies: clinical vs genetic phenotypes (5 min). Challenges in the preclinical research of heart failure / cardiomyopathy models (10 min).  
**Student 1:** Discuss potential or theoretical ways by which an abnormal protein in the nuclear envelope of all the cells in the body, produces a phenotype that is restricted in cardiac and skeletal muscle only (10 min)  
**Student 2:** If you had an unlimited budget, what would you do to determine whether this disease could be cured (10 min)?  
**Objective:** To understand the difficulties/limitations of developing therapies of complex genetic diseases.  
**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 |
| Cancer | A 63 yr man is diagnosed with an aggressive form of brain cancer. Genetic sequencing identified 7 new mutations in the tumour suppressor gene p53 within the tumor.  
**Facilitator:** Discuss the case. Discuss the mutational theory of cancer and its relevance in cancer diagnosis and treatment – what is an oncogene? (5 min). Of the multiple mutations in a given cancer, how can we decide which are the most important and which are attractive therapeutic targets? (5 min). Discuss the CRISPR/CAS9 technique (5 min). |
| **Heart Failure** | **Student**: 3 independent gene mutations (cancer-specific – not somatic) characterize a very aggressive form of brain cancer. Two of them cause a down-regulation of the relevant genes and one causes an up-regulation of the relevant gene. Describe 3 ways that an experimental therapy can address these abnormalities. (don't be specific – discuss the general principles of the approaches).

**Objectives**: To understand the features of an “oncogene” (or a disease-specific abnormal gene)

**Readings**: *Multiple mutations and cancer. Lawrence A. Loeb et al., PNAS (2003); 100(3), 776-781.* |

| Heart Failure | **Heart Failure**
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. What are the challenges and benefits of cardiac rehabilitation (supervised graded exercise and intense control of blood pressure, diet and other risk factors) and what are the challenges of research in this field, in the modern era (15min)?

**Student**: How would you conduct a “trial” in a rat model of myocardial infarct in order to study the mechanism of the benefits of rehabilitation? What would be the biggest challenges?

**Objectives**: The criteria required for designing appropriate “pre-clinical” trials.


| Heart Failure | A 45 yr old man presents with heart failure, decades after he was treated with a chemotherapeutic drug for a curable cancer as an adolescent.

**Facilitator**: Discuss the case. What are the challenges in developing relatively “selective” anticancer drugs? What are the current limitations in preventing chemotherapy-induced heart failure (15 min)?

**Student 1**: You have been provided with a candidate Drug X that has been shown to reduce lung cancer progression. The molecular pathway for Drug X is potent inhibition of Enzyme A, which is highly expressed in lung cancer but is also expressed in low amounts in the heart. How would you design a pre-clinical study (both in cells and animals) to address the selectivity of Drug X? How would you determine if Drug X may result in cardiotoxicity? (10 min)

**Student 2**: In your pre-clinical study Drug X was effective in decreasing lung cancer in 8 out of 10 mice (10 mice in the treatment group and 10 in the vehicle control group). Contrary to the 8 responding mice, Drug X increased tumor growth in 1 mouse to a higher degree compared to vehicle-treated mice and did not affect the tumor in another mouse (similar to vehicle controls). Should you remove these 2 mice from your analysis? If so, what criteria should you use? (10 min)

**Objective**: The criteria for evaluating drug specificity, off-target effects as well as “outliers” in animal studies.

**Readings**: |
**Debate**

Two teams of 2 students each (which will be randomly selected during the first session) will debate (pro vs con) on a given controversial subject. At the end of the presentation and discussion, all students will vote. The winning team will get an iPad (or $500 each).

**Arthritis**

30 yr old fit woman presents with swollen, red and painful joints.

**Facilitator:** Discuss the case. Challenges of preclinical research in RA (5 min). Principles of preclinical research in common disease lacking appropriate animal models (5 min). What is the value of proteomic analysis of human samples (5 min).

**Student 1:** You have a collection of serum and fluid from joints of 100 patients with mild, 100 patients with moderate, 100 patients with severe RA and 50 healthy patients. You have a collaborator that can perform a complete proteomic analysis of the samples. How would you design your approach in identifying a biomarker of disease progression? (10 min)

**Student 2:** How would you decide which of the top abnormal proteins are a potential therapeutic target worth pursuing experimentally?

**Objectives:** To understand the value and limitations of human tissues/samples in preclinical research.

**Readings:**
- *The Pathogenesis of Rheumatoid Arthritis: I McInnes* at al. NEJM (2011);365:2205-19
- *Therapeutic Strategies for Rheumatoid Arthritis: J. O’Dell* NEJM (2004);350:2591-602

**Stroke**

A 60 yr old woman with atrial fibrillation presents to the ER 6 hours after the onset of right-sided weakness, where she is given a neuroprotective agent as part of a clinical trial.

**Facilitator:** Discuss the case. Rationale and challenges in the use of neuroprotective agents in acute stroke as a classic example of translational research failure (15 min)?

**Students:** Despite promise in pre-clinical 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.

**Student 1:** List potential reasons that suggest that animal research is the weak link in translational research failures

**Student 2:** List potential reasons that clinical research is the weak link in translational research failures

**Objective:** To understand the basis of failures in translational research.

**Readings:**
- *Acute Ischemic Stroke: B. van der Worp* et al NEJM (2007);357:572-9

**Statistics**
### Brief lectures on statistical analysis using parametric and nonparametric tests for pre-clinical animal studies and in-vitro cell analysis.

1. principles of very low sample size analysis
2. practical example 1
3. practical example 2

**Objectives:** To understand the appropriate statistical tests for pre-clinical animal studies or in-vitro cell analysis.

### Cancer

37 yr old female with lung cancer is resistant to conventional therapy. A genetic screen suggests she has a single nucleotide polymorphism in a gene that encodes a protein downstream of the molecular pathway targeted by this therapy.

**Facilitator:** Discuss the case. Discuss the co-clinical trial project and its ability to improve the efficacy of drug treatments in early phase clinical trials (15 min).

In a parallel design clinical trial, 300 cancer patients were exposed to drug A (n=150) or drug B (n=150). Both groups had mixed responses. Genetic analysis showed that an SNP in gene X caused resistance to treatment in drug A. And another SNP in gene Y identified good responders to drug B.

**Student 1:** You believe that Drug A is ineffective in decreasing tumor growth in patients that have an SNP in gene X. Design a pre-clinical study (in animals) that would validate this hypothesis and define the precise mechanism of this resistance.

**Student 2:** You believe that Drug B is the ideal therapy for decreasing tumor growth selectively (i.e. with minimal side effects) in patients that have the SNP in gene Y. Design a pre-clinical study (in animals) that would validate this hypothesis and explain the increased response to the drug.

**Objective:** To appreciate the advantage of genetically engineered mouse models (that mimic patients) for screening of drug response.

**Readings:**

*A co-clinical platform to accelerate cancer treatment optimization. Andrea Lunardi and Pier Paolo PandolfiTrends in Molecular Medicine January 2015, Vol. 21, No. 1*

### Abstracts/Summaries

Abstract/summary writing session (5 Students). (a complete paper will be given and students will be called to write a 200 word abstract). Needs to be submitted by Tuesday December 5th.

### Grant Review

Grant review session (all students will write a proof-of-principle grant (150 word abstract + 3 pages + 1 page figures + 1 page references) based on their areas of choice (in any of the CIHR pillars of research).

### Review and FINAL EXAM
MED 604: Vascular Medicine

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".

**Objectives - General**

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-health services" continuum.

**Specific Objectives**

- **Statistics core**: Correlation and Dependence, Regression analysis, Subgroup analysis, Combined endpoints, Survival analysis with Cox and logistic regression
- **Novel Clinical Trial design**
- **Early-phase clinical trial design**
- **Cost-benefit analysis in outcomes research**
- **Biomarker discovery principles**
- **Ethics of clinical research**
- **Quality assurance in the writing of a scientific paper**
- **Proof-of-principle research: effective grant writing**

**Sessions**

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<td>Peripheral Vascular Disease</td>
<td>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 she is also found to have extensive aortic, carotid and coronary disease.</td>
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<td><strong>Facilitator:</strong> Despite the vasculature being a single organ, vascular diseases in different organs (heart, brain, limbs, eye, skin etc) are essentially approached as different entities and often managed by different specialties. <strong>Why is that and what are the challenges of this approach in discovery research? Discuss &quot;correlation and dependence&quot; in statistics.</strong></td>
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<td><strong>Student:</strong> Describe your approach in trying to pursue the hypothesis that the presence of peripheral vascular disease predicts the presence of coronary artery disease in the same patient. What kind of resources or tools would you need? – try to be specific.</td>
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| **Erectile Dysfunction** | A 35 yr old man with hypertension and hyperlipidemia presents with erectile dysfunction (ED) and depression.  
**Facilitator:** The magnitude of the clinical problem and its vascular basis (5 min).  
The challenges in the preclinical and clinical research of ED. **Discuss “regression analysis” in statistics.**  
**Student:** Describe a research protocol in which to study the hypothesis that ED is an independent risk factor for mortality among all other vascular disease risk factors (e.g. hypertension, smoking, hyperlipidemia.) Be specific.  
**Readings:**  
Erectile dysfunction. McVary KT. NEJM. (2007); 13;357:2472-81 |
|------------------------|--------------------------------------------------------------------------------------------------|
| **Stroke**             | A 40 yr old man (married with 3 kids, owner of a business with 20 employees) with new atrial fibrillation, presents with signs of a large thromboembolic stroke in his GP office in Northern Alberta, within 45 minutes from the onset of symptoms. He is 4 hrs away from the closest hospital where imaging and possible thrombolytic therapy could be offered. In the absence of any timely intervention he develops permanent right upper and lower limb paralysis and dysphasia (he cannot talk).  
**Facilitator:** Discuss the case. What are the challenges in the management of acute stroke in a country like Canada (5 min). **Can a dollar value be used to quantify the loss of a human life? Should this be used in our reasoning for investing in costly medical infrastructure (10 min)?**  
**Student:** representatives from 40 remote North Alberta communities form a petition to the provincial government demanding the creation of 2 comprehensive satellite stroke centers (with CT availability, telehealth stations and nurses and physicians able to deliver thrombolytic therapies) to cover most of remote Northern Alberta and a population of 50,000. The estimated total cost is ~100 million, Describe the kind of evidence required to convince the government that funding of such a provincial program is beneficial and cost effective.  
**Readings:**  
WHO GUIDE TO IDENTIFYING THE ECONOMIC CONSEQUENCES OF DISEASE AND INJURY -  
Mortality Risk Valuation (United States environmental Protection Agency)  
https://www.epa.gov/environmental-economics/mortality-risk-valuation#means |
| **Chronic Angina**      | An 84 yr old woman with severe arthritis, presents with worsening chest pain with minimal activity. She has documented diffuse coronary artery disease. She is already on 14 different medications, she is ambulatory and lives independently  
**Facilitator:** 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 (10 min).**  
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.  
**Student 1 (10 min):** Describe an animal model that could best model the patient in your case.  
**Student 2 (10 min):** What kind of endpoints would you use is such a model, when developing therapies for angina that could target the elderly?  
**Readings:**  
| 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. He also asks for advice on enrollment on new clinical trials for hypertension.  
**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 (5 min). **Discuss Novel Clinical Trials design - part I**  
Describe the principles of a 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.  
**Student 1 (10 min):** in preclinical animal research  
**Student 2 (10 min):** in clinical research involving patients  
**Readings:**  
* Is it the blood pressure or the blood vessel? Cohn, J.N., Journal of the American Society of Hypertension (2007); 1: 5-16.  
* Adaptive designs for Clinical Trials. Bhatt et al. NEJM 2016; 375:65-74 July 7, 2016DOI: 10.1056/NEJMra1510061 | | 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. Non-standard risk factors for vascular disease (5 min). Challenges in the studies of endothelial function and novel clinical biomarkers (10 min).  
Describe the principles and essential features of a translational research program for the discovery of a novel blood-based biomarker of endothelial dysfunction.  
**Student 1 (10 min):** in preclinical research (discover the biomarker)  
**Student 2 (10 min):** in clinical research (validate the biomarker)  
**Readings:**  
**Facilitator:** The molecular basis of PAH and the challenges in translational research in PAH, limiting the development of effective therapies (5 min). **Principles of early phase clinical trial design for investigational new drugs** (10 min)  
**Student 1 (10 min):** 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. |
### Student 2 (10 min): Describe preclinical research principles in the development of pulmonary hypertension therapies: assuming a good rodent model, what kind of endpoints will you be checking in response to experimental therapies, and how can you achieve selectivity of the therapies to the pulmonary circulation?

**Readings:**
* Translational Challenges in Pulmonary Arterial Hypertension Research and A Vision for change, Sutendra et al. Science Translational Medicine, 2013
* Michelakis E. et al, “Inhibition of pyruvate dehydrogenase kinase improves pulmonary arterial hypertension in genetically susceptible patients”, Science Translational Medicine, 2017

### Debate 1

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

### Statistics Core

**Statistics Core**
1. Survival analysis with Cox and logistic regression
2. How to use and interpret combined endpoints
3. How to conduct and interpret subgroup analysis in clinical trials

### Acute Myocardial Infarction

A 55-year-old man presents with acute anterior MI and undergoes placement of a drug-eluding stent in the proximal left anterior descending artery, under a novel anticoagulation therapy (as part of a clinical trial). Although the stent placement was successful, he developed a large brain bleed that left him comatose.

**Facilitator:** What are the challenges in determining the optimal anticoagulation strategy to use during the very traumatic procedure of a stent placement in a coronary artery? **Discuss Novel Clinical Trial Designs – part II.**

**Student:** The patient participated in an industry-sponsored trial studying the benefits of a novel antiplatelet agent during acute coronary interventions. The physician that enrolled the patient in the trial did not mention to the patient and his wife that the physician and his institution would receive $20,000 in order to enroll this patient to the clinical protocol (this is relatively common practice). Do you think this was appropriate? Justify your response.

**Readings:**
Acute Myocardial Infarction. Anderson and Morrow. NEJM 2017; 376:2053-2064
DOI: 10.1056/NEJMr1606915

### Features of a How to write a scientific paper in the modern era: satisfying the long “quality assurance” pre-submission checklists of most leading journals
Grant Review Session

Debate 2

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 #1-2:** A global “life intervention” approach to improve diet and exercise in ALL Canadians, in order to prevent cardiovascular disease.

**Student #3-4:** 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 (i.e. patients with aneurysms, bypass vessels etc).

Review and FINAL EXAM
### MODULE III: Immunity, Inflammation, Infection


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<td><strong>Asthma 1</strong>&lt;br&gt;Molecules to Animals</td>
<td>25 year old female with long-standing asthma and frequent exacerbations despite preventive measures. <strong>Facilitator:</strong> Discuss the case (5 min). How can murine models of allergic airway inflammation be used to develop therapies for allergic asthma (10min)&lt;br&gt;<strong>Student:</strong> 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.&lt;br&gt;&lt;br&gt;<strong>Reading:</strong>&lt;br&gt;1. Holmes Am et al, Animal Models of asthma: value, limitations and opportunities for alternative approaches. <em>Drug Discov Today.</em> 2011; 16(15-16):659-70.&lt;br&gt;2. Perrin S. Preclinical research: Make mouse studies work. <em>Nature</em> 2014; 507:423-425&lt;br&gt;3. Book Chapter 2.1.6</td>
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<td><strong>Asthma 2</strong>&lt;br&gt;Animals to Humans</td>
<td><strong>Facilitator:</strong> 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)&lt;br&gt;<strong>Student:</strong> 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&lt;br&gt;&lt;br&gt;<strong>Reading:</strong> Book Chapter 3.1, 3.2, 3.3, 3.4</td>
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<td><strong>Asthma 3</strong>&lt;br&gt;Humans to Populations</td>
<td><strong>Facilitator:</strong> Briefly discuss asthma treatment, and give an overview of the findings of Reading 1: *How to measure survival in clinical trials&lt;br&gt;<strong>Student:</strong> Give a framework for assessing causality (the causal relationship between a drug and a harmful outcome). Discuss the Bradford Hill criteria. Based on this discussion, give your opinion as to whether beta-agonists increase the risk of death.&lt;br&gt;&lt;br&gt;<strong>Reading:</strong>&lt;br&gt;1. Nelson et al. The Salmeterol Multicenter Asthma Research Trial. A comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. <em>Chest</em> 2006;129:15-26.&lt;br&gt;2. Drug Therapy: Asthma; Fant a C.H. NEJM (2009); 360:1002-1014&lt;br&gt;3. Book Chapter 6</td>
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<td><strong>Virology 1</strong>&lt;br&gt;Molecules to Animals</td>
<td>49 year old female post-kidney transplant presents with fever, elevated liver function tests, and diarrhea and is diagnosed with CMV disease.&lt;br&gt;<strong>Facilitator:</strong> Discuss the case (5 min). The challenges of developing effective vaccines for diseases that affect immunocompromised individuals (10 min); optimizing preclinical studies&lt;br&gt;<strong>Student:</strong> 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?&lt;br&gt;&lt;br&gt;<strong>Reading:</strong>&lt;br&gt;1. Cytomegalovirus in solid organ transplantation. Razonable R et al. Am J Transplant. 2013 Mar;13 Suppl 4:93-106.&lt;br&gt;2. Rieder F and Steininger C. Cytomegalovirus vaccine: phase II clinical trial results. <em>Clin Microbiol Infect.</em> 2014, Suppl 5:95-102.&lt;br&gt;3. McVoy MA et al, A cytomegalovirus DNA vaccine induces antibodies that block viral entry into fibroblasts and epithelial cells. <em>Vaccine.</em> 2015, 33:7328-36.</td>
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<td><strong>Virology 2</strong></td>
<td>A 39 year old male with chronic undetected hepatitis C infection presents with liver failure.&lt;br&gt;<strong>Facilitator:</strong> Discuss the case (5 min). The challenges and creative approaches in developing animal...</td>
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### Animals to Humans
- **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:**
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 (5 min). 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:**
2. Book Chapter: 2.1.3, 2.1.7, 2.2

### Inflammation 2

#### Animals 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:**

### 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:**
| **Ethics committee review (animal and human)** | 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** | 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 |

| **EXAM** |  |
MODULE III: Principles of Translational Medicine: Metabolism and Metabolic Syndrome

The aim of this course is to explore important principles of translational medicine. To accomplish this task, articles in the field of metabolism, including obesity, diabetes, hypertension, dyslipidemia and the metabolic syndrome will be used. This course is designed to align graduate students and medical residents with the current trends in preclinical, clinical research and medical practice 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.

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| Cellular metabolism and human disease | **Facilitator:** A practical and focused review of the essentials of cell metabolism will be presented with an emphasis on human disease. Examples of the importance of cellular metabolism in the pathogenesis of cancer, vascular disease, myocardial disease and diabetes will be discussed (30 min)  
**Student:** Present a theoretical framework by which circulating and imaging biomarkers of mitochondrial function can be developed for cancer and vascular disease (15 min) |
| Diabetes - 1 | **Facilitator:** A 30 year old woman with newly diagnosed type I Diabetes and family history of cancer asks whether her metabolic disease can increase her risk of cancer and whether this risk can be passed on her children. The molecular basis of type I diabetes will be discussed. The newly discovered axis between metabolism and epigenetic mechanisms and the immediate relevance to human disease (including cancer) will also be discussed. This discussion will broaden the understanding of the impact of metabolic diseases beyond the current paradigm. (30 min)  
**Student:** Describe the design of a preclinical study that aims to address the hypothesis that uncontrolled diabetes in the mother will increase the probability of cancer in her offspring for at least 2 generations. Do not look to see whether this has been done in the literature. Assume that you have access to any kind of genetically engineered mice that you may need (even if such a mouse is not described in the literature yet. (15 min)  
**Readings:**  
* Diabetes Mellitus and the beta cell: the last 10 years. Aschroft et al. Cell (2012); 148: 1160-70  
| Diabetes - 2 | **Facilitator:** A 45 year-old man with diabetes and hypertension has a blood pressure of 160/90 mmHg. Discuss the case and the importance of risk factors for primary prevention of coronary disease in patients with Diabetes. Discuss the ACCORD trial – specifically, how should one proceed when a trial shows a null result for the primary endpoint, but has a statistically significant reduction in an important secondary endpoint.  
**Student:** The ACCORD trial is an example of a factorial design trial. Discuss this type of study design, describe its pros and cons and how it may explain the study result. ACCORD was also a non-blinded study. Discuss different levels of blinding, or lack thereof, the risk of bias in non-blinded studies and when its ‘ok’ to conduct an un-blinded study.  
**Readings:**  
* ACCORD study supplement  
<p>| Obesity - 1 | <strong>Facilitator:</strong> A 30 year old woman who is overweight by 15 Kg from her optimal weight is asking you about her risk of cardiovascular disease and cancer, because she is very concerned form her readings |</p>
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<td>on the internet. She swims for 1 hour 3-4 times a week. Her blood pressure and all her blood tests are normal. Discuss the molecular links between obesity, CV disease and cancer (20 min)</td>
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<td>Student:</td>
<td>The obesity paradox describes a potential protective effect of non-morbid obesity for a number of human diseases including CV disease, cancer or renal disease to name a few. Would a preclinical or a clinical study be the optimal way to prove or disprove this concept? Justify your decision and describe a summary of your research approach following either a preclinical or clinical study. (15 min)</td>
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<td>Obesity -2</td>
<td>Facilitator: 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”. Discuss the case and the relative importance of pharmacotherapy in the treatment of obesity. Discuss the challenges in clinical research on the role of pharmacotherapy in obesity (20 min)</td>
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<td>Student:</td>
<td>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? (15 min)</td>
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* 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 |
| Metabolic Syndrome -1 | Facilitator: A 70-year-old obese man with metabolic syndrome and coronary disease has a blood pressure of 160/70. He has started losing weight and his lipids and glucose levels are very well controlled. You need to lower his BP but are uncertain as to how much it should be reduced. You are considering his enrollment in a clinical trial that compares intensive versus standard blood pressure control. The importance of blood pressure control in the metabolic syndrome and secondary prevention of coronary artery disease will briefly be discussed. The findings and implications of the SPRINT trial will also be discussed: What is allocation concealment in randomized controlled trials? How is it done? Why is it so important? |
| Student: | SPRINT is a very controversial trial. Many clinicians have decided not to adopt the findings. Generalizability is a major concern. What is generalizability? Why is it important? List and discuss all of the ways that the generalizability of a randomized controlled trial may be compromised using examples from the SPRINT trial and its findings. |
| Readings: | * Metabolic syndrome: from epidemiology to systems biology. A. Lusis et al Nature Reviews Genetics. 9, 819-830  
* Schulz KF. Assessing allocation concealment and blinding in randomised controlled trials: why bother? |
| Metabolic Syndrome -2 | Facilitator: An overweight 45 year old man with a 15 pack year history of smoking and no other significant past medical history participates in a clinical study on the natural history of atherosclerosis and is found to have elevated CRP levels. He asks you what is the meaning of this biomarker as he is very concerned from his readings on the internet. Discuss the importance of inflammation in the metabolic syndrome and the challenges in proving whether inflammation is a result or a contributing cause of metabolic syndrome. (20 min) |
| Student: | There is evidence that inflammatory cytokines can cause insulin resistance in skeletal muscle. There is also evidence that a primary metabolic disturbance (like insulin resistance) can cause...
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<td>activation of T and other inflammatory cells. Describe a research project using in vitro and in vivo animal studies to show whether inflammation is upstream or downstream from a metabolic disturbance (like the one caused by insulin resistance) (15min)</td>
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|         | **Readings:**<br>* From C-Reactive Protein to Interleukin-6 to Interleukin-1: Moving Upstream To Identify Novel Targets for Atheroprotection. Ridker PM. Circ Res. 2016;118(1):145-56.  
* Metabolic Syndrome: A Clinical and Molecular Perspective, D Moller et al, Annual Review of Medicine (2005); 56: 45-62 |
| Hyperlipidemia | **Facilitator:** 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. The relative importance of genetics versus environmental factors in the pathogenesis of hyperlipidemia will be discussed. The challenges or preclinical research and animal models for the pathogenesis and treatment of human hyperlipidemia (20 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. |
|         | **Readings:**<br>* Rethinking Primary Prevention of Atherosclerosis-Related Disease: C. Napoli, et al, Circulation. (2006);114:2517-2527  
| Ethics-Metabolic Syndrome | **A 70 year old Asian woman presented with type II Diabetes, hyperlipidemia and hypertension. While her diabetes and hyperlipidemia have been managed by the appropriate therapy her BP found to be is 200/70 in several occasions. She is asked to enter a randomized controlled trial that will compare an antihypertensive drug to placebo. Should she?**

**Facilitator:** Discuss the case (5 min). What is informed consent. Discuss its history and significance. |
|         | **Student:** Discuss the concept of equipoise in randomized controlled trials. Give examples in clinical medicine where equipoise was not met. Review the design and results of the Syst-China trial. In the context of the year this trial was performed, was it an ethical trial? |
| Grant Writing | **The one-page summary is the most critical part of a grant writing process. Two students will be assigned to write a 1-page summary of a grant. Two grants (a clinical and a basic research one) will be circulated before the class and these students will present their 1-page summary for critique and discussion.**

**Grant Writing - 1**  
HV-EM-RP  
*Proof of principle* of “feasibility” grants are critical for the career of young investigators. 5 students will be asked to write a 3 page grant proposal based on specific instructions and the critique of the grants will be presented during the session. |
| Grant Writing - 2 | **Practical short**  
Faculty will be present short talks with a focus on practical issues for research |
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<td>1. The five things you need to know for sample size calculations in preclinical and clinical research (20 min)</td>
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<td>2. Statistical analysis: parametric and non-parametric data statistical testing (20 min)</td>
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<td>3. ANOVA and post hoc statistical corrections (20 min)</td>
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<td>Debate 1</td>
<td>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.</td>
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<td>Human randomized controlled trials in this area are not available and difficult to do. For this debate,</td>
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<td><strong>Student #1:</strong> 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.</td>
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<td><strong>Student #2:</strong> 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.</td>
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<td>Debate 2</td>
<td>Clinical practice guidelines differ dramatically in their approach to the treatment of dyslipidemia. The US guidelines recommend a ‘fire and forget’ approach, in which drugs are started at moderate to high doses if risk is high and no further monitoring is recommended. The Canadian guidelines recommend that LDL levels be followed and that drug therapy be titrated such that LDL levels are lowered below target.</td>
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<td><strong>Student #1:</strong> should argue that the American approach is correct, that the only evidence that matters when crafting clinical practice guidelines is the ‘hard endpoint’ evidence from human statin trials, that the LDL hypothesis is not the primary reason for statin benefit, and that we don’t need to consider animal model data and/or observational human data.</td>
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<td><strong>Student #2:</strong> should argue that the Canadian approach is correct, that we should consider ALL the data when making clinical practice guidelines and the data justify a treat-to-target approach using LDL levels as the surrogate endpoint.</td>
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<td><strong>FINAL EXAM</strong></td>
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