		Design an appropriate pre-clinical study to investigate the efficacy of this new vaccine. What biomarkers and endpoints (either blood-based or imaging) would you use to assess the validity of this treatment? What would make a potential biomarker attractive for clinical translation? Reading: Rosenberg et al., Cancer Immunotherapy: moving beyond current vaccines: Nature Medicine. 2004 Sep; 10(9): 909-15. Mak IWY et al. Lost in translation: animal models and clinical trials in cancer treatment. American Journal of Translational Research. 2014; 6(2): 114-118.
Week 3 **October 1** **Faculty** Jickling **Student:** Igor Zoric	***Biomarkers 2*** ***Stroke***	A 55 year old female has 30 minutes of right sided weakness and numbness. She has a history of migraines and this was thought be the aura component of her migraine. Seven days later she has a large stroke leaving her paralyzed on the right side and unable to speak. Facilitator (25 min): Discuss the case. Discuss the role a biomarker could play to aid in the diagnosis of stroke. Discuss the steps involved in translating a marker of disease to a clinical biomarker including sensitivity, specificity, clinical utility, prediction analysis, validation. Student (15 min): You have a well-validated animal model of stroke. You start screening the factors that change in the blood stream of the animal within minutes after the induction of stroke (embolization of a cerebral artery) measuring proteins and small molecules. Among the hundreds of factors that change, 10 show a significant increase and 5 show a significant decrease. Describe the rationale of your approach to identify which of these factors are the most attractive and deserve further studies as potential biomarkers for the very early diagnosis of stroke. Reading: Drucker E et al. Pitfalls and limitations in translation from biomarker discovery to clinical utility in predictive and personalized medicine. EPMA J. 2013; 4(1). Sara A et al. Translating RNA sequencing into clinical diagnostics: opportunities and challenges. Nature Reviews Genetics 2016; 17, 257–271
Week 4 **Oct 8** **Faculty** Kinnaird **Student:** Maryam Soleimani	***Biomarkers 3*** ***Prostate Cancer***	A 64 year old man is referred to the Urology clinic with an elevated PSA of 5.4. He has a family history of prostate cancer in his father and breast cancer in his mother. He asks if he has prostate cancer and how we would find out if he does? Facilitator (25 minutes): Discuss principles of risk assessment in disease. Does risk outweigh harm? Discuss use of biochemical, imaging, and genetic biomarkers in prostate cancer diagnosis and management. Student (15 minutes): You have a new ultrasound device that can detect prostate cancer in animal models with a sensitivity of 95% and a specificity of 30%. How would you design an early phase trial to determine the diagnostic accuracy of this new device in humans? Reading: Hung et al., PSA and Beyond: Biomarkers in Prostate Cancer. BCMJ, vol 56, No. 7. September 2014.
Week 5 **Oct 15** **Faculty** Jickling **Student:**	***Assessing Risk Reduction*** ***Influenza***	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 (20 min): Brief background on influenza, vaccine efficacy and current expert consensus indications for vaccination. Discuss the concepts of relative risk and absolute risk. Student (15 min): The target population for flu vaccination has evolved from administration only to high-risk individuals, 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'.

Robert Kay		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
Week 6 **Oct 22** **Faculty** Sutendra **Student:** Bruna Dutra	***Assessing Correlation*** Myocarditis	A 30-year-old male has mild chest pain and fever, and subsequent blood work (troponin) and imaging studies (coronary angiography, MRI, ECHO) suggest that the patient has myocarditis. He asks about the chance that he will develop chronic heart failure. Facilitator (20 min): Discuss the case. Is there an ideal biomarker for diagnosing heart failure and correlating with the severity of disease? Discuss correlation plots, including the Pearson Correlation Coefficient. Student (15 min): You wish to identify a novel biomarker that would predict the occurrence of heart failure (i.e. prior to clinical symptoms or functional changes in cardiac function). Design the ideal pre-clinical study/model to identify such a biomarker. What would you look for and how would you screen for this candidate biomarker? How would you validate this biomarker identified in pre-clinical models in the clinical setting? Reading: Eugene Braunwald. Biomarkers in Heart Failure. NEJM. 2008; 358:2148-2159. Cooper LT Jr. Myocarditis. N Engl J Med. 2009;360(15):1526-38.
Week 7 **Oct. 29** **Faculty** Jickling **Student:** Ali Nomani	***Principles of bedside-to-bench research*** ***Neuro-inflammation***	A 58 year old female presents with vision loss and bilateral leg weakness that is worsening over the past 4 days. Her MRI brain is normal but her spinal fluid suggests inflammation. Facilitator (20 min): Discuss the case and the clinical approach to what may be a novel, not previously described disease. Describe how you would accurately phenotype it and how would you approach potential "causal" versus "associative" findings at the early stages of a molecular/genetic work-up. Student (15 min): You have several patients with very unique clinical phenotype suggesting a novel neuro-inflammatory disease. The mechanism of this disease remains as yet unknown. Describe your approach to study the disease and investigate potential mechanism. What principles will you need to follow in order to establish a preclinical model of the new disease? What would this model look like? (don't look into the literature – it may have not been described yet)
Week 8 **Nov 5** **Faculty** Jickling **Student:** Danielle Munsterman	***Biomarkers 4*** ***COVID-19***	A 74yr female presents with new fever and cough. Her nasal swab is PCR positive for COVID19. Over the subsequent 6 days she experiences worsening renal function and respiratory function requiring intubation and intensive care admission. Facilitator (20 min): Discussion of risk stratification biomarkers. Student (15 min): You have an immunoglobulin therapy to help reduce COVID19 injury to the lungs. It is costly and in limited supply so is only available to a very small fraction of patients with COVID19. Design a biomarker study to select which patients are most likely to benefit from the therapy to prevent respiratory failure.
Week 9 **Nov 12** **Faculty** Sutendra Jickling	***Ethics of animal and human research***	Facilitators (10min x 2):Briefly describe the ACUC animal review panel and human ethics review panel processes. Critical components of an animal protocol and a human ethics protocol will be presented by the facilitators in this session. Student 1 (10 min): You have a disease model (for example injection of monocrotaline that causes pulmonary hypertension and predictable death within 5 weeks from heart failure) and you want to evaluate an experimental drug in terms of its ability to prolong survival. But the ethics committee objects and tells you that since death will come predictably it is inhumane to let the animals die from an agonizing death with worsening symptoms. You reply that this is what

Student 1: Saymon Tejay **Student 2:** Anita Dahiya		happens in humans: they typically die from agonizing deaths with many symptoms in incurable diseases and you want to model the real disease. But the committee still forbids you from having a protocol where the animals (particularly in the placebo group) will be left to die in order to study your drug's effects on survival. What can you do in this case to best study your drug? Student 2 (10 min): A clinical trial evaluates an experimental therapy in a rare and deadly disease. In the protocol the sponsors propose to pay the patients enrolled $1000 each, in order to motivate participation. They argue that their experience tells them that these patients are two few and too sick and unless they motivate participation the will not be able to complete the trial and an opportunity to find a cure will be lost. The money is the company's (a private company), not public. The ethics committee does not allow in general enrolled patients to receive payments in clinical trials. What do you think? Justify your opinion.
Week 10 **Nov 19** **Faculty** Sutendra **Student:** Moin Tinwala	***Biomarker 4*** *Cardiotoxicity*	A 58-year-old female is taking the chemotherapeutic Herceptin for HER2 positive breast cancer, but is worried about her chances of developing cardiac dysfunction as a direct consequence of her cancer treatment. She asks if there are specific ways to detect if she would be more susceptible for developing cardiotoxicity. Facilitator (20 min): Discuss the case along with challenges in predicating which patients are more prone to chemotherapy-induced cardiotoxicity. Discuss the principles and importance of tumor-secreted factors. Student (15 min): You have access to tumor cell lines that grow indefinitely (and pure tumor biopsies) from patients that have developed cardiotoxicity and those that have not. Design a pre-clinical study to identify candidate tumor-secreted factors that could increase the risk of developing cardiotoxicity.
Week 11 **Nov 26** **Faculty** Sutendra Jickling **Group Discussions**	***Biomarker Identification and Validation from Pre-Clinical models to the Clinical Setting***	The group will be split into two different teams (you will be informed of your team in the previous session). We will expand on the previous discussions from the prior session. We have identified a novel Tumor-Secreted Factor (TSF) that appears to positively correlate (in pre-clinical models) with mice that develop chemotherapy-induced cardiotoxicity (CIC). **Team A** (Pre-Clinical) will provide details on how they will directly determine if the candidate TSF is either directly involved in the development of CIC or a mere consequence. What in-vitro and in-vivo assays will you use to validate that this TSF is involved in CIC susceptibility? How will you elucidate this mechanism of action? **Team B** (Clinical) will provide details on how they will validate and design a prospective clinical trial to address that this TSF is a good biomarker and predictive for CIC susceptibility in patients.
Week 12 **Dec 3** **Team A** Joseph Tatuene **Team B** Ali Nomani	**Debate**	Debate Topic: Conflict of Interest (COI) is a serious problem in medical research. Many clinicians receive consultancy fees and/or research funds when participating in industry sponsored clinical research. At times these fees can reach tenths (and in some cases hundreds) of thousands of dollars. Also, many basic scientists develop for-profit spin-off companies (based on their patents) to promote and sell a product, with significant financial gains (for themselves and their institution). There is ample evidence to suggest that financial incentives can bias academics (both clinical and basic researchers) in the way they conduct and particularly they interpret and communicate research findings. This is a problem if these academics can influence public opinion (colleagues, regulatory agencies, public) by means of a) publishing an influential paper, or b) participating in high impact committees (like "guidelines / consensus statement committees or regulatory agencies committees). To address this concern the following measures are currently taken: a) all authors of a paper have to declare any association with companies from which they receive money

		b) the membership of many (but not all) committees requires that all members need to make their COI public and >50% of the members need to have no significant conflicts of interest (e.g. the second "rule" is a requirement for American Heart Association guidelines committees but not for many Canadian "guidelines" committees). Most of the times these measures are based on the assumption that simply "declaring the COI" is an adequate measure since the "readers" can "make their own conclusions". Argue for the following statement: **Team A:**"We agree that the current status of "declaring COI" is adequate in medical research – no further measures are needed." **Team B:**"We disagree that "declaration of COI" alone is adequate since declaring COI does not eliminate the COI and the relevant bias – further, stricter measures are needed." Team A: 15 min presentation Team B: 15 min presentation Team A: 3 min rebuttal Team B: 3 min rebuttal Discussion and audience vote: 25 minutes
Week 13 **Dec 10** **Faculty** Jickling Sutendra **Grant Review** **Panel A:** Kiandokht Bashiri/ Bruna Dutra **Panel B:** Robert Kay/Igor Zoric	**Grant Review Panel**	All students will be provided with recent grants from the facilitators. Two students will present the grants and provide strengths/weaknesses for each grant. Only one grant can be funded and the panel will vote (based also on the summary page) which grant should be funded. The **objective** of this session is to stimulate a grant review panel for all to assess how a grant is reviewed in a peer-review panel.
Week 14 **Dec 17**		FINAL EXAM