MED 604 Translational Research Training Program, Module II

Co-ordinators: Drs. G. Jickling, G. Sutendra and E.D. Michelakis

The course aim is to understand the principles in the conduct of early-phase versus large clinical trials and the requirements for successful translation of preclinical research: traditional and novel trial designs, endpoints, statistical challenges, regulatory and funding challenges, structure of translational teams and knowledge translation will be discussed. 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 entire Translational Medicine Program

Med 602, Module I: The course aim is to understand principles of preclinical (animal and human tissue-based) research and models of human disease that promote translation to early phase clinical trials.
Med 604, Module II: The course aim is to understand the principles in the conduct of early-phase versus large clinical trials and the requirements for successful translation of preclinical research: traditional and novel trial designs, endpoints, statistical challenges, regulatory and funding challenges, structure of translational teams and knowledge translation will be discussed.
Med 606, Module III: The course aim is to recognize the role of biomarkers (genetic, biochemical and imaging) in clinical research, including early phase trials and clinical care. Principles for the discovery of novel biomarkers at the preclinical and clinical level will be discussed.
Med 608, Module IV: The course aim is to discuss the principles of candidate drug targets in disease and drug design. The importance of drug target validation at the cellular level, preclinical level and in clinical studies as well as the financial and social implications of drug development will be discussed.

Objectives for Med 604, Module II Course – Winter 2022 Term

- Novel clinical trial design
- Early-phase clinical trial design
- Cost-benefit analysis in outcomes research
- Ethics of clinical research
- Quality assurance in the writing of a scientific paper
- Statistics: Correlation, regression, survival analysis
- Effective grant writing

Companion Book: Principles of Translational Science in Medicine: From Bench to Bedside. Edited by Martin Wehling
Second Edition; ISBN: 978-0-12-800687-0
(available at the UofA library, at the Dept of Medicine Res Office and uploaded as PDF at program's site)

SESSION		SESSION DETAILS
Week 1 **Jan 13** **Faculty** Michelakis Sutendra Jickling	**Essentials of Grant Writing**	1. Introduction to Med 604: **Michelakis** 2. Assessment for the long "quality assurance" pre-submission checklists of most leading journals. 3. Fundamental aspects of Grant writing and assessment. The objectives and expectations of Module II will be described. Principles of grant writing, along with resubmission of unsuccessful grant and peer review process will be discussed. Every trainee is expected to submit a 3-page hospital foundation style grant to be discussed at the last session of the course.
Week 2 **Jan 20** **Faculty** Michelakis **Student 1:**	***Human Ethics I: Clinical trials***	A 30-year-old woman suffers from a rare form of lymphoma that has failed all standard therapies. An industry sponsored clinical trial just published impressive results of a new drug on the same form of lymphoma with the patient. This was a small early-phase clinical trial (not placebo controlled) but had very robust positive results (80% of the 40 patients enrolled had an almost complete resolution of the tumor) but the drug is a few years before it can be approved in the USA and Canada. The patient has 6 months to live at best. The parents are asking the government for exception and permission to use the drug for their daughter. Facilitator: The history of ethics regulation of human clinical research (10 min) The basis of the COI around physicians that are paid from industry to conduct clinical trials (10 min)

Saymon Tejay **Student 2:** Alexandra Saunders		Student 1: Should the government make an exception and allow the company to offer the drug to this patient? Student 2: A patient participated in an industry-sponsored trial studying the benefits of a novel cancer grant. 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 enrol this patient to the clinical protocol (this is relatively common practice). Do you think this was appropriate? Justify your response.
Week 3 **Jan 27** **Faculty** Michelakis **Student 1:** Majid Sikosana **Student 2:** Amy Morrison	**Challenges of clinical research in the elderly**	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 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: 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? (15 min) Student 2: You speculate that **Protein X** is induced in the myocardium of elderly patients and is *causative* for susceptibility to left ventricular dilation. How would you investigate this in a preclinical model, but also in elderly human patients? Readings: Can J Cardiol. 2004; Suppl A:7A-16A. Canadian Cardiovascular Society Consensus Conference 2002: Management of heart disease in the elderly patient
Week 4 **Feb 3** **Faculty** Jickling **Student:** Joseph Lunyera	***Human Ethics II:*** Health care delivery	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 - http://www.who.int/choice/publications/d_economic_impact_guide.pdf* Mortality Risk Valuation (United States environmental Protection Agency) https://www.epa.gov/environmental-economics/mortality-risk-valuation#means
Week 5 **Feb 10**	***Complex Diseases and clinical trials***	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.

Faculty Michelakis **Student 1:** Amro Qaddoura **Student 2:** Margret Michaels		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: In preclinical animal research (15 min) Student 2: In the clinical setting (15 min) 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. * Adaptive designs for Clinical Trials. Bhatt et al. NEJM 2016; 375:65-74July 7, 2016DOI: 10.1056/NEJMra1510061
Week 6 **Feb 17** **Faculty** Michelakis **Student:** Nishaka William	***Biomarkers I and precision medicine-designed trials***	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 a disease that causes remodeling (and stenosis) of pulmonary arteries but spares systemic blood vessels. 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 in rare diseases** (10 min) Student: Speculate on the reason(s) for which this disease (pulmonary hypertension) affects the pulmonary arteries (causing proliferative vascular remodeling resembling in-stent restenosis) but spares all the other blood vessels in the body. You will not find an answer in the literature. Speculate using logic and try to justify your opinion. This concept is critical for the rationale used in the design of early phase trials for pulmonary hypertension in order to achieve specificity of the therapies for the pulmonary, but not systemic arteries. 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).
Week 7 **Feb 24** **Faculty** Jickling **Student 1:**	***Biomarkers II***	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. Challenges in the studies of endothelial function and novel clinical biomarkers – basic principles of biomarker discovery (20 min). Students: 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: in preclinical research (discover the biomarker) (15 min)

Abdulellah Almohaya **Student 2:** Luke Gagnon		Student 2: in clinical research (validate the biomarker) (15 min) 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.
Week 8 **Mar 3** **Faculty** Sutendra **Team 1:** Benson Weyant & David Li **Team 2:** Muizz Wahid & Jashan Saini	***Co-Clinical Trial Design***	This session will incorporate the principles discussed in Med 602 and clinical trial designs discussed this semester. The co-clinical trial occurs at the same time in both the patient and the pre-clinical animal model. In this case, we will design a co-clinical trial for a specific form of melanoma that initial genetic sequencing revealed a functional mutation resulting in a gain of function mutation for the oncogene BRAF (V600E). In addition, the patient has an SNP for loss of function for p53. The preclinical team already has several mouse models available for the co-clinical trial study, including p53-deficient mice, immune-deficient or immune-competent models for human tumor engraftment. Furthermore, biopsies from the patient will be provided every month. The initial treatment plan for this patient is the "relatively" selective inhibitor of BRAF (V600E) Vemurafenib. However, it is well known that resistance to this drug can occur as early as 6 months after therapy. Facilitator: Discuss the case. Briefly review the co-clinical trial concept and its ability to improve the efficacy of drug treatments in early-phase clinical trials. (10 min) Team 1: Design this co-clinical trial from the perspective of the preclinical side. What information would you need from clinical team? How would you design the animal trial? What would be your endpoints? What drugs would you test in these animals? Is there a potential to find a novel therapy against this cancer? What is the plan if resistance to therapy occurs (and is expected)? Think about sequencing the tumor serially. (15 min) Team 2: Design the trial from the perspective of the clinical team. What would you look for in the patient during the treatment regime? What are your endpoints? What information would you need from the preclinical team while following this patient? What is the plan if resistance to therapy occurs? (15 min) Readings: *A co-clinical platform to accelerate cancer treatment optimization. Andrea Lunardi and Pier Paolo Pandolfi. Trends in Molecular Medicine January 2015, Vol. 21, No. 1
Week 9 **Mar 10** **Faculty** Michelakis **Student:** Robert Kay	***Novel clinical trial designs: adoptive clinical trials***	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: Speculate on the potential design of clinical trials in a situation like the one described in the clinical case, i.e. how could you design a trial to see whether a new drug (i.e. an anticoagulant) prevents in-stent restenosis while the potential adverse effects (i.e. bleeding) are minimized during the duration of the trial Readings: Acute Myocardial Infarction. Anderson and Morrow. NEJM 2017; 376:2053-2064 DOI: 10.1056/NEJMra1606915
Week 10 **Mar 17** **Faculty**	***Statistics***	Facilitator: Presentations on important statistical tests that are essential for small clinical trial designs, including correlation will be presented and discussed (30 min).

Sutendra **Student:** Christine Salama		Student: It appears that Transcription Factor X (TFX) can increase the metastatic potential of a cancer cell. Utilizing the co-clinical trial concept (discussed above), design a pre-clinical/clinical study to assess if tumor biopsies from patients that express high vs low levels of TFX results in increased metastatic rate (15 min).
Week 11 **Mar 24** **Faculty** Paulden **Student:** McDonald Isaiah	***Health Economics and clinical trials***	A 47-year female has breast cancer. She is concerned about her risk of recurrent breast cancer. Chemotherapy would reduce this risk; however, she is worried about the side effects. Facilitator: Discuss the case and how a new biomarker assay could help guide the decision to be treated with chemotherapy in breast cancer. Discuss the role of a cost analysis to implement a new biomarker in practice. Student: An ideal biomarker should be: specific, sensitive, reproducible, cheap and simple. Rank these 5 features in terms of importance in its clinical use for a relatively common and deadly disease like cancer and justify your reasoning. Reading: Paulden M et al. Cost-Effectiveness of the 21-Gene Assay for Guiding Adjuvant Chemotherapy Decisions in Early Breast Cancer. Value in Health 2013; 16(5) 729-739.
Week 12 **Mar 31** **Faculty** Kinnaird **Student 1:** Elise Kammerer **Student 2:** Monica Dahiya	***Designing a small clinical trial for a new diagnostic test***	A 55-year-old man is diagnosed with Gleason Grade Group 1 (low risk) prostate cancer. Active Surveillance is suggested as the management strategy. He asks, "What are the chances this cancer gets worse?" Facilitator: Describe current strategies to prognosticate cancer outcomes using prostate cancer active surveillance as a model Student 1: Design an early phase clinical trial for a new test (imaging or genomic or blood test) that may predict the development of aggressive prostate cancer in the future. Student 2: What is decisional regret? Why are patient quality of life outcomes important in clinical trials and how are they assessed? Briefly describe how you would capture patient quality of life in a prostate cancer clinical trial that compared active surveillance against surgery.
Week 13 **Apr 7** **All**	***Grant writing II*** ***Review of grants***	Grant review session (small group discussions headed by each of the 3 facilitators) of the grants submitted (deadline for grant submission Friday Apr 1st, 12:00 p.m. (noon)).
Apr 14		**FINAL EXAM** Winter term examinations are held within the period of April 13-26

MED 606 - Principles of Translational Medicine, Module III

The aim of this course is to explore the translational aspects of preclinical and clinical research covering all CIHR pillars of research. It is designed to help graduate students and medical residents to better understand translational research or even become effective translators of discovery and knowledge themselves.

Objectives of the whole program (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-health services" continuum.

Objectives of MED 606

While the clinical examples that will be used will mainly come form diseases of cardiovascular, cancer, inflammation and immunity (but also include example of other diseases like stroke) the emphasis will not be on the clinical aspects of these diseases. Rather, these diseases will often provide a platform in which some of the following research concepts will be developed:

- **Biomarker discovery principles**
- **Principles of statistical analysis in high sample sizes, survival analysis, risk reduction assessment and correlation plots**
- **Features of Biomarker validation in pre-clinical models and clinical setting**
- **Features of effective pre-clinical models (bench to bedside and bedside to bench)**
- **Principles for human and animal ethics protocols**

Companion Book: Principles of Translational Science in Medicine: From Bench to Bedside. Edited by Martin Wehling
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	SESSION	SESSION DETAILS
Week 1 **Sept 15** **Faculty** Jickling **Student** none	***Introduction***	**Introduction to MED 606** Background on Biomarkers and Precision Medicine. Discussion of Biomarker Development using examples from Clinical Practice Students: Before class think of a biomarker used in the disease you study. What type of biomarker is it? How is it used? How was it developed?
Week 2 **Sept 22** **Faculty** Jickling **Student:** Majid Sikosana	***Biomarkers 1*** *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 3 **Sept 29** **Faculty** Sutendra **Student:** Matthew Cooper	***Biomarkers 2*** *Cancer Immunotherapy*	A 42-year-old male had surgery to remove an aggressive form of melanoma. As an adjuvant therapy to prevent the potential recurrence of this cancer the patient is given a vaccine that is designed to stimulate the body's immune system against this form of cancer. Facilitator (20 min): Discuss the case. Briefly discuss the principles of immunotherapy and the development of vaccines in cancer as well as the basic principles of appropriate pre-clinical models for cancer treatment. Students (15 min): A new candidate vaccine needs to be tested for its effectiveness against melanoma. The vaccine is based on a unique protein expressed on the surface of melanoma cells but in no other cells. Thus, it sensitizes immune cells to attack and kill all cells expressing this protein, as if they were foreign. You have 3 well-validated models of melanoma where human or mice melanoma tumors grow fast in mice. 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 4 **Oct 6** **Faculty** Sutendra **Student:** Shivani Mandal	***Biomarker 3*** *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 5 **Oct 13** **Faculty** Jickling **Student:** Sarina Falcione	Companion Diagnostics	Facilitator: Discussion of biomarkers to improve patient selection for drug therapy. What are the advantages and disadvantages of using a biomarker to improve "precision" of which patients should receive a treatment. Student: A new study has just been funded to evaluate a drug designed to inhibit metastasis (spread) of lung cancer. The study will randomize 1000 lung cancer patients with no metastasis to the study drug + standard care versus standard care alone. The primary outcome is the rate of metastasis at 1 year. A request for ancillary applications is put out with a budget of $500,000. The request is to develop a biomarker that can improve patient selection of who responds to the drug. Design a biomarker study to address this request. What biomarker will you use? How will you divide the cohort to test your proposed biomarker?

		Reading: Nature Reviews Rheumatology volume 14, pages 354–362 (2018)
Week 6 **Oct 20** **Faculty** Sutendra **Student:** David Li	**Statistics – Part 1** ***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. 27** **Faculty** Jickling **Student:** Majid Sikosana	***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 3** **Faculty** Fahlman **Student:** Almohaya Abdulellah	***Biomarkers 4*** *Proteomic Analysis for Biomarker Identification*	A 34yr female presents with weakness of arm and leg muscles, double vision, drooping eyelids and difficulties with speech, chewing, swallowing and breathing. Her preliminary diagnosis appears to be Myasthenia Gravis. Facilitator (20 min): Discuss a novel proteomic approach for identification and validation of a universal biomarker for Mysasthenia Gravis. Student (15 min): Design an appropriate biomarker-based protocol for validating a proteomic biomarker as specific for this condition, while addressing the importance of using a reference/control disease in addition to healthy control patients when comparing this candidate biomarker from the target disease.
Week 9 **Nov 10** **Faculty** Sutendra Michelakis **Student 1:**	***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 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

Joseph Nanoa **Student 2:** Benson Weyant		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 17** **Faculty** Kinnaird **Student:** Arno Qaddoura	***Biomarker 5*** *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 11 **Nov 24** **Faculty** Michelakis **Student:** Narmeen Umar	***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 (10 min – 7 slides): The target population for flu vaccination has evolved from administration only to high-risk individuals, to administration to most of the population. **Student:** Does the evidence support this? What factors should be weighted when deciding on mass vaccination? Discuss Rose's 'Prevention Paradox'. 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 12 **Dec 1** **Faculty** Michelakis **Team A** Luke Gagnon **Team B** Alexander Saunders	**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: 5 min rebuttal Team B: 5 min rebuttal Discussion and audience vote: 20 minutes
Week 13 **Dec 8** **Faculty** Michelakis **Student:** Bohlouli Solmaz	**Biomarker 7** *Asthma*	25-year-old female with long-standing asthma has frequent exacerbations despite preventive measures. Although the exacerbations are mostly mild, they seriously impact her quality of life. <u>Facilitator (20 min):</u> Discuss 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). <u>Student (15 min – 10 slides):</u> You have identified a new blood-based biomarker in asthma and your data from a small clinical study indicate that it may be able to predict asthma exacerbations, but it appears that it may also be associated with the severity of the disease. Design a prospective study to separate the two (i.e. a) predict disease exacerbations, b) is associated with the severity of the disease – the more severe the disease the higher its levels) and validate its clinical use. <u>Reading:</u> Book Chapter 3.1, 3.2, 3.3, 3.4
Week 14 **Dec 15**		**FINAL EXAM**

MED 608 - Principles of Translational Medicine, Module IV

The aim of this course is to explore the translational aspects of preclinical and clinical research covering all CIHR pillars of research. It is designed to help graduate students and medical residents to better understand translational research or even become effective translators of discovery and knowledge themselves.

Objectives of the whole program (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 and large clinical trials: understand the challenges in the conduction of early-phase versus large clinical trials and the requirements for successful translation of preclinical research: traditional and novel trial designs, endpoints, statistical challenges, regulatory and funding challenges, structure of translational teams, knowledge translation.

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. Drug Development: Identifying candidate drug targets, along with drug design and validation of dug targets will be discussed at the cellular level, along with pre-clinical models and clinical studies.

Objectives of MED 608

While the clinical examples that will be used will mainly come form diseases related to metabolism, the emphasis will not be on the clinical aspects of these diseases. Rather, these diseases will often provide a platform in which some of the following research concepts will be developed:

- **Identification of candidate drug targets in complex multifactorial diseases**
- **Economics and ethics of Drug Development**
- **Features of effective pre-clinical models (bench to bedside and bedside to bench)**
- **Principles of designing small pilot studies, early phase and large clinical trials**
- **Principles of knowledge translation in preclinical and clinical studies**
- **Communication skills and effective grant writing**

Companion Book: Principles of Translational Science in Medicine: From Bench to Bedside. Edited by Martin Wehling Second Edition; ISBN: 978-0-12-800687-0
(available at the UofA library, at the Dept of Medicine Res Office and uploaded as PDF at program's site)

SESSION		SESSION DETAILS
Week 1 **Jan 12** **Faculty** Sutendra Michelakis Jickling	**Essentials of Grant Writing** ***Group Session***	1. Introduction to Med 608 2. Fundamental aspects of Grant writing and assessment. The objectives and expectations of Module IV will be described. Principles of grant writing, along with resubmission of unsuccessful grant and peer review process will be discussed. Every trainee is expected to submit a 3-page hospital foundation style grant to be discussed at the last session of the course.
Week 2 **Jan 19** **Faculty** Sutendra	***Metabolism and Human Disease*** ***Group Session*** ***Objective:*** Drug target identification in complex diseases	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, obesity, diabetes and neurodegenerative diseases will be discussed (30 min). *Class Discussion Topic (30 min):* Mitochondrial function and its relevance to essential cellular and organ function in both health and disease have opened new and exciting therapeutic windows in a multitude of metabolic diseases, including cancer and vascular disease. There are very few examples of drugs and therapies targeting mitochondria at this point. Be prepared to discuss the theoretical advantages and challenges of developing therapies that target mitochondria for human disease. For example, how can one effectively target mitochondria in a diseased tissue/organ without affecting healthy tissues, since mitochondria are important for all cells and organs in the body?

		Trainees will be asked to offer and support their opinions during the group discussion. Readings: * Mitochondria: in sickness and in health. Cell. 2012 Mar 16;148(6):1145-59 PMID: 22424226 * Mitochondria in vascular health and disease. Annual Rev Physiol. 2013;75:95-126. PMID: 2365280
Week 3 **Jan 26** **Faculty** Michelakis	***Metabolism and Human Disease -2*** ***Group Discussions***	*Facilitator:* Discuss the principles of translational research utilizing mitochondrial targeted therapies in a variety of diseases, including vascular remodeling, heart failure and cancer as examples. How to start a translational research program will also be discussed *(30 min)*. *Class Discussion (30 min):* Trainees should be prepared to build on previous discussions on drug targets, including what would you like to know at the cellular level (for novel drug targets) prior to translating these findings to patients. What should you focus on when you first start a translational research program. **Trainees will be asked to offer and support their opinions during the group discussion.**
Week 4 **Feb 2** **Faculty** Paulden **Student:** Matthew Cooper	***Drug Development*** ***Objective:*** Economics and ethics of drug development	Facilitator: Discuss the mechanisms that regulate the cost of new drugs in the modern era (20 min). Student: A rare disease (affecting ~1000 children in Canada) is caused by the genetic lack of Protein X. A small company is the only one in the world that makes clinically-approved recombinant Protein X that has been shown to alleviate the symptoms of the affected children and dramatically improve their survival. The company sells this therapy for $170,000/year/patient. When asked by the government to decrease the price (by decreasing the profit margin from 500% to 200%), the company threatened to stop production of recombinant protein for that country. No other company is able to produce recombinant Protein X. Do you think this is appropriate? Is this ethical? What do you think can or should be done? (15 min). Readings: * Drug-Development Challenges for Small Biopharmaceutical Companies. N Engl J Med 2017; 376:469-474 PMID: 28146666 * The High Cost of Prescription Drugs in the United States: Origins and Prospects for Reform. JAMA. 2016 Aug 23-30;316(8):858-71. PMID: 27552619
Week 5 **Feb 9** **Faculty** Michelakis **Student:** Amro Qaddoura	***Obesity Clinical Studies*** ***Objective:*** Clinical drug development in common and complex diseases (off target effects)	A 35-year-old obese 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 and the challenges of clinical drug development in the treatment of obesity (20min). 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 (15 min)? 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
Week 6 **Feb 16** **Faculty** Michelakis **Student:** Solmaz Bohlouli	***Metabolic Syndrome - 1*** ***Pre-Clinical Studies*** ***Objective:*** Causality and drug target identification	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 and whether there are any drugs that would decrease CRP levels. Facilitator: Discuss the importance of inflammation in the metabolic syndrome and the concept of "cause and effect" in complex diseases (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 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). Readings: * 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. * Inflammation, atherosclerosis, and coronary artery disease. GK Hansson. NEJM. (2005); 352: 1685– 1695. * Metabolic Syndrome: A Clinical and Molecular Perspective, D Moller et al, Annual Review of Medicine (2005); 56: 45-62.
Week 7 **Feb 23** **Faculty** Jickling **Student:** Catherine-Elisabeth Boutet	***Metabolic Syndrome - 2*** ***Clinical Studies*** ***Objective:*** Strengths and challenges of large randomized trials – knowledge translation	A 70-year-old obese man with metabolic syndrome and coronary disease has a blood pressure of 160/70 mmHg. 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 in order to prevent a stroke. You are considering his enrollment in a clinical trial that compares intensive versus standard blood pressure control. Facilitator: The importance of blood pressure control in the metabolic syndrome and secondary prevention of coronary artery disease or stroke 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. 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 * Definition of Metabolic Syndrome. S Gundy et al. Circulation (2004); 109:433-438 * The SPRINT Research Group. A randomized trial of intensive versus standard blood pressure control. *N Engl J Med* 2015;373:2103-2116. * Schulz KF. Assessing allocation concealment and blinding in randomized controlled trials: why bother?
Week 8 **Mar 2** **Faculty** Jickling **Student:** Matthew Cooper	***Diabetes-2*** ***Clinical Studies*** ***Objective:*** Strengths and challenges of large clinical trials – trial design	A 45-year-old man with diabetes and hypertension has a blood pressure of 160/90 mmHg. Facilitator: 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 Group. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575-1585. * ACCORD Study Group. Effects of combination lipid therapy in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1563-1574.
Week 9 **Mar 9** **Faculty** Michelakis **Student:** Maria Guadalupe	***Diabetes-1*** ***Pre-Clinical Studies*** ***Objective:*** Genetics and environmental interactions in complex diseases	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 onto her children. Facilitator: 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 (20 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 * Metabolic control of epigenetics in cancer. A. Kinnaird et al: Nat Rev Cancer. 2016 Nov;16(11):694-707;
Week 10 **Mar 16** **Faculty** Sutendra **Student:** Joseph Nanoa	***Drug Discovery-1*** ***Objective:*** Drug target identification in complex diseases - II	A 32-year-old female who has pulmonary arterial hypertension (PAH), has just been diagnosed with lung cancer. She enquires if there are any therapies that may be beneficial against both diseases. Facilitator (30 min): Discuss the principles in identifying potential drug targets in metabolic diseases. Student (15 min – 10 slides): You represent a drug company. An academic researcher who has discovered a new pathway that is activated in cancer approaches you. The researcher would like you to identify the best potential target in their pathway to develop a drug against cancer. The researcher has strong evidence that **Mitochondrial Protein A**, which is preferentially induced in cancer, binds and *inhibits* **Enzyme Y**, which can no longer phosphorylate and suppress **Transcription Factor B**, which is highly active in cancer, and increases the expression of proliferative and apoptosis resistance genes. Discuss which of the three potential targets in this mechanism pathway you would target with a new drug that you will develop. Explain your rationale. Also, discuss how you would validate that this drug is effective and specific to your target. Readings: * Mitochondria: in sickness and in health. Cell. 2012 Mar 16;148(6):1145-59 PMID: 22424226
Week 11 **March 23** **Faculty** Sutendra **Team 1** Joseph Nanoa,	***Drug Discovery Group Sessions*** ***Objective:*** Drug discovery: validation of *efficacy* and *specificity*	The purpose of this session is to promote creative discussion on identifying the best drug target from the previous session (**Week 10**), along with the principles of confirming the specificity of the drug and validating the efficacy, specificity and relevance in pre-clinical models and patients. Facilitator: Provide a brief description of how drug discovery occurs at molecular stage and characterization of prospective drugs at the in-vitro stage (10 min). **Team 1** will approach the drug discovery platform from a basic-scientist standpoint. This team will propose the best principles to validate the drug *specificity* and *efficacy* in a pre-clinical animal model (20 min).

Matthew Cooper, Maria Guadalupe **<u>Team 2</u>** Solmaz Bohlouli, Amro Qaddoura, Catherine-Elizabeth Boutet Noman Ishque		**Team 2** will approach the drug discovery platform from a clinical perspective. This team will design the clinical trial to demonstrate the safety and efficacy of the drug that is required for it to be approved for use in clinical practice (20 min).
Week 12 **Mar 30** **Faculty** Fahlman **Student:** Noman Ishque	***Drug Discovery-2*** ***Objective:*** Describe an approach to signal a therapeutic protein target for degradation	An ideal therapeutic target in an aggressive form of cancer has been identified (named **Protein A**), however, no current small molecules are able to inhibit Protein A. Utilizing the cells' ability to tag and degrade proteins could be a viable option and will be the focus of this session. <u>Facilitator (20 min):</u> Discuss the principles of utilizing the cells degradation system as a novel and viable option for eliminating (in a targeted manner) a specific protein. <u>Student (25 min – 15 slides):</u> **Protein A** is a potential therapeutic target in cancer and appears to promote both cancer progression and metastasis. Design a pre-clinical study to validate if this novel proteolysis targeting technology (against **Protein A**) is both *specific* and *effective* in promoting cancer regression and preventing cancer metastasis. <u>Readings:</u> PROTAC: An Effective Targeted Protein Degradation Strategy for Cancer Therapy. Front Pharmacol. 2021 May 7; 12:692574.
Week 13 **Apr 6** **Faculty** Kinnaird **Student:** Amro Qaddoura	***Clinical trials for a known cancer predisposing mutation*** ***Objective:*** Describe an approach to targeting a germline mutation in cancer	A 69-year-old man presents with metastatic prostate cancer progresses despite adequate androgen blockade. His father had prostate cancer and his mother and sister both have breast cancer. He enquires if there could be a genetic linkage and if this can be treated. <u>Facilitator (20 min):</u> Discuss the principles in identifying potential genetic drug targets in cancer using prostate cancer as a model. <u>Student (25 min – 15 slides):</u> Describe differences between germline and somatic mutations as they relate to diagnosis and treatment. Why may germline mutations be favorable for clinical trial design and therapeutic targeting across a spectrum of cancer? Design an early phase trial for a new drug for high-risk prostate cancers that have a DNA damage response mutations (such as BRCA2). <u>Readings:</u> PROfound trial. N Engl J Med 2020; 382:2091-2102
Week 14 **Apr 13** **Faculty** Sutendra Jickling Michelakis	**Grant Review** ***Group Sessions*** ***Objective:*** Communication skills / grant writing	Grant review session (small group breakout discussions headed by each of the 3 facilitators) of the grants submitted (deadline for grant submission Friday April 7th, 12 noon).
Week 14 **Apr 20**		FINAL EXAM – open book and remotely with eClass

MED 602 Translational Research Training Program, Module 1

Co-ordinators: Drs. G. Sutendra, G. Jickling and E.D. Michelakis

The course aim is to understand principles of preclinical (animal and human tissue-based) research and models of human disease that promote translation to early phase clinical trials. 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 entire Translational Medicine Program

Med 602, Module I: The course aim is to understand principles of preclinical (animal and human tissue-based) research and models of human disease that promote translation to early phase clinical trials.
Med 604, Module II: The course aim is to understand the principles in the conduct of early-phase versus large clinical trials and the requirements for successful translation of preclinical research: traditional and novel trial designs, endpoints, statistical challenges, regulatory and funding challenges, structure of translational teams and knowledge translation will be discussed.
Med 606, Module III: The course aim is to recognize the role of biomarkers (genetic, biochemical and imaging) in clinical research, including early phase trials and clinical care. Principles for the discovery of novel biomarkers at the preclinical and clinical level will be discussed.
Med 608, Module IV: The course aim is to discuss the principles of candidate drug targets in disease and drug design. The importance of drug target validation at the cellular level, preclinical level and in clinical studies as well as the financial and social implications of drug development will be discussed.

Objectives for Med 602 Course – Fall 2023 Term

- 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 co-clinical trials
- Principles and approaches to intellectual property protection (patents)
- Principles for translational research from cells to animals to patients

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SESSION		SESSION DETAILS
Week 1 **Sept 14** **Faculty** Michelakis **Student:** No Presentation		**Introduction to Med 602** Facilitators will present the principles of Translation Research. The objectives of Module I will be described, along with the expectations for the students. **Basic to Clinical to Basic:** A continuum of research concept will be discussed, where animal research leads to a clinical trial and then more animal work is conducted to explain the findings (**Michelakis**). A project will be discussed where metabolic modulators reversed pulmonary hypertension in animals, leading to a clinical trial with unexpected results (i.e., not predictable based on preclinical research), requiring a return to animal research to understand the clinical results (10 min).
Week 2 **Sept 21** **Faculty** Jickling **Student:**	***Multiple Sclerosis*** *bench-to-bedside*	A 21 yr woman, triathlon athlete, presents with double vision and a tingling sensation in her hands. 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).

Maria Guadalupe Contreras Real		Student: Immunotherapies shown to be effective in animal models of MS have subsequently been found to have severe side effects when trialed in humans. These side effects were not described in animal research (they didn't occur in animals or they occurred but not realized or understood). *How would you design animal studies to improve drug success and predict potential side effects in humans? You need to discuss broad concepts rather than specific actions* (15 minutes). **Objective: To understand the principles of "bench-to-bedside" translational research.** Readings: * Therapies for multiple sclerosis: translational achievements and outstanding needs. Trends in Molecular Medicine. 19 (5) 309-319. 2013.
Week 3 **Sept 28** **Faculty** Sutendra **Student:** Solmaz Bohlouli	***Cancer*** *bench-to-bedside*	A 55 yr old 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: How would you use preclinical models to decide whether or not some (or all) of these abnormalities are "causal" for cancer? How would you use preclinical models to determine which of these mutations is the most attractive to develop a potential therapeutic target against (15 min)? **Objective: Principles and challenges of modeling the natural history of a disease using preclinical models** Readings: * Barrett's Esophagus: Stuart J. Spechler et al., N Engl J Med (2014) 371, 836-845 *Residual Embryonic Cells as Precursors of a Barrett's-Like Metaplasia: Xia Wang et al. Cell (2011); 145(7), 1023-1035.
Week 4 **Oct 5** **Faculty** Sutendra **Student:** Joseph Nanoa	***Technology*** *Biofuel Cell*	Mitochondria are organelles that can generate a membrane potential (i.e., battery) that is used to power ATP synthase, a multicomplex protein that generates ATP (the currency of the cell). The need for alternative bio-degradable energy-driven devices is of particular interest to several government and other agencies. Biofuel cells are electrochemical devices that utilize enzymatic activity for the transformation of energy into electrical power. Facilitator: Provide examples of how mitochondria can be used in biofuel cell technology and its implications for medical/technological devices (20 min). Student: How would you use this new biodegradable technology for medical purposes? What devices would you first test this technology in? How would you design a pre-clinical study to test if such a technological device would be economically, environmentally and medically effective? How would you assess the lifespan of this new device? (10 min) **Objectives: To understand the how-to setup an appropriate experimental investigation in pre-clinical models** Readings: Gellett et al., Biofuel Cells for Portable Power. Electroanalysis. 2008. DOI: 10.1002/elan.200980013.

		https://www.bbc.com/news/technology-11084136 https://experiment.com/projects/can-our-cell-s-mitochondria-power-a-cell-phone https://www.chemistryworld.com/news/bio-battery-based-on-cellular-power-plant/3000531.article
Week 5 **Oct 12** **Faculty** Sutendra **Student 1:** Mike Clarke **Student 2:** Mya Schmidt	***Cancer and Co-Clinical Trials*** *bedside to bench*	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, resulting in drug-resistance. Facilitator: Discuss the case. Discuss the co-clinical trial concept and its ability to improve the efficacy of drug treatments in early-phase clinical trials (15 min). Students: 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 a somatic SNP (i.e. a gene variant) in gene X was associated with resistance to treatment in drug A. And another SNP in gene Y was found in 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*. (10 min) 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. (10 min). **Objective: To appreciate the advantage of genetically engineered mouse models (that mimic patients) for screening of drug response before applying the drugs to specific patients.** Readings: *A co-clinical platform to accelerate cancer treatment optimization. Andrea Lunardi and Pier Paolo Pandolfi. Trends in Molecular Medicine January 2015, Vol. 21, No. 1
Week 6 **Oct 19** **Faculty** Michelakis **Student:** Alisha Rullay	***Heart Failure*** *bedside-to-bench*	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 sessions in a specialized rehabilitation center?" 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 (10min)? Student: How would you conduct a "trial" in a rat model of myocardial infarction in order to study the mechanism of the benefits of rehabilitation? What would be the biggest challenges (15min)? **Objectives: The criteria required for designing appropriate "pre-clinical" trials**. Readings: *Cardiac Rehabilitation and Secondary Prevention of Coronary Heart Disease: P. Ades; N Engl J Med, Vol. 345, No. 12 2001.
Week 7 **Oct 26** **Faculty** Jickling	***Stroke*** *bench-to-beside*	A 60 yr old woman with atrial fibrillation presents to the Emergency Department 6 hours after the onset of right-sided weakness, where she is given a neuroprotective agent as part of a clinical trial, in an effort to limit ongoing necrosis of brain tissue. Facilitator: Discuss the case. Rationale and challenges in the use of neuroprotective agents in acute stroke as an example of intense translational research that has failed to produce any clinical benefits in patients, despite the success in animal models (15 min)?

Student: Todoran Raluca		Student: Despite promise in pre-clinical research, neuroprotective drugs aiming to limit the damage in the brain after the onset of stroke, have failed in when applied to humans. Discuss potential reasons for this. List potential reasons that suggest that animal research is the weak link in translational research failures (i.e. the animal research did not mode well enough the disease and/or overstated the results). List potential reasons that clinical research is the weak link in translational research failures (i.e. the neuroprotective agents could have shown benefits, which was not revealed because of suboptimal trial designs). (15 min). **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 * Improving the translation of animal ischemic stroke studies to humans. Jickling GC. Metab Brain Dis. 2015;30(2):461-7.
Week 8 **Nov 2** **Faculty** Sutendra **Student:** Catherine Jarvis	***Cancer*** *bedside-to-bench*	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). Student: 3 independent gene mutations (cancer-specific –somatic; i.e. they are only found in the cancer cells within a human tumor and not in any other cells of the body) characterize a very aggressive form of brain cancer (based on biopsies from 300 affected patients). Two of them cause a down-regulation of the encoded proteins and one causes an up-regulation of the encoded protein. Describe an approach that an experimental therapy can address these abnormalities (don't be specific – discuss the general principles of the approaches). Design an in-vitro cellular experiment to address if the mutation results in a functional change of the protein. What could you do and what would you look for at the protein level (15min). **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.
Week 9 **Nov 9** **Faculty** Michelakis **Student 1:** Matthew Cooper **Student 2:** Catherine Boutet	***Debate***	Each student will debate (pro vs con) on a given controversial subject. At the end of the presentation and discussion, all students will vote. Some clinicians argue that -when possible- an available drug should be directly tested in humans with a randomized placebo-controlled trial (after it passes the required toxicity studies in early phase trials). Their point is that the drug is only relevant to disease if it shows benefits in patients, even if we don't know its precise mechanism of action (i.e. " what does it matter what the mechanism is, if the drug shrinks a tumor, prolongs survival and does not have significant toxicity, particularly since animals often do not predict clinical responses?). In contrast, translational scientists argue that "if the mechanism of the drug is not known first, long term significant toxicities cannot be predicted and the industries funding the clinical trials take a big risk since, after millions of funds are spent, the drug may be withdrawn". **Student 1:** Animal research should typically be conducted first, to define mechanism of disease and then used to guide human studies (15 min + 5 min follow-up).

		Student 2: Human studies should be conducted first, whenever possible, to identify relevant human targets and potential beneficial effects, that can then be evaluated further in animal models if needed (15 min + 5 min follow-up).
Week 10 **Nov 16** **Faculty** Michelakis **Student:** Suen Akinfolarin	***Heart Failure*** *bedside-to-bench*	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 the gene encoding 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: If you had an unlimited budget, what would you do to determine whether this disease could be cured? Discuss broad ideas, concepts and general approaches – not specific actions. Design a pre-clinical study to definitely prove the mutation identified in this patient is sufficient to directly cause the cardiomyopathy (15 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 **Objective: to understand the process in developing new diagnostic tests.**
Week 11 **Nov 23** **Faculty** Kinnaird **Student:** Samina Khan	***Cancer*** *bedside-to-bench*	A 65-year-old man is diagnosed with recurrent prostate cancer 5 years after external beam radiation therapy. He has new back pain and is concerned that it has metastasized. Facilitator: Discuss the case. What are the principles of staging cancers. What are techniques that are used to stage cancer. How can you achieve level 1 evidence for a new imaging test (20min)? Student: How would you develop a new imaging test to diagnose cancer? What unique features of cancer might be 'targets' for your imaging test? Think broadly (do not read the literature). If you had unlimited supplies, how would you create the most sensitive of tests for cancer diagnosis? How would you conduct a "trial" in an animal model for a new imaging test? What are the requirements for showing the accuracy of a new diagnostic test (15 min)? **Objective: to understand the process in developing new diagnostic tests.**
Week 12 **Nov 30** **Faculty** Sutendra **Student:** Aliy Jokha Yusuf	***Heart Failure*** *bench to bedside*	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: 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 cells but is also expressed in low amounts in the heart. *How would you design a pre-clinical study (both in cells and animals) to enhance the selectivity of Drug X for the tumor versus the heart* (15 min)*?* **Objective: The criteria for evaluating drug specificity, off-target effects as well as "outliers" in animal studies.**

		Readings: A. Albini *et al.*, Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst* **102**, 14-25 (2010).
Week 13 **Dec 7** **Faculty** Jickling **Student 1:** Saswat Sahoo **Student 2:** Matthieu Zolondek	***Neurology*** *bench to bedside*	A 70-year-old retired school teacher with hypertension is experiencing gradually worsening memory. She has had imaging of her brain over the past 5 years showing increased injury to the white matter (white matter hyperintensities on MRI brain). Faciliator: Discuss the case. Discussion of how to identify the factors promoting progression of cerebral white matter hyperintensities and the role of omics based methods. Student 1: You conduct a study screening the immune system in patients with progressive white matter injury. In your precision medicine research program, you test 100,000 genes, metabolites and peptides and find 40 molecules are associated with progression of disease. Discuss the strategy/strategies you want to use in your experiments and analysis to reduce the chance of false discovery and ensure the molecules you identified are a true finding (10 min)? Student 2: You believe molecule SP is critical to promoting progression of white matter injury and dementia in patients. Design an animal experiment to test the effect of SP on white matter injury (10 min). Readings: Silbert, L.C., et al., Cognitive impairment risk: white matter hyperintensity progression matters. Neurology, 2009. 73(2): p. 120-5. Noble, W. How does multiple testing correction work?. Nat Biotechnol 27, 1135–1137 (2009).
Week 14 **Dec 14**		**FINAL EXAM**