MSC 1000H: Foundations in Translational Research

Course Description

“For Academia, translational research represents a general desire to test novel ideas generated from basic investigation with the hope of turning them into useful clinical applications” (Littman, 2007).

There are many perspectives on what constitutes Translational Research (TR) in health sciences. Most views incorporate the idea that TR is the harnessing of knowledge from discovery (fundamental science) to produce new drugs, devices, diagnostics, and treatment options. TR can also mean the translation of research into processes and practices that deal with policy and intervention; and TR can mean simply the transition of knowledge across disciplinary boundaries of research. From these perspectives, the aim of TR is to help ensure that treatments and knowledge improve human health. However, translation also includes processes through which feedback from the community and clinicians can inform research in the fundamental sciences. Thus, effective translation constitutes bi-directional movement of knowledge across disciplinary silos, furthering the understanding of biologic mechanisms, techniques and approaches that support prevention, diagnosis and treatment of disease.

This lecture, discussion and case-based course will survey the landscape of TR across the health sciences. The course will help students distinguish how areas of fundamental and applied investigation are linked in the TR continuum and articulate the knowledge skills necessary to move ideas and projects across these domains.

Course Structure

This course will involve 12 three-hour sessions (36 contact hours). Class time will include an one hour lecture overview on the session theme, an additional hour talk by a guest with expertise related to the week’s topic; and a final hour devoted to group discussion and work related to the development of translational case studies that will unfold across the in-class sessions.

The course will include assessment of individual and group work. Each student will prepare an annotated bibliography and paper. Working in groups, students will complete a case study, and will present this orally and in writing. Each assignment is described below and students will receive more detailed assignment instructions in class.

Course Goals

To examine the range of TR disciplines, introduce key issues and encourage analysis of the field through case studies and critical reflection.
# Grading Scheme

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Weight</th>
<th>Due Date</th>
<th>Type</th>
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</thead>
<tbody>
<tr>
<td>1 Topic Pitch</td>
<td>10%</td>
<td>Week 6</td>
<td>Individual</td>
</tr>
<tr>
<td>2 Annotated Bibliography</td>
<td>15%</td>
<td>Week 4</td>
<td>Individual</td>
</tr>
<tr>
<td>3 Paper</td>
<td>30%</td>
<td>Week 11</td>
<td>Individual</td>
</tr>
<tr>
<td>4 Group Case Study</td>
<td>30%</td>
<td>Week 12</td>
<td>Collaborative</td>
</tr>
<tr>
<td>5 Participation</td>
<td>15%</td>
<td>On Going</td>
<td>Individual</td>
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## Assignment Details

### 1. Paper Pitch (10%)

Students will select an aspect of Translational Research and give 5 minute pitches for papers on the topics of their choice. The pitch will outline their thesis, describe how they envisage development of their thesis involving translation between two or more domains of research, or translational phases.

### 2. Annotated Bibliography (15%)

Based on feedback from the Paper Pitch, students will develop a brief literature survey of the topic. Student research should not include more than 3 readings from the course readings or supplementary material. Each student will present a topic to the course director for written approval before starting. Once topics are approved, students will write 10 – 12 annotated reviews of key readings on their topics. The reviews should identify central points and themes of each resource and discuss key research questions or directions the source may represent for each student’s own research interests.

### 3. Paper (30%)

Preparation of the paper will provide an opportunity to explore the bridging aspects of Translational Research in relation to an area of work/research. Building on the literature survey and extending and bridging the concepts below, students will write a thesis-based discussion paper. One or more of the following translational issues must be addressed in development of the thesis:

- Health Policy
- Biomarker, Drug or Device Discovery
- Intellectual Property
- Commercialization
- Implementation Science
- Reverse Translation
- Knowledge Translation
- Medical Advocacy

The paper should be 8 – 10 pages in length.

### 4. Group Case Study (30%)

Students will work on TR case studies in teams of 5. The case studies will be presented in 4 parts. Each part will include a description of specific developments and problems to be considered at that stage in the case.

Discovery. The first stage of each case will involve a novel discovery, confounded by limitations of
experimental design and/or biological complexity. These may include issues such as differences in biological response related to species, gender or age, off-target drug action, or genetic heterogeneity. Teams will be confronted with choices in how to proceed toward validating the idea, or discovery. They will consider when to disclose and publish this knowledge and how to evaluate its potential scope and significance. Each discovery will be based on an actual historic example of TR.

**Application:** Students will consider steps required to develop their discovery to a range of possible endpoints, which may include a therapeutic, device, biomarker, policy, or procedure. They will face choices regarding patents, prior art, licensing and conceptualizing the market landscape for their discoveries. They will begin to confront scenarios that force personal and professional decisions concerning the turnover of responsibility for development of the project.

**Development and Implementation:** Issues encountered at the development stage will include the regulatory and procedural steps necessary to establish efficacy and safety, process development, validation and testing. Students will be led to think through funding for their ventures and to perform a SWOT analysis of the competitive landscape. They will also be obliged to consider how the discoveries might best be positioned to reach appropriate stakeholders.

**Evaluation, Reverse Translation and Exits:** Students will be asked to consider how their case project might be packaged into a viable venture, embedded in regulatory frameworks, communities of practice or other relevant contexts. They will consider goals, and how evaluation of progress toward goals can iteratively inform processes of re-discovery, re-development and re-implementation.

Students will prepare written group notes, documenting their reflections at each stage of the evolving case study narrative. At the end of the term, teams will use this material to present the completed case study to the class as a whole. Teams will have 10-12 minutes for their presentation and will also be required to distribute the material in written abstract form to class members. They will also use their notes to compile a report outlining challenges and choices the group encountered during the exercise. The report will be 5-8 pages in length (excluding any figures or appendices).

The group presentation will be worth 15% of the final grade. The group report will account for another 15% of each student’s final grade.

**5. Participation (15%)**

Participation will be based on a student’s contribution to discussions in each session.

**Detailed Class Schedule**

**Week 1: What is Translational Research? An Overview**

This seminar charts the TR landscape and introduces concepts such as the “valley of death”, phases of translation, and key issues in fostering translational research, including funding and assessment. The lecture will cover the “translation bridge”—the steps involved in crossing the valley of death between bench and community. The translational bridge metaphor will be loosely used as the organizing structure for the remainder of the course.

**Readings:**


***Annotated Bibliography Assignment will be described***

**Week 2: Health, Disease and Disability**
This session will provide a high level context for TR by discussing evolving concepts of health, disease and disability. The seminar will engage with paradigms for understanding origins and treatment of disease and will explore topics like: What is disease? What differentiates curing from healing? What role do “consensus disorders” have in modern medicine? Major modern health challenges will be considered, including infection, acute, chronic and degenerative diseases, psychiatric issues, disability, disease prevention, and public health. Strategies for developing and evaluating models of disease will be discussed.

Readings:

**Week 3: Biomedical Science & Target Identification**
This session will consider the role of modern biomedical science in identifying new targets, elucidating pathways, and developing screening strategies. The role of genetic tools and new ‘omics’ strategies will be presented. The discussion will look at how personalized medicine addresses sources of variation in disease presentation through an analysis of biochemical and genetic causes. It will also look at the development and validation of biomarkers that are necessary for assessing disease progression and phenotype and for predicting response to treatment.

Readings:

**Week 4: Drug Development**
This session will deal with the drug development process. The range of drug classes will be surveyed including: small molecules, inhibitors, activators, biologics, and siRNA. Identification of druggable vs non-druggable targets will be discussed, as will side effects, medicinal chemistry and issues of drug delivery. The formal drug approval process will be reviewed and differentiated from the medical device approval pathway. Issues of drug repurposing and orphan disease targeting will be discussed as translational strategies have become increasingly common in recent years.

Readings:

***Paper Pitch***

**Week 5: Clinical Observation**
This lecture will explore the nature of observational evidence in diagnosis, prognosis and outcome. The presentation will explore hierarchies of evidence, including anecdotal case reports, observational studies, expert opinion and randomized control trials. Sampling issues, considerations of correlation vs causation,
statistical power and bias will be discussed. Students will be asked to consider how clinical observations may lead to new questions at the bench or new interventions, practices and policies in practice and in society at large.

Readings:

***Annotated Bibliography Due***

*Week 6: Measuring Disease*
The ‘success’ of translation is often tied to evaluation. For example, has the intervention ‘improved’ outcomes? Has the translation ‘improved health’, reduced costs, or reduced suffering? Evaluation requires ways of qualifying and quantifying disease. Different ways of quantifying disease from physical exams to clinical lab tests, patient self-reporting, and biomarkers. Strategies for identifying, evaluating and driving adoption of new measurements will be discussed.

Readings:

*Week 7: Defining and Characterizing Relevant End Points*
TR is often schematically represented as a circular endeavour, but bridging a gap or mobilizing knowledge implies a goal, or endpoint. This lecture will explore different endpoints in TR. It will address the use of validated *in vitro* and *in vivo* testing for on-target effects, side effects, surrogate endpoints, and progression-free survival vs survival. Approaches for defining and evaluating endpoints for health policy interventions at the population level (e.g. data mining) will be discussed. The challenge of measuring prevention will be discussed.

Readings:

*Week 8: Products, Commercialization and IP*
You have your target, compound or idea... now what? Turning widgets into start-ups. This lecture will address challenges and pitfalls of moving an idea into a funded start-up. The lecture will discuss entrepreneurship, intellectual property rights, patents and funding mechanisms.

Readings:
**Week 9: Health Policy**
This lecture will look at diverse and often divergent stakeholder interests of the political process in policy making and consider how collaboration between scientists, clinicians, advocacy groups and government agencies could lead to robust policies that not only improve human health but also reduce social and economic burdens on the health care system. The talk will encompass how governmental bureaucracy is organized and where policy is actually formed.

Readings:

**Week 10: Knowledge Translation & Implementation**
This session will introduce the field of knowledge translation. The lecture will outline how knowledge is disseminated, adopted in practice and evaluated post-implementation. The talk will explore implementations and interventions, barriers to use and adoption, and explore practical strategies for monitoring, evaluating and sustaining knowledge use.

Readings:

**Week 11: Reverse Translation**
This lecture will touch on the later stages of translating knowledge into populations and touch on approaches to medicine through big data epidemiology. The lecture will also explore how patient and community insights are harnessed to inform the design of research questions in clinical and fundamental research.

Readings:

***Paper Due***

**Week 12: Translational Research Frontiers?**
This lecture will explore challenges and frontiers in TR including incentives and rewards; changing institutional momentum; and the impact that changes in funding have on research practice.

Readings:
Supplementary Reading List:
<table>
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<tr>
<th>Year</th>
<th>Author(s)</th>
<th>Title</th>
<th>Journal</th>
<th>Volume</th>
<th>Pages</th>
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<tr>
<td>2011</td>
<td>Luciano, J. S., Andersson, B., Batchelor, C. R., Bodenreider, O., Clark, T., Denney, C. K., ... &amp; Dumontier, M.</td>
<td>The Translational Medicine Ontology and Knowledge Base: driving personalized medicine by bridging the gap between bench and bedside</td>
<td>J Biomed Seman</td>
<td>2(2)</td>
<td>S1</td>
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<tr>
<td>2006</td>
<td>Malinowski, M. J., &amp; Rao, R.</td>
<td>Legal limitations on genetic research and the commercialization of its results</td>
<td>Am J Compar Law</td>
<td>45</td>
<td>65</td>
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<td>2003</td>
<td>Marincola, F. M.</td>
<td>Translational medicine: a two-way road</td>
<td>J Transl Med</td>
<td>1(1)</td>
<td>1</td>
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<td>2007</td>
<td>Marincola, F. M.</td>
<td>In support of descriptive studies; relevance to translational research</td>
<td>J Transl Med</td>
<td>5(1)</td>
<td>21</td>
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<td>2011</td>
<td>Marincola, F. M.</td>
<td>The trouble with translational medicine</td>
<td>J Int Med</td>
<td>270(2)</td>
<td>123-127</td>
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<td>2010</td>
<td>McGaghie, W. C.</td>
<td>Medical education research as translational science</td>
<td>Sci Transl Med</td>
<td>2(19)</td>
<td>19cm8</td>
</tr>
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<td>2011</td>
<td>Michie, S., van Stralen, M. M., &amp; West, R.</td>
<td>The behaviour change wheel: a new method for characterising and designing behaviour change interventions</td>
<td>Implement Sci</td>
<td>6(1)</td>
<td>42</td>
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<td>2008</td>
<td>Plebani, M.</td>
<td>The changing scenario in laboratory medicine and the role of laboratory professionals in translational medicine</td>
<td>Clinica Chimica Acta</td>
<td>393(1)</td>
<td>23-26</td>
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<td>2008</td>
<td>Rogowski, W. H., Hartz, S. C., &amp; John, J. H.</td>
<td>Clearing up the hazy road from bench to bedside: a framework for integrating the fourth hurdle into translational medicine</td>
<td>BMC Health Serv Res</td>
<td>8(1)</td>
<td>194</td>
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<td>2010</td>
<td>Sarkar, I. N.</td>
<td>Biomedical informatics and translational medicine</td>
<td>J Transl Med</td>
<td>8(1)</td>
<td>22</td>
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<td>2005</td>
<td>Sonntag, K. C.</td>
<td>Implementations of translational medicine</td>
<td>J Transl Med</td>
<td>3(1)</td>
<td>33</td>
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<td>2010</td>
<td>Szalma, S., Koka, V., Khasanova, T., &amp; Peraksils, E. D.</td>
<td>Effective knowledge management in translational medicine</td>
<td>J Transl Med</td>
<td>8(1)</td>
<td>68</td>
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<td>2006</td>
<td>van der Greef, J., Hankemeier, T., &amp; McBurney, R. N.</td>
<td>Metabolomics-based systems biology and personalized medicine: Moving towards n=1 clinical trials</td>
<td>Pharmacogenomics</td>
<td>7(7)</td>
<td>1087-1094</td>
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<td>2006</td>
<td>Wehling, M.</td>
<td>Translational medicine: can it really facilitate the transition of research “from bench to bedside”?</td>
<td>Eur J Clin Pharmacol</td>
<td>62(2)</td>
<td>91-95</td>
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<tr>
<td>2008</td>
<td>Wehling, M.</td>
<td>Translational medicine: science or wishful thinking?</td>
<td>J Transl Med</td>
<td>6(1)</td>
<td>31</td>
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<td>2008</td>
<td>Wolff, S. H.</td>
<td>The meaning of translational research and why it matters</td>
<td>JAMA</td>
<td>299(2)</td>
<td>211-213</td>
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<tr>
<td>2011</td>
<td>Xu, L., &amp; Anchordoquy, T.</td>
<td>Drug delivery trends in clinical trials and translational medicine: Challenges and opportunities in the delivery of nucleic acid-based therapeutics</td>
<td>J Pharmaceut Sci</td>
<td>100(1)</td>
<td>38-52</td>
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<tr>
<td>2010</td>
<td>Yu, X., Schneiderhan-Marra, N., &amp; Joos, T. O.</td>
<td>Protein microarrays for personalized medicine</td>
<td>Clin Chem</td>
<td>56(3)</td>
<td>376-387</td>
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<tr>
<td>2007</td>
<td>Zerhouni, E. A.</td>
<td>Translational research: moving discovery to practice</td>
<td>Clin Pharmacol &amp; Therap</td>
<td>81(1)</td>
<td>126-128</td>
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Academic Rationale

This is the foundational required course for the MHSc in Translational Research in Health Science. Its purpose is to examine the range of TR disciplines, introduce key issues and encourage analysis of the field through case studies and critical reflection.

Learning Outcomes

This course is intended to provide students with exposure to the ‘breadth’ of TR issues. Students will be assessed on their ability to:

- Identify key debates that result from often divergent stakeholder views;
- Make informed judgments on complex issues in the context of TR;
- Assess a complex translational problem; and
- Demonstrate an understanding of the landscape from bench to community in Translational Research in Health Science including key stages and challenges.