Foundations in Biomedical Sciences
Module Vg: Translational Genetics and Genomics

Spring 2012
Tuesdays, 9:30 – 11:20 AM
Fridays, 2:00 – 3:00 PM

Course description

This course will explore the process by which insights from basic science research ultimately lead to new strategies for patient care with a focus on examples from genetics and more recent genome-wide experimental approaches. The course will cover examples of translational research using genetic, epigenomic, transcriptomic, proteomic, approaches in human and/or model systems. Research that leads to new approaches for establishing disease diagnosis, prognosis, therapy, and personalized medicine will be discussed. The ethical and societal implications of these developments will also be considered.

The course will be aimed towards first year Ph.D. students in the Division of Graduate Medical Sciences. The class will be taught by members of the Division in a variety of Departments utilizing a combination of traditional lectures and discussion sections focusing on primary research to total 3 hours of class time per week. In the discussion section, several papers from the primary literature that illustrate the theme of that week's lecture will be discussed. Students will be evaluated on their classroom participation, discussion session participation, a mid term paper that critically describes work in an area of translational research, and a final presentation that proposes new directions for translational research in a field of their choosing. These exercises will be designed to test the students' ability to explain the translational research process and demonstrate how individual research findings build on one another to move a field forward through examples that are connected by the central theme of translational research that ultimately impacts patient care.

Course Learning Objectives

By the end of this course, students should be able to:
1. Identify examples of translational research in genetics, genomics and proteomics and related fields.
2. Assess the potential translational development of ongoing research.
3. Propose translational research strategies that might be appropriate for the research that they have experienced and may wish to undertake for doctoral thesis.

Course Managers:

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Grading: This class is designed to instill awareness of methods for translational research in genetics and genomics and to assist students in incorporating these techniques in their own developing research projects. Participation in discussion of the topics is critical to the process of developing and incorporating critical thinking in this field.

Students will write a mid-term research paper selected from two or three topics (each with 3 or 4 readings) critiquing the research and discussing the translational trajectory of research around that topic.

Students will prepare a final research poster on a research topic of their choosing. Each student will be asked to describe previous work in that field in the context of translational research and propose additional research that would further advance the research toward impacting patient care. Students will be encouraged to design the poster around their specific area of research interest, anticipated future lab affiliation and dissertation topic.

Group Discussion participation	20%
Mid term paper (Research Paper on examples of translational research)	35%
Final Project (Poster presentation describing the translational path for a research project of the student's choosing).	45%
Total	100%

Dates	Classes February 14 – May 1, 2012 Tuesday Lecture 9:30am – 11:30am Friday discussion groups 2:00 – 3:00pm	Instructor
Feb 14, 17	**Introduction to the field, translational uses of proteomics (glycomics, lipidomics, etc.)** Translational research using Mass Spectrometry in a wide range of applications including: Amyloid, Carbohydrates, Electron Capture Dissociation, Glycosaminoglycans, High Pressure MALDI, Lipid Antigens. Wada et al. Comparison of Methods for Profiling O-glycosylation: HUPO Human Disease Glycomics/Proteome Initiative Multi-Institutional Study of IgA1. *Mol Cell Proteomics* **2010**, *9*, 719-727 Palaima et al. The Caenorhabditis elegans bus-2 mutant reveals a new class of O-glycans affecting bacterial resistance. *J Biol Chem* **2010**, *285*, 17662-72. Jones et al. Strong IgG antibody responses to Borrelia burgdorferi glycolipids in patients with Lyme arthritis, a late manifestation of the infection. *Clin Immunol* **2009**, *132*, 93-102. Connors et al. Cardiac amyloidosis in African Americans: comparison of clinical and laboratory features of transthyretin V122I amyloidosis and immunoglobulin light chain amyloidosis. *Am Heart J* **2009**, *158*, 607-14.	Cathy Costello, PhD
Feb 21, 24	**Translational Pharmacogenomics and ALS** A key challenge facing scientists is to move basic research discoveries into the clinic. This lecture will present a basic research discovery related to Amyotrophic Lateral Sclerosis, and then describe how this discovery was used to generate a high throughput assay for drug discovery. I will then convey the course of the drug discovery process, including identification of lead compounds and validation of these compounds in secondary assays, including in vivo validation. Mitchell, J.D. and G.D. Borasio, Amyotrophic lateral sclerosis. Lancet, 2007. 369: 2031-41.Acc. #:17574095. Neumann, M., D.M. Sampathu, L.K. Kwong, A.C. Truax, M.C. Micsenyi, T.T. Chou, J. Bruce, T. Schuck, M. Grossman, C.M. Clark, L.F. McCluskey, B.L. Miller, E. Masliah, I.R. Mackenzie, H. Feldman, W. Feiden, H.A. Kretzschmar, J.Q. Trojanowski, and V.M. Lee, Ubiquitinated TDP-43 in frontotemporal lobar degeneration and amyotrophic lateral sclerosis. Science, 2006. 314: 130-3.Acc. #:17023659. Liu-Yesucevitz, L., A. Bilgutay, Y.J. Zhang, T. Vanderwyde, A. Citro, T. Mehta, N. Zaarur, A. McKee, R. Bowser, M. Sherman, L. Petrucelli, and B. Wolozin, Tar DNA binding protein-43 (TDP-43) associates with stress granules: analysis of cultured cells and pathological brain tissue. PLoS One, 2010. 5: e13250.Acc. #:20948999. Liu-Yesucevitz, L., G.J. Bassell, A.D. Gitler, A.C. Hart, E. Klann, J.D. Richter, S.T. Warren, and B. Wolozin, Local RNA Translation at the Synapse and in Disease. J Neurosci, 2011. in press.	Ben Wolozin, MD, PhD
Feb 28, March 2	**Translational Research in Neurodegenerative disease** Cloning the Huntington disease gene, Creating cell-culture models and transgenic model organisms, identification and significance of neuronal intranuclear inclusion bodies, utility and pitfalls in testing therapeutics in model organisms and systems, clinical trial outcomes and prospects.	Richard Myers, PhD

HDCRG. A novel gene containing a trinucleotide repeat that is unstable on Huntington's disease chromosomes. Cell 1993;72:971-983.

Mangiarini L., et al. Exon 1 of the HD gene with an expanded CAG repeat is sufficient to cause a progressive neurological phenotype in transgenic mice. Cell 1996;87:493-506.

Beal MF, Ferrante RJ. Experimental therapeutics in transgenic mouse models of Huntington's disease. Nat Rev Neurosci. 2004; 5:373–384.

Beal MF. Neuroprotective effects of creatine. Amino Acids. 2011;40:1305-1313.

Mar 6, 9	**Point of care molecular diagnostics** Cancer is self, gone awry, with uncontrolled growth and the loss of normal patterns of cell behavior. Cancer is not one disease but many, highly adaptive and heterogeneous. Following the sequencing of the human genome, we have developed technology that can advance our ability to prevent, detect, and target treatment, to improve our fundamental understanding of tumor biology. Here we will discuss the risks, benefits and limitations of the clinical setting for point of care molecular diagnostics in cancer.	Jennifer Rosen, MD

Update of phase I study of imatinib (STI571) in advanced soft tissue sarcomas and gastrointestinal stromal tumors: a report of the EORTC Soft Tissue and Bone Sarcoma Group. van Oosterom AT, Judson IR et al; European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. Eur J Cancer. 2002 Sep;38 Suppl 5:S83-7. PMID: 12528778

A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. Paik S, Shak S, Tang G, Kim C, Baker J, Cronin M, Baehner FL, Walker MG, Watson D, Park T, Hiller W, Fisher ER, Wickerham DL, Bryant J, Wolmark N. N Engl J Med. 2004 Dec 30;351(27):2817-26. Epub 2004 Dec 10.

Initial sequencing and analysis of the human genom**e**. Lander ES, Linton LM et al; International Human Genome Sequencing Consortium. Nature. 2001 Feb 15;409(6822):860-921. Erratum in: Nature 2001 Aug 2;412(6846):565. Nature 2001 Jun 7;411(6838):720. Szustakowki, J [corrected to Szustakowski, J]

Wiley Interdiscip Rev Nanomed Nanobiotechnol. 2010 Sep-Oct;2(5):450-60. The NCI Alliance for Nanotechnology in Cancer: achievement and path forward. Ptak K, Farrell D, Panaro NJ, Grodzinski P, Barker AD.Office of Cancer Nanotechnology Research, Center for Strategic Scientific Initiatives, National Cancer Institute, NIH, 31 Center Dr, Bethesda, MD 20892, USA.

Surgery. 2005 Dec;138(6):1050-6; discussion 1056-7. A six-gene model for differentiating benign from malignant thyroid tumors on the basis of gene expression. Rosen J, He M, Umbricht C, Alexander HR, Dackiw AP, Zeiger MA, Libutti SK.Surgery Branch, Center for Cancer Research, National Cancer Institute, National Institute of Health, Bethesda, MD 20892,

Mar 13, 16	**Genome Instability and Targeted Cancer Therapy** Cancer is often preceded by a loss of genomic integrity leading to the activation of oncogenes and loss of tumor suppressor genes via point mutation, gene fusion, amplification and chromosomal loss. Identification of oncogenes that are frequently activated in tumors has led to the development of several successful targeted therapies for treating cancer in patients with these specific genomic alterations. The example of trastuzumab for the treatment of Her2+ breast cancer will be discussed.	Marc Lenburg, PhD

Coussens, L. et al. Tyrosine kinase receptor with extensive homology to EGF receptor shares chromosomal location with neu oncogene. Science 230, 1132–1139 (1985).

Slamon, D.J. et al. Human breast cancer: correlation of relapse and survival with amplification of the HER-2/neu oncogene. Science 235, 177–182 (1987).

Hudziak, R.M. et al. Increased expression of the putative growth factor receptor p185HER2 causes transformation and tumorigenesis of NIH 3T3 cells. Proc Natl Acad Sci U S A 84, 7159-63 (1987).

Carter, P. et al. Humanization of an anti- p185HER2 antibody for human cancer therapy. Proc Natl Acad Sci U S A 89, 4285-9 (1992).

Slamon D.J. et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 344,783-92 (2001).

Mar 20, 23	**Pharmacogenetics and transcriptomics of lung disease** Asthma is a common chronic diseases for which beta-agonists and corticosteroids are cornerstones of treatment. There has long been concern that regular use of beta-agonist inhalers might have a paradoxical adverse effect on persons with asthma, possibly even increasing the risk of a fatal outcome. Functional polymorphisms in the beta2-adrenergic receptor (ADRB2) gene may be clinically useful for stratifying patients according to their risk of experiencing adverse effects of regular beta-agonist therapy although clinical trials have not established a clear role as a clinical tool. Gene variants related to corticosteroid function may influence treatment response. A functional variant of the glucocorticoid-induced transcript 1 gene (GLCCI1) has been studied for response to inhaled corticosteroid in asthmatics. Gene expression profiling in tumor tissue versus normal tissue have guided treatment of a number of types of cancer, including lung cancer. However, gene expression profiles in unaffected (i.e. non-tumor) airway epithelial cells that identify persons with a high likelihood of having lung cancer (e.g. those with a small lung nodule discovered on a chest CT scan) may lead to more accurate risk assessment, effective targeting of invasive screenings, such as surgical resection of nodules, to patients most likely to have cancer. mRNA microarray technology has yielded expression profiles associated with the presence of lung cancer, providing potential clinical utility in screening and diagnosis. Gene expression patterns in peripheral whole blood may be also detect early-stage adenocarcinoma of the lung. Wechsler ME et al. Effect of beta2-adrenergic receptor polymorphism on response to longacting beta2 agonist in asthma (LARGE trial): a genotype-stratified, randomised, placebo-controlled, crossover trial. Lancet. 2009 Nov 21;374(9703):1754-64. PubMed PMID: 19932356; PubMed Central PMCID: PMC2914569. Reihsaus E,et al. Mutations in the gene encoding for the beta 2-adrenergic receptor in normal and asthmatic subjects. Am J Respir Cell Mol Biol. 1993 Mar;8(3):334-9. PubMed PMID: 8383511. Tantisira KG et al. Genomewide association between GLCCI1 and response to glucocorticoid therapy in asthma. New Engl J Med 2011; 365: 1173-1183. Spira et al. Airway epithelial gene expression in the diagnostic evaluation of smokers with suspect lung cancer. Nat Med. 2007 Mar;13(3):361-6. PMID: 17334370. Rotunno et al. A gene expression signature from peripheral whole blood for stage I lung adenocarcinoma. Cancer Prev Res (Phila). 2011 Oct;4(10):1599-608. PMID: 21742797.	George O'Connor, MD, MS Jerry Brody, MD

Mar 27, 30	**Genetics of autoimmune disease** Genome-wide association studies (GWAS) have uncovered a large number of common variants contributing to the risk for autoimmune disease. Using the examples of rheumatoid arthritis and psoriasis, we will discuss how GWAS results have converged on NFKB-related pathways as a common pathway in autoimmune pathogenesis. We will also discuss the importance of careful phenotype definition for generating meaningful GWAS results, using rheumatoid arthritis and vitiligo as examples, and explore the concept of missing heritability. Lastly, we will review how GWAS results in psoriasis spurred the development of ustekinumab and other drugs targeting the IL-23 pathway, and discuss how GWAS may be informative for tailoring therapy in autoimmune diseases. Wellcome Trust Case Control Consortium (2007) Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. Nature 447(7145): 661–678 (students should focus on the rheumatoid arthritis and IBD sections) NALP1 in vitiligo-associated multiple autoimmune disease (2007) Jin, Y et al, N Engl J Med. 356(12):1216-25. Estimating missing heritability for disease from genome-wide association studies (2011) Lee SH, Wray NR, Goddard ME, Visscher PM. Am J Hum Genet. 88(3):294-305. Epub 2011 Mar 3. Personalized medicine in rheumatoid arthritis: miles to go before we sleep (2011) Plenge RM, Bridges, SL, Arthritis Rheum. 2011 Mar;63(3):590-3. doi: 10.1002/art.30126.	Julia Charles, MD, PhD
Apr 3, 6	**Pharmacogenomics, as it impacts drug metabolism, drug action and toxicity.** Individual differences in drug metabolism reflect both environmental and genetic factors, with the latter having a significant impact on drug metabolism, drug action and toxicity in different individuals and patient populations. This lecture will overview basic principles of drug metabolism and the enzymes and genes that carry out these processes. Select examples of drugs whose metabolism is subject to genetic polymorphisms that affect drug action and toxicity will be examined, along with their clinical implications. Johansson I, Ingelman-Sundberg M. Genetic polymorphism and toxicology--with emphasis on cytochrome p450. Toxicol Sci. 2011 Mar;120(1):1-13. Daly AK. Pharmacogenetics and human genetic polymorphisms. Biochem J. 2010 Aug 1;429(3):435-49.	David Waxman, PhD
Apr 10, 13	**Commercialization in the translational research process** The productivity of pharmaceutical research has dropped dramatically in the past decade with many of the FDA approved drugs being "me-too". Academic drug discovery research by contrast has originated 31% novel drug candidates. Industry has taken note of this and is increasingly collaborating with academia. For example Boston University is one of 18 U.S. universities who have signed an agreement with Pfizer biologics drug development. Additionally, Dr. Francis Collins, Director of	Vinit Nijhawan

	National Institute of Health has recognized the need for a new approach and has created NCATS (National Center for Advancing Translational Sciences) that BU's CTSI will fall under. The lecture will detail these macro trends and will also present the translational/commercialization process for drug discovery. Herrera, V. L. M. et al. Spontaneous combined hyperlipidemia, coronary heart disease and decreased survival in Dahl salt-sensitive hypertensive rats transgenic for human cholesteryl ester transfer protein. Nature Med 12, 1383-1389 (1999). Ruiz-Opazo N, Lopez L V, and Herrera V L M. The dual AngII/AVP receptor gene N119S/C163R variant exhibits sodium-induced dysfunction and cosegregates with salt-sensitive hypertension in the Dahl salt-sensitive hypertensive rat model. Molecular Medicine 8: 24-32, 2002. Kaneko, Y, Herrera, V. L. M., Didishvili, T. & Ruiz-Opazo, N. Sex-specific effects of dual ET-1/AngII receptor (Dear) variants in Dahl salt-sensitive/resistant hypertension rat model. Physiol Genomics 20, 157-164 (2005).	
Apr 17, 20	**Is there an ethical or legal obligation to return research results in genomic and genetic research?** Are genomic researchers legally or ethically obligated to give information discovered about subjects through research to the subjects? Should they be? In this session we will explore the answer to those questions and its implications. Bunnik EM, Schermer M and Janssens AC, Personal genome testing: Test characteristics to clarify the discourse on ethical, legal and societal issues. *BM C Medical Ethics* **12**:11 (14 June 2011). http://www.biomedcentral.com/content/pdf/1472-6939-12-11.pdf Berg JS, Khoury MJ, and Evans JP, Deploying whole genome sequencing in clinical practice and public health: Meeting the challenge one bin at a time. *Gen in Med* 2011; 13: 499-504. Kohane, IS and Taylor PL, Multidimensional results reporting to participants in genomic studies: Getting it right. *Sci. Tansl. Med*. 2010; 2:(37): 37cm19. http://stm.sciencemag.org.ezproxy.bu.edu/content/2/37/37cm19.full.pdf Van Ness B, Genomic research and incidental findings. *J. L. Med & Ethics*; 2008 36:292-297. http://onlinelibrary.wiley.com.ezproxy.bu.edu/doi/10.1111/j.1748-720X.2008.00272.x/pdf Clayton, EW, Incidental Findings in Genetics Research Using Archived DNA. *J.L.Med. & Ethics* 2008; 36: 286–29. http://onlinelibrary.wiley.com.ezproxy.bu.edu/doi/10.1111/j.1748-720X.2008.00271.x/pdf	Winnie Roche, JD, MPH
Apr 24	**Translational research in the private sector.** This class will bring together several local scientists working in the private sector in pharmaceutical, genetic start-ups companies, and related industries involved in translational research. Each scientist will discuss his or her experience of the similarities and differences between the way translational research is done in academia and the private sector. Discussion will focus on strategies for academic / private sector collaboration, as well as practical skills that could be useful specifically for scientists interested in transitioning to the private sector. Walter Newman, PhD (Proteostasis Therapeutics Inc.)	Richard Myers, PhD Marc Lenburg, PhD

	Jason Laramie, PhD (formerly of Pfizer, Complete Genomics Inc.) Christopher Smith, PhD (Genedata, Inc.) Douglas Jeffery, PhD (Novartis, Inc.)
Apr 27	**Pre-poster Session discussion** This session will allow students to get feedback on their planned poster projects.
May 1	**Poster Session**