HST 140/ BCMP 218 – Molecular Medicine
Fall 2013, Tuesdays 1-3 PM
Location *(see schedule)*: HMS (MEC 227) or MIT (E25-117)

Faculty: **Irving London**, imlondon@mit.edu
Assistant: Ken Pierce, 6-7-258-7656, kpierce@mit.edu

George Q. Daley, george.daley@childrens.harvard.edu
Assistant: Kathryn Entner, 617-919-2015, Kathryn.Entner@childrens.harvard.edu

David Cohen, dcohen@partners.org
Assistant: James Macdiarmid, 617-525-5092, jmacdiarmid@partners.org

TA: **Daisy Robinton**, robinton@fas.harvard.edu

This course introduces students to a variety of topics in molecular medicine. The course is conducted as a seminar to study various human diseases and the underlying molecular, genetic or biochemical basis for the pathogenesis and pathophysiology of the clinical disorders. Lectures are presented by faculty experts engaged in current research in these fields. Seminars are conducted by the students, with tutorial and supervision by faculty.

Requirements: Attendance is mandatory and any absences must be excused in advance by one of the course directors. Participation is required in all scheduled sessions, given the interactive nature of the course. All students will give two 20-minute presentations on a research paper selected by the lecturers.

Credits: Harvard units: 2 (P) / MIT units: 2-0-4 [P/D/F] (H-level credit). Grading is pass/fail unless your program requires a letter grade.

Website: http://mycourses.med.harvard.edu (please contact TA if you do not have access)

09/10/2013 – *Gleevec and the Triumph of Target-Directed Chemotherapy*
Speaker – George Daley; Model student presentation: Daisy Robinton
Location – MEC 227
****Please come prepared having read the following articles for the first class meeting****

Review: Brian J. Druker, Translation of the Philadelphia chromosome into therapy for CML. **Blood** 112: 4808 – 4817 (2008).

Commentary: Dolgin E, As leukemia options grow, drugs jockey to be first-line therapeutics. **Nature Medicine** 19(1):7 (2013).

Readings:

1. Cortes JE et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. **N Engl J Med**, 29;367(22):2075-88 (2012).
2. Notta F, Mullighan CG, Wang J, Poeppl A, Doulatov S, Philips LA, Ma J, Minden, MD, Downing JR, Dick JE. Evolution of *BCR-ABL1* lymphoblastic leukaemia-initiating cells. **Nature**, 469: 362-367 (2011).

09/17/2013 – *Sex: Cells, Chromosomes, Development and Disorders*

Speaker – David Page
Location – MIT E25-117

Review: Bluma J Lesch and David C Page. Genetics of germ cell development. **Nature Reviews Genetics** 13: 781-94 (2012).

Readings:

1. Dokshin GA, Baltus AE, Eppig JJ, Page DC. Oocyte differentiation is genetically dissociable from meiosis in mice. **Nature Genetics** (2013). doi:10.1038/ng.2672
2. Lange J, Skaletsky H, van Daalen S KM, Embry, SL, Korver CM, Brown LG, Oates RD, Silber S, Repping S, Page DC. Isodicentric Y chromosomes and sex disorders as byproducts of homologous recombination that maintains palindromes. **Cell** 138: 855-69 (2009).

09/24/2013 – *Protein Homeostasis in Health and Disease*
Speaker – Susan Lindquist
Location – MIT E25-117

Review: Lindquist SL and Kelly JW. Chemical and biological approaches for adapting proteostasis to ameliorate protein misfolding and aggregation diseases: progress and prognosis. **Cold Spring Harb Perspect Biol** (2011).

Readings:

1. Santagata S, Mendillo ML, Tang YC, Subramanian A, Perley CC, Roche SP, Wong B, Narayan R, Kwon H, Koeva M, Amon A, Golub TR, Porco JA Jr, Whitesell L, Lindquist S. Tight coordination of protein translation and HSF1 activation supports the anabolic malignant state. **Science** 341(6143):1238303 (2013).
2. Taipale M, Krykbaeva I, Koeva M, Kayatekin C, Westover KD, Karras GI, Lindquist S. Quantitative analysis of Hsp90::client interactions reveals principles of substrate recognition. **Cell** 150(5):987-1001. PMID: 22939624 (2012).

10/01/2013 – *Drug Delivery and Targeting*
Speaker – Robert Langer
Location – E25-117

Review: Robert Langer. Drug Delivery and Targeting. **Nature** 392: 5-10 (1998).

Readings:

1. R Langer & J Folkman. Polymers for the Sustained Release of Proteins and Other Macromolecules. **Nature** 263: 797-800 (1976).
2. Rosen HB, Chang J, Wnek GE, Linhardt RJ, Langer R. Bioerodible Polyanhydrides for Controlled Drug Delivery. **Biomaterials** 4: 131-133 (1983).

10/08/2013 – *Defining Pathways that Regulate Stem Cell Self-Renewal and Migration*
Speaker – Len Zon
Location – MEC 227

Review: Orkin SH and Zon LI. SnapShot: hematopoiesis. **Cell**. 132(4):712 (2008).

Readings:

1. North TE, Goessling W, Walkley CR, Lengerke C, Kopani KR, Lord AM, Weber GJ, Bowman TV, Jang IH, Grosser T, Fitzgerald GA, Daley GQ, Orkin SH, Zon LI. Prostaglandin E2 regulates vertebrate haematopoietic stem cell homeostasis. **Nature** 447(7147):1007-11 (2007).
2. Trompouki E, Bowman TV, Lawton LN, Fan ZP, Wu DC, DiBiase A, Martin CS, Cech JN, Sessa AK, Leblanc JL, Li P, Durand EM, Mosimann C, Heffner GC, Daley GQ, Paulson RF, Young RA, Zon LI. Lineage regulators direct BMP and Wnt pathways to cell-specific programs during differentiation and regeneration. **Cell** 147 (3):577-89 (2011).

10/15/2013 – *Title TBA*
Speaker – Barbara Kahn
Location –MEC 227

Review: TBA

Readings:

1. TBA
2. TBA

10/22/2013 – *Personal Genomes and Guide RNA Genome Therapeutics*
Speaker – George Church
Location – MEC 227

Review: Mali P, Esvelt KM, Church GM. A versatile tool for engineering biology: Cas9 as the Unifactor. **Nature Methods** (submitted).

Readings:

1. Guye P, Busskamp V, Lewis NE, Sanjana NE, Li Y, Zhang F, Ron Weiss R, Church GM. Early transcriptional changes in Neurogenin-induced human stem cell derived neurons. **Neuron** (submitted)
2. Mali P, Yang L, Esvelt KM, Aach J, Guell M, DiCarlo JE, Norville JE, Church GM. RNA-guided human genome engineering via Cas9. **Science** 339:823-6 (2013).

10/29/2013 – *Defining the mutational vulnerabilities of HIV for rational design of vaccines*
Speaker – Arup K. Chakraborty
Location – MIT E25-117

Review: Virgin, H, Walker, B.D. Immunology and the elusive AIDS vaccine, **Nature** 464, 224-231 (11 March 2010).

Readings:

1. V. Dahirel et al. Coordinate linkage of HIV evolution reveals regions of immunological vulnerability. **Proc Nat Acad Sci** 108, 11530-11535 (2011)
2. Ferguson et al., Translating HIV Sequences into Quantitative Fitness Landscapes Predicts Viral Vulnerabilities for Rational Immunogen Design. **Immunity** Volume 38,

Issue 3, 606-617 (2013).

11/05/2013 – *The Biology of Non-Coding RNAs*
Speaker – Phil Sharp
Location – MIT E25-117

Review: Gurtan AM, Sharp PA. The role of miRNAs in regulating gene expression networks. **J Mol Biol** doi: 10.1016/j.jmn.2013.03.007 (2013).

Readings:

1. Heravi-Moussavi A, Anglesio MS, Cheng SW, Senz J, Yang W, Prentice L, Fejes AP, Chow C, Tone A, Kalloger SE, Hamel N, Roth A, Ha G, Wan AN, Maines-Bandiera S, Salamanca C, Pasini B, Clarke BA, Lee AF, Lee CH, Zhao C, Young RH, Aparicio SA, Sorensen PH, Woo MM, Boyd N, Jones SJ, Hirst M, Marra MA, Gilks B, Shah SP, Foulkes WD, Morin GB, Huntsman DG. Recurrent somatic DICER1 mutations in nonepithelial ovarian cancers. **N Engl J Med** 366(3): 234-42 (2011).
2. Gurtan AM et al. Let-7 represses Nr6a1 and a mid-gestation developmental program in adult fibroblasts. **Genes Dev** 15;27(8): 941-54 (2013).

11/12/2013 – *Induced Pluripotent Stem Cells in Disease and Therapy*
Speaker – George Q. Daley
Location –MEC 227

Review: Daisy A. Robinton & George Q. Daley. The promise of induced pluripotent stem cells in research and therapy. **Nature** 481: 295-305 (2012).

Readings:

1. Hanna J et al. Treatment of Sickle Cell Anemia Mouse Model with iPS Cells Generated from Autologous Skin. **Science** 318: 1920-23 (2007).
2. Tulpule A et al. Pluripotent Stem Cell Models of Shwachman-Diamond Syndrome Reveal a Common Mechanism for Pancreatic and Hematopoietic Dysfunction. **Cell Stem Cell** 12, 1-10 (2013).

11/19/2013 – *Programmed Cell Death in Development and Disease*
Speaker – Bob Horvitz
Location – E25-117

Reviews: H. Robert Horvitz. Worms, Life and Death (Nobel Lecture). **Chem Bio Chem** 4: 697-711 (2003).

Readings:

1. MO Hengartner & HR Horvitz. C. elegans Cell Survival Gene *ced-9* Encodes a Functional Homolog of the Mammalian Proto-Oncogene *bcl-2*. **Cell** 76: 665-676 (1994).
2. Tse C, Shoemaker AR, Adickes J, Anderson MG, Chen J, Jin S, Johnson EF, Marsh KC, Mitten JM, Nimmer P, Roberts L, Tahir SK, Xiao Y, Yang X, Zhang H, Fesik S, Rosenberg SH, Elmore SW. ABT-263: A Potent and Orally Bioavailable Bcl-2 Family

Inhibitor. **Cancer Res** 68: 3421-3428 (2008).

11/26/2013 – *von Hippel-Lindau Disease as a Model for Studying Oxygen Sensing and Cancer Metabolism*
Speaker – Bill Kaelin
Location – MEC 227

Review: Kaelin WG, Jr. & Ratcliffe PJ (2008) Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. Mol Cell 30(4):393-402.

Readings:
1. Ivan M, Kondo K, Yang H, Kim W, Valiando J, Ohh M, Salic A, Asara J, Lane W, & Kaelin WG, Jr. (2001) HIFalpha targeted for VHL-mediated destruction by proline hydroxylation: implications for O2 sensing. **Science** 292:464-468.
2. Losman JA, Looper RE, Koivunen P, Lee S, Schneider RK, McMahon C, Cowley GS, Root DE, Ebert BL, & Kaelin WG, Jr. (2013) (R)-2-hydroxyglutarate is sufficient to promote leukemogenesis and its effects are reversible. Science 339(6127):1621-1625.

12/3/2013 – *Congenital Heart Disease: Many Genes Lead to a Broken Heart*
Speaker – Christine Seidman
Location – MEC 227

Review: Fahed AC, Gelb BD, Seidman JG, Seidman CE. Genetics of congenital heart disease: the glass half empty. **Circulation Research** 112(4):707-20 (2013).

Readings:
1. Zaidi S et al. *De novo* mutations in histone-modifying genes in congenital heart disease. **Nature** 498(7453):220-3 (2013).
2. Cordell et al. Genome-wide association study of multiple congenital heart disease phenotypes identifies a susceptibility locus for atrial septal defect at chromosome 4p16. **Nature Genetics** 45(7):822-4 (2013).

12/10/2013 – *Human Genetic Variation and Disease*
Speaker – David Altshuler
Location – MIT E25-117

Readings may change

Review: Altshuler D, Daly MJ, Lander E. Genetic Mapping in Human Disease. **Science 322(5903): 881-888 (2008).

**Readings:
1. Voight et al. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomization study. **The Lancet** 380(9841): 572-80 (2012).
2. Jonsson T et al. A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline. **Nature** 488: 96-99 (2012).