<u>HG803: Advanced Topics in Genetics</u> -- Syllabus Winter 2019

Wednesdays, 3pm-5pm
Location: **THSL** (Taubman Medical Library); **Room 6320 (all classes except for Apr 17, which is in Med Sci II, Room 3817)**
Course Director: Jeff Innis (innis@umich.edu)

• Week 1 (Jan. 9, 2019): Therapy of Genetic Disease I -- Innis
Topic: Correction of Genetic Disease by Modification of Endogenous Gene Expression

1. Systemic administration of PRO051 in Duchenne muscular dystrophy. NM Goemans et al. (2011) *New England Journal of Medicine* 364: 1513-1522

2. The LSD1 inhibitor RN-1 induces fetal hemoglobin synthesis and reduces disease pathology in sickle cell mice. Cui S, et al. (2015) *Blood* 126: 386-396.

Addl paper of interest: Correction of sickle cell disease in adult mice by interference with fetal hemoglobin silencing. J Xu et al. (2011) *Science* 334: 993.

3. Topoisomerase inhibitors unsilence the dormant allele of *Ube3a* in neurons. Sung-Huang H, Allen JA, Mabb AM et al. (2011) *Nature* 481: 185. Review to go with Reference 3: Mabb AM, Judson MC, Zylka MJ, and Philpot BD. 2011. Angelman syndrome: insights into genomic imprinting and neurodevelopmental phenotypes. *Trends in Neurosciences* 34: 293

• Week 2 (Jan. 16): Therapy of Genetic Disease II -- Innis
Topic: Success with Small Molecule Approaches in Seemingly Intractable Genetic Diseases

1. Lovastatin corrects excess protein synthesis and prevents epileptogenesis in a mouse model of Fragile X syndrome. EK Osterweil et al. (2013) *Neuron* 77: 243-250.

<u>Addl paper of interest</u>: Effect of lovastatin on behavior in children and adults with Fragile X syndrome: an open-label study. A. Caku, Pellerin D, et al. (2014) *American Journal of Medical Genetics* 9999:1-9; DOI 10.1002/ajmg.a.36750.

2. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. BW Ramsey et al. (2011) *New England Journal of Medicine*. 365: 18.

<u>Addl paper of interest</u>: Ivacaftor potentiation of multiple CFTR channels with gating mutations. Yu H, Burton B, Huang C-J et al. (2012) *Journal of Cystic Fibrosis* 11: 237.

3. Sustained therapeutic reversal of Huntington's disease by transient repression of Huntington synthesis. Kordasiewicz HB, Stanek LM, et al. (2012) *Neuron* 74: 1031. Review to go with Ref. 3: Lu X-H and Yang XW. 2012. "Huntington Holiday": Progress toward and antisense therapy for Huntington's disease. *Neuron* 74: 964-966.

• Week 3 (Jan. 23): Therapy of Genetic Disease III -- Innis
<u>Topics: RNAi, ASOs, and Genetic Ablation/Small Molecule Pathway Targeting;</u> i) Targeting dominant disorders with RNAi - cardiomyopathy ii) Antisense oligonucleotide treatment of SMA iii) Protective effect of loss or inhibition of DLK in ALS and Alzheimer disease

1. Allele-specific silencing of mutant *Myh6* transcripts in mice suppresses hypertrophic cardiomyopathy. Jiang J *et al.* (2013) *Science* 342: 111-114.

2. Treatment of infantile-onset spinal muscular atrophy with nusinersen: a phase 2, open-label, dose-escalation study. Finkel RS et al. (2016) *The Lancet* 388: 3017-3026.

3. Loss of dual leucine zipper kinase signaling is protective in animal models of neurodegenerative disease. Le Pichon CE et al. (2017) *Sci Transl Med*, Aug. 16; 9(403).

• Week 4 (Jan. 30): Therapy of Genetic Disease IV -- Keegan

Topics: i) Alteration of splicing ii) Interference with post-translational processing or mutant protein interactions

1. Splicing-directed therapy in a new mouse model of human accelerated aging. Osorio FG *et al.* (2011) *Sci Transl Med* 3: 106ra107.

2. Clinical trial of a farnesyltransferase inhibitor in children with Hutchinson-Gilford progeria syndrome. Yang SH *et al.* (2012) *PNAS* 109: 16666-16671.

- **Background:** *Protein farnesyltransferase inhibitors and progeria.* Meta M *et al.* (2006) *Trends Mol Med.* 12(10):480-7.

3. Interruption of progerin-lamin A/C binding ameliorates Hutchinson-Gilford progeria syndrome phenotype. Lee S-j et al. (2016) *J Clinical Investigation* 126: 3879-3893.

• Week 5 (Feb. 6): Somatic Mosaicism in Human Genetic Disease -- Keegan

Topics: i) Focal cortical dysplasia ii) Megalencephaly syndromes iii) CLOVES syndrome

1. Somatic mutations in *TSC1* and *TSC2* cause focal cortical dysplasia. Lim JS et al., (2017) *Am J Human Genetics* 100: 454-472.

2. *De novo* germline and postzygotic mutations in *AKT3*, *PIK3R2* and *PIK3CA* cause a spectrum of related megalencephaly syndromes. Riviere J-B et al. (2012). *Nature Genetics* 44: 934-940.

3. Somatic mosaic activating mutations in *PIK3CA* cause CLOVES syndrome. Kurek KC et al. (2012). *Amer J Hum Genet* 90: 1108-1115.

- **Background:** *A genomic view of mosaicism and human disease.* Biesecker LG and NB Spinner. (2013) *Nature Reviews Genetics* 14: 307-320.

• Week 6 (Feb. 13): Genome Engineering with CRISPR/Cas9 -- Saunders

Topics: i) Off target effects ii) Genome scale transcriptional manipulation iii) Genome editing

1. A high-fidelity Cas9 mutant delivered as a ribonucleoprotein complex enables efficient gene editing in human hematopoietic stem and progenitor cells. CA Vakulskas et al., (2018) *Nature Medicine*, 24:1216-1224.

2. The new frontier of genome engineering with CRISPR-Cas9. J Doudna and E. Charpentier. (2014) *Science* 346:1077 and 1258096-1 – 1258096-9.

3. Induction of fetal hemoglobin synthesis by CRISPR/Cas9-mediated editing of the human B-globin locus. C. Antoniani et al., 2018. *Blood* 131:1960-1973.

• Week 7 (Feb. 20): Cryptic and Complex Genome Rearrangements and Heterogeneity in Autism and Neuropsychiatric Diseases -- Mills

Topics: i) Exploring the genetic basis of neuropsychiatric and autism disorders

1. Cryptic and complex chromosomal aberrations in early-onset neuropsychiatric disorders. Brand M *et al.*, (2014) *Am J Hum Genet* 95(4): 454-61

2. Multiplatform discovery of haplotype-resolved structural variation in human genomes. Mark JP Chaisson *et al.*, (2018) *bioR$_x$iv* posted June, 2018.

3. Whole-genome sequencing of quartet families with autism spectrum disorder. Yuen et al., (2015) *Nature Med* 21: 185-191.

• Week 8 (Feb. 27): Models of Human Brain Development -- Bielas
Topics: i) 3-dimensional human forebrain spheroids pluripotent stem cells– ii) Gyral folding in brain development

1. Assembly of functionally integrated human forebrain spheroids. Birey F et al., (2017) *Nature* 545: 54-59.

2. Induction of expansion and folding in human cerebral organoids. Li Y et al. (2017) *Cell Stem Cell* 20: 385-396.

• Week 9 (Mar. 13): New Technologies to Measure and Predict Variant Effects -- Kitzman
Topics: i) Relative pathogenicity ii) Insight from macromolecular interaction perturbations ii) Amino acid resolution applied to protein interaction profiling

1. A general framework for estimating the relative pathogenicity of human genetic variants. Kircher et al., (2014) *Nature Genetics* 46: 310-315.

2. Identification of *cis*-suppression of human disease mutations by comparative genomics. DM Jordan, SG Frangakis et al., (2015) *Nature*.

3. Protein interaction perturbation profiling at amino-acid resolution. Woodsmith J et al., 2017. *Nature* Methods. Oct. 16; PMID 29039417.

• Week 10 (Mar. 20): Genome Structural Variation, Genomics and Recurrence Risk -- Kidd
Topics: i) Inversions ii) Evolutionary toggling iii) Risk for disease determined by structural haplotypes

1. A common inversion under selection in Europeans. Stefansson H et al. (2005). *Nature Genetics* 37: 129-137.

2. Evolutionary toggling of the MAPT 17q21.31 inversion region. Zody MC et al. (2008). *Nature Genetics* 40: 1076-1083.

3. Structural haplotypes and recent evolution of the human 17q21.31 region. Boettger LM et al. (2012). *Nature Genetics* 44: 881-885.

• Week 11 (Mar. 27): Modeling Epigenetic Regulation Through X-Chromosome Inactivation -- Kalantry
Topics: i) Roles of Xist, RLM and RNF12 in X inactivation

1. Female mice lacking Xist RNA show partial dosage compensation and survive to term. Yang L et al., (2016) *Genes Dev* 30: 1747-1760.

2. RLIM is dispensable for X-chromosome inactivation in the mouse embryonic epiblast. Shin, J., Wallingford, M. C., Gallant, J., Marcho, C., Jiao, B., Byron, M., et al. (2014). *Nature* 511(7507), 86–89. doi:10.1038/nature13286

3. The trans-activator RNF12 and cis-acting elements effectuate X chromosome inactivation independent of X-pairing. Barakat, T. S., Loos, F., van Staveren, S., Myronova, E., Ghazvini, M., Grootegoed, J. A., & Gribnau, J. (2014). [Mol Cell. 2014] - PubMed - NCBI. *Molecular Cell* doi:10.1016/j.molcel.2014.02.006

Review. X chromosome regulation: diverse patterns in development, tissues and disease. X Deng et al. (2014). *Nature Reviews Genetics* 15(6), 367–378. doi:10.1038/nrg3687

• Week 12 (Apr. 3): Stepwise Evolution of the Sex Chromosomes -- Mueller

Topics: i) Evolution of the X ii) Dosage sensitive regulation iii) Is the whole Y chromosome required?

1. Four evolutionary strata on the human X chromosome. BT Lahn and DC Page (1999) *Science*. 286:964–967

2. Mammalian Y chromosomes retain widely expressed dosage-sensitive regulators. Bellott DW, et al. (2014) *Nature* Apr 24;508(7497):494-9

3. Two Y genes can replace the entire Y chromosome for assisted reproduction in the mouse. Yamauchi Y, et al. (2014) *Science* 343:69–72

• Week 13 (Apr. 10): Complexity of Histone Modifications and State of the Art Methods of Characterization -- Iwase

Topics: i) Asymmetrically modified nucleosomes ii) Decoding modified nucleosomes iii) Recombinant antibodies to histone post-translational modifications

1. Examining the roles of H3K4 methylation states with systematically characterized antibodies. RN Shah *et al.* (2018) *Mol Cell* 72: 162-177.

2. The histone H3-H4 tetramer is a copper reductase enzyme. N Attar et al. (2018) *bioR$_x$iv* posted June, 2018.

3. A mechanism for preventing asymmetric histone segregation onto replicating DNA strands. C Yu *et al.* (2018) *Science* 10.1126/science.aat8849.

• Week 14 (Apr. 17): Computational and Functional Identification of Transcriptional Regulatory Elements Important for Human Development and Disease -- Antonellis

Topics: i) Creation of functional neurons from iPS cells ii) Genetic etiologies of brain malformations iii) Genome editing in stem cells

1. Identification and characterization of multi-species conserved sequences. Margulies EH *et al.* (2003) *Genome Research* 13: 2507-2518.

2. A systematic comparison reveals substantial differences in chromosomal versus episomal encoding of enhancer activity. Inoue F *et al.* (2017) *Genome Research* 27: 38-52.

3. Enhancer variants synergistically drive dysfunction of a gene regulatory network in Hirschsprung disease. Chatterjee S *et al.* (2016) *Cell 167*: 1-14.

HG803 requirement:

Please complete the course evaluation for each module at the end of the course. Your input is essential for improving class organization and content! Please email Jeff Innis (innis@umich.edu) if you have any questions regarding the class.