HG803: Advanced Topics in Genetics -- Syllabus Winter 2021

Wednesdays, 3pm-5pm
Location: **Virtual**
Course Director: Jeff Innis (innis@umich.edu)

• Week 1 (Jan. 20, 2021): Therapy of Genetic Disease I -- Innis
Topic: Correction of Genetic Disease by Modification of Endogenous Gene Expression

1. Reactivation of PTEN tumor suppressor for cancer treatment through inhibition of a MYC-WWP1 inhibitory pathway. Lee Y-R, et al. (2019) *Science* 364: eaau0159.

2. 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. 27): Genome Engineering with CRISPR/Cas9 -- Saunders
Topics: i) Genome editing; prime editing ii) Deletions and rearrangements induced by DSB

1. Public health concerns over gene-drive mosquitoes: will future use of gene-drive snails for schistosomiasis control gain increased level of community acceptance? DO Famakinde, (2020). *Pathog Glob Health*. 2020 Mar;114(2):55-63. doi: 10.1080/20477724.2020.1731667. Epub 2020 Feb 26. PMID: 32100643.

2. Reducing resistance allele formation in CRISPR gene drive. J Champer et al., 2018. *Proc Natl Acad Sci U S A.* 2018 May 22;115(21):5522-5527. doi: 10.1073/pnas.1720354115. Epub 2018 May 7. PMID: 29735716.

3. CRISPRoff enables spatio-temporal control of CRISPR editing. J Carlson-Stevermer et al., 2020. *Nat Commun.* 2020 Oct 7;11(1):5041. doi: 10.1038/s41467-020-18853-3. PMID: 33028827

• Week 3 (Feb. 3): Therapy of Genetic Disease II -- Keegan
Topics: i) Interference with mutant protein interactions, ii) CRISPR/Cas9 for progeria

1. 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.

2. Development of a CRISPR/Cas9-based therapy for Hutchinson-Gilford progeria syndrome. Santiago-Fernández et al. (2019) *Nat. Medicine* 25: 423-426 (including extended data).

• Week 4 (Feb. 10): Somatic Mosaicism in Human Genetic Disease -- Keegan
Topics: i) CLOVES syndrome ii) Therapy in PIK3CA-related overgrowth syndromes

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

2. Targeted therapy in patients with PIK3CA-related overgrowth syndrome. Venot Q et al. (2018). *Nature* 558: 540-546.

• Week 5 (Feb. 17): 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 6 (Feb. 24): NO CLASS – Well-Being Break

• Week 7 (Mar. 3): 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 8 (Mar. 10): New Technologies to Measure and Predict Variant Effects -- Kitzman
Topics: i) Relative pathogenicity ii) Saturation genome editing

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

2. Accurate classification of BRCA1 variants with saturation genome editing. GM Findlay et al., (2018) *Nature* 562:217-222.

• Week 9 (Mar. 17): Cryptic and Complex Genome Rearrangements and Heterogeneity in Autism and Neuropsychiatric Diseases -- Mills
Topics: i) Exploring the genetic basis of neuropsychiatric and autism disorders

Review: Structural variation in the sequencing era. SS Ho et al., 2020. *Nat Rev Genet.* 2020 Mar;21(3):171-189. doi: 10.1038/s41576-019-0180-9. Epub 2019 Nov 15.PMID: 31729472

1. Multiplatform discovery of haplotype-resolved structural variation in human genomes. Mark JP Chaisson *et al.*, (2019) *Nature Commun*. 10:1784.

2. Dissecting the causal mechanism of X-linked dystonia-parkinsonism by integrating genome and transcriptome assembly. T Aneichyk et al., (2018) *Cell* 172(5): 897-909.

• Week 10 (Mar. 24): Modeling Epigenetic Regulation Through X-Chromosome Inactivation
Topics: i) Roles of Xist, RLM and RNF12 in X inactivation **-- Kalantry**

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

1. 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

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

• Week 11 (Mar. 31): Stepwise Evolution of the Sex Chromosomes -- Mueller
Topics: i) Evolution of the X and Y chromosomes ii) Is the whole Y chromosome necessary?

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

2. 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 12 (Apr. 7): Complexity of Histone Modifications and State of the Art Methods of Characterization -- Iwase
Topics: i) Asymmetrically modified nucleosomes ii) Decoding modified nucleosomes

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

2. Histone serotonylation is a permissive modification that enhances TFIID binding to H3K4me3. LA Farrelly *et al.* (2019) *Nature* 567: 535.

• Week 13 (Apr. 14): Paternal Epigenetic Inheritance -- Hammoud
Topics: i) Developmentally critical gene chromatin ii) Transgenerational effects of histone disruption

1. Distinctive chromatin in human sperm packages genes for embryo development. S Hammoud *et al.* (2009) *Nature* 460: 473-479.

2. Disruption of histone methylation in developing sperm impairs offspring health transgenerationally. K Siklenka *et al.* (2015) *Science* 350: 651 (summary); aab2006-1 - 12.

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.