Neurobiology of Developmental Brain Disorders
Department of Human Genetics, HG 480/580

Meeting Time and Location: Winter Semester, Tu/Th, 1-2:30 THSL 6215

Course Director: Stephanie Bielas - sbielas@umich.edu/(734) 647-8890

Participating Faculty: Shigeki Iwase - siwase@umich.edu/(734) 647-8832 and Kenneth Kwan – kykwan@umich.edu/(734) 615-2444

Course Description:
This seminar and discussion course is focused on cellular and molecular aspects of mammalian developmental neurobiology. Genetic and epigenetic principles underlying the emergence and maintenance of the mammalian nervous system will be explored in the context of human disorders that lead to structural brain abnormalities, intellectual disability and autism. The intent of this course is to present current topics in developmental neuroscience in the context of human genetics and mammalian models of brain development.

Undergraduate Prerequisites:
BIO225 and BIO305

Graduate Student Requirement:
In addition to the activities described below, students will write a 300 word analysis of a primary research paper to receive graduate level credit. This assignment should reflect a graduate level evaluation of the published research, emphasizing a logical analysis and interpretation of the data. These skills will be discussed and honed throughout the course.

Online office hours:
Any organizational/administrative or course content questions can be raised during online office hours. I will be available in the Canvas Chat Room **Monday and Wednesday afternoons from 3-5 PM**.

Grading:
Your grade will be based on a possible total of **500 points.**

In-Class Quizzes (**200 points**): 40% of your grade will be based on performance on quizzes, which will occur first thing prior to presentations. These quizzes will assess your in-depth understanding of material from the previous days' lectures, and the reading(s) assigned for that weeks discussion. Quizzes will be open-book (paper) - *i.e.*, you will be able to refer to the previous day's lecture notes and the assigned paper in framing your response to quiz questions. **Your 12 highest quiz scores of 15 quizzes total will count toward the final total of 200 points. If you miss a quiz for any reason (medical, family, personal), there will be no make-up assignment; that quiz grade will be one of two dropped from your total.**

*** 15 minutes of class time will be allotted for you to complete the quiz.**

Participation (**100 points**): 20% of your grade will be based on your contribution to in-class discussion of assigned readings. **Preparing for discussion will improve your grades on in-class quizzes, and active participation will make subsequent discussion more interesting and productive**. You should come to discussion sections ready to discuss how experiments in the papers were carried out, how the authors interpreted their data, and how their findings fit with prior hypotheses. You will be expected to raise technical and conceptual questions about the authors' research strategy, and to propose alternative strategies, critical next experiments, or alternate interpretations of data.

Presentations/Student-led discussions (**200 points**): 40% of your grade will be based on three short 25 minute presentations on an assigned scientific paper. Each of the three instructors will moderate 5 student presentation classes with 2 presentations per class. **Successful presentations will address the following criteria:**

- Summarize what is currently known about the problem (5 points).
- Explain why addressing the issues presented in the scientific papers are important and of general interest to neuroscience (6 points).
- State the hypothesis when a hypothesis is being tested, or the major goal of the work if the paper is discovery-based (5 points).
- Describe the experiments being used to address the scientific issues (20 points).
- Explain the strengths and weaknesses of experimental strategy being used to address their research question (10 points).
- Describe the potential outcomes of their experiments (predicted and not predicted) and how they interpret the data (10 points).
- Explain any caveats, describe alternative strategies, and subsequent future directions (6 points).
- Adhere to the time limit (5 points).

Class Schedule:

Date:	Lecture or discussion topic:	Required reading:
	Instructor: Stephanie Bielas	
Th 4 Jan	Introduction to the course, roles human genetics and mouse models have played in informing us about mammalian neurodevelopment (Lecture 1). Stephanie Bielas	
Tu 9 Jan	General Principles of CNS development and neurogenesis (Lecture 2)	
Th 11 Jan	***Quiz 1***; Discussion of: Evolution of mammalian neurogenesis	Hansen et al. 2010 Nature & Qian et al. 2016 Cell
Tu 16 Jan	***Quiz 2***; Discussion of: Modeling human brain size	Li et al. 2017 Cell Reports; Harding et al. 2016 AJHG & Li et al. 2016 AJHG
Th 18 Jan	Genetics and molecular biology of cortical neuron migration (Lecture 3)	
Tu 23 Jan	***Quiz 3***; Discussion of:	Poirier et al. 2013 Nature

	Cortical neuronal migration	Genetics & Koizumi et al. 2006 Nature Neuroscience
Th 25 Jan	Genetics of epigenomic regulation of brain development (Lecture 4)	
Tu 30 Jan	***Quiz 4***; Discussion of: Epigenomic mechanisms of brain development	Yang et al. 2012 Cell & Nitarska et al. 2016 Cell Reports
Th 1 Feb	Role of cilia in brain development (Lecture 5)	
Tu 6 Feb	***Quiz 5***; Discussion of: Cilia in brain development	Cantegral et al. 2008 AJHG & Higginbotham et al. 2013 Nature Neuroscience
	Instructor: Shigeki Iwase	
Th 8 Feb	Introduction of intellectual disability; cellular and molecular basis (Lecture 6)	
Tu 13 Feb	***Quiz 6***; Discussion of: Identification of mutations in ID patients and modeling ID with mouse models.	Pirozzi F, et al. 2011 Human Mutation & Khelfaoui M, et al. 2007 Journal of Neuroscience.
Th 15 Feb	Introduction of epigenetics (Lecture 7) Shigeki Iwase	
Tu 20 Feb	***Quiz 7***; Discussion of: Discovery of “writers” and “readers”of epigenetic marks.	Rea S, et al. 2000 Nature & Lachner M et al. 2001 Nature
Th 22 Feb	IDs associated with defective "writing" or "erasing" of epigenetic marks (Lecture 8)	
Tu 27 Feb	Spring Break	
Th 1 Mar	Spring Break	
Tu 6 Mar	***Quiz 8***; Discussion of: Mouse models of Rubinstein-Taybi syndrome and gene regulation triggered by neuronal activity.	Alarcon JM, et al. 2004 Neuron & Malik AN, et al. 2014 Nature Neuroscience
Th 8 Mar	***Quiz 9***; Discussion of: Kabuki syndrome caused by a “writer” and “eraser” mutation.	Ng SB, et al. 2010 Nature Genetics & Van Laarhoven PM, et al. 2015 Hum. Mol. Gen. .
Tu 13 Mar	IDs associated with defective "reading" of epigenetic marks. (Lecture 9)	
Th 15 Mar	***Quiz 10***; Discussion of: Molecular mechanism of ATRX syndrome and reversal of Rett syndrome symptoms in developed brain.	Iwase S, et al. 2011 Nature Structural Molec Biology & Guy J et al. 2007 Science.
	Instructor: Kenneth Kwan	
Tu 20 Mar	An introduction to autism spectrum disorders (Lecture 10)	

Th 22 Mar	***Quiz 11***; Discussion of: Transcriptomic analysis of autistic brain reveals convergent molecular pathology.	Stoner et al. 2014 Nature & Voineagu et al. 2011 Nature
Tu 27 Mar	The genetics of autism (Lecture 11)	
Th 29 Mar	***Quiz 12***; Discussion of: Sporadic autism exomes reveal a highly interconnected protein network of de novo mutations.	Rubeis et al. 2014 Nature & Willsey et al. 2013 Cell
Tu 3 Apr	Syndromic forms of autism (Lecture 12)	
Th 5 Apr	***Quiz 13***; Discussion of: FMRP stalls ribosomal translocation on mRNAs linked to synaptic function and autism and mutations causing syndromic autism define an axis of synaptic pathophysiology.	Darnell et al. 2011 Cell & Osterweil et al. 2013 Neuron
Tu 10 Apr	Language disorders and human brain evolution (Lecture 13)	
Th 12 Apr	***Quiz 14***; Discussion of: Human-specific transcriptional regulation of CNS development genes by FOXP2 and the human language-associated gene SRPX2 regulates synapse formation and vocalization in mice.	Enard et al. 2009 Cell & Sia et al. 2013 Science
Tu 17 Apr	***Quiz 15***; Discussion of: Species-dependent posttranscriptional regulation of NOS1 by FMRP in developing cerebral cortex and a humanized version of Foxp2 affects cortico-basal ganglia circuits in mice.	Kwan et al. 2012 Cell & Bae et al. 2014 Science