Sex Differences in Human Disease

BIOL 490-003

Class Days and Time: Tuesday and Thursdays
11:00 AM-12:15 PM
Locations: Peabody - Rm 0216
Instructor: Frank L. Conlon, Ph.D.
Email: frank_conlon@med.unc.edu
Office Hours: TBA (or by appointment)

Course Description:

Many human disease states including, cancer, cardiovascular disease, dementia, chronic kidney disease, obesity, auto-immune disease and others show a difference in the pathology and treatment between males and females. To facilitate a deeper understanding of the basis of these disease states, the class will progress from a basic understanding of the mechanism of sex determination to its hormonal and genetics outcomes. The course will be based on primary literature and discuss experimental evidence for student to gain an understanding of sexual disparities in the development and potential treatments of disease.

Prerequisites:

BIOL 202 or BIOL 205

Topics will include:

- Primary sex determination
    - Testis development
    - Ovary development
- X-Chromosome inactivation
- Gonadal sex hormones and their effect on gene expression
- Evidence for sexual dimorphism in human disease
- Female prevalent disease; dementia
- Male prevalent disease; cardiovascular disease

Expectations:

Students will be expected to do assigned readings before class. This is essential for class participation, which is a major component of the final grade. Participation is a must in this course. You will be expected to contribute to class discussions on a daily basis, and you will be expected to work in groups.

Course Objectives:

Upon completion of the course, students will be able to:

1. Develop an in-depth understanding of sexual development and sexual dymorphism.
2. Understand the basis and uses of a variety of laboratory techniques used to study sexual development and sexual dymorphism, and to gain an awareness of how these techniques have contributed to our knowledge in the field.
3. Comprehend the causes, symptoms and treatments of a variety of sexually dimorphic disease states.
4. Apply the skills necessary to critically analyze data presented in the primary scientific literature.
5. Communicate via both written and oral dissemination of the knowledge gained in the course.
6. Propose solutions to address unanswered questions in sexual dymorphism in development and disease.

Textbook

This class is based on primary scientific and medical literature. There is no textbook.

Readings (current or historic scientific papers):

Will be assigned and made available as pdf files through Sakai.

Course Policies

1. Exams

There will be 3 exams. All exams will consist of essay questions assessing your understanding of course readings, lectures and discussions. Each exam covers 1/3 of the content of the course, and the final exam (also an essay exam) is cumulative. You will have plenty of opportunities during class discussions to practice responding to essay exam questions so that you are adequately prepared to do so by the time the first midterm exam takes place

2. Attendance

All students are expected to:

–be on time for all class periods.

–attend all classes.

–meet deadlines for homework and other assignments.

3. Participation
Classes will consist of lectures, discussions and student-centered learning activities that focus on a scientific paper relevant to that week's unit. 25% of your final grade will be determined by the level of your participation in these activities and classroom discussions. Keep in mind that simply showing up for these activities does not earn you an "A" for a discussion grade. You must actively participate to earn the "A". Active participation has two components: 1) engaging in the activities assigned for that class; and 2) asking any questions about concepts presented in the unit or scientific paper that are "murky" to you. You are not expected to understand everything addressed in assigned readings before showing up for class each week. You are however, expected to ask questions if something is unclear.

Remember: It is difficult to participate if you are not present. Thus, attendance is mandatory, and your discussion grade will be negatively affected by absences. The ONLY acceptable excuses for missing class are documented illness or family emergencies. Unexcused absences will incur grade penalties.

During discussion, students are expected to:
–be courteous and respectful to other participants and ideas.
–adhere to the Honor Code.

4. Homework and Quizzes
Homework will be assigned in advance as much as possible; however, the flexible and dynamic nature of this class may make it difficult to do so far in advance.

5. Grading:
75% Exams. There will be three exams, two mid-semester exams and one final exam. Each exam will count for 25% of your final grade. The final exam will be cumulative, with an emphasis on untested material.
25% Participation, homework & class preparedness

Grade Scale
90n and above: A
80-89: B
70-79: C
60-69: D
Less than 60: F

Please note that I reserve the right to make changes to the syllabus, including project due dates and test dates (excluding the officially scheduled final examination), when unforeseen circumstances occur. These changes will be announced as early as possible so that students can adjust their schedules.

HONOR CODE: All work done in this class must be carried out within the letter and spirit of the UNC Honor Code. You must sign a pledge on all graded work certifying that no unauthorized assistance has been given or received. You are expected to maintain the confidentiality of examinations by divulging no information about any examination to a student who has not yet taken that exam. You are also responsible for consulting with your professors if you are unclear about the meaning of plagiarism or about whether any particular act on your part constitutes plagiarism. Please talk with the professor if you have any questions about how the Honor Code pertains to this course.

Course Copyright Information:

All course materials including your notes and assignments are covered by University Copyright Policy http://policies.unc.edu/files/2013/05/Copyright.pdf

Unauthorized sale, duplication, or posting is a violation of the Honor Code.

Date	Class Schedule
Thursday January 9	**Sex differences in Disease** Introduction and Outline
Tuesday January 14	**Sex Determination: Evolution and Sex Chromosomes 1** Bellott et al., (2010) Convergent Evolution of Chicken Z and Human X Chromosomes by Expansion and Gene Acquisition. *Nature*. 466(7306):612-616.
Thursday January 16	**Sex Determination: Evolution and Sex Chromosomes 2** Bellott et al., (2014) Mammalian Y chromosomes retain widely expressed dosage-sensitive regulators. *Nature*. 508, 494–499.
Tuesday January 21	**Sex Determination: Somatic versus Gonadal** Burgoyne, Buehr, Koopman, Rossant, McLaren (1988) Cell-autonomous action of the testis-determining gene: Sertoli cells are exclusively XY in XX—XY chimaeric mouse testes. *Development*. 102: 443-450.
Thursday January 23	**Sex Determination: SRY Testis Development** Gubbay et al., (1990) A gene mapping to the sex-determining region of the mouse Y chromosome is a member of a novel family of embryonically expressed genes. *Nature*. 346: 245–250.
Tuesday January 28	**Sex Determination: Ovary Development** Colvin et al., 2001 Male-to-female sex reversal in mice lacking fibroblast growth factor 9. *Cell.* 104: 875-889.
Thursday January 30	**Tuner Syndrome** Ganger et al., (2016) Anatomy of turner syndrome. *Clin Anat.* 2016 Jul;29(5):638-42.
Tuesday February 4	**Dosage Compensation: X-Chromosome Inactivation** Brockdorff et al., (1991) Conservation of position and exclusive expression of mouse Xist from the inactive X chromosome. *Nature*. 351: 329–331.
Thursday February 6	**Escaping X-Chromosome Inactivation in Mouse** Yang et al., (2010) Global survey of escape from X inactivation by RNA-sequencing in mouse. *Genome Res*. 20(5):614-22.
Tuesday February 11	**Escaping X-Chromosome Inactivation in Human** Tukiainen et al., (2017) Landscape of X chromosome inactivation across human tissues. *Nature*. 550(7675):244-248.
Thursday February 13	**Cancer** 1. Clocchiatti et al., (2016) Sexual dimporphism in cancer. *Nat Rev Cancer*. 2016 May;16(5):330-9. 2. Dunford A, et al., (2016). Tumor-suppressor genes that escape from X-inactivation contribute to cancer sex bias.

	Nat. Genet. 49, 10–16.
Tuesday February 18	**Exam #1**
Thursday February 20	**It is not all genetic** Snell and Turner (2018) Sex Chromosome Effects on Male–Female Differences in Mammals. *Curr Biol*. 2018 Nov 19;28(22):R1313-R1324.
Tuesday February 25	**Hormonal Control of Sex 1** Jost, (1970) Hormonal factors in the sex differentiation of the mammalian foetus. *Phil Trans. Roy. Soc. Lond*. 259, 119-130.
Thursday February 27	**Hormonal Control of Sex 2** Short, (1970) The Bovine Freemartin: a new look at an old problem. *Trans. Roy. Soc. Lond*. 259, 141-147.
Tuesday March 3	**Hormonal Control of Sex 3** Zangen et al., (2011) XX Ovarian Dysgenesis is Caused by a PSMC3IP/HOP2 Mutation that Abolishes Coactivation of Estrogen-Driven Transcription. *Am J Hum Genet.* 89(4):572-579.
Thursday March 5	**Hormonal Control of Neural and Behavior** Phoneix et al., (1959) Organizing Action of Prenatally Administered Testosterone Propionate on the Tissues Mediating Mating Behavior in the Female Guine Pig. *Endocrinology* 65: 369-382.
Tuesday March 10	**Spring Break**
Thursday March 12	**Spring Break**
Tuesday March 17	**Separating Hormonal verses Genetic Influence in Neural and Behavioral Traits 1** Burgoyne and Arnold (2016) A primer on the use of mouse models for identifying direct sex chromosome effects that cause sex differences in non-gonadal tissues. *Biol Sex Differ*. 2016 Dec 13;7:68.
Thursday March 19	**Separating Hormonal verses Genetic Influence in Neural and Behavioral Traits 2** Gatewood et al., (2006) Sex chromosome complement and gonadal sex influence aggressive and parental behaviors in mice. *Journal of Neuroscience.* 26(8):2335-42
Tuesday March 24	**Sex Differences in Neural Homeostasis 1** 1. Luders et al., (2009) Why sex matters: brain size independent differences in gray matter distributions between men and women. *J Neurosci.* Nov 1;29(45):14265-70. 2. Babapour et al., (2019) Nature and implications of sex differences in AD pathology. *Nat Rev Neurol.* Jan;15(1):6-8.
Thursday March 26	**Sex Differences in Neural Homeostasis 2** Damoiseaux et al., (2012) Gender modulates the APOE ε4 effect in healthy older adults: convergent evidence from functional brain connectivity and spinal fluid tau levels. *J. Neurosci.* 32, 8254–8262.
Tuesday March 31	**Exam #2**

Thursday April 2	**Sex Differences in Allergy and Infection 1** Christou et al., (2019) Sexual dimorphism in SLE: above and beyond sex hormones. *Lupus* Jan;28(1):3-10.
Tuesday April 7	**Sex Differences in Allergy and Infection 2** Liang et al., (2017) A gene network regulated by the transcription factor VGLL3 as a promoter of sex-biased autoimmune diseases. *Nat Immunol.* 2017 Feb;18(2):152-160.
Thursday April 9	**Sex Differences in Viral Infection** Smith-Bouvier DL (2008) A role for sex chromosome complement in the female bias in autoimmune disease. *J Exp Med.* May 12;205(5):1099-108.
Tuesday April 14	**Sex Differences in Viral Vaccines** Klein, S. L., Jedlicka, A. & Pekosz, A. (2010) The Xs and Y of immune responses to viral vaccines. *Lancet Infect. Dis.* 10, 338–349 (2010).
Thursday April 16	**Sex Differences in Cardiac Homeostasis and Disease 1** Trexler et al., (2017) Transcriptome and Functional Profile of Cardiac Myocytes Is Influenced by Biological Sex. *Circ Cardiovasc Genet.* Oct;10(5).
Tuesday April 21	**Sex Differences in Cardiac Homeostasis and Disease 2** Deegan et al., (2019) The developmental origins of sex-biased expression in cardiac development. *Biol Sex Differ.* Sep 5;10(1):46.
Thursday April 23	**The Future**