BSCI 243.01 Genetics of Disease
Fall 2007
Date: MWF 11:10a-12p
Location: Room U5202, MRB3

Instructor
Dr. Joshua Gamse
U5231 BSB/MRBIII
936-5574
josh.gamse@vanderbilt.edu

Office hours: You can drop in without an appointment Tuesday and Wednesday, 1-3 pm. Other times can be arranged, just email me in advance.

Course overview: This course will focus on the biology of human genetic disorders, using a case-study format. Review and research articles from scientific journals will be a main resource, while the textbook will serve as a reference for understanding techniques and concepts from the papers. Each week, we will tackle a different human genetic disease. We will cover 1. the biology of the disease, at the molecular, cellular, and organismal level, 2. the methods used to identify the gene(s) involved, and/or 3. therapeutic strategies that are being used or developed to treat the disease. In parallel, during the semester you will be researching a human genetic disease of your choice. You will present a paper on the disease to the class, and write a mock grant proposal for research on the disorder.

Blackboard: Papers and reading assignments will be posted before each class session on Blackboard. Be sure to check Blackboard on a regular basis!

Textbook: Strachan and Read, Human Molecular Genetics 3

Further reading: These books on human genetics are available in the Science & Engineering Library. They aren't required for the course; they're lighter reading on this subject.

Mutants: On Genetic Variety and the Human Body, Armand Marie Leroi
When a Gene Makes You Smell Like a Fish, Lisa Seachrist Chiu

Prerequisite: Bsci 210 (Genetics). Knowledge of the basic principles of classical and molecular genetics is expected. We will review these concepts at the start of the class, but you are responsible for remembering those concepts that have faded from your mind!

Course objectives: This course is designed to increase your knowledge of genetics as it is applied in the laboratory, and your fluency in genetics, both written and verbal. You will learn how different experimental approaches can be used to solve problems, and how to think in a critical manner about experimental design and data. These skills will be

applied to the final proposal, where you will design hypothetical experiments to explore as-yet unanswered questions in human genetics.

Format: Each week, on Monday and Wednesday I will give a short (~30 minute) lecture on the genetic disorder we will be studying, as well as topics in human genetics relevant to the particular disease.
On Wednesday and Friday, we will discuss papers assigned for that week. The articles will cover the disease of the week, including 1. how the disease gene was identified, 2. the pathophysiology of the disease, and/or 3. therapeutic approaches. Some discussions will be led by you (see below for details).

Additionally, on Mondays, there will be a short (~20 min) presentation on a genetic disorder, given by one of you (starting September 12). See below for more about this presentation.

Weekly assignments: For each class session, there will be textbook reading and/or research papers to analyze. Papers will be available on Blackboard in the "Course Information" section. You are responsible for printing out the papers, reading them and making notes on the papers as you read them, and bringing them to class. On occasion, if an electronic copy of a paper is unavailable, I will distribute paper copies in advance.

Along with the papers, I will post study questions to guide your reading and to prompt discussion. The topics covered in the questions are the most important points of the papers. As you read the paper, answer the questions. They won't be graded but I may call on you at random to answer them in class!

If you don't understand something in the reading, look up the concept in your text and on the web (see Useful Links below). If you can't find the answer, contact me. Because discussion is a significant portion of your grade, come prepared to explain anything covered in the reading, even on weeks that you aren't leading the discussion.

> TIPS ON HOW TO READ A RESEARCH PAPER: To start, read the abstract and introduction to get the context and the general questions to be addressed. Then read the discussion to understand how the findings fit within the context. You now know the start and end point of the paper, so delve into the results section to see what experiments led from one point to the other. Each figure will depict a major finding/set of findings. For each figure, read the associated portion of the text AND the figure legend to determine the specific question addressed, the technique used, and the data generated. Don't bother with the Materials and Methods unless you need clarification on particular reagents used. Look up unfamiliar terminology in the textbook and online, but don't get bogged down – I don't expect you to get every detail as you are initially getting used to reading research papers!

Leading discussion: Once during the semester, you will lead discussion on one of the papers assigned (this will usually be a paper assigned for Friday discussion), using the

study questions as a starting point for discussion. Following your leading of discussion, I will give you feedback.

Research on a human disorder:

Over the course of the semester, you will independently research and write a mock grant proposal on a human genetic disease. It must be a disease that is not otherwise covered in the course. **Please let me know what disease you will research by September 14, 4 pm by email,** so that there are no duplicates within the class. You are welcome to choose any human genetic disease. I have also made a list of a number of such diseases if you would like some choices, and you can look through the list at the Genes and Disease website (see below).

Formal presentation: You will give one formal presentation during the semester. It will be 20 minutes long and focus on the disease you have chosen. You will choose a primary research paper on the disorder to present. You should spend about 10 minutes on background information about the disease, and 10 minutes on analysis of the paper. Following your presentation, I will give you feedback.

When you are deciding on your paper, please come to me for advice and suggestions. **NOTE: I must approve the article you choose, and you must make your choice at least 7 days prior to your presentation.**

For your presentation, you will have access to a Mac or a PC with projector and PowerPoint software. Please send me your Powerpoint presentation afterwards, so I can make it available to the class.

Hints: you shouldn't try to present the whole paper. Pick the 1-3 figures that are most important to the take-home message, and discuss them in detail.

Mock Grant Proposal: You will write a paper in the style of an NIH grant proposal. The proposal will be approximately 2000-3000 words (not including bibliography). Use double spacing, 12 point font, 1 inch margins. You will research a human genetic disorder by reading reviews as well as original research papers, and propose the next questions to address. This will include explaining the experiments that you would perform to answer these questions.

You should take advantage of the online databases OMIM and PubMed (see below) to learn about the disease and find articles about current research. **Do NOT plagiarize work from other sources or you will receive a failing grade for the grant proposal.**

The sections of this paper will be **due at different points during the semester**, as noted below. I will provide feedback on the sections after you hand them in, and based on this feedback, you will revise the sections and hand in the final grant proposal that I will grade.

The paper will include the following sections:

Abstract: this should be 1-2 paragraphs (~300 words), similar to the abstract section of a research paper. It briefly introduces the disease, the specific aspect of the disease that you wish to research, and what sorts of experiments you will do. This is a broad overview, without too many details. **DUE: 4 pm October 1 by email, in Word or PDF format.**

Introduction: This is where you will go into more depth regarding what is known about the disease. This is similar to the introduction of a paper (~1000 words). You will start off very generally introducing the disease, and gradually work towards the particular problem that you would like to study. You will cite the papers of other researchers here, explaining what they have done and how this illuminates our knowledge of the disease's biology. The last paragraph of the introduction should lead in to the specific problem you're interested in. For instance, for Huntington's disease, you would discuss the symptoms of the disease, the identification of the disease gene and the nature of mutations in the gene, and finally discuss what is know about how polyglutamine repeats cause cell toxicity (if this was the topic you were going to propose for experiments). This section is similar to the Introduction of a research article. **DUE: 4 pm October 15 by email, in Word or PDF format.**

Hypotheses and experiments: this is the meat of the proposal. Given what is already know about the disease, what experiments should be done next to investigate an interesting aspect of the disease? You will propose 2-4 experiments (~1500 words). For each experiment, you will propose a hypothesis, stating a prediction based on what is already known. This should be a few sentences. Then you will explain how you will do the experiment to test the hypothesis in a couple of paragraphs. An example of one such experiment: for Huntington's disease, you might hypothesize that chaparone proteins can suppress toxicity due to aggregation of long polyglutamine repeats, and test the hypothesis by overexpressing a polyglutamine repeat in cells, then additionally overexpressing a chaparone to see if it reduces toxicity. **DUE: 4 pm November 5 by email, in Word or PDF format.**

Bibliography: The bibliography should be in alphabetical order by the surname of the first author of the paper. The bibliography is **due along with the final version of the paper.** You should be adding references to the bibiliography as you write the introduction/significance and hypotheses/experimental methods sections.

> The format of bibliography entries should be:
>
> Author Last Name, Initials (Year of publication). Title of paper. *Journal* **Volume,** starting page-ending page.

Example:
Adamus, G., Zam, Z. S., Arendt, A., Palczewski, K., McDowell, J. H. and Hargrave, P. A. (1991). Anti-rhodopsin monoclonal antibodies of defined specificity: characterization and application. *Vision Res* **31**, 17-31.

Final paper: Abstract, Introduction, hypotheses/experimental methods and bibliography, revised according to my feedback, will be due **4pm November 14 by email, in Word or PDF format.**

More in depth discussion of how to write can be found in A Short Guide to Writing about Biology by Jan Pechenik. It is available in the library and I have a copy as well.

Peer reviews: You will receive the grant proposals of two of your classmates by email. For each review, you should write a ~400 word critique for EACH of the proposals. You should evaluate the clarity and completeness of the background and significance, and assess the plausibility, logic, and value of the proposed experiments. **Due: 4 pm on December 7 by email, in Word or PDF format.**

Final Exam: The final exam will be take home. You will read a research article on a disease that we studied during the semester, and answer a set of short answer questions. **Due: December 18 by email, in Word or PDF format.**

Method of Evaluation

Grades will be based on the following distribution

Participation in discussions: 10%
Performance as a discussion leader (1 session): 10%
In class presentation: 15%
Paper (mock grant proposal): 30% (based on revised final paper)
Peer review of other students' grant proposals: 10% (5% each)
Final exam: 25%

Useful links:

NCBI Genes and Disease. A list of many major genetic diseases organized by organ system affected. It includes links to fact sheets, articles, etc. This is a good starting place to find an interesting disease to research.
http://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=gnd.TOC&depth=2

OMIM (Online Mendelian Inheritance in Man). A complete database of genes and diseases in humans, containing an exhaustive amount of information. This is a good place for in depth information on the disease that you choose.:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM

PubMed. A complete database of abstracts of biomedical research articles, and links to PDFs of the papers. The OMIM links to articles connect you to this database. It's a good place to continue searching for information about your disease:
http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=PubMed

Online Medical Dictionary. A searchable dictionary of biology and medical terms. Helpful when you run across an unfamiliar term in an article:
http://cancerweb.ncl.ac.uk/omd/

Class schedule:

Class	Date	Topic
1	Aug. 29	Introduction to class; meiosis and chromosomes (Ch. 2)
2	Aug. 31	Genes and pedigrees (Ch. 4)
3	Sept. 3	Gene cloning (Ch 5), nucleic acid hybridization (Ch. 6)
4	Sept. 5	Gene expression (Ch. 7)
5	Sept. 7	Gene mapping (Ch. 13)
6	Sept. 10	Hutchingson-Gilford progeria introduction: RNA processing, post translational modification (ch 1), gene mapping (ch. 14)
7	Sept. 12	Hutchingson-Gilford progeria
8	Sept. 14	Hutchingson-Gilford progeria **Choice of disease for presentation/grant proposal due 4pm**
9	Sept. 17	Down syndrome introduction; chromosomal abnormalities (Ch 2); deletion syndromes (ch. 16)
10	Sept. 19	Down syndrome
11	Sept. 21	Down syndrome
12	Sept. 24	Huntington's disease introduction; repeat expansion (ch. 11); cellular pathology (ch 16) – Instructor this week: Robert Taylor
13	Sept. 26	Huntington's disease
14	Sept. 28	Huntington's disease
15	Oct. 1	ALS/Lou Gehrig's disease introduction; cell-cell interactions (ch. 3); cellular pathology (ch. 16) **Abstract of mock grant proposal due 4pm**
16	Oct. 3	ALS/Lou Gehrig's disease
17	Oct. 5	ALS/Lou Gehrig's disease
18	Oct. 8	Alzheimer's disease introduction; mouse models of disease (ch. 20); susceptibility genes (ch 15)
19	Oct. 10	Alzheimer's disease
20	Oct. 12	Alzheimer's disease

21	Oct. 15	Breast Cancer introduction; cancer genetics (ch. 17) **Introduction section of grant proposal due 4pm**
22	Oct. 17	Breast Cancer
23	Oct. 19	Breast Cancer
	Oct 22 – Fall Break	
24	Oct. 24	Narcolepsy introduction; positional cloning (ch. 14)
25	Oct. 26	Narcolepsy
26	Oct. 29	Prader-Willi syndrome introduction; control of gene expression (ch. 10); DNA methylation and imprinting (ch. 10)
27	Oct. 31	Prader-Willi syndrome
28	Nov. 2	Prader-Willi syndrome
29	Nov. 5	Bardet-Biedl syndrome introduction; proteomics (ch. 19) **Hypotheses/experiments section of grant proposal due 4pm**
30	Nov. 7	Bardet-Biedl syndrome
31	Nov. 9	Bardet-Biedl syndrome
32	Nov. 12	Sickle cell anemia introduction; gene therapy (ch 21)
33	Nov. 14	Sickle cell anemia **Complete revised grant proposal due 4 pm**
34	Nov. 16	Sickle cell anemia
	Nov 19 – 23 Thanksgiving	
35	Nov. 26	Cystic fibrosis introduction; heterozygote advantage (Ch. 4); genetic testing (Ch. 18)
36	Nov. 28	Cystic fibrosis
37	Nov. 30	Cystic fibrosis
38	Dec. 3	Leber hereditary optic neuropathy (LHON) introduction; genetics of mitochondria (ch 9, 11) ; multifactoral causes of disease (ch 4)
39	Dec. 5	LHON

40	Dec. 7	LHON **Peer reviews due 4 pm**
41	Dec. 10	Ethical implications of technology I (ch. 21)
42	Dec. 12	Ethical implications of technology II (ch. 21)
Final	Take home exam	Due Dec. 18th 4 pm