BI423/523 Human Molecular Genetics, Winter 2011

Alice Barkan, Instructor (abarkan@uoregon.edu)

Time: MWF 11-11:50 am
Place: 12 Pacific Hall
Office Hours: Tues 3-4, Fri 3-4, 280 Onyx

This course will focus on selected topics in human molecular genetics that illustrate fundamental and fascinating genetic principles. My goals for this course are to help students to increase their breadth of knowledge by exploring current topics in human molecular genetics; to develop an appreciation for the excitement and dynamic nature of this field; to develop skills associated with reading the primary research literature, evaluating data, formulating hypotheses, and devising experiments to test hypotheses; to improve written and oral communication skills; and to enjoy discussing topics in molecular genetics that are directly relevant to human health.

Readings and Class Format

Background readings are available in a text by Strachan and Read (Human Molecular Genetics, 4rth edition). The text is available for purchase at the U of O Bookstore and two copies have been placed on reserve in the Science Library. These readings are optional but recommended. Each topic will be introduced in one or two lectures and will then be explored in more depth through discussion of several research articles. *PDF files of the assigned papers and of lecture handouts are available on-line through BLACKBOARD.* The lecture handouts are provided to facilitate your note-taking. Please bring printouts of the relevant lecture handouts and papers to class.

Graded Assignments

There will be five graded sets of "Discussion Questions". These questions are posted on Blackboard, and will frame our discussions of the research articles. These assignments will help you focus on the relevant issues while reading the papers, they will prepare you to participate actively in discussions, and they will help you to refine your writing skills.

Some of the questions will be short answer, factual questions. However, most will concern data interpretation, implications, and future experiments. Please bring a draft of the answers to class on the day the papers are discussed. You will turn in your answers in a subsequent session so that you can incorporate what you learned during the discussion. *ANSWERS MUST BE TYPED! You should aim to provide concise answers that address the key points but that do not include extraneous information.*

I will post verbatim (anonymous) copies of particularly good answers as "answer keys" for each set of questions. Answers will be graded on a "check", "check-plus" or "check-minus" basis (with occasional "check-plus-plus's" awarded for exceptionally well-done assignments).

In addition, each student will work in a small group (2 or 3 students) to present one research article to the class. *The articles that will be the subject of student presentations are indicated in italics in the course schedule.* Preferences regarding the choice of topic will be honored to the greatest extent possible.

Graduate students in the class are required to develop a Research Proposal in which a scientific controversy is summarized , and experimental approaches to resolve the controversy are outlined. The proposal should be 6-8 double-spaced type-written pages (not including references) and will be due at 5 pm on Tuesday of Finals Week. Graduate students are also required to take the Final Exam.

Undergraduates can choose to develop a research proposal, or can take the Final Exam. *The Research Proposal option requires Instructor approval by the beginning of Week 8.* All students will take a Midterm Exam.

I do not use a strict formula for calculating grades in this class. However, a rough breakdown of the weight of each assignment is as follows: Contribution to discussions- 15%; written answers to discussion questions- 35%; oral presentation 15%; Midterm quiz 17%; Final exam or research proposal 18%

The University of Oregon is working to create inclusive learning environments. Please notify me if there are aspects of the instruction or design of this course that result in barriers to your participation. You may also wish to contact Disability Services in 164 Oregon Hall at 346-1155 or disabsrv@uoregon.edu.

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(Dates are subject to change)

Date		Background Reading	Papers for Discussion
Mon 1/3	The human genome: Chromosomal organization Gene content	Strachan: 44-47; 235-239; Chapter 9 Snyder and Gerstein (2003) Defining genes in the genomic era. Science 300: 258-260.	Lecture
Wed 1/5	Human Genome cont'd: The "Epigenome" Mobile elements Complex Genes: Alternative Splicing, Promoters, etc Noncoding RNAs	Strachan: 362-364; 372-374. Gerstein et al. (2007) "What is a gene-post ENCODE?" Genome Research 17: 669-681. J Qiu. (2006) Unfinished symphony. Nature 441: 143-145.	Lecture
Fri 1/7	Discussion: Genome-wide tools for finding genes and analyzing their expression	ML Metzker (2010) Sequencing technologies – the next generation. Nat. Rev. Genet. 11: 31-46.	Kapranov et al (2007) RNA maps reveal new RNA classes and a possible function for pervasive transcription. Science 316: 1484. Affymetrix/ENCODE project (2009) Post-transcriptional processing generates a diversity of 5'-modified long and short RNAs. Nature 457: 1028-1032.
Mon 1/10	Human Genome Discussion cont'd:		Kim et al (2005) A high-resolution map of active promoters in the human genome. Nature 436: 876-880.
Wed 1/12	Tools for Reverse Genetics: RNA silencing and manipulation of the mouse genome.	Strachan, 389-391; 503-504; 643-644; 648-654 Capecchi (2005) Gene targeting in mice. Nat Rev Gen 6: 507-512.	lecture
Fri 1/14	Dosage Compensation: X chromosome inactivation	Strachan 365-367. Wutz (2007) Xist function: bridging chromatin and stem cells. Trends in Genet. 23: 457-464. Leeb and Wutz (2010) Mechanistic concepts in X inactivation underlying dosage compensation in mammals. Heredity 105: 64-70.	lecture

Date	Topic	Background Reading	Papers for Discussion
1/17	No class: MLK day		
Wed 1/19	X-inact Discussion		Wutz and Jaenisch (2000) A shift from reversible to irreversible X inactivation is triggered during ES cell differentiation. Molec Cell 5: 695-705.
Fri 1/21	X-inact Discussion cont'd		Shibata and Lee (2004) Tsix transcription-versus RNA-based mechanisms in Xist repression and epigenetic choice. Current Biology 14:1747-1754.
Mon 1/24	X-inact Discussion cont'd *Student presentation*		*Monkhorst et al (2008) X inactivation counting and choice is a stochastic process: Evidence for involvement of an X-linked activator. Cell 132: 410-421.* *With brief reference to:* *Royce-Tolland et al (2010) The A-repeat links ASF/SF2-dependent Xist RNA processing with random choice during X inactivation. Nat Struct Mol Biol. 17:948-54.*
Wed 1/26	*Student presentation*	Koziol MJ, Rinn JL. RNA traffic control of chromatin complexes. (2010) Curr Opin Genet Dev. 20:142-8.	*Zhao et al (2008) Polycomb proteins targeted by a short repeat RNA to the mouse X chromosome. Science 322: 750-756.* *With brief reference to:* *Maenner et al (2010) 2-D structure of the A region of Xist RNA and its implication for PRC2 association. PLoS Biol. 8:e1000276 (It will be sufficient to read only the Abstract, Intro, and Discussion)*
Fri 1/28	Sex Determination	Strachan: 320-325 Sekido and Lovell-Badge (2008) Sex determination and SRY: down to a wink and a nudge? Trends in Genet 25 19-29.	lecture
Mon 1/31	Sex Determ : discussion *Student presentation*		*Kim et al (2006) Fgf9 and Wnt4 act as antagonistic signals to regulate mammalian sex determination. PLOS Biology 4: 1000-1009*
Wed 2/2	Sex Determ: Disc cont'd *Student presentations*	(*optional:* R Veitia (2010) FOXL2 *versus* SOX9: A lifelong "battle of the sexes". Bioessays 32: 375-380)	*Sekido and Lovell-Badge (2008) Nature 453: 930. Sex determination involves synergistic action of SRY and SF1 on a specific Sox9 enhancer.* *Uhlenhaut et al. (2009) Somatic Sex Reprogramming of Adult Ovaries to Testes by FOXL2 Ablation. Cell 139: 1130-1142.*

date	topic	background reading	papers for discussion
Fri 2/4	Diseases of Unstable Repeat Expansion	Strachan: pp 423-425 La Spada and Taylor (2010) Repeat expansion diseases: progress and puzzles in disease pathogenesis. Nat Rev Genetics 11: 247-259.	lecture
Mon 2/7	How does repeat expansion cause disease? Toxic RNAs.		Kanadia et al (2003) A muscleblind knockout model for myotonic dystrophy. Science 302: 1978-1980.
Wed 2/9	*Student presentation*		*Du et al (2010) Aberrant alternative splicing and extracellular matrix gene expression in mouse models of myotonic dystrophy. Nat. Struct Mol Bio 17: 187-193.*
Fri 2/11	*Student Presentations*		*Steffan et al (2004) SUMO modification of Huntingtin and Huntington's Disease Pathology. Science 304: 100-104.* *Subramaniam et al (2009) Rhes, a striatal specific protein, mediates mutant-Huntingtin cytotoxicity. Science 324: 1327-1330.*
Mon 2/14	*Student presentation: Approaches to gene therapy as applied to repeat expansion diseases.*	*Cooper (2009) Neutralizing toxic RNA. Science 325: 272-273.*	*Wheeler et al (2009) Reversal of RNA dominance by displacement of protein sequestered on triplet repeat RNA. Science 325: 336-339.* *Hu et al. (2009) Allele-specific silencing of mutant huntingtin and ataxin-3 genes by targeting expanded CAG repeats in mRNAs. Nature Biotech. 27: 478-484.*
Wed 2/16	GUEST LECTURE: Jen Phillips. Zebrafish models for human genetic diseases	Lieschke and Currie (2007) Animal models of human disease: zebrafish swim into view. Nat Rev Genet 8: 353-367.	
Fri 2/18	Jen Phillips, continued	Saihan et al (2009) Update on Usher Syndrome, Curr Opin Neurol 22:19-27.	
Mon 2/21	**MIDTERM EXAM**		

date	topic	background reading	papers for discussion
Wed 2/23	Genetics of Cancer	Strachan Chapter 17 Hanahan and Weinberg (2000) The hallmarks of cancer. Cell 100: 57-70.	Lecture
Fri 2/25	Genetics of Cancer Cont'd		Hahn et al (1999) Creation of human tumor cells with defined genetic elements. Nature 400: 464-468.
Mon 2/28	Cancer Discussion cont'd: the molecular basis of metastasis	Yang et al (2006) Exploring a new twist on tumor metastasis. Cancer Res 66:4559-4562	Yang et al (2004) Twist, a master regulator of morphogenesis, plays an essential role in tumor metastasis. Cell 117: 927-939.
Wed 3/2	Cancer Epigenetics *Student Presentation*	Feinberg et al (2006) The epigenetic progenitor origin of cancer. Nat. Rev. Genetics 7:21-33. *Reprise from X inactivation: Koziol MJ, Rinn JL. RNA traffic control of chromatin complexes. (2010) Curr Opin Genet Dev. 20:142-8.*	Croce et al (2002) Methyltransferase recruitment and DNA hypermethylation of target promoters by an oncogenic transcription factor. Science 295: 107901082. *Gupta et al 2010. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 464: 1071-1077.*
Fri 3/4	Guest Lecture: Albert Edwards. Identifying Human Disease Genes	Strachan Chapter 16 Altshuler et al (2008) Genetic mapping in human disease. Science 322: 881-888.	
Mon 3/7	Albert Edwards, continued		
Wed 3/9	*Student Presentation: Personal Genomics*	Flintoff (2008) Towards an individual view. Nat Rev Genet. Strachan Chapter 19 http://www.personalgenomes.org/	*Pelak et al. (2010) PLOS Genetics, The Characterization of Twenty Sequenced Human Genomes*
Fri 3/11	**FINAL EXAM**	There will be NO FINAL EXAM DURING FINAL'S WEEK.	