BI423/523 Human Molecular Genetics, Fall 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 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 through discussion of several research articles. *PDF files of the assigned papers and of lecture handouts are available on-line through BLACKBOARD.* 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" 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 **bold italics** in the course schedule.* Preferences regarding the choice of topic will be honored to the greatest extent possible.

There will be a Midterm Exam and a Final Project. The Final Project will involve identifying an unanswered question that arose from one of the papers we discussed, and outlining a series of experiments that could be used to address that question. Each student will present a brief summary of their question and experimental approach on the last day of class, and will write a 2-page abstract and experimental outline that will be due on Wednesday of Finals Week. Guidelines for this project will be provided as the time approaches. There will be NO Final 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 exam 20%; Final project 15%.

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.

BI423/523 Human Molecular Genetics, Fall 2011
(Dates are subject to change)

Date		Background Reading	Papers for Discussion
Mon 9/26	The human genome: Chromosomal organization and gene content	Strachan: 44-47; 235-239; Chapter 9	Lecture
Wed 9/28	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. ML Metzker (2010) Sequencing technologies – the next generation. Nat. Rev. Genet. 11: 31-46	Lecture
Fri 9/30	Discussion: Genome-wide tools for finding genes and analyzing their expression	Wang et al (2009) RNA-Seq: a revolutionary tool for transcriptomics. Nat Rev Genet. 10:57-63.	Encode Consortium (2011) A user's guide to the encyclopedia of DNA elements (ENCODE). PLOS Biol. 9: e1001046
Mon 10/3	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 10/5			John et al (2011) Chromatin accessibility pre-determines glucocorticoid receptor binding patterns. Nat Genet 43:264-269
Fri 10/7	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
Mon 10/10	Dosage Compensation: X chromosome inactivation	Strachan 365-367. Augui et al (2011) Regulation of X-chromosome inactivation by the X-inactivation centre. Nat Rev Genet 12: 429-442.	lecture

Date	Topic	Background Reading	Papers for Discussion
Wed 10/12	X chromosome inactivation	*We will not discuss this paper in depth. Read to understand the general questions addressed, general approach, and major take home messages.* Shibata and Lee (2004) Tsix transcription-versus RNA-based mechanisms in Xist repression and epigenetic choice. Current Biology 14:1747-1754.	Lecture/Discussion
Fri 10/14	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.
Mon 10/17	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 summary of: Jonkers I, Barakat TS, Achame EM, Monkhorst K, Kenter A, et al. (2009)* *RNF12 is an X-Encoded dose-dependent activator of X chromosome inactivation. Cell 139: 999–1011.*
Wed 10/19	*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 summary of: Hasegawa et al (2010) The matrix protein hnRNP U is required for chromosomal localization of Xist RNA. Dev Cell 14: 469-76.*
Fri 10/21	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 10/24	Sex Determ : discussion		***Kim et al (2006) Fgf9 and Wnt4 act as antagonistic signals to regulate mammalian sex determination. PLOS Biology 4: 1000-1009***

Date	Topic	Background Reading	Papers for Discussion
Wed 10/26	Sex Determ: Disc cont'd *Student presentation*	(*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.***
Fri 10/28	Sex Determ: Disc cont'd *Student presentation*		***Uhlenhaut et al. (2009) Somatic Sex Reprogramming of Adult Ovaries to Testes by FOXL2 Ablation. Cell 139: 1130-1142.***
Mon 10/31	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
Wed 11/2	How does repeat expansion cause disease? Toxic RNAs.		Kanadia et al (2003) A muscleblind knockout model for myotonic dystrophy. Science 302: 1978-1980.
Fri 11/4	*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.***
Mon 11/7	*Student Presentation: Mitochondrial dysfunction and Huntington's Disease*	Bossy-Wetzel et al (2008) Trends Neurosci 31: 609-616. Mutant huntingtin and mitochondrial dysfunction.	***Song et al (2011) Mutant huntingtin binds the mitochondrial fission GTPase dynamin-related protein-1 and increases its enzymatic activity. Nat Med 17: 377-82.***
Wed 11/9	*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.***
Fri 11/11	*Student presentation: Repeat expansion and inherited prion disease*	*Frost and Diamond (2009) The expanding role of prion phenomena in neurodegenerative disease. Prion 3: 74-77.*	***Stevens et al. (2009) Early onset prion disease from octarepeat expansion correlates with copper binding properties. PLOS Pathogens 5: e1000390***
Mon 11/14	**MIDTERM EXAM**		

date	topic	background reading	papers for discussion
Wed 11/16	Genetics of Cancer	Strachan Chapter 17 Hanahan and Weinberg (2000) The hallmarks of cancer. Cell 100: 57-70.	Lecture
Fri 11/18	Genetics of Cancer Cont'd		Hahn et al (1999) Creation of human tumor cells with defined genetic elements. Nature 400: 464-468.
Mon 11/21	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 11/23	Cancer Epigenetics *Student Presentation*	*Reprise from X inactivation: Koziol MJ, Rinn JL. RNA traffic control of chromatin complexes. (2010) Curr Opin Genet Dev. 20:142-8.*	***Gupta et al 2010. Long non-coding RNA HOTAIR reprograms chromatin state to promote cancer metastasis. Nature 464: 1071-1077.***
Fri 11/25	No Class	Thanksgiving Holiday	
Mon 11/28	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 Gen 8:353-367.	
Wed 11/30	Jen Phillips, continued	Saihan et al (2009) Update on Usher Syndrome, Curr Opin Neurol 22:19-27.	
Fri 12/2	*PROPOSAL OUTLINE SUMMARIES*	*Each student will present **3** slides that summarize the hypothesis and experiments to be outlined in their final paper.*	***2 minutes each!***
WED 12/7	**FINAL PAPERS DUE AT NOON**	(There will NOT be a Final Exam)	