

BIO 395F - GRADUATE GENETICS

Syllabus - Fall 2010

Dr. Janice Fischer

Prof: Janice Fischer (jaf@mail.utexas.edu)

TA: Xuanhua Xie (xuanhuaxie@mail.utexas.edu)

Objective: The purpose of this course is for you to learn how scientists use genetics to find answers to biological questions. Thus, the focus is on modern genetic techniques used in each of the most popular model systems.

Prerequisites: A solid knowledge of undergraduate genetics is absolutely necessary and is a prerequisite for taking this class. There will be only a very brief (~5 classes) review of key concepts. You **MUST** have taken an undergraduate Genetics class, equivalent to BIO 325, the undergraduate class offered here at UT. If you have not, you **MUST** take BIO 325 before you take this class. (FYI - I teach BIO325 in the Spring and Summer in the mornings and at night.) There is simply no way that you can understand this class if you have never had a solid undergraduate Genetics class.

Reference Material: If you need to get back up to speed on any basic concepts, any good undergraduate genetics textbook will be fine. If you don't own an undergraduate Genetics textbook, you might consider buying one to use as a reference. The latest edition (4th) of Hartwell et al. (McGraw-Hill) is a very good one. So is the Griffiths et al. (Freeman) book.

For each lecture, journal articles will be provided (reviews and original literature) which serve as background reading to help you understand the lecture material. The recommended articles will be posted on Blackboard as pdf files in folders labeled with the Lecture number.

There will also be a number of different papers specifically assigned for reading each week. The papers are chosen to illustrate one or more specific concepts relevant to the topics discussed in class that week.

Also, Xerox copies of the overheads used in each class will be handed out at the beginning of each class. These are for you to take class notes on - they are not meant to be class notes by themselves.

An important thing to remember is that this is a graduate class, and thus the majority of the responsibility for what you learn lies with you. The expectation is

that you are in this class because you want to learn about genetics. Thus, it is assumed that you will read the background literature provided to support the lecture material, and that you will take the initiative to seek out other reading and other help if you need it, either on your own, or with assistance from Janice, Paul, or Xuanhua.

Class Attendance: You are expected to attend class, be awake, and participate. While attendance will not be taken formally, it will be impossible for you to pass this class if you do not attend class. This class takes place from August 26 through December 13, with the period between December 3 and December 12 to be used to study for the final exam. If you would like me to hold question and answer sessions during that time, I will be happy to do so. You can study for the final in another galaxy if you like, but you must be present here in Austin, Texas on December 13 in order to take the Final Exam.

Integration with MOL190: Most of you are also taking MOL190 this semester. This class is integrated with MOL190. Starting with Week 3, the topics that we focus on during a given week will be those covered in MOL 190 the following week. You will receive a separate MOL190 syllabus from Paul Macdonald, and a separate MOL190 grade. You will not be at a major disadvantage if you are not taking MOL190, as the specific material covered in that class will be posted on Blackboard. If you are not signed up for MOL190, you are welcome to audit that class so as not to miss out on those discussions, but you certainly do not have to do that to do well in BIO395F.

Assignments: You will be given a reading assignment of two or more research articles each week. These are listed at the end of this syllabus and the articles will be posted on Blackboard. In MOL190, you will be presenting and listening to others present discussions of specific aspects of these papers. The MOL190 presentation topics, in the form of questions that you will answer, will be posted for everyone to see on the BIO395F Blackboard site. For BIO395F, you are responsible not only for the lecture material, but also for understanding the material in the MOL190 presentations; this means not only your own presentation, but everyone else's as well.

About the Assigned Papers: The papers you read and the questions you present answers to in MOL190 were chosen for their direct relevance to the topics covered in the previous week of this class. (1) This is not a current literature class; some of the papers were written before you were born, and others are more recent. Many of the assigned papers are landmarks in their fields. (2) Often, the focus of the MOL190 presentations will NOT be the main scientific point of the paper. Do not be alarmed by this. Again – the papers were chosen to illustrate specific concepts, and those are the aspects of the paper that will be discussed in MOL190 and that you

will be responsible for understanding in BIO395F. (3) As we cover more material, we will revisit some papers to concentrate on additional aspects of those articles.

Exams: There will be four take-home midterm exams, and also a 3-hour comprehensive final exam. The exams will cover lecture material, and also the papers and material presented in MOL 190. You will have two weeks to complete each exam. Exam I covers the material in part I, Exam II covers the material in part II, etc. The Course Schedule Summary below contains due dates for each exam. I will post each exam on Blackboard two weeks before the date that it is due. You can work on the exams together and get help from anyone or anything you want. They are meant to be learning experiences. Each exam will have instructions and helpful hints. As these are take-home exams and you are graduate students, my standards for you are high, as I assume that yours are for yourselves. Clear thinking and clear writing are the same things. Science requires clear thinking, and in addition to imparting useful information in an organized way, thinking clearly and logically is what your classes are meant to be training you to do. That training never ends the whole time that you are a scientist - this is only the beginning - so get used to it.

There is also a comprehensive final exam, the date of which was determined by the University, and this is indicated on the Course Schedule Summary Below.

DO NOT MEMORIZE ANYTHING FOR THIS CLASS. ANY STUDYING YOU DO THAT FEELS LIKE MEMORIZING IS A WASTE OF YOUR TIME. EXAMS WILL TEST WHAT YOU UNDERSTAND, NOT WHAT YOU CAN MEMORIZE.

Grades: Your grade will be computed as 50% the average of your take-home exams and 50% the final exam, or 100% the final exam, whichever gives you the higher grade. As B- is considered passing for a graduate class, the class average will be considered a B+. This means that if your grades are much below the class average, this is a sign that you need to change something in your behavior to better your performance.

Getting Help: Janice Fischer will have office hours by appointment made through e-mail **ANYTIME**. My office is MBB 1.312AA. I am happy to help you with any specific problems you have in understanding the lecture material or the assigned papers during this time. If it is your turn to present for MOL190, I'm happy to help you with that, but you need to come prepared. By this I mean that I expect you to have spent a lot of time thinking about the answer to the question and your presentation, and have specific questions. In other words, I'm not going to simply tell you the answers and do the work for you.

All I ask is that you don't wander into my office without a prior appointment. I promise not to do that to you, either.

If you miss a class, please get one of your classmates to go over it with you, as I cannot give you the lectures you miss personally in my office.

I will do my best to answer simple questions through e-mail.

Xuanhua Xie is your TA. He will be present at each class. Xuanhua's role is to help you understand the material presented in class and the assigned papers. He can be contacted via e-mail (xuanhuaxie@mail.utexas.edu). Xuanhua will hold Discussion Sections and he will distribute and post on Blackboard a hand-out describing where and when they are and what will go on there. What happens at Discussion Section is largely up to you. Tell Xuanhua what kind of help you need, and he will provide it.

CLASS SCHEDULE SUMMARY WITH EXAM DATES:**CLASS TAKES PLACE AUG 26 – DEC 13****I. BRIEF REVIEW of UNDERGRADUATE GENETICS**

- Aug 26 TH 1. Mendel
 Aug 31 TU 2. Genotype and phenotype I
 Sept 2 TH 3. Genotype and phenotype II
 Sept 7 TU 4. Linkage Analysis
 Sept 9 TH 5. Mutant classification [Exam I posted](#)

II. MODERN GENETIC METHODOLOGY

- Sept 14 TU 6. Linkage and mapping in multicellular diploids I
 Sept 16 TH 7. Linkage and mapping in multicellular diploids II
 Sept 21 TU 8. Methods for generating transgenic organisms
 Sept 23 TH 9. Methods of mutagenesis **Exam I due**
 Sept 28 TU 10. Reverse genetics I
 Sept 30 TH 11. Reverse genetics II [Exam II posted](#)

III. HOW TO IDENTIFY GENES INVOLVED IN A PROCESS**A. SYSTEMATIC SCREENS FOR A PHENOTYPE**

- Oct 5 TU 12. Systematic mutant screens and linkage analysis in bacteria
 Oct 7 TH 13. Systematic mutant screens and linkage analysis in yeast
 Oct 12 TU 14A. Systematic mutant screens in *C. elegans* and *Drosophila*
 Oct 14 TH 14B. Systematic mutant screens in *C. elegans* and *Drosophila*
Exam II due
 Oct 19 TU 15A. Systematic mutant screens in mice, zebrafish, Arabidopsis
 Oct 21 TH 15B. Systematic mutant screens in mice, zebrafish, Arabidopsis
[Exam IIIA posted](#)

B. FINDING ADDITIONAL PATHWAY COMPONENTS

- Oct 26 TU 16. Modifier screens I: Synthetic lethality
 Oct 28 TH 17. Modifier screens II: Sensitized backgrounds
 Nov 2 TU 18. Modifier screens III: Suppression
 Nov 4 TH 19. Modifier screens IV: Using Transgenes **Exam IIIA due**
 Nov 9 TU 20. Enhancer trapping and gene trapping

IV. WHERE AND WHEN DO GENES ACT?

- Nov 11 TH 21. Mosaics I: Methods for generating mosaics [Exam IIIB posted](#)
 Nov 16 TU 22. Mosaics II: Methods/Using mosaics to answer biological questions
 Nov 18 TH 23. Mosaics III: Using mosaics to answer biological questions
 Nov 23 TU 24. Temperature-sensitive alleles and hypomorphs **Exam IIIB due**
 Nov 25 TH THANKSGIVING BREAK

V. ORDERING GENE FUNCTION

- Nov 30 TU 25. Epistasis I: Basic principles of ordering genes in a pathway
 Dec 2 TH 26. Epistasis II: Specific applications of epistasis analysis
 Dec 3 – Dec 12 : Question and Answer Sessions by Request

COMPREHENSIVE FINAL EXAM: MONDAY DECEMBER 13, 2-5 pm

CLASS SCHEDULE

I. BRIEF REVIEW of UNDERGRADUATE GENETICS

Week 1

Aug 26 TH 1. Mendel

Week 2

Aug 31 TU 2. Genotype and phenotype I
 Sept 2 TH 3. Genotype and phenotype II

Week 3 * assigned papers start this week (see list below)

Sept 7 TU 4. Linkage Analysis
 Sept 9 TH 5. Mutant classification

II. MODERN GENETIC METHODOLOGY

Week 4

Sept 14 TU 6. Linkage and mapping in multicellular diploids I
 Sept 16 TH 7. Linkage and mapping in multicellular diploids II

Week 5

Sept 21 TU 8. Methods for generating transgenic organisms
 Sept 23 TH 9. Methods of mutagenesis

Week 6

Sept 28 TU 10. Reverse genetics I
 Sept 30 TH 11. Reverse genetics II

III. HOW TO IDENTIFY GENES INVOLVED IN A PROCESS

A. SYSTEMATIC SCREENS FOR A PHENOTYPE

Week 7

- Oct 5 TU 12. Systematic mutant screens and linkage analysis in bacteria
 Oct 7 TH 13. Systematic mutant screens and linkage analysis in yeast

Week 8

- Oct 12 TU 14A. Systematic mutant screens in *C. elegans* and *Drosophila*
 Oct 14 TH 14B. Systematic mutant screens in *C. elegans* and *Drosophila*

Week 9

- Oct 19 TU 15A. Systematic mutant screens in mice, zebrafish, Arabidopsis
 Oct 21 TH 15B. Systematic mutant screens in mice, zebrafish, Arabidopsis

B. FINDING ADDITIONAL PATHWAY COMPONENTS

Week 10

- Oct 26 TU 16. Modifier screens I: Synthetic lethality
 Oct 28 TH 17. Modifier screens II: Sensitized backgrounds

Week 11

- Nov 2 TU 18. Modifier screens III: Suppression
 Nov 4 TH 19. Modifier screens IV: Using Transgenes

Week 12

- Nov 9 TU 20. Enhancer trapping and gene trapping

IV. WHERE AND WHEN DO GENES ACT?

Nov 11 TH

21. Mosaics I: Methods for generating mosaics

Week 13

Nov 16 TU

22. Mosaics II: Using mosaics to answer biological questions

Nov 18 TH

23. Mosaics III: Using mosaics to answer biological questions

Week 14

Nov 23 TU

24. Using temperature-sensitive alleles and hypomorphs

Nov 25 TH

THANKSGIVING BREAK

V. ORDERING GENE FUNCTION

Week 15

Nov 30 TU

25. Epistasis I: Basic principles of ordering genes in a pathway

Dec 2 TH

26. Epistasis II: Specific applications of epistasis analysis

ASSIGNED PAPERS – Additional background reading is on Blackboard

* will be presented in MOL190
 Questions about the other papers listed may appear on exams.

Week 3: Mutant Classification

*Struhl G. (1981) A homeotic mutation transforming leg to antenna in *Drosophila*.
Nature 292, 635–638.

*Baker NE, Rubin GM. (1989) Effect on eye development of dominant mutations in
Drosophila homologue of the EGF receptor. *Nature* 340, 150–153.

Demir E, Dickson BJ (2005) *fruitless* splicing specifies male courtship behavior in
Drosophila. *Cell* 121, 785–794.

Week 4: Linkage and Mapping

*Chen B, Chu T, Harms E, Gergen JP, Strickland S (1998) Mapping of *Drosophila*
 mutations using site-specific male recombination. *Genetics* 149, 157–163.

*Jakubowski J, Kornfeld K (1999) A local, high-density, single-nucleotide
 polymorphism map used to clone *C. elegans cdf-1*. *Genetics* 153, 743–752.

Zhai RG, Hiesinger PR, Koh T-W, Verstreken P, Schulze KL, Cao Y, Jara-Nejad H,
 Norga KK, Pan H, Bayat V, Greenbaum MP, Bellen H. (2003) Mapping *Drosophila*
 mutations with molecularly defined P element insertions. *PNAS* 100, 1086–
 10865.

Week 5: Transgenic Organisms

*Schwartzberg PL, Goff SP, Robertson EJ. (1989) Germ-line transmission of a *c-abl*
 mutation produced by targeted gene disruption in ES cells. *Science* 246, 799–
 803.

*Rubin GM, Spradling AC. (1982) Genetic transformation of *Drosophila* with
 transposable element vectors. *Science* 218, 348–353.

Kurita K, Burgess SM, Sakai N. (2004) Transgenic zebrafish produced by retroviral
 infection of *in vitro*-cultured sperm. *PNAS* 101, 1263–1267.

Week 6: Reverse Genetics

*Kuhn R, Schwenk F, Aguet M, Rajewsky K. (1995) Inducible gene targeting in mice. *Science* 269, 1427-1429.

*Rong YS, Golic KG. (2000) Gene targeting by homologous recombination in *Drosophila*. *Science* 288, 2013-2018.

Choi CM, Vilain S, Langen M, Van Kelst S, De Geest N, Jiekun Y, Verstreken P, Hassan BA. (2009) Conditional mutagenesis in *Drosophila*. *Science* 324, 54.

Week 7: Systematic Mutant Screens in Bacteria and Yeast

*Oliver DB, Beckwith J. (1981) *E. coli* mutant pleiotropically defective in the export of secreted proteins. *Cell* 25, 765-772.

*Li R, Murray AW. (1991) Feedback control of mitosis in budding yeast. *Cell* 66, 519-531. See also ERRATA that came out later for this paper.

Ngheim Y, Cabrera M, Cupples CG, Miller JH. (1988) The *mutY* gene: A mutator locus in *E. coli* that generates G•C-to-T•A transversions. *PNAS* 85, 2709-2713.

Week 8: Systematic Mutant Screens in Nematodes and Drosophila

*Ferguson EL, Sternberg PW, Horvitz HR. (1987) *Nature* 326, 259-267.

*Nusslein-Volhard C, Wieschaus E. (1980) *Nature* 287, 795-801.

Week 9: Systematic Mutant Screens in Zebrafish, Mice, Arabidopsis

*Dosch R, Wagner DS, Mintzer KA, Runke G, Wiemelt AP, Mullins MC. (2004) Maternal control of vertebrate development before the midblastula transition. *Dev Cell* 6, 771-780.

*Kile BT, Hentges KE, Clark AT, Nakamura H, Salinger AP, Liu B, Box N, Stockton DW, Johnson RL, Behringer RR, Bradley A, Justice MJ. (2003) Functional genetic analysis of mouse chromosome 11. *Nature* 425, 81-85.

Mayer U, Torres Ruiz RA, Berleth T, Misera S, Jurgens G. (1991) Mutations affecting body organization in the *Arabidopsis* embryo. *Nature* 353, 402-407.

Amsterdam A, Burgess S, Golling G, Chen W, Sun Z, Townsend K, Farrington S, Haldi M, Hopkins N. (1999) A large-scale insertional mutagenesis screen in zebrafish. *Genes Dev* 13, 2713-2724.

Week 10: Modifier Screens-Synthetic Lethality / Sensitized Backgrounds

*Simon MA, Bowtell DDL, Doson GS, Laverty TR, Rubin GM. (1991) Ras1 and a putative guanine nucleotide exchange factor perform crucial steps in signaling by the Sevenless protein tyrosine kinase. *Cell* 67, 701-716.

*Ooi SL, Shoemaker DD, Boeke JD. (2003) DNA helicase gene interaction network defined using synthetic lethality analyzed by microarray. *Nature Genetics* 35, 277-286.

Week 11: Modifier Screens - Suppression / Using Transgenes

*Rogge RD, Karlovich CA, Banerjee U. (1991) Genetic dissection of a neurodevelopmental pathway: *Son of sevenless* functions downstream of the Sevenless and EGF receptor tyrosine kinases. *Cell* 64, 39-48.

*Fares H, Greenwald I. (2001) Genetic analysis of endocytosis in *C. elegans*: coelomocyte uptake defective mutants. *Genetics* 159, 133-145.

Week 12: Enhancer Trapping and Gene Trapping

*Leighton PA, Mitchell KJ, Goorich LV, Lu X, Pinson K, Scherz P, Skarnes WC, Tessier-Lavigne M. (2001) Defining brain wiring patterns and mechanisms through gene trapping in mice. *Nature* 410, 174-179.

*Scott EK, Mason L, Arrenberg AB, Ziv L, Gosse NJ, Xiao T, Chi NC, Asakawa K, Kawakami K, Baier H. (2007) Targeting neural circuitry in zebrafish using GAL4 enhancer trapping. *Nature Methods* 4, 323-326.

McClure KD, Schubiger G (2007) A screen for genes that function in leg disc regeneration in *Drosophila melanogaster*. *Mech Dev* 125, 67-80.

Pignoni F, Hu B, Zipursky SL (1997) Identification of genes required for *Drosophila* eye development using a phenotypic enhancer-trap. *PNAS* 94, 9220-9225.

Week 13: Mosaics

*Simske JS, Kim SK. (1995) Sequential signaling during *C. elegans* vulval induction. *Nature* 375, 142-146.

*Tomlinson A, Kimmel BE, Rubin GM. (1988) *rough*, a *Drosophila* homeobox gene required in photoreceptors R2 and R5 for inductive interactions in the developing eye. *Cell* 55, 771-784.

Seydoux G, Greenwald I. (1989) Cell autonomy of *lin-12* function in a cell fate decision in *C. elegans*. *Cell* 57, 1237-1245.

Mlodzik M, Hiromi Y, Weber U, Goodman CS, Rubin GM. (1990) The *Drosophila seven-up* gene, a member of the steroid receptor gene superfamily, controls photoreceptor cell fates. *Cell* 60, 211-224.

Also Revisit:

Week 3

Struhl G. (1981) A homeotic mutation transforming leg to antenna in *Drosophila*. *Nature* 292, 635-638.

Week 10

Simon MA, Bowtell DDL, Dodson GS, Lavery TR, Rubin GM. (1991) Ras1 and a putative guanine nucleotide exchange factor perform crucial steps in signaling by the Sevenless protein tyrosine kinase. *Cell* 67, 701-716.

Week 14: Temperature sensitive alleles and hypomorphs

Hartwell LH, Culotti J, Reid B (1970) Genetic control of the cell-division cycle in yeast, I. Detection of mutants. *PNAS* 66, 352-359.

Mullins MC, Rubin GM. (1991) Isolation of temperature-sensitive mutations of the tyrosine kinase receptor *Sevenless* (*sev*) in *Drosophila* and their use in determining its time of action. *PNAS* 88, 9387-9391.

Zeidler MP, Tan C, Ballaiche Y, Cherry S, Hader S, Gayko U, Perrimon N. (2004) Temperature-sensitive control of protein activity by conditionally splicing inteins. *Nature Biotechnology* 22, 871-876.

Week 15: Epistasis

Anderson KV, Jurgens G, Nusslein-Volhard C. (1985) Establishment of dorsal-ventral polarity in the *Drosophila* embryo: genetic studies on the role of the *Toll* gene product. *Cell* 42, 779-789.

Bowman JL, Sakai H, Jack T, Weigel D, Mayer U, Meyerowitz EM. (1992) *SUPERMAN*, a regulator of floral homeotic genes in *Arabidopsis*. *Development* 114, 599-615.

Struhl G. (1981) A gene product required for correct initiation of segmental determination in *Drosophila*. *Nature* 293, 36-41.