Biology 76/176: Advanced Genetics

Fall 2014
Lecture: M, W, F 11:15-12:20; x-hour Tu 12:00-12:50

C. Robertson McClung
323 Life Sciences Complex

Office Hours: Monday-Friday 2:00-4:00 PM
or by appointment

Course Content

This course provides in-depth coverage of the analysis of gene inheritance and function. Biology 76 will build on material covered in Biology 13, emphasizing the use of model organisms to obtain information relevant to important problems.

Text

There will be no text, but your text from earlier Genetics classes (e.g., Russell iGenetics 3e) might prove useful as a resource.

Evaluation

Your grade will be based on five written assignments—study guides based on the analysis of a paper from the primary literature. The first will be worth 10% (to ease you into it) and the remaining four will be worth 20% each. In addition, 10% of your grade will be based on class participation. This includes attendance (to paraphrase Woody Allen, 80% of success is showing up) as well as your willingness and ability to contribute meaningfully to class discussion. Examples of this would include your providing a clear explanation of a figure from the assigned reading to the class or asking thought-provoking questions about the topics under consideration. The four assignments that will be discussed in class will be due at **the beginning** of the class in which they are to be discussed. The method of submission is electronic—email me your file before class begins. The fifth assignment will be due at 5 PM on Nov 25 (the last day of final exams). **Late assignments will be penalized** 25% of the earned grade per day or part thereof unless a prior arrangement is finalized **in writing**.

Please note that the Discussions with the graduate students (BIOL 176) will be held Tuesdays in X-hour (12:00-12:50 PM) and the Discussions with the undergraduates (BIOL 76) will be held Wednesdays in the regular class time (11:15-12:20), EXCEPT on Oct 14/15, when the undergraduates will meet on Tuesday and the graduate students on Wednesday.

Disability Notice

Students with disabilities who may need disability-related academic adjustments and services for this course are encouraged to see me privately as early in the term as possible. Students requiring disability-related academic adjustments and services must consult the Student Accessibility Services office (205 Collis Student Center, 646-9900,

Student.Accessibility.Services@Dartmouth.edu). Once SAS has authorized services, students must show the originally signed SAS Services and Consent Form and/or a letter on SAS letterhead to their professor. As a first step, if students have questions about whether they qualify to receive academic adjustments and services, they should contact the SAS office. All inquiries and discussions will remain confidential.

Religious Holidays

Some students may wish to take part in religious observances that occur during this academic term. If you have a religious observance that conflicts with your participation in this course, please meet with me as soon as possible to discuss appropriate accommodations. For example, Rosh Hashanah is Sept. 25-26, Yom Kippur is Oct. 4, and Eid-al-Adha is Oct. 5.

The Honor Principle

Academic honesty is essential. The following is quoted directly from the Dartmouth College Student Handbook: "Fundamental to the principle of independent learning are the requirements of honesty and integrity in the performance of academic assignments, both in and out of the classroom. Dartmouth operates on the principle of academic honor, without proctoring of examinations. Any student who submits work which is not his or her own, or commits other acts of academic dishonesty, violates the purposes of the college and is subject to disciplinary actions, up to and including suspension or separation." The complete text of the Academic Honor Principle is in the Student Handbook. Please read it carefully. Graduate students should consult the Graduate Student Handbook, with particular emphasis on The Honor Principle and Code of Conduct. Any violations of the Honor Principle within the context of Biology 76/176 will be referred to the Committee on Standards or to the Dean of Graduate Studies, respectively.

Awareness of the Academic Honor Principle is not intended to inhibit discussion of the class material among the students. Indeed, such discussion is worthwhile and constitutes a valuable component of the learning process and is encouraged on the first four study guide assignments. However, the study guides must be written independently. Two assignments by two individuals who had discussed the assignment almost certainly will reflect ideas developed by the two together, but each student must phrase their assignment in their own words and acknowledge the "helpful discussions" with their collaborators. Do not share computer files! To do so constitutes plagiarism. The **Fifth Assignment** is in open book format (all written resources are permitted) but is to be **done entirely on one's own (no collaboration**).

Schedule (subject to change)

	Topic	Reading (list in progress)
1. Sep 15	Introduction/Genetics in the Genomics Age	
Section 1, Forward Genetics		
2. Sep 16	Mutation Rates & Mutant Selections	(Lang and Murray, 2008; Ossowski et al., 2010)
3. Sep 17	Mutant Screens: Heterochrony in Worms	(Ambros and Horvitz, 1984)
Sep 19-24	No Class	
4. Sep 26	Complementation, Suppression, Enhancement, Epistasis	
5. Sep 29	Conditionally Lethal Mutations	
6a. Sep 30	GR Study Guide 1 (10%)	(Lee et al., 1993; Reinhart et al., 2000)
6b. Oct 1	UG Study Guide 1 (10%)	(Lee et al., 1993; Reinhart et al., 2000)
7. Oct 3	Cystic Fibrosis	
8. Oct 6	Sex determination in Drosophila I	(Keyes et al.; Erickson and Quintero, 2007; Salz, 2011)
9a. Oct 7	GR Suppression/Epistasis in Cystic Fibrosis	(Kiesewetter et al., 1993; Sosnay et al., 2013)
9b. Oct 8	UG Suppression/Epistasis in Cystic Fibrosis	(Kiesewetter et al., 1993; Sosnay et al., 2013)
10. Oct 10	Sex determination in Drosophila II	(Johnson et al., 2010)
11. Oct 13	Anteroposterior polarity in Drosophila I	(Nusslein-Volhard et al., 1987)
12a. Oct 14	UG Study Guide 2 (20%)	(Goodwin and Ellis, 2002; Large and Mathies, 2007; Farboud et al., 2013)
12b. Oct 15	GR Study Guide 2 (20%)	(Goodwin and Ellis, 2002; Large and Mathies, 2007; Farboud et al., 2013)
13. Oct 17	Anteroposterior polarity in Drosophila II	(Cha et al., 2002)
Section 2, Reverse Genetics		
14. Oct 20	RNAi in *C. elegans* and plants	(Fire et al., 1998)
15a. Oct 21	GR Anteroposterior polarity in *C. elegans*	(Griffin et al., 2011)

15b. Oct 22 UG Anteroposterior polarity in *C. elegans* (Griffin et al., 2011)

16. Oct 24 T-DNA in Arabidopsis (Alonso et al., 2003)

17. Oct 27 Gene replacement in Yeast (Giaever et al., 2002; Giaever and Nislow, 2014)

18a. Oct 28 GR Study Guide 3 (20%) (Zhang et al., 2009)
18b. Oct 29 UG Study Guide 3 (20%) (Zhang et al., 2009)

19. Oct 31 Transgenic Mice (knockouts/knockins) I (Mansour et al., 1988)

20. Nov 3 Transgenic Mice (knockouts/knockins) II (Imayoshi et al., 2010) (Garcia-Cao et al., 2012)

21a. Nov 4 GR: CRISPR-mediated activation and repression (Gilbert et al., 2014)
21b. Nov 5 UG: CRISPR-mediated activation and repression (Gilbert et al., 2014)

22. Nov 7 The quest for stem cells and scientific fraud (Takahashi and Yamanaka, 2006; Maherali et al., 2007; Cyranoski, 2014b, a; Obokata et al., 2014b; Obokata et al., 2014a)

Section 3, Quantitative Genetics (still under construction)

23. Nov 10 Quantitative Trait Loci (Nuzhdin et al., 1998)

24a. Nov 11 GR Study Guide 4 (20%) (Pasyukova et al., 2000; De Luca et al., 2003)
24b. Nov 12 UG Study Guide 4 (20%) (Pasyukova et al., 2000; De Luca et al., 2003)

25. Nov 14 eQTL to be determined

26. Nov 17 Genome-Wide Association Studies to be determined

27. Nov 18 Molecular breeding to be determined

28. Nov 25 GR & UG Study Guide 5 (20%) (paper to be determined; no meeting, but assignment due by 5 PM)

Reading List (still in progress)

Alonso, J.M., Stepanova, A.N., Leisse, T.J., Kim, C.J., Chen, H., Shinn, P., Stevenson, D.K., Zimmerman, J., Barajas, P., Cheuk, R., Gadrinab, C., Heller, C., Jeske, A., Koesema, E., Meyers, C.C., Parker, H., Prednis, L., Ansari, Y., Choy, N., Deen, H., Geralt, M., Hazari, N., Hom, E., Karnes, M., Mulholland, C., Ndubaku, R., Schmidt, I., Guzman, P., Aguilar-Henonin, L., Schmid, M., Weigel, D., Carter, D.E., Marchand, T., Risseeuw, E., Brogden, D., Zeko, A., Crosby, W.L., Berry, C.C., and Ecker, J.R. (2003). Genome-wide insertional mutagenesis of *Arabidopsis thaliana*. Science **301:** 653-657.

Ambros, V., and Horvitz, H.R. (1984). Heterochronic mutants of the nematode *Caenorhabditis elegans*. Science **226:** 409-416.

Cha, B.-J., Serbus, L.R., Koppetsch, B.S., and Theurkauf, W.E. (2002). Kinesin I-dependent cortical exclusion restricts pole plasm to the oocyte posterior. Nature Cell Biol. **4:** 592-598.

Cyranoski, D. (2014a). Papers on 'stress-induced' stem cells are retracted. Nature**:** doi:10.1038/nature.2014.15501.

Cyranoski, D. (2014b). Stem-cell pioneer blamed media 'bashing' in suicide note. Nature**:** doi:10.1038/nature.2014.15715.

De Luca, M., Roshina, N.V., Geiger-Thornsberry, G.L., Lyman, R.F., Pasyukova, E.G., and Mackay, T.F.C. (2003). Dopa decarboxylase (*Ddc*) affects variation in *Drosophila* longevity. Nature Genetics **34:** 429-433.

Erickson, J.W., and Quintero, J.J. (2007). Indirect effects of ploidy suggest X chromosome dose, not the X:A ratio, signals sex in *Drosophila* PLoS Biol. **5:** e332.

Farboud, B., Nix, P., Jow, M.M., Gladden, J.M., and Meyer, B.J. (2013). Molecular antagonism between X-chromosome and autosome signals determines nematode sex. American Zoologist **27:** 1159-1178.

Fire, A., Xu, S.-Q., Montgomery, M.K., Kostas, S.A., Driver, S.E., and Mello, C.C. (1998). Potent and specific genetic interference by double-stranded RNA in *Caenorhabditis elegans*. Nature **391:** 806-811.

Garcia-Cao, I., Song, Min S., Hobbs, Robin M., Laurent, G., Giorgi, C., de Boer, Vincent C.J., Anastasiou, D., Ito, K., Sasaki, Atsuo T., Rameh, L., Carracedo, A., Vander Heiden, Matthew G., Cantley, Lewis C., Pinton, P., Haigis, Marcia C., and Pandolfi, Pier P. (2012). Systemic Elevation of PTEN Induces a Tumor-Suppressive Metabolic State. Cell **149:** 49-62.

Giaever, G., and Nislow, C. (2014). The Yeast Deletion Collection: A Decade of Functional Genomics. Genetics **197:** 451-465.

Giaever, G., Chu, A.M., Ni, L., Connelly, C., Riles, L., Veronneau, S., Dow, S., Lucau-Danila, A., Anderson, K., Andre, B., Arkin, A.P., Astromoff, A., El Bakkoury, M., Bangham, R., Benito, R., Brachat, S., Campanaro, S., Curtiss, M., Davis, K., Deutschbauer, A., Entian, K.D., Flaherty, P., Foury, F., Garfinkel, D.J., Gerstein, M., Gotte, D., Guldener, U., Hegemann, J.H., Hempel, S., Herman, Z., Jaramillo, D.F., Kelly, D.E., Kelly, S.L., Kotter, P., LaBonte, D., Lamb, D.C., Lan, N., Liang, H., Liao, H., Liu, L., Luo, C.Y., Lussier, M., Mao, R., Menard, P., Ooi, S.L., Revuelta, J.L., Roberts, C.J., Rose, M., Ross-Macdonald, P., Scherens, B., Schimmack, G., Shafer, B., Shoemaker, D.D., Sookhai-Mahadeo, S., Storms, R.K.,

Strathern, J.N., Valle, G., Voet, M., Volckaert, G., Wang, C.Y., Ward, T.R., Wilhelmy, J., Winzeler, E.A., Yang, Y.H., Yen, G., Youngman, E., Yu, K.X., Bussey, H., Boeke, J.D., Snyder, M., Philippsen, P., Davis, R.W., and Johnston, M. (2002). Functional profiling of the *Saccharomyces cerevisiae* genome. Nature **418:** 387-391.

Gilbert, Luke A., Horlbeck, Max A., Adamson, B., Villalta, Jacqueline E., Chen, Y., Whitehead, Evan H., Guimaraes, C., Panning, B., Ploegh, Hidde L., Bassik, Michael C., Qi, Lei S., Kampmann, M., and Weissman, Jonathan S. (2014). Genome-Scale CRISPR-Mediated Control of Gene Repression and Activation. Cell **159:** 647-661.

Goodwin, E.B., and Ellis, R.E. (2002). Turning clustering loops: sex determination in *Caenorhabditis elegans*. Curr. Biol. **12:** R111-R120.

Griffin, Erik E., Odde, David J., and Seydoux, G. (2011). Regulation of the MEX-5 gradient by a spatially segregated kinase/phosphatase cycle. Cell **146:** 955-968.

Imayoshi, I., Sakamoto, M., Yamaguchi, M., Mori, K., and Kageyama, R. (2010). Essential Roles of Notch Signaling in Maintenance of Neural Stem Cells in Developing and Adult Brains. J. Neurosci. **30:** 3489-3498.

Johnson, M.L., Nagengast, A.A., and Salz, H.K. (2010). PPS, a large multidomain protein, functions with Sex-Lethal to regulate alternative splicing in *Drosophila*. PLoS Genet. **6:** e1000872.

Keyes, L.N., Cline, T.W., and Schedl, P. The primary sex determination signal of Drosophila acts at the level of transcription. Cell **68:** 933-943.

Kiesewetter, S., Macek, M., Davis, C., Curristin, S.M., Chu, C.-S., Graham, C., Shrimpton, A.E., Cashman, S.M., Tsui, L.-C., Mickle, J., Amos, J., Highsmith, W.E., Shuber, A., Witt, D.R., Crystal, R.G., and Cutting, G.R. (1993). A mutation in CFTR produces different phenotypes depending on chromosomal background. Nature Genet. **5:** 274-278.

Lang, G.I., and Murray, A.W. (2008). Estimating the per-base-pair mutation rate in the yeast *Saccharomyces cerevisiae*. Genetics **178:** 67-82.

Large, E.E., and Mathies, L.D. (2007). Chromatin regulation and sex determination in *Caenorhabditis elegans*. Trends Genet. **23:** 314-317.

Lee, R.C., Feinbaum, R.L., and Ambros, V. (1993). The *C. elegans* heterochronic gene *lin-4* encodes small RNAs with antisense complementarity to *lin-14*. Cell **75:** 843-854.

Maherali, N., Sridharan, R., Xie, W., Utikal, J., Eminli, S., Arnold, K., Stadtfeld, M., Yachechko, R., Tchieu, J., Jaenisch, R., Plath, K., and Hochedlinger, K. (2007). Directly reprogrammed fibroblasts show global epigenetic remodeling and widespread tissue contribution. Cell Stem Cell **1:** 55-70.

Mansour, S.L., Thomas, K.R., and Capecchi, M.R. (1988). Disruption of the proto-oncogene *int-2* in mouse embryo-derived stem cells: a general strategy for targeting mutations to non-selectable genes. Nature **336** 348-352.

Nusslein-Volhard, C., Frohnhofer, H.G., and Lehmann, R. (1987). Determination of anteroposterior polarity in *Drosophila*. Science **238:** 1675-1681.

Nuzhdin, S., Keightley, P.D., Pasyukova, E.G., and Morosova, E.A. (1998). Mapping quantitative trait loci affecting sternopleural bristle number in *Drosophila melanogaster* using changes in marker allele frequencies in divergently selected lines. Genet. Res. **72:** 79-91.

Obokata, H., Wakayama, T., Sasai, Y., Kojima, K., Vacanti, M.P., Niwa, H., Yamato, M., and Vacanti, C.A. (2014a). Stimulus-triggered fate conversion of somatic cells into pluripotency. Nature **505:** 641-647.

Obokata, H., Sasai, Y., Niwa, H., Kadota, M., Andrabi, M., Takata, N., Tokoro, M., Terashita, Y., Yonemura, S., Vacanti, C.A., and Wakayama, T. (2014b). Bidirectional developmental potential in reprogrammed cells with acquired pluripotency. Nature **505:** 676-680.

Ossowski, S., Schneeberger, K., Lucas-Lledó, J.I., Warthmann, N., Clark, R.M., Shaw, R.G., Weigel, D., and Lynch, M. (2010). The rate and molecular spectrum of spontaneous mutations in *Arabidopsis thaliana*. Science **327:** 92-94.

Pasyukova, E.G., Vieira, C., and Mackay, T.F. (2000). Deficiency mapping of quantitative trait loci affecting longevity in Drosophila melanogaster. Genetics **156:** 1129-1146.

Reinhart, B.J., Slack, F.J., Basson, M., Pasquinelli, A.E., Bettinger, A.E., Rougvie, A.E., Horvitz, H.R., and Ruvkun, G. (2000). The 21-nucleotide *let-7* RNA regulates developmental timing in *Caenorhabditis elegans*. Nature **403:** 901-906.

Salz, H.K. (2011). Sex determination in insects: a binary decision based on alternative splicing. Curr. Op. Genet. Dev. **21:** 395-400.

Sosnay, P.R., Siklosi, K.R., Van Goor, F., Kaniecki, K., Yu, H., Sharma, N., Ramalho, A.S., Amaral, M.D., Dorfman, R., Zielenski, J., Masica, D.L., Karchin, R., Millen, L., Thomas, P.J., Patrinos, G.P., Corey, M., Lewis, M.H., Rommens, J.M., Castellani, C., Penland, C.M., and Cutting, G.R. (2013). Defining the disease liability of variants in the cystic fibrosis transmembrane conductance regulator gene. Nature Genet. **45:** 1160-1167

Takahashi, K., and Yamanaka, S. (2006). Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell **126:** 663-676.

Zhang, E.E., Liu, A.C., Hirota, T., Miraglia, L.J., Welch, G., Pongsawakul, P.Y., Liu, X., Atwood, A., Huss III, J.W., Janes, J., Su, A.I., Hogenesch, J.B., and Kay, S.A. (2009). A genome-wide RNAi screen for modifiers of the circadian clock in human cells. . Cell **139:** 199-210