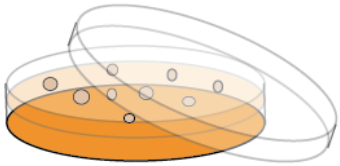
BIOL 494-01
SEMINAR IN STEM CELL BIOLOGY



FALL 2009

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Course meets: MWF Noon-1 pm in Olin Rice 270

Course Description

Stem cells are cells that are capable of dividing without differentiating into a specific cell type. Sources of stem cells include embryos, adult tissues, and most recently, adult cells that have been genetically engineered back into an embryonic state. Because of the developmental plasticity or pluripotency of these cells, the biomedical field has been interested in developing methods to direct the development of stem cells into specific cell and tissue types with the longterm goal of treating or replacing diseased tissue. This course will entail extensive reading and discussion of the primary literature of stem cell research to gain some historical perspective as well as an up-to-date view of the current state of the field. Several methodologies used to generate and/or study stem cells, such as cell culturing techniques, transgenic approaches, and microarrays will be covered in some depth, as will related concepts such as cell signaling and differential gene expression. We will also read and discuss a variety of perspectives on the socio-ethical issues associated with stem cell research and its potential therapeutic applications. Three discussion/lecture hours per week. Pre-requisites: Cell Biology & Genetics II or Genetics (BIOL 260) and Cell Biology (BIOL 265); junior or senior standing.

Introduction

The study of stem cells is exploding. The potential of stem cells for studying and treating numerous diseases, including neurological disorders such as Parkinsons, blood disorders such as sickle cell anemia, and those due to deteriorating/aging tissues and organs has been hyped for over a decade but may be realized within the next few to several years. Literally thousands of papers are being published each year in the field of stem cell biology. We will be reading and discussing in depth just a *dozen* of these research papers. Each paper addresses one or more specific research questions in the field and represents a breakthrough in regards to that question(s). The papers I've chosen for this semester primarily focus on the newest major player in the field: induced pluripotent stem (iPS) cells. These cells were first "discovered" (or some would argue "generated" or as the name reflects "induced") in 2007 but have drawn much attention because they appear to have the same potential as embryonic stem (ES) cells but lack many of the ethical concerns engendered by ES cell research. Although the dozen papers for the seminar course have

been chosen and posted on Moodle, I reserve the right to substitute a paper for one currently listed in the syllabus. The field is moving so fast that I may find a more suitable paper for a given week's topic than currently posted. If I do so, you will have a minimum of two weeks' advance notice.

Learning Goals and Objectives

Broadly speaking, any seminar such as this emphasizes *critical reading and thinking skills*, as reflected by a semester-long effort to understand, analyze, and critique a body of primary scientific work in the context of a field of knowledge, in this case the field of stem cell biology. Moreover, this course entails extensive *writing* and *discussion*. Both writing and discussion should be viewed as *tools* that help you to better understand the scientific literature, by deconstructing a paper (getting into the real nitty gritty), debating the merits of its methodological approaches and/or interpretation of experimental results, and finally contextualizing the research in the broader constellation of published work. In addition to these broader learning goals, I hope by the end of the semester that students will be able to (1) demonstrate familiarity with many of the *methodologies* used in the field of stem cell research, and (2) *critically assess* claims of the pluripotency of specific types of stem cells, as well as their therapeutic potential.

Format of the Course

The course is structured so that we cover a different paper from the primary literature each week. In general, I will provide a lecture on Mondays that provides some essential background and/or explains new methodologies relevant to the week's discussion. I will often assign a review article that should be read prior to Monday's lecture and that will place the primary research paper in context. On Wednesdays and Fridays we will discuss the week's research paper. (Papers 7 and 11 are exceptions as they fall during Fall Break and Thanksgiving Break, respectively. These papers will be discussed on Monday and Wednesday during those weeks.) The discussion will be facilitated by a set of questions that we will address in each paper (described in detail under "Reading Response Guidelines"). Your answers to these questions will need to be posted on Moodle by midnight Monday each week (Saturday for papers 7 and 11). The final 10 minutes of each Friday's class will be devoted to an evaluation of the week's discussion.

Expectations and Evaluation

Pre-seminar preparation:	35%
Seminar participation:	45%
Note-Taking:	10%
Essay:	10%

Pre-seminar preparation: See "Reading Response Guidelines"

Seminar participation: We will get the most out of this seminar if everyone has read the paper carefully and critically, has done their background research, and comes prepared ready to share their ideas, interpretations, and questions. The pre-seminar preparation will help in getting everyone ready for the discussion, but then it will be important that *all*

contribute to the *conversation*. I can, and will, call on individuals by name if necessary, but we are aiming for a more natural free-flowing discussion. If you find early in the semester that it is difficult for you to volunteer your thoughts during the discussion, talk with me and we will work on strategies that might help you feel more comfortable speaking in class. This is a skill that is most likely to be important for the rest of your professional life, and you would do well to view this as an opportunity to hone it. It will also be important to *listen* to what each of us has to contribute; you can demonstrate *active listening* by directly responding to another student's point or question. This also helps to generate a vigorous discussion and a respectful attitude toward your colleagues. Thus, significant participation (Grade B+ to A) will consist of (a) *asking*, *answering*, and *facilitating* pertinent and significant questions regarding the paper and directing those comments to your colleagues (as opposed to me, the instructor), (b) being able to describe each figure (and the results more broadly) of the paper in terms of how the data were generated, how the data are represented in the figure, and what conclusions the authors draw from the results, (c) being able to recall the content of the paper in the context of the larger field of research, and (d) being able to articulate what is unclear. Marginal participation (Grade C+ to B) will be measured in terms of unwillingness to speak up and/or respond to questions, inability to recall and place in context the content of the paper, and lack of evidence of preparedness. An unexcused absence or near silence will result in a grade of C or lower and an unexcused absence will result in no credit for participation. I will evaluate participation at the end of each week.

Note-Taking: We will have an official note-taker for each day in which we discuss a paper from the primary literature (generally Wed and Fri). The job of the note-taker will be to listen and take notes on the conversation. The note-taker needs to function as an "expert listener" rather than someone who is not engaged with the topic and merely writes down what people say. After the class period, I will photocopy your notes for that day and give them back to you. You will then post on Moodle a summary (2 pages max) of the discussion within two days. Note-takers will be assigned alphabetically (by first name) and each of you will have the opportunity to function as note-taker twice.

Essay: The final week of the course will be devoted to a more in-depth analysis and discussion of the "promise" of stem cells. What have we learned during the course of the semester from the dozen papers we've covered? What new breakthroughs were published during the semester? What ethical controversies/concerns remain? Prior to the final week of classes, I will post a question that addresses these issues and for which you will write a formal response in the form of a thesis-governed essay. For this assignment, students should view writing as a tool to explore and express ideas, develop the ability to synthesize and critically evaluate information from multiple sources and viewpoints, and apply such information to the construction of a persuasive argument. A rough (but complete) draft of your essay will be due the final week of the semester and a final polished draft will be due by noon, December 19th.

PLEASE NOTE: The only acceptable excuses for missing a discussion day are severe personal illness, a family emergency, or other event of similar nature, or participation in a sporting event or other official Macalester activity.

Reading Response Guideline

(The following approach and guideline to running an undergraduate seminar was developed by David Matthes and Devavani Chatterjea.)

Pre-seminar preparation in the form of reading responses will count for 35% of your grade in this course. I will ask you to turn in each week, by Monday midnight (or Saturday midnight in the case of papers 7 and 11), a written response to a set of questions based on the research paper we are discussing that week. Turning in 11 of the 12 sets of responses earns you 10% of points toward your final grade. The rest of the points will be awarded based on detailed evaluation of at least 6 of your responses. You will not know in advance which 6 responses I will grade (but I will be working off a matrix that simulates random selection); in the event of an excused absence a week where your response is due to be graded, I will grade a different week's response and you will not be penalized.

Pre-seminar reading responses: A few general guidelines for reading and writing about any paper including the ones for this course:

- Demonstrate that you prepared yourself to read the paper; i.e. you read, used and cited reviews and/or other papers in the field when you wrote your responses. This means that you need *time* to not only read the paper but look up additional sources. This is one of the reasons that your responses are due a couple days before we begin discussion and why the research papers are posted on Moodle well in advance. Don't procrastinate!
- Show that you looked up terms you did not understand (by citing sources you checked), and if you still did not understand them, explain that and also make it clear how that left gaps in your understanding of the paper.
- Be thoughtful, perceptive, original, and critical in your deconstruction of the paper. An important way to do this is to be precise in your commentary and invoke concrete examples, data points, graphs, figures, etc. from the paper. Paraphrasing the discussion section will be a waste of your time.

What goes into the response for this class? In order to keep things varied and interesting for all of us, you will not be asked to answer the same questions every week. Instead we will work off a matrix where you will be responsible for a subset of the questions that frame our reading of the paper. As a group, we will always have a complete set of responses to the paper and your personal contribution to the discussion will be very important as not all your colleagues will have considered the same questions as you.

<u>The Questions</u>:

(a) What is the main experimental question? Can you identify a specific experimental hypothesis as well as a larger contextual hypothesis (i.e. one that involves an important concept/problem in the field)?
(b) What experimental approaches and methodologies were used to address their main question? What would you say is the key figure in the article and why?
(c) How did this work move the field forward? What paradigms in the field did this paper extend, deepen, overturn?

(d) Who are the authors (academic background/training, field(s) of expertise, institutional affiliation)? What other labs are working on closely related questions? (These others are likely to be collaborators and/or competitors.) What (and where) have they published recently?
(e) What are the logical next experimental questions that need addressing? What did this research group do next based on the results of this study (if they've had time to publish since the paper under discussion)?
(f) What is the principle weakness or limitation of this study? Are the conclusions supported by the study? Were the most appropriate techniques used? Were all appropriate controls included?
(g) Were there other ways to address the question? Is there a "blind spot" in the study that you can identify? For example, because of the way the study is set up, are there questions that were not asked or that may never be asked?

Grading the responses: Excellent responses (Grades B+ to A) will incorporate all of the criteria listed above but clearly do so with evidence of your original intellectual involvement in learning. Adequate responses (Grades C+ to B) will typically have "checked off" most of the criteria but might be missing evidence of higher order connective and critical thinking. Responses with lots of room for improvement (Grade C or lower) will typically have addressed, often in a cursory fashion, some but not all of the criteria listed above.

The Matrix:

Student order (alphabetical by first name): 1-12

Paper

Student	1	2	3	4	5	6	7	8	9	10	11	12
1	ab	cd	ef	ga	bc	de	fg	ab	cd	ef	ga	bc
2	bc	de	fg	ab	cd	ef	ga	cd	ef	ga	bc	de
3	cd	ef	ga	bc	de	fg	ab	ef	ga	bc	de	fg
4	de	fg	ab	cd	ef	ga	bc	ga	bc	de	fg	ab
5	ef	ga	bc	de	fg	ab	cd	ab	cd	ef	ab	bc
6	fg	ab	cd	ef	ga	bc	de	bc	de	fg	bc	cd
7	ga	bc	de	fg	ab	cd	ef	cd	ef	ga	cd	de
8	ab	cd	ef	ga	bc	de	fg	de	fg	ab	de	ef
9	bc	de	fg	ab	cd	ef	ga	ef	ga	bc	ef	fg
10	cd	ef	ga	bc	de	fg	ab	fg	ab	cd	fg	ga
11	de	fg	ab	cd	ef	ga	bc	ga	bc	de	ab	ab
12	ef	ga	bc	de	fg	ab	cd	bc	cd	ef	bc	bc

The Papers (schedule/dates posted on Moodle; subject to change with 2 weeks notice)

#1: Thomson JA *et al.* (1998) Embryonic stem cells lines derived from human blastocysts. *Science* 282, 1145-47

#2: Takahashi, K *et al.* (2007) Induction of pluripotent stem cells from adult human fibroblasts by defined factors. *Cell* 131(5), 861-72.

#3: Hanna, J *et al.* (2008) Direct reprogramming of terminally differentiated mature B lymphocytes to pluripotency. *Cell* 133(2), 250-64.

#4: Zhao, X-Y *et al.* (2009) iPS cells produce viable mice through tetraploid complementation. *Nature* advance online publication 23 July 2009 | doi:10.1038/nature08267

#5: Deng, J *et al.* (2009) Targeted bisulfite sequencing reveals changes in DNA methylation associated with nuclear reprogramming. *Nature Biotechnology* 27(4), 353-60.

#6: Zhou, H. *et al.* (2009) Generation of induced pluripotent stem cells using recombinant proteins. *Cell Stem Cell* 4, 381-384.

#7: Karumbayaram, S *et al.* (2009) Directed differentiation of human-induced pluripotent stem cells generates active motor neurons. *Stem Cells* 27(4), 806-11.

#8: Ebert, AD *et al.* (2009) Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature* 457(15 Jan 09, doi:10.1038/nature07677)

#9: Wernig, M *et al.* (2008) Neurons derived from reprogrammed fibroblasts functionally integrate into the fetal brain and improve symptoms of rats with Parkinson's disease. *PNAS* 105(15), 5856-61.

#10: Amariglio, N *et al.* (2009) Donor-Derived Brain Tumor Following Neural Stem Cell Transplantation in an Ataxia Telangiectasia Patient. *PLoS Medicine* 6(2), 221-31.

#11: Amoh, Y *et al.* (2009) Human hair follicle pluripotent stem (hfPS) cells promote regeneration of peripheral-nerve injury: An advantageous alternative to ES and iPS cells. *J Cell Biochem* (1 Aug) 107(5), 1016-20.

#12: Qiao Zhou, Q *et al.* (2008) In vivo reprogramming of adult pancreatic exocrine cells to bold beta-cells. *Nature* 455, 627-632.