Experimenting with Hybridoma Technology in the Immunology Lab

Newell Innovative Teaching Award Application 2014

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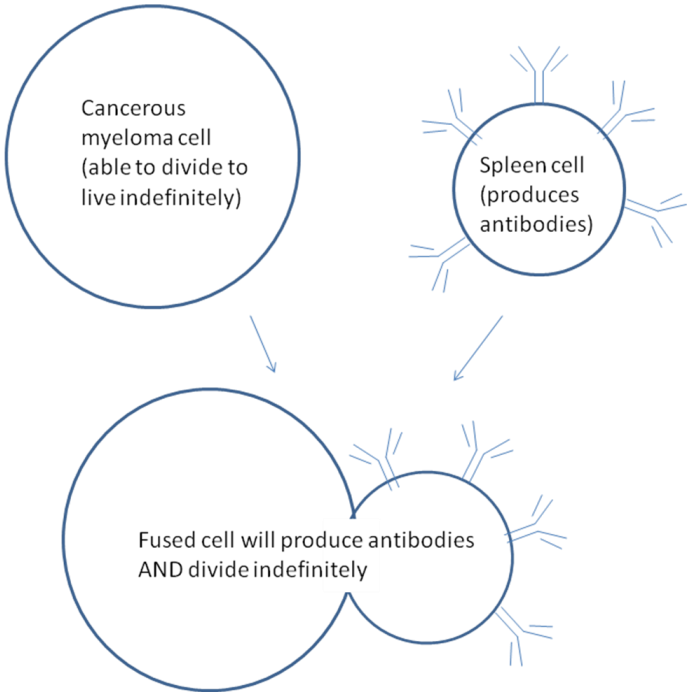
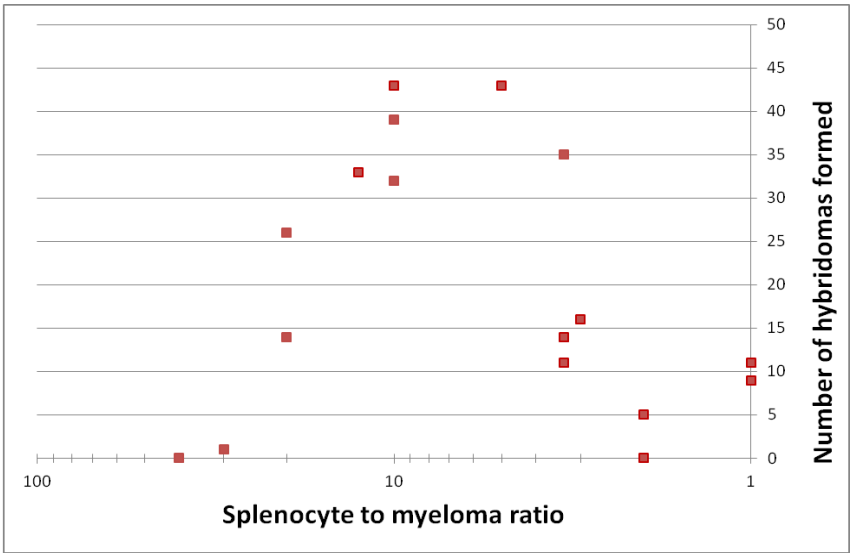
Description of the project

My Fall 2013 Immunology (BIO320) class consisted of 29 students divided into two laboratory sections (BIO320L). These students carried out a semester-long research project under my supervision. In particular, they tested the effect of changing the ratio of myeloma cells to spleen cells in the formation of hybridoma cell lines. This allowed undergraduates, most of whom had not had any previous research experience, to participate in a set of experiments in which the outcomes were not known by me, their teacher, at the outset. They were able to see patterns emerging from the data they produced, and to participate in discussions of the best way to proceed with design of the next weeks' experiment in light of incoming data.

Hybridoma cell lines are formed by fusing an antibody-producing cell from the spleen of a mouse with a cancerous myeloma cell. The resulting hybrid cell has the antibody-producing trait from the former and the growth properties of the latter. This allows for the production of large amounts of a single type of antibody, called a monoclonal antibody, and these antibodies may be used in research or as drugs. Monoclonal antibodies are able to recognize and bind to one specific molecule that was injected into the mouse that provided the spleen cells. Many of the newer cancer drugs are monoclonal antibodies, and their ability to bind specifically has reduced many of the unpleasant side effects of cancer treatment. Hybridoma technology was developed in the 1970's, and its inventors were subsequently awarded the 1984 Nobel Prize in Physiology or Medicine for this work.



Although hybridoma technology is widely used today, the science behind it is poorly understood and attempts to make hybridoma cell lines often fail for unknown reasons. A better understanding of why the process fails or succeeds would be helpful to researchers who use this technology. One book gives instructions for the procedure with the warning that while sometimes the procedure works on the first try, sometimes it must be repeated 5-10 times for success[1]. The same book claims that the ratio of spleen cells to myeloma cells has little effect on the success of the procedure. However, one of my research students, while doing another project, produced some results that suggested that the ratio actually is important. While that student did not have time to follow up on the lead, the students in my Immunology class were able to perform the experiments needed to rigorously test the effect of varying the cell ratio. They found that the optimal cell ratio is about 10 spleen cells for every myeloma cell, and that hybridoma formation drops off if this ratio is higher or lower (see graph below).



Innovation

Most undergraduate Immunology labs give students the opportunity to do a variety of procedures relevant to the subject. But they are usually "canned labs" in that the expected outcome is known by the professor in advance. In my Immunology lab, students participated in a semester-long experimental project, in that I as their instructor did not know what results to expect from the experiments, and we had to adjust plans for each week's new experiments as data from previous weeks came in. Many

[1] Goding, J. Monoclonal Antibodies: Principles and Practice, 3rd ed. Academic Press, 1996. Pg 154.

undergraduate Biology programs provide an opportunity for students to do an independent research project, and therefore participate in real experimental science. However, those projects are typically separate from the lab courses like mine which are attached to specific lecture courses and that meet at a defined time each week. Therefore my Immunology lab was unusual in that I was able to combine research experience with a lab course. While this might seem an obvious improvement over canned labs, it is simply not practical at most universities. Union's policy of giving load credit to faculty for actual hours met in science labs is extremely unusual, and it allowed me to invest a great deal of time to take care of the myeloma cell line and the mouse colony, to do library research to figure out what experiments have already been done, and to prepare the various reagents that the students needed to finish the experiment in the time allotted for lab. A professor elsewhere who receives the standard 1 or 1.5 hours of load credit for a lab that meets three hours a week would not be able to replicate what I'm doing here, and so in that sense my innovation is specific to Union.

Several students commented on another difference between my course and their other lab courses. Because they had to do the same kind of experiment multiple times in order to get the needed data, they were able to master the procedures needed for that experiment. In this case, the procedures were fairly challenging for undergraduates; they needed to be able to remove the spleens from the mice using sterile tools and maintain sterility throughout the process of fusing the cells together. In more typical Immunology labs, the goal is to expose the students to as many different types of procedures as possible. This is a good goal, but it comes at the expense of mastery of any of the procedures. I was actually initially a little worried that the students would be bored doing the same thing multiple times, but the repetition turned out to have an unanticipated benefit.

Success and potential for improvement

My main hope in designing this lab was that students would get excited about doing research. Content can be more efficiently conveyed in lecture than lab, but a hands-on project that replicates and expands on Nobel-winning research has much more potential to draw students in and get them interested in science. In this, I think I've succeeded. I had many students interested in further building on the research begun in this course for their independent research projects. I ended up turning some away because of constraints of time and space. One of the students from this lab is currently writing up our results for publication, even though the course is over and therefore he will not receive a grade for the work. During the course, students were enthusiastic about what they were learning, and because the

procedures relate back to the Immunology lecture, I was able to draw connections in my lectures back to what we were doing in lab.

Another success is the collection of a surprisingly large amount of data in a short period of time. Undergraduate research is mostly done to expose students to the experience. But when students are working independently, they are more likely to make mistakes than when a professor is watching over their shoulders the entire time. Another factor that may have helped us collect so much data is that the students seemed excited by early results and therefore motivated to get even more data to finish the project by the end of the semester.

There were a few bumps along the semester. Labs were split into two groups, and I supervised the group doing the actual fusion of the cells. The other group was left alone to test hybridomas formed from previous experiments to verify the presence of antibodies. Although they had done this procedure once under supervision, they still made a number of mistakes when trying to do it by themselves. In order to help future students, I can improve the written instructions left for them, but this is not the same as personal supervision, and I can't be in both places at once. Because the test can be repeated the next week, this is not a serious problem, and mistakes can be learning opportunities for students.

Another aspect of the course that I would like to improve is how the course is graded. I created a grading rubric and each student was able to practice the fusion procedure once and do it for credit twice. This created anxiety for some students, because with only two grading points the stakes were high for each one. The lab grade is combined with their lecture grade, and it is possible for a low lab grade to bring down a student's overall grade. I would like to incorporate a written component, in which students would work throughout the semester on different parts of a potentially publishable research paper. This would spread their grades out and also encourage the students to think in terms of sharing their results with the larger scientific community.