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Essay

Implementation of a Project-Based Molecular Biology Laboratory Emphasizing Protein Structure–Function Relationships in a Large Introductory Biology Laboratory Course

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In introductory laboratory courses, many universities are turning from traditional laboratories with predictable outcomes to inquiry-inspired, project-based laboratory curricula. In these labs, students are allowed to design at least some portion of their own experiment and interpret new, undiscovered data. We have redesigned the introductory biology laboratory course at Brandeis University into a semester-long project-based laboratory that emphasizes concepts and contains an element of scientific inquiry. In this laboratory, students perform a site-directed mutagenesis experiment on the gene encoding human γD crystallin, a human eye lens protein implicated in cataracts, and assess the stability of their newly created protein with respect to wild-type crystallin. This laboratory utilizes basic techniques in molecular biology to emphasize the importance of connections between DNA and protein. This project lab has helped engage students in their own learning, has improved students' skills in critical thinking and analysis, and has promoted interest in basic research in biology.

BACKGROUND TO THE LAB COURSE REDESIGN

The laboratory portions of introductory science courses are designed to teach students basic protocols, providing them a visual and physical representation of the subject matter they learn in the lecture classes. The laboratory classes are also meant to give students hands-on experience with the scientific process and, in college classes, experience with research as a field.

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The National Research Council (2003) suggested that other opportunities for gaining a better understanding of science could be achieved through project-based laboratory courses. These courses help to students to think more like scientists by simulating the actual research lab environment where students design their own project and interpret their own independent results. This report and many other studies have further suggested that the incorporation of active-learning strategies such as critical thinking, data interpretation, group collaborative work, and problem-solving skills into both lecture and laboratories of introductory science classes will increase student retention of information and will facilitate overall interest in pursuing science careers and majors (National Science Foundation, 1996; commentary in Handelsman *et al.*, 2004; Regassa and Morrison-Shetlar, 2007).

Studies have shown that student retention of key concepts is increased when project-based learning strategies are implemented (Cianciolo *et al.*, 2006; Lord and Orkwiszewski, 2006; Rissing and Cogan, 2009). These laboratories often have elements of independent and critical thinking, asking students to develop and troubleshoot their own experiments. The

design and implementation of project-based labs in higher-level undergraduate biology courses has been extremely successful in increasing student interest in advanced topics such as development, bioinformatics, and molecular biology (D'Costa and Shepard, 2009; Lau and Robinson, 2009). These models allow for a fair amount of independent student research, but the class size is limited in these studies.

When developing project-based labs for introductory biology courses with high enrollments, several models have been developed. Short, 2- or 3-wk modular concept-based laboratories can be used to enhance student learning in large introductory biology courses (Halme *et al.*, 2006). Similarly, multiweek experiments relating interconnected concepts in genetics and molecular biology have also been shown to be effective (Aronson and Silviera, 2009). In most models, given the true experimental nature of the lab, the incorporation of multiple success points and a reasonable amount of experimental overlap within the class or group has been critical to allow all students the opportunity to continue performing a multiweek laboratory even if the student "makes a mistake" while performing the procedure (Hanauer *et al.*, 2006).

We have redesigned the cell biology portion of the introductory biology lab curriculum at Brandeis University into a semester-long, project-based laboratory. Focusing on a human health concern, students must use what they learned and performed in the previous weeks' experiments to understand the material in the current experiment. This laboratory exposes students in a high-enrollment course to basic techniques in molecular biology with an inquiry-based introductory experiment that emphasizes the importance of the relationship between DNA and protein.

DESCRIPTION OF THE REDESIGNED COURSE

University and Course Profile

Brandeis is a private, liberal arts university in Waltham, MA, with an entering first-year class of about 800 students. Of the 800 students, more than half enter with an intention to pursue a career in the allied health professions. All of these students are required to take the core science courses including introductory chemistry, biology, organic chemistry, and physics and the accompanying laboratory courses.

Biol18b and Biol18a are the introductory-level biology laboratory courses that accompany the sophomore-level general biology lectures in cell biology and genetics, respectively. The laboratory courses are independent entities complete with their own weekly 1-h, 20-min lecture and weekly 4-h laboratory session. Each semester, about 200 students enroll in the course, which is in the top five in enrollment figures for the university. The weekly lectures are led by the course professor, and the laboratory is led by both a graduate and an undergraduate teaching assistant (TA) in sections of 24 students each. Each student is assessed a $20 laboratory fee per course that covers the majority of the cost of the consumables used during the semester.

Laboratory Design

Historically, the introductory biology laboratories at Brandeis were modular, traditional labs in which students would perform straightforward lab protocols to obtain predictable results on topics such as β-galactosidase enzyme kinetics, mitochondrial respiration, and photosynthesis. These labs provided little opportunity for our students to think conceptually or creatively about a scientific problem and were often met with minimal enthusiasm and interest.

In Fall 2007, we informally surveyed our faculty to determine which concepts and techniques in molecular and cellular biology they felt were critical to student understanding and success in both upper-level courses and in advanced undergraduate research projects within their basic research labs. Core concepts that were emphasized by faculty included the central dogma, protein structure–function relationships, and nucleic acid structures. In addition, the faculty thought that basic knowledge of the polymerase chain reaction (PCR), gel electrophoresis, and pipette strategies were important techniques for our introductory students to learn. With these responses in mind, we began redesigning the cell biology semester of the course (Biol18b) into a semester-long research-based project that encompassed many of the most crucial concepts and techniques. The course was designed with the following student-centered objectives in mind:

1. To give students experience designing experiments and interpreting newly generated scientific data;
2. To facilitate student understanding of basic concepts in cell biology specifically, including central dogma and protein structure–function relationships;
3. To give students experience in the application of certain techniques in molecular biology, specifically including pipetteman use and measurement, gel electrophoresis, and PCR; and
4. To encourage student interest in basic research and science by exposure to a project-based lab allowing students to design their own experiment and interpret their results.

Given the overwhelming interest of our students in pursuing health-related professions, we chose a research project with a distinct connection to human health and disease. Over the course of the semester, our students perform a site-directed mutagenesis experiment on the gene encoding human γD crystallin (HγD-Crys) loosely based on published methodologies (Kosinski-Collins and King, 2003). HγD-Crys is an extremely stable eye lens protein consisting of 173 amino acids, found at high concentration in the human lens, which is important for lens function and establishing the appropriate refractive index in the eye for visual acuity (Oyster, 1999; Benedek, 1997). HγD-Crys is expressed only in utero and during childhood and therefore must remain stable throughout a person's life. Several mutations that destabilize the native structure of HγD-Crys have been identified that are directly responsible for congenital cataracts (Pande *et al.*, 2000, 2001, 2005). A list of apparatus utilized in these experiments is given in Table 1.

In the first lecture before our students began lab, the professor introduced the topic and the research problem that was to be pursued throughout the semester. A detailed breakdown of the topics and techniques covered in each week of the lab is given in Table 1. Although we retained the basic laboratory/lecture format of the course, we added a weekly, hour-long "concept review" given our focus on making conceptual connections throughout the course. The professor offered this voluntary 1-h concept review session immediately following

Table 1. Outline of 10-wk project-based labs utilized in Biol18b

Week No.	Procedures performed	Apparatus utilized	Techniques/Concepts discussed
1	Analysis of HγD-Crys structure Selection of mutation SDM Primer Design	Computers	Protein modeling Protein structure–function relationships
2	PCR	Thermocycler	DNA in vitro amplification
3	Agarose gel electrophoresis Ethidium bromide staining Gel analysis	DNA gel boxes Gel scanner	Structure of DNA Electrophoretic mobility
4	Transformation into competent cells	Water baths Incubators	Recombinant bacterial systems Plasmid structure Antibiotic resistance
5	Plasmid purification DNA concentration determination	Microcentrifuge UV/Vis Spectrometer	Bacterial cell structure Centrifugation UV Absorbance of DNA
6	DNA sequencing Selection of mutant plasmid Transformation into competent cells	Water baths Incubators	Structure of DNA and nucleotides Triplet code, translation
7	Expression of recombinant proteins	Incubators	Bacterial expression systems Limiting reagents Carrying capacity
8	Purification of cell lysate	Ultracentrifuge	Sonication Lysozyme function Centrifugation Soluble versus insoluble proteins
9	Purification of recombinant HγD-Crys from cell lysate with Ni-NTA SDS–PAGE	Microcentrifuge Spin columns Protein gel boxes	Column chromatography Acrylamide gels Native and denaturing protein gels
10	Analysis of gel Protein concentration determination Determination of mutant protein stability with respect to wild type	UV/Vis Spectrometer Fluorimeter[a]	UV absorbance of proteins Protein purity Fluorescence spectroscopy[a]

[a]Stability assays could be performed with solution turbidity aggregation scans or native gel electrophoresis instead of fluorescence spectroscopy.

lecture each week. In most of these sessions, the professor proposed real or imaginary data to the students based on the previous week's laboratory procedure and asked them to think critically about how to interpret the data or to troubleshoot what may have gone wrong during the procedure to get that result.

Upon entering the lab, students were asked to use a protein modeling program to analyze the structure of the HγD-Crys protein. In this course they used StarBiochem (Massachusetts Institute of Technology, 2010) to observe the different levels of structure found in the protein (accession number 1HK0) and made predictions of which amino acid(s) they felt was (were) important for the protein's extreme stability. StarBiochem was chosen as our protein viewing software because it presents protein structure in a manner cohesive with the way we present levels of structure in lecture, specifically representing primary, secondary, tertiary, and quaternary structure in order. Each pair of students then chose a residue that they wanted to mutate to test their hypothesis and defended their choice in front of their lab section of 24 students, presenting a rationale to convince their peers of their choice. Each section voted on which mutation they all made such that each partner pair within any one section was working on the same mutagenesis project. This facilitated overlap in the class and functioned as backup in the cases of experimental mistakes among partners.

Over the course of the next 4 wk, the students performed a site-directed mutagenesis (SDM) experiment on a plasmid containing a His-tagged version of HγD-Crys. This procedure involved the design of SDM primers, PCR amplification, transformation into competent cells, and plasmid purification, followed by DNA sequencing and analysis.

After successfully incorporating their mutation into the coding sequence of HγD-Crys, the students began a 3-wk process of purifying their recombinant protein. The students transformed the plasmid with the proper sequence into competent cells capable of producing large amounts of protein, cultured cells, induced protein production, purified their protein using Ni-NTA column chromatography, and analyzed the efficiency of their purification using SDS–polyacrylamide gel electrophoresis (PAGE) gels. During the final week of the semester, the students analyzed their recombinant protein using fluorescence spectroscopy and compared the stability of their mutant with respect to that of wild-type HγD-Crys. The use of a fluorimeter is cost prohibitive for many larger institutions with high-enrollment classes, but native gel comparison between mutant and wild-type crystallin or UV/Vis solution turbidity assays with conventional Spec20s could be substituted for these experiments (Kosinski-Collins and King, 2003). Over the past 3 yr, our students have successfully created and purified 20 mutants of HγD-Crys never reported before in the literature.

In preparation for lab each week, the students were asked to answer four or five prelab questions designed to emphasize both conceptual and procedural information about the week's

lab. The students were also asked to write a scientific purpose for each lab that placed that particular week's experiment into the context of the semester-long project. The students were asked to relate multiple week procedures to one another and write purposes that explained the "who, what, where, how, and why" of each individual lab to emphasize course-long conceptual connections. The students were strongly discouraged from writing "learning purposes" (i.e., "to learn how to perform a PCR") for each week through professor and TA feedback. In addition, each week the students were required to answer approximately five open-ended postlab questions that guided them through the interpretation of their data and helped them draw reasonable conclusions based on their own specific results. An example set of questions designed to troubleshoot PCR is presented in Supplemental Material A.

For evaluation purposes, the class included two 80-min exams each written with a focus on conceptual information, data interpretation, and troubleshooting experimental procedures. The students were also asked to write a full scientific lab report for their entire semester-long project at the end of the course in journal format.

Evaluation Design

To assess understanding in response to the project-based format of the course, students were given the option to complete a written evaluation at the beginning of the second semester of the course (Biol18a) reflecting on their work in the previous semester of the laboratory (Biol18b). The questions focused on gauging student interest in basic research in biology and probing student perception of the project-based course format. Because there was no control group to assess learning in a more conventional laboratory format, we focused our assessment on student perception and interest in the new course structure including assignment/laboratory design and class structure. The evaluation also included basic retention questions to evaluate understanding of central concepts and basic laboratory techniques. All of our students were taking a lecture course in cell biology that emphasized many fundamental concepts covered in Biol18b concurrently with our laboratory course so we chose to focus our assessment only minimally on content understanding and retention because we felt it would be extremely difficult to separate learning gains in the laboratory from learning gains in the lecture.

The evaluation was taken anonymously and bonus participation points were awarded to those completing the survey within the first 2 wk of the second semester of the laboratory course. This meant that 10 wk had lapsed between the last experiments of the project-based course and the time of assessment. The 10 wk included the winter break and therefore most of our students were not reviewing material and/or taking additional courses during this time.

Of the 176 students enrolled in the course, 138 completed the survey (78.5%). Students were asked to evaluate each question with a numerical score of 1 (least valuable) to 7 (most valuable). A detailed version of the student survey is given in Supplemental Material B. Positive values are indicative of responses of 5 or higher on a scale of 1–7 for each question, respectively.

WHAT WE LEARNED FROM COURSE MODIFICATIONS

Of the students electing to take the survey, 79.0% were sophomores, 12.3% were juniors, 3.6% were seniors, 2.2% were freshmen, and 3.0% were students enrolled in postbaccalaureate studies. The top reasons why students enrolled in Biol18b were that the course was required 1) for their major and 2) in further study in health-related fields (81.1% and 71.7%, respectively). Approximately half of the students also said they took the course for general interest in addition to the university or prehealth requirement.

Student Perception of Performing Guided, Basic Research Projects

On the basis of our survey results, students generally appreciated the fact that they were performing experiments as they are done in research settings, without having a concrete set of expected results (Table 2). Almost three-quarters of the students who participated in the survey found that performing an experiment that has not been done before was at least somewhat valuable. Fourteen percent found this to be extremely valuable. When asked about their interest in performing guided, self-designed experiments, more students felt this was extremely valuable (18%), and 64% of students thought this was at least somewhat valuable. Student perception of being able to troubleshoot experiments in real time also showed a similar trend, with 72% of the total reporting some value to this and 20% ascribing a high level of value to this aspect of the project.

More than two-thirds of students also reported that they would be interested in taking another course that allowed them to design their own experiment. Since the implementation of the project-based format in the introductory course, we have noted a marked increase in the number of students interested in the upper-level Project Lab (Biol155a) offered to junior and senior life science majors. The enrollment has more than doubled in Biol155a in 2 yr from the institution of the HγD-Crys experiment and another project-based lab in the genetics semester of the introductory biology laboratory. To accommodate this level of interest, Project Lab is now offered in both the Fall and Spring semesters. We have also observed an increase in the number of undergraduate students interested in pursuing technician positions in research laboratories.

Student Connection of Concepts in Biology and Laboratory Techniques

The fundamental concept emphasized in the semester-long project-based lab was the connection between DNA and protein. The students were asked to design a mutation in a nucleic acid primer complementary to the crystallin gene that would ultimately be translated into a mutated amino acid in the HγD-Crys protein. When asked to explain the central dogma in an open-ended response question, we categorized student responses as "correct," "incorrect," or "unreadable." (For sample student responses see Table 3.) The student response was determined to be correct if it indicated that the student could demonstrate how the connection is made between these biological molecules. Of the readable responses,

Table 2. Summary of student responses to survey questions

Question asked	*n*	Percent of students responding for each value		
		Of little value (score 1–3)	Of moderate value (score 4)	Of high value (score 5–7)
1. How valuable was it to your learning to perform an experiment that had never been performed before?	133	12	13	75
2. To what extent did designing your own experiment affect your interest in the semester-long project?	128	13	19	68
3. How valuable was being able to troubleshoot real scientific experiments to your learning?	130	9	15	76
4. How useful were prelab questions in helping you understand the purpose of the lab?	133	11	12	77
5. How useful were postlab questions in helping you understand the purpose of the lab?	133	6	14	80
6. How useful were the lab reports in understanding the purpose of your experiment?	133	12	5	83
7. How useful were the rewrites in (better) understanding your experimental purpose?	132	16	12	72
8. How useful were postlab questions in helping you understand the data and concepts presented in lab?	132	5	7	88
9. To what extent did writing a Discussion section help you interpret and understand your data?	133	7	15	78

53% of our students understood the relationship between DNA and protein at the end of the course, while 47% of our students still had misconceptions about this idea even after completion of the semester-long project. We also noted that, of the students who answered correctly, 70% classified themselves as confident with their answer. Although their answers indicated that students could reiterate the connections between these three types of biomacromolecules, it was unclear whether the students actually understood these connections and in which class they gained this information. Future assessment strategies will focus on how this relates to initial knowledge of the concept of central dogma before entering this course, with an emphasis on separating learning gains from the concurrent lecture and laboratory.

Table 3. Sample student central dogma responses

Student response to the question: What is the central dogma in biology?	Scored as correct
DNA -> RNA -> Protein	Yes
Figuring out how organisms function	No
States that information is transfered to protein but cannot flow back to nucleic acid	Yes
DNA (replication) -> RNA (transcription) -> protein (translation)	Yes
The central dogma of biology is protein synthesis	Yes
The central dogma of biology is that all living organisms have genetic material (DNA and RNA) that produce proteins	Yes
Gene is transcribed to RNA (mRNA) and translated into protein	Yes
The central dogma of biology refers to the process of DNA replication, transcription from DNA to RNA, and the translation of RNA to protein	Yes
DNA translated to RNA, RNA transcribed to protein	No
The process of transcription and translation and shifting from DNA to RNA to protein	Yes

We also wished to address students' comfort with and understanding of standard laboratory protocols by presenting them with a question concerning serial dilutions. This is a technique that students needed to use in the laboratory and were tested on in multiple formats throughout the semester. Given a sample setup for calculations, 60% of students were able to determine the correct answer despite the 10-wk lapse between the course and completing the assessment. This indicated that the majority of our students understood the concept of serial dilution and retained it even after class was completed.

Student Perception of Value of Pre- and Postlab Questions

Because students were performing experiments that did not have set, expected results, they were required to think more about the science performed rather than whether the results were "right or wrong." Student understanding of the experimental purpose, design, and data interpretation were assessed by weekly pre- and postlab exercises preliminary to a comprehensive lab report.

Students found pre- and postlab questions to be useful in determining the purpose of each experiment, with 74% of students reporting a positive value for prelabs and 77% for postlabs (Table 2). When it came to writing the lab report, 80% of students reported a positive value in helping to understand the purpose and 36% ranked this with the highest value (Table 2). Seventy percent of students also reported that being able to rewrite their lab report helped them better understand their purpose (Table 2).

We also wanted to address the value of experiential learning in being able to connect students' experiments with their understanding of the concepts presented in the labs themselves. Of students participating in the survey, the vast majority (85%) reported that the postlab questions concerning the data and experiment they just performed helped to connect their data with the concepts. Students also felt that writing

lab reports was valuable to understanding their data, with 76% reporting a positive value for this exercise (Table 2).

Student Understanding of Conceptual Connection in the Project-Based Laboratory

Part of the prelab was a written purpose with strict criteria established during the semester. The students were asked to define the "who, what, how, and why" of the week's experiment in the context of the semester-long project, specifically avoiding "learning purposes." Our students were graded depending on their ability to connect individual labs and procedures assigned together each week in context with the overall semester-long experiment. In other words, they were evaluated with respect to their understanding of how each week's experiment was applicable to assess the stability of their new mutant crystallin protein. Two points were awarded for knowledge of the experiment at hand, two points were awarded for understanding of how it fit into the larger multiple-week experiment, and one point was given for scientific/grammatical correctness. For instance, for week 9, during which students performed column chromatography to purify their own protein, a purpose describing the use of Ni-NTA to purify mutant crystallin obtained during site-directed mutagenesis to be used in subsequent stability assessment studies would have been given a perfect score of 5. Individual interviews with our course TAs anecdotally revealed that their students' purposes improved drastically with respect to content and understanding throughout the course of the semester.

Surprisingly, in the postclass assessment, we found that only 54% of the students wrote a purpose demonstrating at least acceptable knowledge of the experiment, acceptable being a score of at least 2 on a scale of 5 based on the same criteria used by the course TAs during the semester (Table 4). Of those answering appropriately, 82% indicated confidence with their answer providing a score greater than 4 on a scale of 7 total points (data not shown). These results indicate that only a slight majority of our students understood the scientific concept behind the semester-long HγD-Crys project even after completion of the course. Future course improvements will seek to improve retention of concepts and the ability to formulate scientific purposes.

Table 4. Sample student purposes for the semester-long experiment

Student response to the prompt: Write a purpose for the 10 week project lab you performed last semester.	Score out of 5[a]
I will design a mutation that will affect the way Human γ-D crystallin functions, and then create and sequence DNA strands with the mutation	2
To see if our mutation caused a cataract	0
Project was performed to create an insoluble protein cataract and replicate it in bacteria	1
To see how incorporation of a mutation in CRYGD using SDM-PCR affects the stability of n HγD-Crys	4
We mutated an amino acid in n HγD-crys in order to create a cataract in a test tube	2
We will see how site directed mutation (V126E) in HγD-Crys affects the protein's structure and stability	2
Mutating the primary stucture of the Human γD crystallin protein and investigating the effect on tertiary structure, stanibility, and function	2
We attempted to mutate the structure of HγD crystallin in a way that would cause it to form a cataract	2
To find a new mutation in the HγD-crystalin protein	1
We observed the stability of the structure of HγD-Crys protein by creating a mutation in the CRYGD gene, amplifyling the mutation and inducing its expression in *E. coli* cells	4

[a]One point given each for the questions that were required: the who, the what, the why, and the how, as well as an additional point for completeness over the 10-wk experiment.

CLOSING THOUGHTS

We have developed a course model for a project-based laboratory in a large introductory biology class. Emphasizing a human health concern, this lab focuses primarily on protein structure–function relationships and the central dogma and teaches important techniques used in modern molecular biology. Our model involves a weekly lecture on fundamental concepts, a weekly professor-led concept review session, and a weekly laboratory experiment assigned over the course of 10 wk in a successive, semester-long inquiry-based research project with a unifying theme. We have found that our students seem to be engaged in the project and that more than two-thirds of them are interested in taking future courses in which they participate in the design of their own research question.

Teaching courses with concept-based project labs exposes students to troubleshooting their data, critiquing their own work, and learning the concepts through data analysis in addition to the classroom lectures. In the beginning of the semester students can be frustrated by not knowing whether their results are "right or wrong," but as the semester progresses students start to appreciate learning in this method and become more comfortable with the component of uncertainty in scientific learning.

The utilization of a highly stable, easily purified recombinant protein like human γD crystallin provides an inexpensive, resilient model protein implicated in human disease that tolerates some level of error on the part of beginner students and TAs. Invariably, protocol mistakes are made by introductory students in large classes due to class size and experience levels, but our model incorporates methodology that allows small lab groups of students to make the same mutation to provide "backups" for the other students in the section in the case that one team's experiment does not work. In addition, larger laboratory classes must have cost-effective protocols that can be scaled up depending on enrollment numbers each semester. Because our model involves collaboration and agreement between students in each section as to which mutation they will make, it limits the number of primers that must be ordered. In addition, our model involves growth of common strains of *Escherichia coli* that have short incubation times and need limited space for growth. The columns in our experiments are an expensive investment at first but may be recharged and reused from semester to semester. The startup costs of this lab only involve investment in apparatus common to typical molecular biology labs including thermocyclers, incubators, spectrometers, pipettemen, and centrifuges.

The introductory laboratories at Brandeis University are not as large as some other introductory courses at other institutions, especially states schools where enrollment numbers are significantly greater than our own. We propose a model for a project-based course that larger universities could adjust depending on the availability of funding and resources. Specifically, we feel simple native gel-based or solution turbidity assays could be used to assess protein aggregation and stability instead of the more cost-prohibitive fluorescence scans.

We have found that exposing students to real-life lab work forces the students to incorporate what is known in the field with their own ideas in order to understand their results. In an introductory course this allows us, as educators, to go more into depth on certain core concepts, like central dogma and protein structure–function relationships, instead of trying to cover every aspect of cell biology only superficially.

We believe that teaching a concept-based, semester-long project lab can be effective at the introductory level, and we hope that this method also strengthens students' interest in their learning as future scientists.

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