



Design of a Lyme Disease Vaccine as an Active Learning Approach in a Novel Interdisciplinary Graduate-Level Course[†]

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A biomedical sciences graduate program needed an introductory class that would develop skills for students interested in a wide variety of disciplines, such as microbiology or cancer biology, and a diverse array of biomedical careers. Faculty created a year-long student-centered course, Scientific Discovery, to serve this need. The course was divided into four modules with progressive skill outcomes. Each module had a focus related to each of the major research areas of the collective faculty: molecular biology, biochemistry, neuroscience, and infectious disease. First-year graduate students enter the program with relevant college-level biology and chemistry coursework but not in-depth content knowledge of any of the focus areas. Each module features a biomedical problem for the students to gain specific content knowledge while developing skills outcomes, such as the ability to conduct scholarly inquiry. In 2015, the theme of the infectious disease module was to create an effective human vaccine to prevent Lyme disease. The module required students to learn fundamental concepts of microbiology and immunology and then apply that knowledge to design their own Lyme disease vaccine. The class culminated with students communicating their creative designs in the form of a “white paper” and a pitch to “potential investors.” By the end of the module, students had developed fundamental knowledge, applied that knowledge with great creativity, and met the skills learning outcomes, as evidenced by their ability to conduct scholarly inquiry and apply knowledge gained during this module to a novel problem, as part of their final exam.

INTRODUCTION

Intended audience

Students accepted into the biomedical science program seek either a Master’s (MS) or Doctorate degree (PhD). The majority of these students have Bachelor’s degrees in science and varying levels of research experience. Once accepted, first-year graduate students take a year-long course, titled Scientific Discovery, that is divided into four eight-week modules. The Scientific Discovery course developed out of a recognition that students taking the previous lecture-based introductory course were not developing the skills

necessary for success in their graduate work and subsequent future careers. The previous lecture-based course was a traditional “professor at the podium” style class, with exams consisting of multiple choice and application-based essays. There was clearly a disconnect between assessments that required application and in-class lectures that did not allow the practice of that application. The emphasis on lecture also did not result in the desired skill outcomes: proficiency in scientific knowledge, ability to conduct scholarly inquiry, communication skills, educational experience, and professional and ethical training.

The new Scientific Discovery course aims to provide students with a basic introduction to biochemistry, molecular biology, neuroscience, and infectious disease through active learning approaches while developing competency in skills that students will need to succeed in scientific careers. These competencies include critical evaluation of scientific literature, development of hypotheses and experimental design, scientific writing, and presenting science to various stakeholders. Progressive competency development is encouraged from Module 1 through Module 4. Each module is focused on one of the major research areas of the collective faculty and further concentrated on a disease- or biomedical-related problem. Sequential modules include

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specific exercises designed to emphasize progressive skill sets. For example, one core competency is hypothesis testing and experimental design. In Module 1, students would explore common methodologies for biomedical laboratories. In Module 2, students might design protocols, including carefully controlled experiments and logical workflows for the biomedical research laboratory. By Module 4, students should be able to develop convincing experimental strategies for competitive research proposals.

Each year, the focused scientific research area remains the same for each module; however, the disease- or biomedical-related problem changes. Module 4 is intended to introduce basic concepts of infectious disease, microbiology, pathogenesis, and immunology to a diverse group of graduate students, some of whom have never taken a specific college-level microbiology or immunology course. The skills-based course competencies of the fourth module are scaled up to a level of mastery, in anticipation that after this module, students should have the skills needed to join a research laboratory in the department and begin taking content-specific courses, depending on their research emphasis.

Using current biomedical-related problems as the focus of the module creates a project-based environment, much like students will experience in their graduate careers as scientists. Narrowing the problem to a specific disease helps to focus student learning. During the first year of this course, the fourth module centered on the topic of arthritis, with the final project composed of a grant proposal, white paper, and pitch on a novel treatment for rheumatoid arthritis. The second year of the fourth module, and the focus of this paper, used Lyme disease as a model. The final project was for each student to develop a concept for a novel Lyme disease vaccine or treatment, write a white paper, and then pitch their white paper to a panel of potential pharmaceutical company investors.

The choice to utilize Lyme disease as the biomedical problem for Module 4 had multiple origins. First, one of the involved faculty members studies the cause of Lyme disease, *Borrelia burgdorferi*. Having an expert on the bacterium as a resource is valuable for the students as they develop their ideas, and the expert can push students' understanding to a deeper level by asking more difficult, nuanced questions. An added benefit for the expert faculty member is the students sometimes generate novel ideas that are worth pursuing in their own research.

Secondly, in the case of Module 4's general topic, students learn basic concepts of microbiology, pathogenesis, and immunology. In order for students to successfully design a vaccine, they would need to understand basic microbiology, pathogenesis, and immunology of the pathogen, *B. burgdorferi*; how this bacterium causes disease; the normal host immune response to the bacterium; and basic concepts of vaccine development. They would then have to integrate what they learned and apply knowledge to the problem at hand.

Thirdly, relevant problems that are novel, or that no one has yet solved, serve to challenge and intrigue the students. The answer to these biomedical problems cannot be found by simply searching the Internet. For graduate students, challenges can also be very interesting and offer a push to expand their creative thinking. Creativity is a skill that is needed in asking complex questions and solving complex problems that students will face in their research and careers. For example, with our chosen biomedical problem: Lyme disease is prevalent across the entire northern hemisphere, including Europe, Asia, and North America (1), with approximately 30,000 cases per year reported to the Centers for Disease Control and Prevention (CDC) in the United States (2). The incidence of Lyme disease continues to increase and is likely underreported (1, 3, 4). While it is readily treatable with antibiotics, serious complications including central nervous system involvement, severe arthritis, and inflammation of the heart can occur (5). Medical costs associated with Lyme disease and its sequelae have been estimated at over US\$700 million per year (6). A vaccine for Lyme disease is currently available for veterinary use; a human vaccine was pulled from the market in 2002 due to declining sales, spurred in part by fears of adverse vaccine events (7). Numerous researchers have developed potential new targets and strategies, including targeting the tick vector or the natural reservoir hosts such as small mammals (e.g., 8–10). Despite these exhaustive efforts, a human vaccine or alternative method for slowing or stopping the spread of Lyme disease remains elusive.

Prerequisite student knowledge

Ideally, students will have completed the following coursework:

1. General Biology with laboratory
2. General Chemistry with laboratory
3. Organic Chemistry with laboratory
4. Physics with laboratory
5. Biochemistry or equivalent
6. Calculus
7. Advanced undergraduate coursework in at least one of the following areas: molecular biology, cell/developmental biology, genetics, neuroscience, biochemistry, microbiology, immunology, anatomy, or physiology.

Learning time

The class met four times per week for eight weeks. These four weekly classes included three two-hour class sessions and a one-hour journal club. Students typically spent 10 to 12 hours outside of class in both group and individual work for the class. Instructor time (preparation and grading) was similar.

Learning objectives

We developed a set of specific objectives for Module 4 in order to measure student progress (Table 1).

PROCEDURE

Materials

See Appendices 1 to 4.

Student instructions

See Appendices 1 and 5 to 7.

Faculty instructions

See Appendices 1 and 5 to 7.

Suggestions for determining student learning

See Appendices 2 to 7.

Sample data

See Table 2.

Safety issues

There are no safety issues associated with this activity.

Overall class structure

Each week included a combination of mini-lectures, guest lectures from outside the department, peer teaching through graded “chalk talks,” and in-class quizzes or activities. “Chalk talks” entailed student groups peer teaching to the rest of

TABLE 1.
Module learning objectives and direct assessment methods.

Learning Objectives	Direct Assessment Methods
1. Compare and contrast the structural similarities and differences between eukaryotes and prokaryotes	Chalk Talks, In-Class Activities, Worksheets, Posttest
2. Outline the basic concepts of bacterial structure and classification	Chalk Talks, In-Class Activities, Worksheets, Posttest
3. Illustrate the general mechanisms microbes use to cause disease	Chalk Talks, In-Class Activities, Worksheets, Posttest
4. Evaluate how specific virulence factors (toxins, effectors) contribute to the disease process	Chalk Talks, In-Class Activities, Worksheets, Posttest
5. Employ information about <i>Borrelia burgdorferi</i> and Lyme disease to thoroughly describe the pathogenic process of one bacterial disease	Chalk Talks, In-Class Activities, Worksheets, Posttest, Vaccine Development
6. Discriminate the different aspects of the innate immune response as it relates to both function and structure	Chalk Talks, In-Class Activities, Worksheets, Posttest
7. Describe the function and structure of the adaptive immune response, with an emphasis on antigen presentation and immunoglobulin production	Chalk Talks, In-Class Activities, Worksheets, Posttest, Vaccine Development
8. Evaluate the interaction of innate and adaptive immune responses	Chalk Talks, In-Class Activities, Worksheets, Posttest, Vaccine Development
9. Assemble a normal host immune response to bacteria, as determined by the bacteria’s residence (intra vs. extracellular)	Chalk Talks, In-Class Activities, Worksheets, Posttest, Vaccine Development
10. Employ advanced peer teaching techniques to further group understanding of biomedical science concepts	Chalk Talks
11. Interpret and evaluate information acquired from actual data generated in the laboratory	In-Class Activities, Worksheets, Posttest
12. Evaluate and review scientific manuscripts	In-Class Discussions, Posttest, Vaccine Development
13. Effectively communicate scientific information through informal “chalk talks”	Chalk Talks
14. Effectively communicate scientific ideas and proposals to stakeholders	In-Class Informal Presentations, End-of-Class Pitch, White Paper Proposal
15. Provide accurate and relevant scientific information to the lay public	End-of-Class Pitch, White Paper Proposal, “What’s Hot” Paper

the class, utilizing only a white board. Students were assigned chalk talk topics two days before class. Faculty members in attendance were from a diverse set of backgrounds to enhance and give depth to the discussions and activities. There were three major writing assignments: a paper targeted to a lay audience, a “What’s hot” journal club paper, and the final white paper. Students were given one week to complete each major writing assignment. A final take-home exam, due within one week, entailed applying knowledge gained in the module to a novel problem: the emergence of Zika virus, and the design of an effective vaccine. The final day of class had the students pitching their vaccine or therapeutic ideas.

Please see supplemental materials for the following: syllabus, which includes daily topics and activity descriptions (Appendix 1), listing of primary literature readings (Appendix 2), homework (Appendix 3), sample in-class worksheets (Appendix 4), chalk talk student information and grading rubric (Appendix 5), white paper project guidelines for students (Appendix 6), oral presentation guidelines for students and grading scheme (Appendix 7). The grading rubric for the white paper was obtained from the University of Delaware: www1.udel.edu/ghw/genre2/rubric-white-paper.pdf. This rubric assesses audience, purpose, organization of writing, reasons for problem/solutions, use of sources, conclusions, unity and coherence, and grammar. *More specifics on daily activities or homework sets may be obtained directly from the corresponding author.*

General timeline

- Week 1: Basic Bacteriology
- Week 2: Innate Immunity and Cells
- Week 3: Adaptive Immune Response
- Week 4: Bacterial Pathogenesis
- Week 5: Lyme Disease and *B. burgdorferi*
- Week 6: Host-Pathogen Interactions/
Vaccine Development
- Week 7: Intellectual Property and Biotechnology
- Week 8: “The Pitch”

Please note that students in each semester of their first year take Scientific Discovery, a six-credit course, Ethics (fall) or Statistics (spring), which are both two-credit courses, and rotate through research laboratories (~20 hrs/per week).

Content background and vaccine or therapeutic development project details (direct assessment measures)

Extensive background information on host-pathogen interactions, Lyme disease and *B. burgdorferi*, and vaccine development was explored via chalk talks, mini-lectures, and various group activities and discussions (weeks 1 to 5). During week 6, each student created a one- to two-page outline of their vaccine or therapeutic strategy and gave a chalk talk to their instructors and classmates to get

feedback. Also during week 6, a discussion was held on the difference between a white paper and grant proposal to set the students up to begin work on their final paper.

During week 7, guest lecturers came to class to discuss intellectual property from a legal and commercial perspective, as well as vaccine development in the biotech industry. The goal of providing this information from the guest lecturers was to help the students craft their pitches and to introduce them to areas of employment outside of academia. The students received their final take-home exam (on the emergence of Zika virus and the design of an effective vaccine) Friday of week 7, with the exam due one week later.

The final week of class consisted of the students’ oral pitches. Students gave their official presentation (20-minute maximum, including time for questions). The audience for the pitches included their classmates, instructors, guest lecturers, and representatives from the University of North Dakota Center for Innovation. Each panel participant completed an assessment form of the individual students, indicating whether the investor thought the project deserved full support, partial support, support with reservations, or no support. This audience was carefully crafted to create an authentic but supportive experience for the students. White papers were due at the end of week 8, after the oral pitches had concluded, to allow students time to make adjustments based on feedback during their pitch.

Student module evaluations (indirect assessment measures)

At the close of each module, an evaluation is sent out to students via an online survey (Qualtrics, Provo, UT). Students respond anonymously to questions relating to the overall competencies applied to the entire year of classes and general questions on the structure, organization, and implementation of the module (Appendix 8).

Sample data

Vaccine proposals (direct assessments). Despite limited exposure to microbiology, immunology, and the intricacies of vaccine design, student proposals were generally well researched and creative. For example, OspA and OspC proteins have been utilized as Lyme vaccine targets, but the students combined them in novel ways with vaccine targets from tick saliva (e.g., Student 5, Table 2). Although many of the same targets were suggested, each student’s vaccine was unique in its choice of delivery, adjuvant, or construction (e.g., chimeric proteins vs. linear peptides) (Table 2).

DISCUSSION

Evidence of student learning

Direct assessments. Student performance on the final white paper was very strong, with scores ranging from 42/50

TABLE 2.
Student white paper topic ideas.

	Idea	Antigens/Targets	Novelty ^a
Student 1	Therapeutic monoclonal IgY (11)	OspA, BBK32 (12, 13)	IgY has not been employed as a therapeutic for Lyme
Student 2	ΦBB-1 bacteriophage (14)		Phage therapy has not been attempted for Lyme disease
Student 3	Multivalent anti- <i>Borrelia</i> vaccine	CheA1, CheA2, OspA (13, 15)	CheA proteins have not been utilized as vaccine targets
Student 4	Multivalent anti- <i>Borrelia</i> and anti-tick vaccine	Chimera of OspA-OspC plus Salp15 (13, 16, 17)	Chimeric proteins have not been utilized as vaccine targets
Student 5	Multivalent anti-tick vaccine	TIX-5, Sialostatin L2, Subolesin (18–20)	TIX-5 proteins have not been utilized as vaccine targets
Student 6	Multivalent anti-tick vaccine	TROSPA, Subolesin, Salp15, 64TRP (17, 20–22)	TROSPA proteins have not been utilized as vaccine targets
Student 7	Multivalent anti- <i>Borrelia</i> and anti-tick vaccine	Salp14, OspA, Salp15 (13, 17, 23)	Combination of antigens is unique
Student 8	Multivalent anti- <i>Borrelia</i> and anti-tick vaccine	OspA, OspC, TROSPA (13, 16, 21)	Combination of antigens is unique

^a PubMed search (1/12/17) with keywords Lyme, IgY; Lyme, bacteriophage; Lyme vaccine, Che; Lyme vaccine, Salp; Lyme vaccine, sialostatin; Lyme vaccine, subolesin; Lyme vaccine, TROSPA.

(1 student) to 50/50 (5 students) and a mean of 48.75 ± 2.765 . In general, students scored slightly higher on the white paper than on the oral pitch; scores on the oral pitch ranged from 43/50 (2 students) to 49/50 (1 student), with a median of 46/50 and a mean of 45.88 ± 2.167 . Student performance in the module overall was also strong, with a minimum percentage score of 87, a median of 93, and a mean of 92.38 ± 2.722 .

Average student performance on homework assignments was over 99% (± 0.625). Student performance on weekly chalk talks (assessed via a standardized rubric, Appendix 5) averaged 94% (± 5.8). Student performance on all other written assignments (including a paper aimed at a lay audience and a newspaper-style article) was 92% (± 5.5).

The students had a final exam in which they had to design a vaccine for Zika virus, a completely unrelated pathogen. The students had to integrate lower-order cognitive skills-based information on host-pathogen interactions and immune responses, and the higher-order cognitive skills they acquired in designing a Lyme vaccine, and apply those successfully to the development of a Zika vaccine. Scores ranged from a low of 27/50 to 48/50, with a mean score of 41/50 (82%).

Student evaluations of module (indirect assessment). Students agreed that they acquired new knowledge, applied that information, and communicated it effectively to multiple audiences (7/8 students agree or strongly agree). The structure of how they acquired the knowledge and application was considered effective (6/8 students agree or strongly agree). Competencies related to scientific

literature trended more toward neutral (4 students agree/strongly agree/4 students neither agree or disagree). As to the structure, organization, and implementation of the module, means ranged above 4 (agree) on all areas assessed, except a slight dip in “communication of module expectations,” with a mean of 3.75.

Students noted components that promoted their learning during the module as “unique writing assignments,” chalk talks, mini-lectures, guest lectures, and an “in-depth background early in the module.” Components that inhibited their learning as noted from the survey included “too many chalk talks,” “not enough time between chalk talks to prepare and improve on chalk talk abilities,” and “lack of feedback on the white paper before presentation.”

Additional student comments indicated a misalignment between the syllabus/schedule and actual class time. Some content was switched from an in-class activity to chalk talks, which increased the burden of chalk talks to the students. In-class activities and homework did not seem appropriate for a graduate level at times, and students indicated they would like more depth and complexity to their assignments. Requests for more feedback and time to polish the white paper project before presenting to outside guests were expressed. There was also a desire to increase the diversity in the topic for the white papers.

Did students achieve module objectives?

Early module objectives consisted of lower-order Bloom’s taxonomy items relating to basic knowledge and

understanding of bacteria and host-pathogen relationships. These objectives then supported the higher-order objectives involved in creating a vaccine or treatment, communicating that idea to various stakeholders, and evaluating peers' projects. Successful completion (greater than 80% grade) of these higher-order objectives indicate the lower-order objectives were achieved. Success was achieved for all students in the class. The module was successful in objectives related to multiple competencies needed for scientific careers based on the success of major end assignments: researching and critically evaluating scientific literature, evaluating potential pitfalls and alternative methods, and communicating effectively through written and oral mediums. We note that repeated chalk talks did not result in an improvement over time, as average scores remained high across the module (8.7/10 to 10/10). Students had opportunities in the previous three eight-week modules to practice this skill and achieve mastery.

Module assessment

Overall, the feedback from students during this second attempt at this class format was an improvement over the previous year. The organization and structure of the class were evaluated more positively. This is likely due to a decrease in the total number of faculty involved in the module and a decrease in the number of large assignments. The previous year had the students writing a white paper and a short grant proposal, with considerable negative feedback on the amount of time required and a decrease in quality of work due to lack of time. The adjustment to having a white paper and no grant proposal, in combination with smaller writing assignments, vastly improved the evaluation of the module as a whole. Students in both years appreciated the unique aspect of writing a white paper and pitching their ideas in a manner that is outside of normal academic communication.

Did students enjoy the module?

In the end, the students did express positive outcomes from the module. The variety of biomedical science disciplines these students are entering (from neuroscience to infectious disease) makes student interest challenging. In addition, students occasionally have a "burnout" attitude by the time they encounter the final module in the class, as evidenced by decreasing enthusiasm for consecutive modules. All things considered, positive comments outweighed negative comments or concerns, and both instructor and overall module evaluations were improved from the previous year. As instructors, we were struck by the students' in-class enthusiasm and creativity and feel that our problem-centered, active learning approach in using a design-a-vaccine activity was both enjoyable and constructive in teaching basic concepts in microbiology and immunology to first-year graduate students.

Possible modifications

Recommendations for future teaching of this module.

Before the next round of Module 4 takes place, concerns to be addressed include: balancing the chalk talks to allow the students adequate time to prepare, increased depth of the learning moments, and requiring faculty to offer more feedback in-between chalk talks in order to help students improve their communication skills. We are also considering expanding the length of time provided for preparation of the white paper and adding more formative evaluation of the white paper and oral presentations to increase the quality of the communication experiences. It is important to note, however, that students were provided summative feedback on their oral pitches within 24 hours, providing them an opportunity (2 to 3 days) to improve their final white paper. The students expressed an interest in having more freedom in the choice of topics for their white paper. This freedom has the potential to be problematic for several reasons: class time is constrained currently for adequate background preparation, and the time needed to properly evaluate and grade their projects would increase due to the grading faculty member's need to acquire background knowledge for each topic. For these reasons, the focus of the module will likely remain on one disease. Lastly, we will also look at creating a more specific end-of-module survey to get better feedback from the students.

Applications for other disciplines and undergraduate teaching.

Although the content stated here about our module is related to the discipline of microbiology and immunology, specifically Lyme disease, core skill competencies can be applied to other disciplines or discipline-specific problems. Indeed, in the two years this module was taught, the competencies remained the same, but each module's focus has changed. Module 4 alone changed from development of new treatments for rheumatoid arthritis to Lyme disease. Assessments are also applicable for other disciplines. For instance, white papers or short project/idea papers are becoming much more commonplace and are therefore authentic written communication assessments. Our course model may also be applicable for upper-level undergraduate courses, with a modification of the level of competency to perhaps a proficiency level. Indeed, one of us (Dr. Condry) has utilized many of the concepts in upper-level microbiology and immunology undergraduate courses; for example, the use of chalk talks as oral presentations in large microbiology classes. To accommodate the large class size, the assignment was moved to a recorded chalk talk with online submission, expectations of content were decreased, and duration of the talk was shortened.

Overall, we feel that students' performance in this module exceeded our expectations and demonstrated the power of active learning strategies. Designing a course around any problem or question in microbiology and utilizing some of the strategies we employed could be adapted to other graduate courses, medical education, as well as undergraduate microbiology.

SUPPLEMENTAL MATERIALS

- Appendix 1: Syllabus
- Appendix 2: Sample primary and review literature
- Appendix 3: Sample homework assignment
- Appendix 4: Sample in-class worksheet
- Appendix 5: Chalk talk grading rubric
- Appendix 6: White paper guidelines
- Appendix 7: Oral presentation guidelines, feedback and grading scheme
- Appendix 8: Module evaluations

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