Creative Teaching Award
Application Cover Sheet 2017-18
Center for Teaching Excellence, Duquesne University

Please type this information, except for signatures.
Turn in <u>one</u> original signed copy. Also, submit it electronically as page one of your dossier.

Name(s) of Applicant(s): Wilson Meng, PhD., and Lauren O'Donnell, Ph.D.

School/Department**:** School of Pharmacy

__X_ By checking here, you affirm that faculty applicants have taught at Duquesne one year or more

List the courses or learning initiatives where the innovation occurred

Course Number & Title (or name of initiative if not a course)	**# of Students**	**Semester/Year**	**Instructor/Facilitator**
PHIN 424: Ability-Based Lab Experience (ABLE) IV	149	Spring 2015	Meng and O'Donnell
PHIN 424: Ability-Based Lab Experience (ABLE) IV	164	Spring 2016	Meng and O'Donnell
PHIN 424: Ability-Based Lab Experience (ABLE) IV	122	Spring 2017	Meng and O'Donnell

Title of Project:
A data-mining practicum for enhancing pharmacy students' understanding of the impacts of genes on medications

Abstract (150 words)
The rapidly expanding knowledge of human genetics makes the practice of medicine more complex than ever. Pharmacists play increasing important roles in deciphering genetic and pharmacological complexities in delivering quality health care. To meet the challenges that our graduates will face in the workplace, a bioinformatics practicum was developed and implemented in the second year of the professional pharmacy curriculum. The exercise was designed to enable the students to apply basic immunological principles to delineate interactions between genes and drugs. Specifically, students were tasked with analyzing patients' reactions to protein-based drugs in relation to major histocompatibility complex (MHC), a family of genes of which thousands of variants have been discovered. The learning goals encompassed activities that allow students to evaluate diverse data sets generated from the Immune Epitope Database. The innovation contributed to student learning by adding to their skills repertoire an aspect of personalized medicine, evidenced by their ability to hypothesize theories to explain original findings.

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Applicant Signature Wilson Meng, Ph.D. Date: 1/12/2018

Applicant Signature L. O'Donnell Lauren O'Donnell, Ph.D. Date: 1/12/2018

Department Chair's Name: David A. Johnson, Ph.D.

Department Chair's Signature Date: 1/10/2018

Dean's Name: J. Douglas Bricker, Ph.D.

Dean's Signature: J. Douglas Bricker Date: 10 Jan 2018

THE INNOVATION

The Epitope Search Practicum is a series of bioinformatics exercises that were designed to address a critical gap in the Pharmacy curriculum: the immunological basis of personalized or "precision" medicine. The Practicum has been offered in three different iterations (Spring 2014, Spring 2015 and 2016, and Spring 2017), with each iteration building upon our observations and reflections in the prior courses (Appendix D1). We took advantage of a freely-available, online bioinformatics tool (The Immune Epitope Database; IEDB.org), which is maintained by the National Institutes of Health and can be utilized by anyone with an internet connection. Although IEDB is typically used for research purposes, we adopted tools from the website in order to design an experiment in which students considered patient outcomes for treatment with biologics, an important and growing class of protein drugs. The key clinical problem is that some patients will develop an immune response against the biologic, thereby interfering with the function of the drug and potentially eliminating it from the body. Currently, there are no tests available to screen for whether patients would be likely to develop an immune response against a biologic drug. In this exercise, students used a patient's genetic make-up (MHC, or major histocompatibility complex, genes) to predict whether the patient's immune system would recognize, and potentially destroy, a biologic drug. Using search algorithms in IEDB, students screened a biologic drug for epitopes, or fragments of the drug that could induce an immune response, in the context of unique MHC genes. In doing so, we have created a novel exercise that reinforces the genetic basis behind the immunological variables in precision medicine.

PURPOSE AND INNOVATIVENESS

The purpose of the practicum is to equip pharmacy students with the skills to analyze the genetic basis of how the human body interacts with biologic drugs, a relatively new but important class of medications. Specifically, the students were asked to evaluate the risk of having an individual's immune cells reacting with a given biologic drug in a way that is unexpected. The practicum falls within the field of pharmacogenomics, which has impacted the way in which cancer and other diseases are treated. Pharmacogenomics uses an understanding of a patient's genetic make-up to tailor therapy to the patient's unique needs. However, few pharmacy schools have incorporated formal settings in which pharmacogenomics competencies can be fulfilled by hands-on experiences. There is an increasing need for pharmacists to actively engage in inter-professional consultations, with nurses, physicians, physical therapists, and other health care workers. Often the first stop for health advice in the community, pharmacists must also provide

accurate and measured information to the public. This aspect of the job is becoming more challenging, as medical and genetic information are readily accessible by the public, via informational portals (e.g. WebMD), or through mail-ordered genotyping (e.g. 23andMe). Thus, we designed this project to offer a mechanism for students to explore the relationship between patient genotypes and therapeutic outcomes.

The innovation centers on that the students were tasked to investigate unknowns in identifying potential gene-drug interactions that were not identified prior to the practicum. This is because the database, IEDB, is constantly being updated by the National Institutes of Health with new verified data. The instructors intentionally refrained from obtaining "answers" in advance, so that the experiments could be performed with the students in "real time". In this way, the students were given ownership of the investigation, insofar new data relevant to the biologic drug might be discovered. While the module does not directly tie in with specific lectures, it serves as a forum for students to consolidate information learned in required courses in the first and second professional years (Appendix D2, Figure 1). The goal is to encourage students to carry forward key concepts to upper level courses and advanced clinical rotations.

With the number of pharmacy programs almost doubled since 2007, the instructors believe that this unique element adds to the competitiveness of the School's pharmacy program among our regional peers. Of the articles that cite IEDB as a resource[1,2], we did not find any papers that utilized IEDB in an educational setting. A recent conference presentation used IEDB in an undergraduate microbiology course, with reported improvement in learning outcomes, but no publications were found for pharmacy schools or other programs[3]. Despite the limited examples of IEDB as an educational tool, we present findings that IEDB can be readily integrated into a classroom or laboratory setting. Equally important is that the experience provides a launching point for pharmacy students to pursue research projects that can lead to a B.S. degree in Pharmaceutical Sciences. It is envisioned that the practicum will serve as the centerpiece of an NIH-funded Research and Education Program (R25) proposal designed for enhancing the professional advancement of our students majoring in pharmacy, nursing, the health sciences, and biomedical engineering. We envision an opportunity to expand the scope of the practicum through interprofessional education (IPE), an emphasis in the University's strategic plan imperative "Transcending Traditional Academic Boundaries" in creating an innovative center in health-related fields.

CONTEXT AND SCOPE

The context of the experience is Precision Medicine, a major conceptual emphasis of the United States health

care enterprise, with initiatives devised and implemented by the Food and Drug Administration and the National Institutes of Health; the concept is endorsed by the American Medical Association (AMA) and the American Pharmacists Association (APhA). The topic is emphasized in the curriculum guide published by the Accreditation Council for Pharmacy Education (ACPE), which sets the accreditation standards for pharmacy education[4]. The gain in genetic information since 2010 has far outpaced revisions of standard textbooks used in pharmacy curricular. Many have perceived an unmet need for pharmacogenomics in the basic science sequence in our curriculum. In this context, we wanted to inculcate in our students the need to embrace complexity, insofar as grasping the underpinnings of individuals responding to a given drug in many different ways. The scope encompassed understanding the interplay among genes, biologic drugs, and infectious diseases.

The practicum serves to connect, or "push-pull", key concepts taught in courses alongside with experientials throughout the curriculum (Appendix D2). We envision that future curricular will be populated with multiple practical modules similar to the one we have developed. The outcomes of more than 400 pharmacy students were assessed in 2015, 2016, and 2017. Over a two-week period, students interrogated whether a biologic drug sequence would be predicted to induce an immune response based upon patient genotype. Results were presented and discussed at the conclusion of the exercise. The assessment included pre-lab quizzes and a final laboratory report. To determine the impact on student understanding of the immunogenicity of biologic drugs, the quality of student data analysis and interpretations were graded. Students answered questionnaires assessing perceived learning gains. The outcomes indicate that clinical immunological questions can be posed in a bioinformatics format.

LEARNING OBJECTIVES

The overall goals of the Epitope Search Practicum are to equip pharmacy students with the skills to perform basic bioinformatics analysis and to develop student understanding of how patient genotype leads to treatment failure with biologic drugs. Students used a hypothetical patient's "major histocompatibility complex" (MHC) genes, which are key to whether the immune system will attack a protein, to predict whether a specific biologic drug would be recognized and potentially eliminated by a patient's immune system. The MHC molecules initiate an immune process that leads to the formation of "anti-drug antibodies" (ADAs), which are the immune component that interferes with the biologic drug. To this end, five learning objectives were defined as **(I)** Explain the how the immune system generates antibodies against foreign proteins, including biologics; **(II)** Describe the role of MHC proteins in antibody

development; **(III)** Explain how anti-drug antibodies could affect clearance of biologics; **(IV)** Hypothesize how anti-drug antibodies could influence treatment failures on biologics; and **(V)** Conjecture how a patient's MHC genotype could predict whether they would develop anti-drug antibodies against biologic drugs.

TEACHING AND LEARNING METHODS

The bioinformatics practicum took place within the "Abilities-Based Laboratory Exercises" (ABLE) course for second-year Doctor of Pharmacy (PharmD) students. The ABLE is a mandatory laboratory series that incorporates clinical and applied subjects from current course work (please see Appendix B for an abbreviated syllabus). PharmD students are enrolled in the ABLE series throughout the 1st-3rd professional years in the program. The bioinformatics practicum was placed within the spring semester of the 2nd professional year in order to coincide with the infectious disease course, where immunity is frequently discussed, and with the rheumatology course, where many of the biologic drugs are introduced. Basic immunology is taught within the "Human Physiology and Pathology" course in the first professional year, so the practicum occurred roughly one year after the concept of MHC molecules and antibody production had been taught in a didactic format.

Students were assigned a pre-lab video that reviewed the basics of MHC function, including a comparison of MHC-I and MHC-II (Video 1), and described the overall clinical issue of anti-drug antibodies (ADAs) in biologic drug therapy (Video 2). Within the videos, an outline was presented to introduce the tasks the students would perform. The practicum was comprised of two sections: 1) an analysis of interactions between a biologic drug and a specific MHC molecule, and 2) a comparison of the biologic drug to similar proteins known to induce an antibody response (Appendix E, Figure 2). By comparing a protein sequence of interest to known proteins within the database, the IEDB analysis provides an initial step toward predicting whether the biologic drug has the potential to be recognized by an MHC molecule and induce an immune response.

At the start of the lab session, a short quiz was administered to test student understanding of the pre-lab videos. The instructors then explained the learning objectives of the lab session and presented a short tutorial (roughly 10 minutes) to explain the IEDB interface, the data output that would be generated from the analyses of the database search, and a worksheet that would be used to record and annotate the datasets. Each lab section was assigned a MHC allele, or gene, to analyze in the lab. MHC alleles were selected by the instructors to include alleles associated with the development of autoimmune disorders, such as rheumatoid arthritis, or alleles without an association with autoimmune

disorders. These MHC alleles were selected in order to include patient populations that would be likely to receive biologic drugs, such as the tumor necrosis factor (TNF) inhibitors, in the class dataset. Within each lab section, students paired off independently for the exercise. Each pair of students picked a biologic drug of their choice from a list provided by the instructors. The students' first task was to examine the protein sequence of the biologic drug for interactions with the assigned MHC molecule. Specifics of the IEDB search parameters and the subsequent data mining are explained in detail in our publication in the *American Journal of Pharmaceutical Education*[5]. Briefly, students were instructed to copy the protein sequence of their chosen biologic drug into the "MHC-II Binding Predictions" tool on IEDB (http://tools.iedb.org/mhcii/.) To limit the parameters of the search to the MHC allele assigned to their lab section, students selected the appropriate allele from the "Select MHC allele" dropdown menu. The instructors informed the students to leave the other search parameters (*e.g.* output of rankings) at the default settings to ensure that the group was viewing uniform datasets. Upon submitting the drug sequence into the search engine, IEDB generates a list of fragments, or epitopes, from the biologic drug that could be recognized by the assigned MHC allele. The predicted epitopes are ranked by a percentile score where lower percentiles equate to good binders to the MHC molecule. The score of a given epitope is generated from averaging of the rankings from several prediction algorithms within IEDB. A percentile cutoff of 10% or lower was used in order to focus student analysis on the epitopes with a greatest likelihood of binding to the MHC molecule. At the conclusion of Part 1, students recorded the number of predicted epitopes that were found from their search into the lab section's Excel sheet in class. The excel sheet was saved by the instructors and used as the starting point for data collation in the next segment.

In the second part of the lab, students compared the predicted epitopes identified from their biologic drug in Part 1 with experimentally validated epitopes in the IEDB database. The goal of this exercise was to identify potential cross-reactive epitopes in the biologic drugs that could be found in environmental stimuli or infectious agents. Despite the specificity of the immune response, cross-reactivity between different proteins is a common occurrence, where the immune response targets two proteins that share structural similarities. Using the predicted epitopes recorded during Part 1, students entered each unique fragment into the "Linear Epitope" search on the IEDB home page. For each match to the queried drug fragment, IEDB returns the protein sequence of the matching fragment, the protein from which the match is derived, the species of origin of the match (*e.g.* human, mouse, pathogen), and the references for the experimental binding data. Students recorded the data from each matching fragment, followed by grouping matches by origin of the protein, and repeating the search with any remaining predicted epitopes from their biologic

drug (please see Appendix E3 for data collection worksheet). If no matches were found in the database, students recorded that there were no matches discovered in a separate chart. Once each pair of students had analyzed their data, they recorded any matching epitopes in a master excel sheet that was projected in the classroom. Thus, each class produced a list of potential cross-reactive epitopes for a given MHC allele from a variety of biologic drugs. The instructors then led a discussion with the class to examine the types of proteins that were identified as potential sources of cross-reactivity, and how prior or coincident exposure to cross-reactive proteins could influence therapeutic outcomes with a given drug. With the exception of the first lab section, subsequent lab sections were also shown the data from prior lab groups as a point of comparison, as each lab section analyzed the same list of drugs within the context of presentation by a different MHC molecule.

After the data collation and group discussion in Part 2, students completed a report based on their findings. The laboratory report included a series of questions that asked the students to apply their findings to a patient case involving treatment with the drug they had analyzed in lab, and to discuss the potential role of the immune response and anti-drug antibodies in treatment failure. The students had one week to complete the report, which was graded by the instructors. The practicum was deemed to be exempt by the University's Institutional Review Board.

INNOVATION'S CONTRIBUTION TO STUDENT LEARNING

Direct evidence of student learning: A pre-laboratory quiz, completion of the practicum exercises, and final laboratory report were graded for all students in the practicum. The quiz was designed to assess whether the students had engaged with the pre-lab video tutorial. It was comprised of brief short answer questions that assessed student understanding of MHC function and cross-reactivity, which is an immune phenomenon where antibodies detect multiple, unrelated proteins. Each lab group was given a different quiz to protect the integrity of assessment, and there were no significant differences between the lab sections ($p>0.05$ by one-way ANOVA). Regardless of the lab section, student performance on the pre-lab quiz was variable (Average = 77.7%; Std. Dev. ±24%). We speculate that the uneven performance on the pre-lab quiz may have been because it was a relatively low stakes assessment in the context of the overall ABLE course (worth only 0.006% of the final grade in the spring ABLE sequence). Another possibility is that the immunological processes described, and the application to antibody development against biologic drugs, may have been difficult to absorb from a short video. Despite the reasons for the wide range of scores on the pre-lab quiz, ~42% of students received >90% on the quiz, suggesting that many of the students grasped the underlying

immunological concepts before entering the lab.

For the final project, we present our data from the 2017 iteration of the exercise, in which we increased our emphasis on predicting therapeutic outcomes for a unique patient. Results from previous years are available in Appendix C (2014-2017) and a time line of changes made to the practicum can be found in Appendix D1. The mean grade on the final laboratory project was an 84.5% (Std. Dev. ±15.0%, n=126). Students completed the data acquisition and analysis from IEDB with relative ease (Average = 92.6%; Table 1), and were able to address corresponding questions about the protein structure (*e.g.* humanized monoclonal antibody, chimeric proteins) and the mechanism of action of their biologic drug of choice. Students performed strongly on sections of the project that required explanations of immunological processes, such as the role of specific immune cells in recognizing foreign proteins (85.1%) and how proteins with regions of sequence similarity could lead to the production of cross-reactive antibodies (89.5%; related to Learning Objectives I and II, Table 2). This suggests that many of the students improved their understanding of these topics in comparison to the pre-lab quiz. In comparison to prior years, students performed better on questions related to hypothetical patient cases, where students were asked to consider how a patient's genotype could affect biologic drug efficacy and stability (Learning Objectives III and IV). We speculate that student performance improved in these sections because the relationship between immune recognition and therapeutic outcomes was broached with the students during an introductory lecture to the lab, thus encouraging the students to link the subjects throughout the exercise. Students struggled most with describing how patient genotype would affect the production of anti-drug antibodies (79.7%; Learning Objectives III and V). This result was surprising in that the students performed well on questions regarding generic antibody production, but we suspect that this section was more challenging for the students as it required a molecular explanation of the role of MHC and its genetic variability as it applied to interactions with biologic drugs. In other words, students were required to bridge the genetic make-up and therapeutic outcome for a patient using molecular processes. Regardless, most students (92.7%) received some partial credit on this section, suggesting that they were able to begin reasoning through some of the steps that can contribute to lack of efficacy with biologic drugs. As instructors, we are continuing to work toward striking a balance between developing the student's understanding of the details of the immunological processes and the "bigger picture" of how patient MHC genotype can be used to predict patient outcomes.

As further evidence of student learning, multiple publications and poster presentations have been made by undergraduate students resulting from the initial laboratory exercise (please see Appendix E for a complete list).

Students further analyzed the initial findings that were collected in the laboratory exercise using other tools in IEDB.org and through a unique search algorithm created in MATLAB[6]. Students also contributed to educational research on the design and analysis of the practicum itself[5]. Furthermore, the practicum is used as training tool for graduate teaching assistants in the School of Pharmacy, who have limited exposure to immunology in their coursework. In training graduate students to assist with the lab, they become proficient in datamining in IEDB.org as well as in teaching the basic immunological principles behind the exercise.

Indirect evidence of student learning: In addition to direct measures of student learning, we also measured perceived learning gains as reported by the students. Pre- and post-lab surveys were provided to the students one week prior to the first lab meeting and one week after the final project was submitted. The surveys were voluntary and anonymous. The response rate was 87% for the pre-lab survey and 92% for the post-lab survey for the 2017 class (Table 2, Appendix C). Additionally, Tables 5 and 6 show survey data for 2015/2016 and 2014, respectively (Appendix C). Nine statements regarding the student's perception of their understanding of different topics raised in the practicum were assessed using a 5-point Likert scale (1=Strongly disagree with the statement; 5=strongly agree with the statement.) The greatest perceived learning gains were reported in understanding how anti-drug antibodies may affect the efficacy of a biologic drug (+1.8) and how anti-drug antibodies may contribute to treatment failures (+1.7; $p<0.001$ by Wilcoxon-Rank test). To our surprise, the highest score in the pre-lab surveys was in regard to the students' understanding of how pharmacogenomics tools could be applied to predict immune response in different patients. Given the relative paucity of pharmacogenomics content in our current curriculum, we did not expect students to express comfort with the subject. However, pharmacogenomics in relation to MHC molecules is briefly discussed in the Infectious Disease course in the context of HIV therapies, which also takes place in the spring of the 2nd professional year. Thus, students would have had multiple exposures to the topic in the same semester, which may explain their initial comfort with the topic and the low perceived improvement (+1.0) for that statement. In essence, students did not express as much of a change in this subject as their comfort level was relatively high before the lab. Nevertheless, students reported a positive trend in their understanding of the subjects presented in the survey.

In conclusion, as science curriculum standards move toward problem-based and inquiry-based laboratory design, this exercise provides an opportunity to ask questions about the interactions of an important class of drugs with the immune system, while improving understanding of how complex immunological processes lead to unique therapeutic responses in patients.