THE PRESENT AND FUTURE OF IMMUNOLOGY EDUCATION

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THE PRESENT AND FUTURE OF IMMUNOLOGY EDUCATION

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The explosion of basic and applied immunology in the first decades of the 21st century has brought forth new opportunities and challenges for immunology education at all academic levels, from professional to undergraduate, medical, graduate and post-graduate instruction. Moreover, developing methods and techniques for educating general audiences on the importance and benefits of immunology will be critical for increasing public awareness and support.

One major immediate challenge consists in accommodating, within the confines of traditional immunology curricula, a body of knowledge that continues to grow exponentially in both size and complexity. Furthermore, the practical toolbox of immunological research has vastly expanded, and even in the present environment of highly interdisciplinary and collaborative science, future immunologists will likely need to be at least conversant in, for instance, computational, structural and system biology, nanotechnology and tissue engineering. At the same time, our perspective of the immune system has progressively developed from primarily a host defense mechanism to a fundamental homeostatic system with organism-wide physiological and clinical significance, and with potentially transformative biotechnological and therapeutic applications. As a consequence, in addition to stand-alone courses, immunology is increasingly integrated into other courses, or distributed longitudinally, throughout a multi-year curriculum. This necessitates inter-disciplinary approaches to reach an expanding range of disciplines, as diverse as neurobiology, cancer biology/oncology, infectious diseases, pharmacology, orthopedics and bioengineering. Creative approaches and pedagogical flexibility will be needed to avoid the pitfall of "one-size-fits-all" instruction, and to tailor level- and discipline-appropriate content to different types of students using multiple teaching formats.

Finally, like most other disciplines, immunology education is also under strong pressure to introduce new didactic strategies that are relevant and meaningful to a generation of students who are "digital natives", comfortable with and expect on-demand and multi-modal learning, diversified sources, and active engagement. Thankfully, the dynamic and interactive behavior of immune system cells, now visualized with striking immediacy by in vivo imaging, has the ability to capture and hold the interest of even the most jaded learner.

The need for an increasingly immunology-knowledgeable workforce – not just academic and industry scientists, but also clinical and research lab technicians, biomedical engineers, and physicians in a growing array of specialties - will also expand job opportunities for immunologists as educators, and for content creators dedicated to generating new didactic tools in this field.

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EDITORIAL
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Editorial: The Present and Future of Immunology Education

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Keywords: immunology, medical, active, learning, education, undergraduate, diversity, laboratory

Editorial on the Research Topic

The Present and Future of Immunology Education

INTRODUCTION

This Research Topic addresses issues relevant to teaching of modern immunology, a field that has exploded in recent years and is constantly evolving. These articles encompass curricular innovation, new pedagogical strategies, and teaching tools for the current and future generations of immunologists. The wide range of articles in this Research Topic illustrate diverse approaches for teaching basic tenets of immunology. Fortunately, immunologists are well-acquainted with diversity. Channeling one of the basic principles of Immunology, it is hoped the readers of this issue will select the Immunology articles that are most helpful to their particular mode of teaching. The articles presented are aimed at practitioners -the faculty members who are teaching and organizing Immunology courses. One of the goals of this issue is to give concrete examples of teaching strategies and concepts that could be modified for their own particular situation. In immunologic terms, this could be thought of as affinity maturation: starting with the ideas presented here, approaches can be actively fine-tuned for the particular situation of the faculty preceptor. Another major aspect of diversity illustrated in the articles presented is that students vary immensely in terms of their background knowledge. There are also fundamentally different educational systems in different countries. Finally, the articles reflect inherent constraints of the course such as the time allotted for the class that impact what is possible to cover in Immunology courses. Indeed, perhaps the major challenge in designing courses is not finding important Immunology subjects amid the myriad of interesting topics to cover (1) but rather what to leave out. We have grouped this editorial into sections for the convenience of the reader with particular interests, but it is important to note that the approaches are more general and can be used at different levels of teaching. While these articles highlight the many different ways to approach teaching immunology, they all reflect the enthusiasm and diversity of the faculty who teach immunology.

DIVERSITY OF APPROACHES IN UNDERGRAD TEACHING

The multitude of pedagogic and stylistic approaches for teaching immunology is revealed in articles describing undergraduate immunology classes. The role of storytelling employs the device of micro

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stories- short narratives designed to harness the affective and cognitive benefits of storytelling in minimal amounts of time (Lukin). These narratives employ concepts of neuroscience to enhance memory formation and emphasize how these can be incorporated to address the diversity of students. On a more global level, the paper by Bruns et al. explores the comparison of immunology as a discipline to neuroscience, which have many intellectual similarities to immunology but is significantly more highly represented in the number of undergraduate majors and discusses the potential reasons why this might occur. This article, as well as a recently published paper (2), details how undergraduate teaching and the curriculum might be changed to enhance Immunology a paradigm for interdisciplinary courses. Chatterjea discusses teaching immunology as a liberal art and emphasizes how immunology is not a single story. Her perspective is captured by the quote that many immunologists would subscribe to "I am grateful that immunology—the beautiful, maddening, messy field that it is—keeps me humble and honest about the work I really want to do with my students and the way in which I want to do it." It reflects both the difficulty and the optimism about teaching immunology that many Immunology professors have. Rawlings describes how to incorporate primary literature at the undergraduate level. While this often occurs at the graduate level, he provides a concrete framework of how to incorporate original articles into undergraduate courses. In a related vein, Stranford et al. offer a compendium of strategies to increase active learning and engagement based on their collective experience of over 90 years of teaching. Acknowledging that no one could be expected to incorporate all of these approaches, they expertly describe multiple strategies that can be employed to promote active learning. Collectively, these papers indicate that whatever strategy one takes, it is important to make a commitment to your chosen approach which needs to be clearly articulated and defined.

CHALLENGES OF LAB COURSES

Many immunologists believe one of the most effective ways to truly learn immunology is thorough lab work. However, lab courses are particularly challenging as outlined in the 3 papers in this Research Topic (Garrison and Bupp; de Vries. et al.; Demaria et al.). They are labor -intensive, require laboratory space rather than classrooms or lecture halls, and often demand sophisticated instruments and specialized supplies. From an institutional standpoint they are extremely expensive. As a result, many schools have greatly reduced the number, or even eliminated, lab courses. Moreover, they require experiments to be done in rather strict timelines (such as 4 hour blocks) compared to "real research" in which the experiments rather than the schedule dictate the experimental design. This is true not only in the actual blocks of lab time but also in the length of the entire class (de Vries. et al.). Concrete strategies to overcome the many obstacles and successfully deliver lab courses are presented (Garrison and Bupp; de Vries. et al.; Demaria et al.) are presented. Ways to provide a realistic experience with an inquiry-based lab experience is illustrated in Demaria et al. In these articles there is an emphasis on how the experiments can be used to help understand the theoretical underpinnings and underlying immunological basis of the experiments as well as their practical applications.

IMMUNOLOGY FOR STUDENTS IN HEALTHCARE PROFESSIONS

Teaching immunology for the healthcare professions can have some advantages compared to most undergraduate courses. Acknowledging there is a wide range of students even among health care pre-professionals, they are often more self-motivated than undergraduates, and in many cases have a stronger background in basic sciences, having already mastered many concepts and techniques in genetics, microbiology, and biochemistry. The stronger background of these students allows the teacher to use their knowledge of these disciplines in introducing immunologic concepts. On the other hand, pre-professionals often have a bias about what they believe is important and are resistant to learning about topics they perceive are not applicable or represent rare cases (Karim). They are particularly motivated by short-term goals such as professional licensure or other test requirements which often drive curriculum. Strategies that help balance these factors are outlined in Haidaris and Frelinger which shares some lessons for teaching medical students in a multidisciplinary medical school course. Teaching medical students or professionals through case studies to promote student engagement with case based scenarios is the topic of two of the articles (Karim) and (Novack). The relative merits of using uncommon cases where the underlying immunology is very clear *versus* more common cases where the immunology is more complex is also addressed. Additional approaches of how to teach immunology to health care professionals include team-based approaches (James et al.) and Just-in-time teaching (JiTT) (Madiraju et al.). These approaches emphasize student engagement and the use of pre-class preparation, and give concrete guidance as how to develop these approaches to promote active learning.

SPECIAL CHALLENGES IN NON-TRADITIONAL STUDENTS AND AUDIENCES

Many of the articles in this Research Topic acknowledge that immunology is a complicated field with an arcane vocabulary and a steep "learning curve". Moreover, it is often non-intuitive while also requiring fundamental knowledge from many other fields. Illustrating immunology concepts is particularly challenging when the audience has little or sometimes no formal training in basic science such as lay audiences. Indeed, such "teaching", is often considered outside the normal teaching

endeavors of immunologists, although it is crucial in maintaining support for scientific research. Ellis and Pennell discuss their efforts to reach general audiences using cancer immunotherapy as the paradigm. How to provide immunology teaching poses other challenges in resource-constrained countries. Kabelitz et al. provide a framework to deliver immunology concepts and information using a combination of online learning modules in conjunction with information presented in an intense course. Importantly, they also provide resources that can be used after the course ends so that individuals can remain current in a rapidly evolving field. In related topics, two of the papers discuss some of the particular issues with attracting and retaining underrepresented groups which has received national attention (3). Smolock and Robert discuss how they restructured their pipeline research to increase trainee success and retention. These include incorporating the many disciplines that are relevant to immunology as well as structural aspects such as skill-building workshops and better cross campus integration with student diversity groups and the Office of Diversity and Inclusion. Riestra et al. discuss high level pedagogy that outline barriers to equitable achievement, including avoiding stereotypes and emphasizing values, relevance, clear paths to achievement, and mastering vocabulary.

COVID-19 EFFECTS OF TEACHING IMMUNOLOGY

It would be remiss to conclude this Research Topic without mentioning the effect of COVID-19 on teaching Immunology. The tragic human and economic cost of the pandemic, and the impressive success of vaccine strategies against it, have highlighted the significance of immunology as a science with direct, practical impact on society. Complex concepts such as antibody titers, neutralization assays, passive immunity using monoclonal antibodies, booster shots, cross reactivity, cytokine storms, and T cell memory have started to enter the general vocabulary of the entire population. At the same time, the need to fight public misinformation from vaccination opponents leading to widespread vaccine hesitancy highlights the great opportunity and challenge of explaining immunology in a way that the general public can understand. Indeed, it has become evident that the general population and even scientists in other disciplines often have fundamental misunderstanding of immunology and the immune response. The articles reflect teaching approaches before the COVID crisis, but like almost all aspects of society, the teaching of immunology has changed dramatically in the past 18 months. These changes range from shifting emphasis on specific teaching topics (e.g., anti-viral responses, immunopathology, vaccine mechanisms), to the adoption of new approaches and technological platforms for remote learning. Which of these changes will endure remains to be seen. However, at the same time, it is clear that certain established principles and methods in teaching Immunology remain very relevant, reflecting not only key ideas and concepts, but also the fundamentals of all teaching: student engagement, active learning, and enthusiasm.

AUTHOR CONTRIBUTIONS

All the authors contributed equally to this editorial. All authors contributed to the article and approved the submitted version.

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HYPOTHESIS AND THEORY
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The Challenge of Teaching Essential Immunology Laboratory Skills to Undergraduates in One Month—Experience of an Osteoimmunology Course on TLR Activation

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Acquiring immunology laboratory skills during undergraduate studies is often a prerequisite for admission to Masters' programs. Many broad liberal arts and sciences honors degree colleges struggle in teaching these essentials since only limited time is usually reserved for this. Here, we describe a new 1-month-course developed to train a small group of honors students in 6 techniques that are useful for immunology research. In essence, 15 students were divided into 3 groups of 5 students where each student became involved in current osteoimmunology research. Osteoimmunology is a relatively new branch of the immunology tree, where the effects of inflammation and the immune system on bone formation and bone degradation is studied. A broad, 3 weeks experiment on the chronic effects of molecules that specifically activate toll-like receptors TLR2 and TLR4 on bone formation or osteoclast differentiation was performed just before the start of the course. Control samples and samples treated with TLR2 (group A), TLR4 (group B), or TLR2+TLR4 (group C) agonists were harvested and analyzed using quantitative PCR, ELISA, biochemistry, microscopy of enzyme-histochemically stained osteoclasts, scanning electron microscopy, and confocal microscopy. Each technique was taught for 2 days by a specialized instructor, who was present at all laboratory activities. The primary research question for each group was: how does the experimental condition affect bone formation or osteoclast formation? The secondary research question specified per technique was: how does this technique answer part of the primary research question? Pedagogically, students were encouraged to collaborate within the group to analyze the obtained data. Secondly, at the end of the course, a representative of each group collaborated to summarize the TLR activation modalities of a technique of choice. Thirdly, each group wrote a report, where introduction and discussion were graded as a group; each technique part was graded individually. The

summary of the results from the 3 treatment modalities was presented orally. The student evaluation of the course was high, students remarked that the course had a curriculum overarching function, since it created an awareness and appreciation for both the joy and the blood-sweat-and-tears aspects of pipetting, and writing research articles, making interpretation of those easier.

Keywords: laboratory work, education–active learning, osteoimmunology, toll-like receptors, osteoclast, mineralization assay

INTRODUCTION

After gaining the essential biomedical knowledge in immunology and molecular cell biology theoretical courses during the first years of an undergraduate program, there is a great urge for hands-on experience; an urge to acquire laboratory skills. This should be satisfied within the curriculum because of two reasons. (1) We should not only train theoreticians since undergraduate courses must connect properly to existing Masters' programs that demand essential laboratory skills. (2) As a teacher-scientist community, we have the obligation to convey our enthusiasm for scientific research to the next generation of biomedical researchers, providing state-of-the-art research within a laboratory context.

Can we design flexible courses, allowing the yearly incorporation of novel immunology/ molecular cell biology research insights? Can we prepare courses in such a way that undergraduate students contribute to the progression of science with visible results? Can we get students hands-on acquainted with a variety of techniques within a short time frame? We asked ourselves these challenging questions when designing the course described below. This course meets the need for flexibility in the rapidly evolving field of osteoimmunology and can be adapted on a yearly basis.

At Amsterdam University College (AUC), the Netherlands, the need for such an undergraduate course was recognized a few years ago. Amsterdam University College is a broad liberal art and science honors college that provides a biomedical track. Since the College does not have laboratory facilities, these were provided by the local dentistry faculty, the Academic Center for Dentistry Amsterdam (ACTA), University of Amsterdam, and Vrije Universiteit (VU) Amsterdam together with the Cellular Imaging microscopy facility of the Amsterdam Medical Center (AMC), University of Amsterdam. We took up the challenge to design a flexible course that can be adapted per year, thus meeting our own desire to be able to line-up with current research of the department. This article tells the story of such a course set-up in the emerging field of osteoimmunology, but in essence, its structure can be applied, and adapted to any immunology course. The course we describe here, Cell Biology, and Physiology Lab, is an existing course, but can be adapted on a yearly basis. The course is evaluated every year at AUC, allowing for improving it further. We have experience in adapting it per year, some of its results can be used by PhD students, or senior scientists from the department.

For scientist-teachers, who are obliged to dedicate some of their precious time to the supervision of a practical course, this time is often considered as "lost," especially when it concerns the supervision of a practical course that is repeated year-after-year without adapting it. Time not spend on own research is lost time, that is a common perception at university. To motivate scientist-teachers that there was some scientific gain in it as well, our course was designed in such a way that the theme of the course connected to the own research interest of the scientist-teachers. Some of the results obtained by students who were for the first time in a laboratory environment could be used, if supervised properly, in research papers of the scientist-teachers. For students, this stirs up the exciting realization that they are involved in cutting-edge research. "You will be the ones who, for the first time will discover ...." Therefore, the benefit for the two stakeholders, students and scientist-teachers, of our tailor-made, and yearly adapted course is symbiotic.

First of all, for students, the course will teach them how to put together solid research data for the different figures of a so-called "almost ready manuscript" at the end of the course. It gives them an appreciation of how to view a central process in immunology research from the perspective of the outcomes of 6 to 7 techniques. They will learn to integrate findings obtained by these techniques. At the end of such a course, students know how to generate, analyze, and weigh results. On top of that, they have gained appreciation of both the excitement of new results and the blood-sweat-and-tears that is inevitably involved in scientific research. Secondly, for the other group of stakeholders, the scientist-teachers, time spent on the course becomes useful time since it contributes not only to leaving a lasting impression on the students, but also to progressing the field and the research progress of the department.

THE SCIENTIFIC BACKGROUND FOR THE COURSE: OSTEOIMMUNOLOGY AND EXPERIMENTAL PERIODONTOLOGY

Around the year 2000, it became more and more clear that the immune system and bone cells communicate. Inflammatory cytokines were shown to activate osteoclasts; T-cells were documented as either contributing to bone loss or to temper bone loss. It was discovered that T-cells and osteoclast precursor cells share transcription factors. Bacterial products were shown to influence both osteoblasts being the bone builders, and osteoclasts being the bone degraders. And after all, osteoclasts were then already known for 20 years to be derived from

hematopoietic cells, more precisely from monocytes. This has led to the coining of the term "Osteoimmunology" (1–3) and also, recently, to redefining cells like osteoclasts as not only degraders of bone, but also as immune cells (4–6).

Periodontitis, the chronic inflammatory disease with loss of the tooth-surrounding bone, is the most common inflammatory bone disease. It is estimated that ∼46% of American adults of 30 years and older have periodontitis, 3.8% of the Americans have a severe form of periodontitis (7). Its etiology comprises the presence of periodontopathogenic bacteria, such as *Porphyromonas gingivalis*, that interact with the cells from the tooth-surrounding tissue, the periodontium, and evoke an inflammatory reaction. Within the tissue, cells will recognize bacterial components with so-called pattern recognition receptors, of which the Toll-like receptors (TLRs) are widely studied (8). In particular, TLR2, and TLR4 are important in recognizing the periodontopathogenic component (9, 10). The recognition of bacterial components evokes an inflammatory response, causing the release of inflammatory cytokines such as interleukin-1β, and TNF-α, attracting a diversity of immune cells to the periodontium. This influx of leukocytes was characterized both in mice (11), reviewed in de Vries et al. (12), and in humans (13, 14). The sequential influx may consist of various innate immune cells such as neutrophils, and monocytes, and at a later stage T-cells from subsequently the Th1, Th2, Th17, and Treg classes, and finally plasma cells that make antibodies against components of the periodontopathogenic bacterial components that may invade the tissue. When enduring, these bacterial components present in the periodontium will eventually activate the monocyte-derived bone degrading cell, the osteoclast. This cell will then degrade the rims of bone between teeth, ultimately leading to tooth loss.

These cellular and bacterial interactions can be mimicked in an immunology/cell biology laboratory. Cells from the periodontium, especially fibroblasts, can be retrieved from extracted wisdom teeth. This surgical waste material is very valuable for the type of research described here. A rim of cells can be retrieved at the occlusal side. This is called the gingiva. More apically, the periodontal ligament can be scraped off the tooth root, and periodontal ligament fibroblasts can be grown from these tiny tissue fragments. The periodontal ligament anchors teeth into bone. The gingiva is the tissue closer to the tooth-epithelium connection and plays a role in anchoring epithelium to the bone, epithelium to tooth by collagenous fibers. The fibroblasts from these tissues, together with peripheral blood mononuclear cells, can be used for the differentiation of osteoclasts (15). Fibroblasts are considered to provide the cytokines macrophage colony stimulating factor (M-CSF) and the osteoclast differentiation factor receptor activator of NF-kappa ligand (RANKL) (16). Gingiva and periodontal ligament fibroblast cultures can be infected with *Porphyromonas gingivalis* to study the induced expression of inflammatory cytokines (17). Recently, it was shown that gingiva fibroblasts not only provide stimuli for osteoclast formation They also retain leukocytes and contribute to the T-cell proliferation as assessed by carboxyfluorescein succinimidyl ester (CFSE) labeling (18).

Apart from their role in catabolic processes, such as osteoclast formation, tooth-associated fibroblasts may also play a role in the regeneration of degraded bone (19). When cultured with vitamin C, needed for proper collagen folding, and with β-glycerophosphate as phosphate source, mineralization nodules are formed (20, 21). Therefore, gingiva or periodontal ligament fibroblasts represent an attractive model to study the effect of external influences on both anabolic and catabolic processes within the same experiment (22, 23).

Noteworthy, these fibroblasts may perceive chronic bacterial stimuli at a periodontitis-affected site of a tooth. Therefore, it is desirable to develop models that mimic such a chronic burden and assess both anabolic or osteogenic on the one hand and catabolic or osteoclastogenic effects on the other hand. Ideally, a co-culture with for instance the periodontitis-associated biofilm could be used, but chronic exposure to bacteria will kill cells in assays that last 21 days and this exposure is likely not biologically relevant, since such high encounter of bacteria likely does not take place within tissues. Biologically more relevant as a chronic exposure model, is the use of defined bacterial cell wall fragments that may leak into the tissue and that specifically target for instance TLR2 or TLR4, so-called TLR agonists. By using specific compounds instead of whole bacteria, it can be determined which activated TLR causes what effect.

THE OSTEOIMMUNOLOGY EXPERIMENT MIMICKING A CHRONIC INFECTION

The experiments for the course were prepared ∼1 month in advance. Gingival fibroblasts from six donors were retrieved from a liquid nitrogen tissue collection of cells cultured from non-inflamed extracted wisdom teeth. These were propagated for ∼1 week until a 175 cm^2 tissue culture flask was confluent at the beginning of the experiment. One day before the start of the experiment, fibroblasts were seeded for osteogenesis or osteoclastogenesis experiments in 48 wells plates. The next day, day 0 of the experiment, either osteogenic medium, or peripheral blood mononuclear cells isolated from a buffy coat were added as previously described in detail (22–24). For the experiments assessing the effects of TLR activation on osteoclast activity, CD14+ monocytes were isolated using MACS technology (25), and seeded on top of bone slices. Experimental conditions were TLR2 agonist (PAM2, a synthetic diacylated lipopeptide; Invivogen, San Diego, CA) or TLR4 agonist (ultrapure LPS from *Porphyromonas gingivalis*; Invivogen, San Diego, CA) or a combination of both, previously titrated (Gerasimos Karlis, TJdV). In total, the experiment lasted 21 days. Cell cultures were refreshed twice a week with culture medium containing solvent or TLR2 or TLR4 or TLR2+4 agonists and supernatant for ELISA was taken every week. Samples were taken throughout the experiment, either by fixing the cells (for confocal, SEM, osteoclast microscopy, or Alizarine red staining), or by lysing the cells by RNAlysis buffer (qPCR), or water (alkaline phosphatase and DNA) or a lysis buffer for biochemical assays. Samples were stored

at 4, −20, or −80°C. To assess the effect of TLR agonists on cell proliferation of peripheral blood mononuclear cells, PBMCs were labeled before experiments with CFSE as described previously (18). Proliferation assays making use of CSFE labeling were analyzed once a week at days 7, 14, and 21. Briefly, cells were detached with trypsin/EDTA and stained with the appropriate cell markers to enable linkage of CSFE fluorescence to leukocyte origin.

THE COURSE OF COURSE: INTEGRATING 7 TECHNIQUES IN A COHERENT WAY

Students enrolled for the course a few month before. A few weeks before the start of the course, students were informed on the theme and the learning objectives of the course. At an introductory morning session, students, and instructors were first introduced to one another where after three groups were formed.

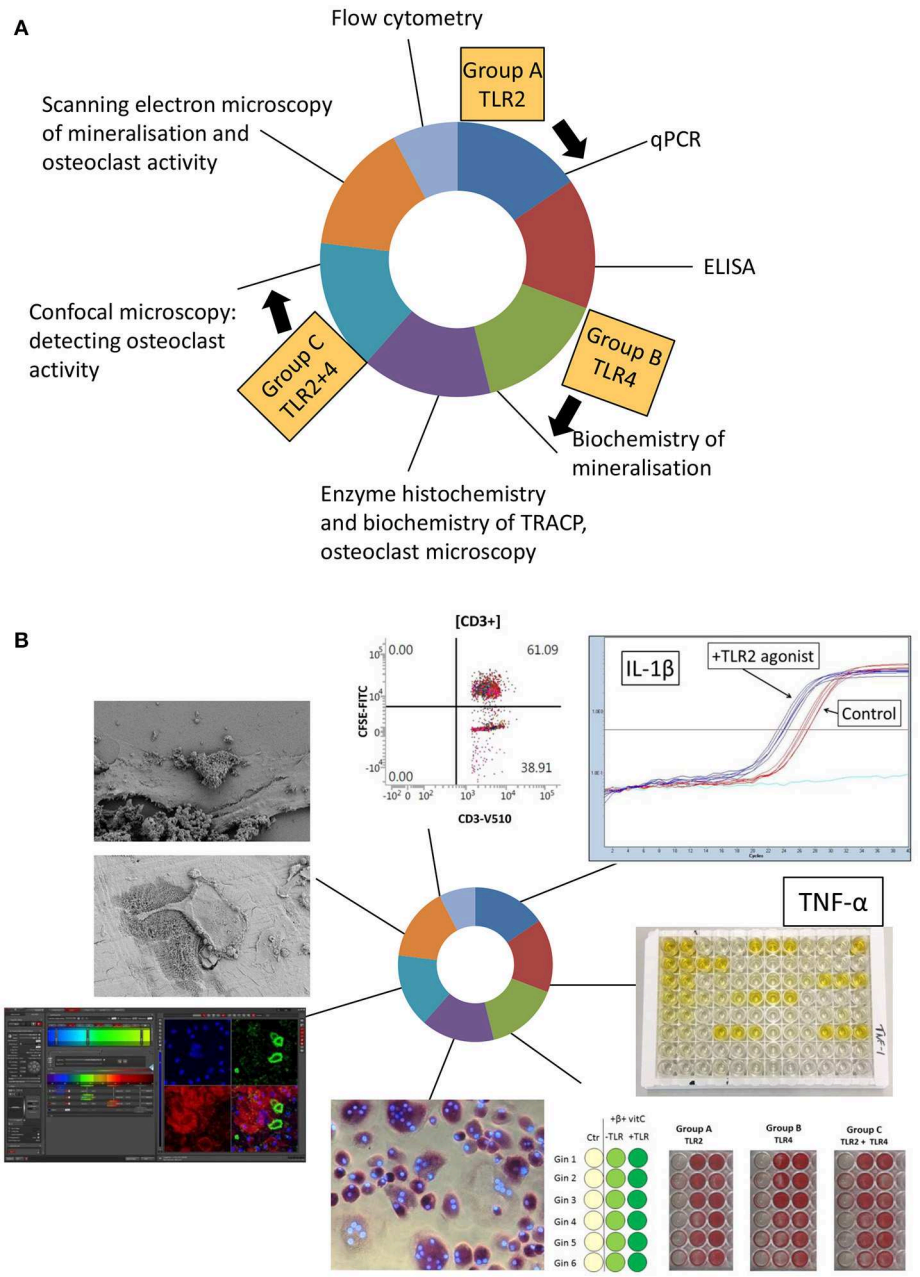

FIGURE 1 | Set-up of the osteoimmunology course. **(A)** Over time, 6 techniques were visited by the three groups, group A (TLR2 agonist), group B (TLR4 agonist), and group C (TLR2+TLR4 agonist) for 2 days in a row. Flow cytometry was demonstrated during a 1 day master class. In principle, the order of these techniques is not relevant, provided that instructors take the time at the beginning of each technique introduction to emphasize the links with the previously examined techniques. **(B)** Illustrated outcomes of the course. All micrographs and graphics were taken during the course.

After a brief introduction on the theme of the course, groups were assigned to analyze the different experimental conditions. Group A would analyze all aspects of TLR2, group B of TLR4, and group C of the combination of TLR2, and TLR4. Each group also analyzed control samples. For the next 3 weeks, groups attended 6 technique modules (**Figure 1**). Each module lasted 2 days and was supervised for these 2 days by the corresponding technique supervisor. To ensure that consistent and usable results were obtained, the same technique supervisor supervised all three groups. Per technique, a short introduction into the technique and instruction for the following 2 days by the instructor preceded the hands-on laboratory work, and the data analysis (**Figure 2**).

Research Questions per Technique Module

The course and the research questions were set-up in such a way that the order of visits of the 6 techniques (**Figure 1A**) was not relevant for fitting the pieces of the scientific puzzle together in the last week of the course.

Research questions per module were formulated beforehand. These are summarized in **Box 1**.

Keyword = Coherence: Per Technique, Between Techniques and Between Experimental Variables

When mimicking scientific research within the course, there should be scientific coherence between its different modules. No technique was carried out just for the sake of the technique. Findings per technique should be compared with outcomes obtained using other techniques, hereby refining, and testing outcomes from multiple perspectives. We thus sought to link the various techniques, encouraging students to find scientific relationships at the end of the course, after completing all modules. Coherence was thus deliberately incorporated in the course. Here, we list 5 examples of coherence (**Box 2**), either within a technique module, between the modules, and between experimental variables (TLR2, TLR4, and TLR2+4 agonists), representing the overall outcomes between groups A–C.

After completing all techniques, time was reserved in the course schedule to meet with the supervisor for individual/personal assistance and feedback on data acquisition, analysis, and interpretation. Students were encouraged to do so, since we (as course supervisors) thought it essential that students can consult us at a very accessible way.

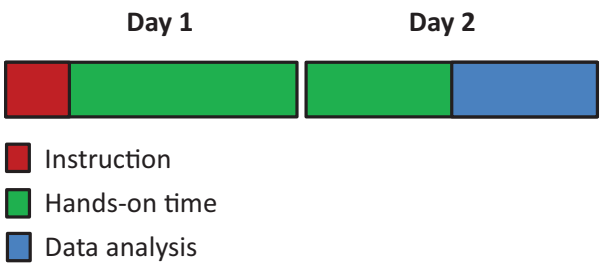

FIGURE 2 | The typical sequence for a 2 day technical training. All 2 day techniques modules started with short instruction of the technique followed by ∼1 day of hands-on training. The last few hours of day 2 were used for data analysis and interpretation.

EDUCATIONAL AND PEDAGOGICAL CONSIDERATIONS

When designing the above-described course, we carefully thought about a variety of educational and pedagogical considerations. What are the features of the teacher-instructors for this course, how are they instructed? Should we evaluate the student's laboratory skills (e.g., pipetting skills)? How do we balance the theoretical and practical aspects of this course? How can we then evaluate the students for this course? How and when should we provide feedback?

The Teachers-Instructors

In contrast to any purely theoretical course, teacher-instructors of this practical course should above all be experienced in laboratory work and should enjoy explaining the designated technique, even three times in a row. They should be skilled in interacting with a critical student audience. Above all this, and special for our course, since it was taught to a group of international students: all (Dutch) instructors should master the English language at a proficient level. Furthermore, all instructors were involved in grading the students (described later).

Evaluate Pipetting Skills?

Students of the honors college AUC are used to a system of continuous assessment. This would mean ∼3 to 4 assignments spread over the whole month. We decided to deviate from this format, since our immunology laboratory skills lab would

BOX 1 | Techniques and research questions per technique.

- **qPCR:**
  What is the effect of TLR activation on gene expression in osteoclast cultures?
- **ELISA:**
  What is the effect of TLR activation on the secretion of inflammatory cytokines?
- **TRACP enzyme quantification, TRACP staining and microscopy:**
  Does TLR activation influence osteoclast formation?
- **Alkaline phosphatase enzyme, Alizarin red staining and calcium deposition:**
  What is the effect of TLR activation on bone formation?
- **Confocal microscopy:**
  Does TLR activation influence osteoclast activity (1)?
- **Scanning electron microscopy:**
  Does TLR activation influence osteoclast activity (2)?
  Does TLR activation lead to differences in mineral deposits?
- **Flowcytometry workshop:**
  Does TLR activation influence T-cell proliferation?

BOX 2 | Examples of coherence.

Example 1:

The production/secretion of the pro-inflammatory cytokine IL-1β was measured by ELISA and by qPCR. Did both techniques give a similar result? What is the interpretation of possible differences?

Example 2:

The effect of TLR activation on mineralization was measured using three techniques (alkaline phosphatase, Alizarin Red staining, as well as calcium deposition over time). These techniques also connected to the analysis of mineral deposits using SEM. Students were invited to find coherence between the techniques, but also to note the effect of TLR activation on differentiation over time.

Example 3:

For the analysis of tartrate resistant acid phosphatase (TRACP)-positive multinucleated cells, both cell counts as well as TRACP enzyme analysis were combined; TLR activation here resulted in fewer osteoclasts and corresponded to less TRACP activity.

Example 4:

There are basically two ways to detect bone resorption using microscopy. Osteoclasts grown on bone slices can be fixed and subsequently bone resorption pits can be assessed using SEM. Alternatively, actin ring formation, typical of resorbing osteoclasts, can be researched using confocal microscopy. These resorption results of the two techniques should in principle be complementary: *in situ* activity can only be shown with actin rings using confocal microscopy, while SEM should be used to study resorption in conjunction to osteoclasts. Examples of the practical are shown in **Figure 1B**.

Example 5:

Having gathered all the data at the end of the third week, students were able to formulate overall effects of TLR2, or TLR4 or by the combination of both on osteoclast formation or on osteogenesis. Furthermore, by connecting per technique to the group members of the other groups, specific TLR2, or TLR 4 or TLR2+4 effects on for example TNF-α expression (ELISA) could be worked out.

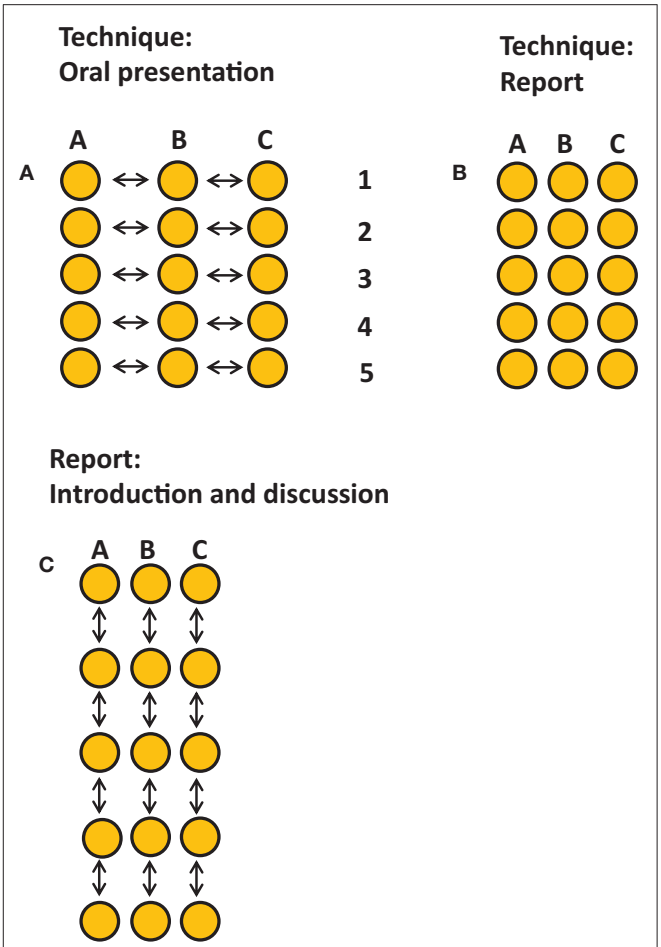

FIGURE 3 | Graphical representation of the assignments. Three assignments took place, each accounted 1/3 of the final grade. Each dot represents one student, arrows indicate interactivity. **(A)** An oral presentation on the results per technique describing the ins-and-outs per technique, techniques 1–5, and the joint outcomes per technique per group presented by representatives for each group. This assessment promoted consultation and collaboration between group members of each group. **(B)** An individual assignment describing the ins-and-outs and the own results of one technique Five techniques were chosen to be covered in the report. **(C)** A group assignment for writing the introduction and discussion. This assignment promoted collaboration and interaction within the group.

benefit from putting all assignments at the end of the course, when all results would be available. Since all assignments we chose were at the end of the course, and since it is a laboratory course, it could be argued whether lab skills should be assessed. We contemplated grading pipetting skills (and some students suggested this) but finally decided against it; it did not seem just to evaluate manual dexterity as some of the students held a pipette for the first time in their life. Furthermore, the design of the course, with its 2 days per module format, did not allow for assessing independent mastery of performing a technique at the per-student-level. These aspects are typically assessed during laboratory internships, where usually several attempts with gradually declining supervision are required before independency is guaranteed.

The Three Assignments

There were three assignments (**Figure 3**). We decided to assess a presentation on the laboratory technique that was chosen by each student. Per laboratory technique, students of the three groups had to collaborate on this, comparing outcomes of TLR 2 (group A), TLR 4 (group B), or TLR 2+4 (group C) activation (**Figure 3A**). Each student had an individual assignment of writing up the results of the chosen technique (**Figure 3B**). Both for the oral evaluation and for the written assignment, students were instructed to introduce the purpose of the chosen technique, and to demonstrate that they master the principle of the technique. Students had to interpret the specific results of their group in the individual written report and had to interpret the results of the three groups during the oral presentation.

All individual reports were combined in the group report that should have the organization of a large research article on the effect of TLR 2 (group A), TLR4 (group B) or the activation of both (group C). As part of the final assignment, each group had to collaborate to write an introduction and a general discussion together. All three assignments counted for

1/3 of the final mark. Oral presentations were scored by all instructors, who were all invited to write down their feedback using a standardized feedback form containing the rubrics and the weight per rubric. Individually written technique was scored by the technique supervisor, and the group work introduction, and discussion were scored by two of the teachers. All three assignments had their own rubrics. The rubrics were known to the students in advance. Course instructors were instructed by the course coordinator (TJdV) on how to fill in the rubrics and how this would lead to the final mark per assignment.

Performance Feedback to Students

Many summer courses, like ours, finish practically on the last days of the summer semester, leaving little room for feedback of the grading since students leave campus immediately after handing in their assignments. From a students' perspective, it is best to receive individual feedback. All remarks on group presentation were known directly after the presentation, but the written individual, and group assignments were marked in the week after the students had left. One person (TJdV) assembled all comments, and wrote a 2-page individualized report justifying the 3 grades that were obtained and sent those reports per email to each student.

STUDENT COURSE EVALUATION

It is a good habit to evaluate all courses, both to the benefit of future students, and to the benefit of teachers. Therefore, student evaluations are a valuable instrument to assess quality and to initiate a plan-do-check-act (PDCA) cycle (26) to improve courses. In our view, course evaluations are only successful when filled in by a large group of participants. The questions of the evaluation were from a general format from the VU University Amsterdam, used by AUC. These included 13 questions on the course (i.e., learning outcomes, relevance, facilities, course information, learning outcomes achieved) 12 questions on the teachers (i.e., quality of teaching, command of English, variation of class activities, whether teacher encourage active participation), and 2 questions on the assessments (continuous assessment useful and whether assessments were a good reflection). Apart from these 1–5 scale evaluation questions, students were offered the possibility to reflect by typing their findings of the course in an open question format. To ensure unbiased and non-repetitive feedback, all students were encouraged to fill in the digital 1–5 scale evaluation form on their laptops prior to the informal evaluation in class. This way, a response rate of 87% (13 out of 15) was achieved.

Overall, the course scored higher than AUC average on 26 out of the 27 aspects that were evaluated. Six out of 27 aspects scored significantly higher than AUC average. Students especially appreciated the dedication and enthusiasm of the instructors, the variety of subjects and the meaningfulness in the broader perspective for the biomedical track. Awareness on how to organize and interpret research was raised. Among points of critique were the relatively late assessments (see The three assignments) and the too short introduction (half a day) of the theme of the laboratory course.

These are a few quotes of appreciation of the course. On a very positive note: "The instructors were super excited and motivated, which was amazing! They were very inspirational and motivated and provided very effective guidance in the lab." Also: "I learned a lot and am happy about it." And: "The atmosphere was great, and they obviously enjoy their work." But then: "All instructors were good, however, the presentations before we started the practical work helped me understand what we were about to do. I would recommend that all instructors do the same in the future." And, in the same line, more critical toward the variation between the teachers: "There were differences between teachers. I preferred when teachers explained the goal of the experiment in the beginning." These points of critique, asking for a synchronized instruction of instructors, will further help improving the course. Also, more emphasis on the theoretical background of the experiment and repetition of this in the context of the technique, was already implemented this year. Finally, another valid point was on spending more time on data analysis: "When it comes to data analysis after the techniques, maybe it is already an idea to introduce graphpad to the groups at the beginning of the course so that little time can be spend on the same day as the experiment which saves time afterwards." This point was taken up as well and the year following the course, more emphasis was placed on statistical analysis of data.

Instructors evaluated the course as well, but informally. This was done before the course started (feasibility of the specific assignment), during the course, and after the course. The level and enthusiasm of students was very much appreciated. Some teachers had a difficult time in bringing across the coherence between the techniques, which was picked-up a year later by putting more emphasis on this aspect. Finally, the course received peer-to-peer feedback by a course coordinator from another laboratory course at AUC.

CONCLUSIONS

The course was to a great extent successful in bringing across new developments in the emerging field of osteoimmunology in a tangible way. Student stakeholders learned the essentials of commonly used immunology laboratory techniques in the context of a current hot topic in immunology with 6 modules of 2 days and a workshop on flow cytometry. Scientist-teacher stakeholders have benefitted from the course since some of the scientific outcomes (quantitative results from osteoclast counts, ELISA, mineralization assays, qPCR, and flow cytometry and illustrative SEM results) of the course will be used in two publications (G. Karlis et al., manuscript in preparation; C. Moonen et al., manuscript under revision). Quite a few students benefited from this course first of all by motivating them to apply for a laboratory internship, which was true for at least 4 out of 15 students in their third year. And, in general, years long experience has shown that experience obtained during laboratory courses such as this one, genuinely helps when applying for

MSc programs and for applications to Medical Schools. Of equal importance: both stakeholders, students and teachers, have had an enjoyable, and even memorable time, therefore time well-spent!

DATA AVAILABILITY

Requests to access the course evaluation data should be directed to the corresponding author at teun.devries@acta.nl.

AUTHOR CONTRIBUTIONS

Course coordinator TdV initiated writing. TS, HvV, JH, PK, CM, and IJ contributed textually and contributed to **Figure 1B**. All authors were instructors of the described course.

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Primary Literature in the Undergraduate Immunology Curriculum: Strategies, Challenges, and Opportunities

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Immunology is a rapidly advancing and expanding field that is regularly highlighted in the lay media, whether it be checkpoint blockade immunotherapy winning the Nobel Prize, CAR-T cells in the treatment of cancer, or the latest anti-inflammatory/immunomodulatory medication advertised directly to consumers. Advances such as these not only transform the way we think about immunology, they also illuminate how knowledge of the immune system can be harnessed to impact public health. Immunology is also a vast subject, with thousands of articles published each year that contribute to our understanding of complex processes such as inflammation, pathogen recognition, and self-tolerance, Taken together, these observations pose significant challenges to teaching immunology in the undergraduate classroom. To meet this challenge, instructors can use primary literature as a means to introduce cutting-edge discoveries that have not yet found their way into textbooks, link what students are learning to what they are exposed to in lay media, and ultimately provide added depth to the students' understanding of the immune system all while illustrating how clinical advances are fundamentally dependent on basic research studies. Furthermore, the addition of primary literature to the curriculum can enhance student enthusiasm for learning immunology and can provide an excellent platform for students to gain critical thinking and analytical skills. Presented here are strategies, challenges, and opportunities in the use of primary literature to effectively augment the immunology curriculum in the undergraduate classroom. Topics include selecting papers to read, teaching students how to read scientific literature, and assessing student learning.

Keywords: primary literature, undergraduate, discussion, strategy, opportunity, challenge

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INTRODUCTION

Primary literature is an enticing pedagogical tool, as its incorporation into the undergraduate curriculum has been shown to improve scientific literacy (1) and enhance critical thinking skills (2), while providing an excellent platform to teach students how to generate a hypothesis, design experiments, and evaluate data (3). In addition to enhancing learning outcomes, primary literature can also bridge the gap between dated information in textbooks and emerging ideas and concepts. A number of strategies for incorporating primary literature into the science curriculum have been investigated (4–7). The goal of this perspective is to present additional strategies to assist

those interested in using a class discussion format to evaluate primary literature as part of the undergraduate immunology curriculum that are aimed to maximize opportunities for student learning and engagement, while minimizing the associated challenges that arise (summarized in **Table 1**). The strategies presented here can be used in isolation or in conjunction with these other methods.

FITTING DISCUSSION OF PRIMARY LITERATURE INTO THE CURRICULUM

As immunology is a very complex subject, most textbooks contain far more content than what can be covered in a single semester. Thus, the challenge is to figure out how many contact hours to devote to primary literature while still providing a comprehensive immunology curriculum. I have found that the selection of three papers to read throughout the semester provides the best balance between the gains of reading primary literature and the number of valuable contact hours used in the process. In terms of contact hour commitment, you should expect to spend at least 1 contact hour laying down the logistics (described below), your expectations for learning outcomes, and providing instruction on how to read a scientific paper. Additional time will be needed to discuss common techniques and model systems (described more below). The actual discussion of each paper can take roughly 2 h, depending on the papers selected and the depth of the discussion. Thus, to discuss 3 papers throughout the semester, you can plan on a total of ∼8 contact hours. Because Immunology at Furman includes a laboratory component, I commit lab sessions as needed without sacrificing too much course content. For reference, Immunology at Furman is comprised of 40 lecture contact hours and 42 lab contact hours; therefore, I commit roughly 10% of total contact hours to primary literature.

TABLE 1 | Summary of challenges and opportunities associated with incorporating primary literature into the undergraduate curriculum.

	Challenges	Opportunities
Fitting primary literature into the curriculum	• Requires significant contact hours • Spacing papers out in curriculum • Deciding on learning outcomes	• Highlight emerging concepts • Provide depth beyond the textbook • Great change of pace for instructor and students • Improving scientific literacy
Selecting papers to read	• Gauging student preparedness • Technical difficulty of the paper • Conceptual difficulty of the paper	• Highlight how scientists gain knowledge • Relate papers to current events • Relate papers to student career aspirations
Implementation	• Achieving student buy in • Getting students to evaluate the actual data	• Teaching students about experimental design • Guest speaker to lead discussion • Improve critical thinking and analytical skills

KNOW YOUR STUDENTS

Before embarking on using primary literature in the immunology curriculum, it is important to have a firm handle on the skills and abilities of your students. At Furman University, Immunology is an upper-level elective course within the Biology major. Students enrolling into the course typically have a strong foundation in genetics and some exposure to cell biology, both gained through three prerequisite courses that serve as the introduction to the major. Students will also know the general anatomy of a scientific paper, but may not have any experience reading a cell/molecular biology paper; therefore, I cannot assume students have a high level of scientific literacy. In terms of interests, the vast majority of students who take Immunology at Furman are on various pre-health career tracks or are interested in biomedical science careers. As such, it is not surprising that students will have the most interest in papers where the translational/clinical link is most apparent. This does not mean that I won't have them read basic science papers, it simply means I will need to help draw the connection between the science and the clinic so they can appreciate the relevance of the paper. This is important, as I have found that if students have "buy in" to what they are reading, they will be more engaged, resulting in a deeper discussion of the paper, and ultimately a deeper understanding of the science.

SELECTING PAPERS TO READ

I have students read one paper from each of the three main thrusts of the Immunology course curriculum: innate immunity, adaptive immunity, and applied immunology. This strategy allows for the papers to be evenly spread out throughout the semester, and also highlights the equal importance of all three areas of immunology. Importantly, this strategy also provides the most flexibility for the instructor in planning out the curriculum and provides a great change of pace for both the instructor and the students.

Great care must be taken in selection of papers to read. The ideal paper will be able to stand alone, in that it has sufficient background in the introduction such that the students can reasonably connect the science to what has been covered in class (or I will adjust coverage in class to make the connection more apparent). The paper will have the right balance between technical difficulty and the complexity of the science itself. Much of this decision will rest on the strengths of the students (see above). I will avoid using papers that are incredibly "data heavy" or have methods that are not clearly spelled out, as undergraduates may have difficulty digesting the data. Ideally, the paper will utilize multiple modalities or approaches to address a clearly articulated hypothesis. I try to select a set of papers that collectively utilize a broad array of techniques so that students are exposed to a variety of data types. When possible, I like to select papers that have timely relevance. For example, choosing a checkpoint blockade paper will not only highlight the recent award of the Nobel Prize to James Allison and Tasuko Honjo, it will allow students to identify with the direct application of their findings in discussing the recently approved therapeutics

based on their discovery. Additionally, such a paper illustrates how clinical advances are absolutely dependent on basic science studies.

The greatest care must be taken in selecting the first paper students will read, as this will set the tone for the remainder of the semester. This selection can be challenging, as students will not have had much exposure to immunology at this point in the semester and even more so if the students are relative novices at reading and discussing primary literature. I like to choose a paper that is visually appealing and has data that is relatively easy to digest. A great example is to use a paper on neutrophil extracellular traps (NETs). In my experience, students have found the idea that a cell will extrude its DNA to trap microbes to be intriguing. Because much of the data is visual in nature, students will be able to not only digest it easily, they will be fascinated by it. Importantly, I cover an overview of cells of the immune system very early in the course, thus students can begin reading the paper almost immediately.

IMPLEMENTATION

Early in the semester, I recommend devoting 1–2 contact hours to covering the basic anatomy of a scientific paper (if needed), common techniques (e.g., flow cytometry, transgenics) and perhaps introduce model systems that are utilized in the selected papers. In addition, this time should be used to lay out overall expectations, including how learning will be assessed. It is important to emphasize to the students that it will take multiple in-depth readings of the paper to understand the science presented. I devote one of the first lab sessions of the semester to these tasks.

Foundational material will need to be covered to prepare students for reading primary literature (e.g., discussing basic functions of neutrophils before assigning a paper on NETs). The instructor need not alter their pedagogy in the delivery of this content. Once foundational material is covered, I will prompt students to start reading the paper and assign them to write a two-page (double spaced) summary of what they read, giving them 2 weeks to complete the assignment. In the assignment, students are instructed to spend approximately half of one page on the introduction, half of a page on the discussion, and the remainder on the results. I do not have students commit a specific section to the methods. Instead, students are to incorporate methods used as they describe the data. For example: "*When T cells were stimulated with IL-2, expression of GeneX increased significantly, as measured by qRT-PCR.*" When laying out expectations for the paper summary, I am transparent with the students about the fact that it will be extremely difficult to summarize the paper in just two pages; the true goal of the assignment is to force students to write concisely and most importantly, attempt to synthesize what they are reading. I also make it clear to the students that simply embellishing the abstract will not meet my expectations for their summary (see section Assessment of Learning below and **Table 2**). Furthermore, expectations regarding plagiarism (which students will have already had exposure in previous courses) and ethical behavior regarding the assignment are reinforced.

Concomitant with assigning the paper summary, I open an online discussion forum for students to post questions about the paper. Students are encouraged to ask both technical questions, as well as questions about the biology. Students are also encouraged to answer each other's questions and engage in discussion about what they are reading. I closely monitor the forum, intervening only when student questions go unanswered or if student replies/discussion gets off track. If the forum lacks activity, I will post questions for students to answer to stimulate discussion. Ideally, students will spend ∼1 week discussing issues on the online forum and use the second week to complete their summary.

In addition to the online forum, I will make every attempt to directly connect course content with what they are reading as we progress through the curriculum. For example, if I assign a paper that utilizes an OT-I transgenic TCR model, I will talk about how expression of the transgene early in thymocyte development results in virtually all T cells expressing the transgenic TCR when I cover TCR rearrangements and control of receptor expression in class. I will also refer to the OT-I model as a means to test signal strength when we discuss thymocyte selection. The goal is to organically interweave the technical aspects of the paper

TABLE 2 | Example questions that can be asked to facilitate discussion of primary literature.

Section	Example questions to facilitate discussion
Abstract/Introduction	• In your own words, can you give a one sentence "elevator pitch" for the main findings of the paper? • What is the main objective of the paper? • What background information would someone need to understand the results of the paper? • What is the overall objective of the study?
Methods/Results	• What biological question is the experiment presented in the figure trying to address? • What are the positive/negative controls? • What are the technical controls? (e.g., loading controls for a western) • What additional controls (if any) are included? • Are any controls missing? • Can you identify any confounding variables? • How does the assay used to generate the data actually measure the phenomenon? • Does the data presented in the figure follow the authors' interpretation? • Is there an alternative/additional experiment you could do to address the same biological question?
Discussion/Critique of paper	• Did the data presented in the paper address the authors' main objective? • Did the authors place their findings into broader context? • What are the main strengths of the paper? • What are the main weaknesses of the approaches used? • What additional experiments could you do to validate the data shown? • If you were to continue this line research, what experiment would you do next?

into what they are learning as a way to show students how immunological concepts can be applied.

The culminating event is the in-class discussion of the paper, for which I will commit at least 2 contact hours. Students are encouraged to bring a copy of their paper summaries to the discussion. The discussion begins by covering the key points in the introduction, making sure that students understand the necessary background information as well as the main objective of the paper. If the paper relies heavily on an advanced technique, a significant amount of time will be spent making sure all students understand how it works, typically expanding on the threads from the online forum. The majority of the discussion will revolve around the results. For each experiment, I will have the students indicate the specific question that is being addressed (and why). Students will then be asked to identify the positive and negative controls and to assess if they are good controls to use for the experiment. Most importantly, I will ask the students to indicate whether the data presented in the figure support the authors' hypothesis. This is critical, as I have found that students will often take the authors' conclusions as absolute truth and typically will not critically evaluate the figures when they write their paper summaries. Importantly, this question forces students to actually think about the data and what it means. Finally, we spend time on the discussion section of the paper, with the goal of putting the findings into broader context. In addition to covering the content the authors' provide, I ask students to identify additional experiments that could be done to support the authors' conclusions, including asking how they might design such an experiment. We also spend time critiquing the science within the paper, as I want to instill in the students that scientists should be critical in evaluating science, even what is presented in a peer-reviewed publication. Examples of questions to ask that may assist in promoting discussion are provided in **Table 3**.

For an incredibly enriching experience, consider bringing in the first author or corresponding author of one of the papers to lead the in-class discussion. In the past, I have invited scientists in the context of a traditional campus visit, where I've had the speaker give a typical "research talk" open to the public in addition to leading the discussion of one of their papers in my Immunology class. Each time I've done this, the students really enjoyed being able to ask more deliberate questions (e.g., "why did you think to do that particular experiment?" or "how did you first generate the hypothesis?"). The guest speaker can also give the students insight into the process of doing science that isn't easily gleaned from reading the paper (e.g., pitfalls encountered and how they were overcome). A few words of caution are in order. First, you should let the speaker know that they will most likely not be able to discuss the entire paper in the context of an hour-long session (the remainder of the paper can be discussed at a future class meeting). Second, be prepared that the discussion may very well turn toward topics such as the speaker's career path. Personally, I welcome these turns, and plan accordingly by anticipating using more total time for the discussion. Finally, I give extra preparation for the students (via taking a more active role in guiding discussion on the online forum prior to the speaker's visit) to ensure that the students will make a good impression on the speaker.

TABLE 3 | Checklist that can be used to develop paper-specific rubrics for grading paper summaries.

Section	Element
Introduction	Background elements described sufficiently to understand the remainder of the summary The relevance of the study/authors' motivation clearly stated Model systems employed are adequately described The objective of the paper is clearly stated
Methods/Results	All experiments (except supplemental data) are described Technique/method used to obtain data for each experiment is mentioned Attempt made at synthesizing information presented in figures
Discussion	How did the authors place the findings into the context of published literature? How do the authors reconcile any differences with published literature (if applicable)? Did the authors adequately address the objective? What weaknesses (if any) does the paper have? Overall critique of the paper
Formatting/Other	Did summary conform to length limit? Is the summary organized logically? Is the writing concise and clear? Check for plagiarism (including from paper abstract)

ASSESSMENT OF LEARNING

Students are formally assessed via three mechanisms: the paper summary, participation in discussion, and on exams. The paper summary serves as the mechanism to ensure that students have deeply read the paper prior to the in-class discussion. When grading their summary of the introduction, I look to see if the student provides enough background to understand the premise of the paper and that they clearly articulate the overall objective. For the results section, I look for completeness: did the student summarize all of the salient experiments in the paper? Did they identify the technique(s) used to obtain the data? I also gauge whether the student was able to synthesize the information they read. When grading the discussion portion, I look to see if the student can place the findings into a broader context, and whether they understood the major points the authors raise. Importantly, throughout the summary, I do not penalize the students for incorrectly interpreting the data or the authors' conclusions, as it is inevitable that some of the concepts or technical aspects may be too difficult for the student to get on their own reading. **Table 2** provides a generalized rubric for grading paper summaries that is augmented with additional elements specific to the particular paper assigned.

Students have the opportunity to participate in the discussion of the paper via two modalities, the online forum and the in-class discussion. I will moderate the online discussion by providing hints or clues to point the discussion in the right direction when questions go unanswered or if student responses are incorrect. If overall activity is low or if there is a particular technical aspect or biological concept that I anticipate students might struggle with, I will proactively post discussion questions that will aid in student understanding. The in-class discussion

follows the same philosophy as the online forum, except the goal is to ensure that students gain a thorough understanding of the paper. We will go through every panel of every figure in the paper (typically not supplemental data). For each figure, I make sure students understand the experimental design and are charged with explaining why the data presented in the figure supports the authors' written conclusions in the text. In terms of grading student participation, I value online participation just as much as participation in the in-class discussion. That said, it is my expectation that every student will engage in the in-class discussion. For both the online forum and in-class discussion, I am interested in seeing thought-provoking questions and well-thought out answers. I am clear with students from the outset that I am interested in quality not quantity. Students can earn up to 30 points throughout the semester for participation, representing 25% of the total points committed to primary literature for the course. Students gain points for either online or in-class participation. During the in-class discussion, I specifically do not allow students who have already maxed out their participation score to respond to questions raised until the rest of the class has had an opportunity to respond. I provide positive reinforcement to all student responses to encourage students to continue participating.

I assess student learning by incorporating questions from the paper on exams. I will typically take a figure from the paper and ask students to evaluate the data, including experimental design. Depending on the paper, I might ask the students follow-up questions about further experiments they might propose. I will also allow students to use a "clean" copy (not marked in any way) of the paper during the exam. In this case, I might ask students to identify the experiment(s) in the paper that address a specific hypothesis.

In terms of points toward the final grade in the course, I make the paper summaries worth 30 points each and students can get up to 10 points for participation in discussions of each paper (online and in-class). If discussing three papers over the course of the semester, collectively this amounts to a bit more than a single exam. I have found this weighting provides sufficient incentive for students to perform at a level needed for a good discussion of the paper and achievement of learning outcomes.

CONCLUDING REMARKS

Successfully incorporating primary literature into the undergraduate Immunology curriculum presents unique challenges and opportunities for the Instructor. Perhaps the most important challenge is to clearly identify the learning goals you wish to achieve. Once the goals are established, great care must be taken to select papers that will meet those goals, are accessible to your students, and will fit into the curriculum. Importantly, implementation must include mechanisms that encourage students to read the literature with the depth necessary to understand the science and provide means to clarify some of the technical and conceptual issues associated with the paper prior to the in-class discussion. If all of the above is done well (a tall task!), you can expect that your students will have learning gains in addition to learning immunology beyond the textbook to include enhanced analytical and critical thinking skills, improved scientific literacy, a greater appreciation for how scientific knowledge is obtained, and greater enthusiasm for learning other aspects of immunology. In my experience, most students can see the immediate benefit of reading and evaluating primary literature as evidenced by unprompted comments such as these on end-of-course evaluations:

> "The journals were one of my favorite parts of the course"
>
> "I loved the papers we had to discuss."
>
> "…the paper discussions were very helpful and will definitely help us in the future as we begin to conduct our own research and review published work in our future careers."
>
> "the papers were well chosen and extremely interesting."
>
> "[Suggestions for improving the course include] additional papers to read"

In addition to all of the above, and perhaps most importantly, the ability to read and understand primary literature will serve your students well beyond the classroom as they will have gained the toolset needed to serve as competent ambassadors of science.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Setting Up an Undergraduate Immunology Lab: Resources and Examples

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Laboratory courses in immunology require a different skill set for their development than lecture courses. They vary widely in their form based on factors like institutional budget and class size, and also in the prioritization of learning goals centered around reinforcing lecture concepts and/or building fundamental skills in the field of immunology. Lab activities can come from a variety of sources including published research protocols, commercial kits, computer-based tools or simulations, and case studies. Each has their own strengths, which will be explored here. There are also important decisions to make about how students will report their data, and what level of guidance in interpreting data is best to enhance student learning and growth. Finally, methods like use of rubrics can help ensure fair and efficient grading, especially with skills-based learning goals. Periodic assessment is important to ensure that activities contribute effectively to student learning and to guide improvements to the lab course over time.

Keywords: lab, ELISA, flow cytometry, epitope prediction, pedagogy

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INTRODUCTION

Why Labs in Undergraduate Immunology Courses?

Lab courses can be expensive and time-consuming for the instructor—why should they be an integral part of any undergraduate immunology course? Well-designed multi-week lab experiments that involve students in experimental design, data analysis, and science-specific communication uniquely reinforce course content, increase student appreciation of the scientific method, and refine communication skills. Additionally, the lab component of immunology courses can expose students to key discipline-specific techniques (such as flow cytometry), which can give those students who might be interested in pursuing laboratory positions an advantage.

Recognizing that students with a wide variety of motivations and career goals will likely be present in any given undergraduate course, it is essential that laboratory activities reinforce content-focused course learning objectives (1). Student participation in labs that are focused on the cellular and humoral components of the immune system forces them to spend more time considering each cell type's unique contribution to the immune response. This understanding provides a strong foundation and can prompt a greater enthusiasm for and an improved understanding of the complete immune response.

Eliminating Potential Roadblocks in the Early Phases of Lab Exercise Design

Clearly establishing the cost expectations for the lab within the context of department budgets is very important. This will determine a number of downstream variables such as use of kits, reagent

availability, and staff support time. It is helpful to budget for the lab to cost at least 10% more than expected for unforeseen costs, especially the first time a lab is implemented. Misunderstandings around cost expectations are a major potential pitfall, especially for new faculty. A frank discussion with the department chair is warranted to establish clarity.

Instrumentation and facility availability are additional potential issues for the selection and design of lab exercises. Flow cytometry exercises are impractical without ready access to a flow cytometer. However, in some cases, access to instrumentation simply enhances an exercise. ELISA assays with visual readouts are more qualitative, whereas access to a plate reader makes them more quantitative. Activities involving cell culture require sufficient cell culture facility capacity to accommodate coursework. Higher level activities like this typically rely on smaller lab spaces designed for research. A lab may be more effective if students are split into smaller groups, which allows the instructor more time with students, but may reduce total lab hours for the course. Additionally, while students can be sub-divided into groups, the instructor cannot. Some activities require close supervision while others can be more independent.

Determining the appropriate level of guidance to offer is important at every phase of the exercise design. Advanced students may benefit from receiving manufacturer's protocols with minimal additional guidance to help them begin to adapt to future independent work in a lab setting, whereas detailed protocols, and analysis guidance may be appropriate for introductory or non-major's courses.

POTENTIAL SOURCES OF MATERIAL FOR LAB EXERCISES

Adapting Protocols From Research Literature: Potential Issues

Work involving human samples is enticing to students with clinical interests, but it can involve its own set of regulatory challenges. Campus rules determine which human samples students may use. Even if students work with their own cells, a blood draw coordinated with the help of a qualified professional (nurse, phlebotomist, or other clinician), together with the processing of cells pose challenges. KG's immunology lab course has used an HLA sequencing protocol from the literature that was initially developed to work with the small amount of cellular DNA present in plasma samples (2). The sensitivity of the amplification protocol allowed the use of cells from cheek swabs as a source of genetic material when the protocol was adapted for HLA typing in the classroom (3). Materials for the classroom exercise included cheek swabs, DNA extraction kits (or chelex resin), PCR mix (beads or liquid), and primers. The products can be sequenced in house or commercially. As such, the cost of implementing this protocol could vary a bit, depending on choices made by each instructor. Although KG's institution does not have its own sequencing facilities, we were able to sequence samples for a reasonable cost at a local research institution. We also regularly perform PCR in multiple labs, so we were able to obtain master mix and primers for nominal costs. The published research protocol was developed to sequence all HLA Class I loci, but our classroom exercise only analyzed the HLA-B locus. Secretory IgA ELISA kits are also available to work with saliva samples (e.g., Abnova). These approaches eliminate the need for a blood draw, but the problem of safe handling of biological materials, and waste disposal still exists (see **Supplementary Materials**). Alternatively, students may work with cell lines or DNA, which can be purchased from ATCC (www.atcc.org). Lastly, it is important to consider the regulatory approvals that may be required, especially if any data collected from or about the students and their experiences in the lab course may be published. Institutional Review Board (IRB) approval may be necessary for research using human samples, even when the research is conducted in a classroom setting. Institutional Animal Care and Use Committee (IACUC) approval is needed for the use of vertebrate animals in the classroom, even if the uses are purely instructional. For tips on the safe handling of mice, consult Assessing the Health and Welfare of Laboratory Animals' website (http://www.ahwla.org.uk/site/tutorials/BVA/BVA05-Mouse/Mouse.html). Sources of specific protocols adapted for undergraduate labs include the Association for Biology Laboratory Education (http://www.ableweb.org/volumes/volume-38/), and CourseSource (https://www.coursesource.org/). Some journals emphasizing laboratory protocols for undergraduate education include CBE—Life Sciences Education and the Journal of Microbiology and Biology Education.

Kits Developed for Classroom Use

Several manufacturers produce kits developed specifically for educational use. Kits are incorporated into the ELISA (Bio-Rad and NeoSci) and Western blot (Bio-Rad) units in KG's lab courses. Edvotek also provides kits to perform immunology experiments. Kits are usually set up to provide a defined number of student workstations or assays (12 workstations of 2–4 students for the Bio-Rad ELISA kit and 8 workstations for the BioRad Western blot kit; the Neo-Sci ELISA kit contains enough reagents for 40 students working individually). The potentially high cost per student (especially when compared to purchasing raw materials to prepare all the necessary reagents) may be offset with a reduction in in-house development time and resources dedicated to reagent preparation, validation, and quality control. The use of kits with an established track record of success also allows the instructor to focus on other aspects of the activity more closely tied to higher order learning goals for students, like data interpretation, and analysis. While kits may not always closely emulate the research lab experience, many clinical assays are kit-based. Students who go on to work in clinical or core labs may benefit from the experience they gain by following detailed protocols closely and carefully.

Kits/Reagents for Flow Cytometry

Flow cytometers can be used in an undergraduate immunology course in a number of ways. A number of manufacturers offer an array of antibodies and kits that can help guide lab design (**Table 1**). As a way to reduce cost, students can work in small

TABLE 1 | Examples of reagents and kits available for use with flow cytometers that may be useful in designing lab activities for undergraduate immunology courses.

Topic	Suggested cell types	Reagent (Manufacturer, Cat. No)	Cost	Students supported by one kit
Cell proliferation	Mouse T cells, B cells, Jurkat cells	CFSE-labeling (Tonbo, 13-0850-U500)	$23/500 μg	Quantity sufficient to label up to 10×10^6 cells on 20 separate occasions; depending on experiment details, quantity sufficient for 60 groups of students
Phagocytosis	Mouse bone-marrow derived macrophages, THP-1 cells	FITC-labeled latex beads for phagocytosis assays (Cayman Chemical, 500290)	$250/750 samples	One kit sufficient for 4 groups of students
Apoptosis	Mouse primary cells, Jurkat cells	Caspase-3/7 Fluorescence Assay Kit (Cayman Chemical, 10009135)	$198/96 wells	One kit sufficient for 6 groups of students
Apoptotic cell clean-up/Lupus	THP-1 cells + any cell as "apoptotic bait"	Efferocytosis Assay Kit (Cayman Chemical, 601770)	$295/kit	Quantity sufficient to label up to 10×10^7 effector cells and 2×10^8 bait cells; depending on experiment details, could support 15 groups of students
Cell viability	Any cell (primary or cell line)	PE Annexin V Apoptosis Detection Kit with 7-AAD (Tonbo, 50-6410-KIT)	$195/100 tests	Depending on experiment details, one kit sufficient for 10 groups of students
Cytokine production	Mouse T or B cells, Jurkat cells	Intracellular cytokine staining kit (protocol is for mouse, but can also purchase kit for use with Jurkat cells) (BD Biosciences, 554715)	$265/250 tests	Depending on experiment details, one kit sufficient for 20 groups of students
Identifying regulatory T cells	Mouse splenocytes	Foxp3 Transcription factor staining kit (ThermoFisher, 00-5523-00)	$165/kit	Depending on experiment details, one kit sufficient for 10 groups of students

groups with a small number of samples and then the results from each group can be pooled for data analysis. Instructors wishing to incorporate flow cytometry may find it useful to first provide archived data for students to practice analyzing, as has been done in other undergraduate laboratory settings (4, 5).

Computer-Based Tools/Simulations

The use of computer-based tools or simulations may permit students to explore areas where a program lacks instrumentation or resources to explore with a hands-on lab activity. In KG's lab course, students learn to use an online epitope prediction algorithm NetCTL (http://www.cbs.dtu.dk/services/NetCTL/). These epitope prediction algorithms are useful to help select a set of peptides for measuring immune responses when the potential number of candidate epitope peptides is large and the budget for peptide synthesis is limited. The lab activity emulates the validation experiments done for this algorithm (6). Other epitope prediction programs are reviewed and summarized in (7, 8). To guide students to identify metrics of success in advance, posing specific analytical questions in the pre-lab materials is helpful (see **Supplementary Materials**).

Case Studies

Case studies are a useful tool in the immunology lab course. Depending on the case study selected, teaching of additional clinical or public health related background material may be needed. Some of the publishers of immunology textbooks produce companion volumes of case studies with additional tools to help incorporate those case studies into an immunology course (e.g., Norton & Co.) Many web-based resources are also available. The National Center for Case Study Teaching in Science provides resources (http://sciencecases.lib.buffalo.edu/cs/). This site includes an interesting case study about the analysis of flow cytometry data (http://sciencecases.lib.buffalo.edu/cs/files/flow_cytometry.pdf) that could be especially helpful for instructors who want to teach the technique but are at an institution that lacks access to an instrument. KG uses a case study developed in the training program for the Epidemic Intelligence Service of the Centers for Disease Control (EIS) (https://www.cdc.gov/eis/casestudies/XscreeningHIV.student.871-703.pdf). This activity requires teaching some additional background on determining the predictive power of clinical assays, but this background is mostly developed in the context of the activity. Use of this activity also introduces students to a component of the US Public Health infrastructure that may offer future training or career opportunities for them.

EXAMPLES OF INQUIRY-DRIVEN LAB MODULES

We present here three Immunology lab modules targeted to upper-level Biology majors. All of the modules span multiple weeks, are inquiry-driven, and gradually involve students in experimental design.

In module one, students induce a sterile inflammatory response by injecting 1 ml of 6% thioglycollate into the peritoneal cavity of mice and follow the immune response over time (3 mice each at 0, 2, 24, and 48 h). Cellular changes in the blood are analysed using blood differentials and in the peritoneal cavity using flow cytometry. Detailed instructor notes and student handouts are provided as **Supplementary Materials**.

The second module is broadly focused on communication between the innate and adaptive immune response; students

analyze the effect of a particular substance on the ability of cultured macrophages to phagocytose latex beads. Students are first introduced to cell culture and are assigned a culture of THP-1 cells to take care of for the week. Next, each group brainstorms a list of substances/compounds that they hypothesize might affect phagocytosis such as garlic extract, honey, particular vitamins/minerals, etc. The class agrees on a substance and designs an experiment to test the effect of the chosen substance on the ability of THP-1 cells to phagocytose FITC-coated beads. Students consult the literature to determine methods of delivery, concentration, and the timing of application of the substance to the culture. Note that if a flow cytometer is not available, an instructor may instead use a fluorescent microscope to assess phagocytosis. Detailed instructor notes and student handouts are provided as **Supplementary Materials**.

The last module builds on the skills the students have practiced in the first two modules. The instructor introduces 1-3 key questions that students choose from. Groups of students present their experimental design ideas and the class votes on one research project (with feedback from the instructor about what is feasible given the number of lab sessions and resources available). In the past, students have chosen to determine if antibiotic exposure influences the isotype or quantity of antibody elicited by vaccination against OVA or KLH antigens using ELISAs. Importantly, to implement this option, instructors must also account for the time needed to order supplies.

MODULAR AND MULTI-DISCIPLINARY APPROACHES TO TOPIC AREAS IN LAB COURSES

In KG's ELISA labs, the technique is approached from several different directions. The qualitative nature of the technique (positive/negative test for an antibody response) is explored using the Neo-Sci kit (Neo/Sci Corporation) with a visual readout. The quantitative nature of the assay is explored using the Bio-Rad kit with a readout requiring a spectrophotometric plate reader. Lastly, the public health implications of the assay are explored using the case study activity developed by EIS.

The objective of the first subset of labs is to teach students about (1) the diagnostic significance of ELISA in clinical settings and (2) the limitations of ELISA tests in clinical settings. It is also an opportunity to introduce students to the challenges involved in discussing scientific results as "clinicians" in understandable terms with other students who role-play as "patients."

The quantitative section involves students generating a standard curve and measuring the concentration of the target in two unknown samples. This activity allows for the assessment of two interlinked outcomes. The first outcome relates to the precision of student pipet technique, which can be evaluated using the reproducibility of replicates in the standard curve. This offers a rare opportunity to make an objective assessment of a skills-based learning goal based on accurate and reproducible pipetting of small volumes. The second is the ability to estimate an unknown quantity using a standard curve. Students at Saint Mary's College of California complete a lab activity in their introductory biology course series involving total protein quantitation using Bradford reagent. With this background knowledge, upper-division students can evaluate the additional advantages of using a protein-specific antibody to quantify a single target protein of interest.

The case study activity supports the exploration of public health uses of ELISA assays. Because this is a more advanced application of the assay, it is done towards the end of unit dedicated to the ELISA. Students are already familiar with the technical aspects of the assay. Because they have seen the effects of pipetting precision on the outcomes of the standard curve and determination of unknowns, they are better able to identify potential technical faults in the assay. This activity helps students to see the changes in predictive value positive and negative in populations with greater or lesser prevalence of a tested antigen (in this case, HIV).

STUDENT PRESENTATION OF LAB DATA

The classic lab report is a commonly used method for instructors to assess student performance in lab. Alternatively, students can make small group or class presentations of their data and analysis, an approach that can increase student accountability for data quality. Additionally, as a way of differentiating the presentations from each other, groups of students can be assigned different discussion questions to incorporate into their presentations (see instructor notes for projects 1 and 2 in **Supplementary Materials** for examples).

Posters are a good way to convey results succinctly with an emphasis on visual impact and clear figure construction. Mock manuscripts with all the sections contained in a typical peer reviewed paper are another approach that can work especially well with advanced students. Ideally, teaching students to write mock manuscripts would begin in the introductory course and be reinforced throughout the curriculum. Posters and presentations can include a peer evaluation component.

ASSESSMENT OF THE VALUE OF LAB ACTIVITY

Designing labs around predefined learning goals enables multi-part lab activities with time for reflecting on progress and interpretation of the data. Sometimes the core principle or skill behind the goal can be taught most effectively with a simpler technique that is easier for students to grasp and more likely to generate meaningful data in their hands. However, teaching students current techniques and valued laboratory skills can translate into jobs for students upon graduation. Evaluating skills and behavior-based learning goals is an interesting area of assessment research, especially in training and evaluating medical residents [(9); American College of Physicians, accessed 2019[1]]. Some of these goals for medical resident evaluation programs are

[1] American College of Physicians. Available online at: https://www.acponline.org/about-acp/about-internal-medicine/career-paths/residency-career-counseling/preparing-for-internal-medicine-board-certification/the-board-certification-process/about-the-residency-performance-and-competency-evaluation-process (accessed 2019).

adaptable to the identification and measurement of skills-based learning goals at the undergraduate level.

Student impacts are measurable in a number of ways. Changes in student knowledge can be measured through pre- and post-testing around any given lab activity. Current student reflections and feedback can be a valuable source of information about the impacts of activities. Periodic assessment by former students who go on to graduate or professional study or work in the biotechnology industry can provide valuable feedback on the relevance of current lab activities and be potential sources of new lab activity ideas. Lastly, it is important to incorporate mechanisms to respond to constructive feedback and update activities as time progresses.

AUTHOR CONTRIBUTIONS

KG contributed experience in running computer simulation, ELISA, and case study labs and wrote these portions of the manuscript. MG contributed experience in running flow cytometry labs and wrote these potions of the manuscript. Both authors contributed collaboratively to other portions of the manuscript.

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SUPPLEMENTARY MATERIAL

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Immunology Education Without Borders

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One of the mandates of the International Union of Immunological Societies (IUIS) is to promote immunological education to young scientists across the globe, including a large focus on those from low and low-to-middle income countries (LIC and LMIC). It strives to achieve this goal through the Education Committee (EDU), which is one of ten committees of the IUIS. To this end, EDU organizes three to four one-week courses per year in close cooperation with regional immunological societies and local organizers. Initially, the focus has been on Africa, addressing the most relevant topics and health issues facing specific countries or regions in the continent. The idea was then extended to Latin America and now also includes courses in Asia. The faculty of all courses is a blend of international and local/regional experts also known for their teaching expertise. The courses are highly interactive, and include "meet-the-speakers" sessions, poster walks, and sessions on grant or PhD project writing, and on practical aspects of becoming a successful scientist. Importantly, all the IUIS-EDU courses use a combination of pre- and during-course on-line learning followed by consolidation of knowledge in a collegial setting. This "flipped" classroom approach ensures that participants have acquired the basic knowledge needed to optimize their participation in the course. Immunopaedia is the IUIS-endorsed immunology learning site used for this purpose. All faculty members are requested to contribute material related to their specific topic while students must learn the on-line material before coming in person to the course. All course participants have free access to all Immunopaedia material indefinitely. The implementation of regional immunology courses targeted to local health issues in areas of the world where PhD students, post-doctoral, and early career scientists often do not have access to open on-line resources and contact with renowned experts in the field has proven to be highly successful. The long-term impact of this structured educational program is already visible through the large number of young scientists who are now connected via Immunopaedia and who are forming networks in regions where there had been very little contact before and building new Immunological Societies.

Keywords: Education Committee, immunology courses, Immunopaedia, IUIS, on-line learning

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INTRODUCTION

The International Union of Immunological Societies (IUIS) is the umbrella organization for regional federations composed of national societies of immunology throughout the world. There are four regional Federations (EFIS, European Federation of Immunological Societies; FAIS, Federation of African Societies of Immunological Societies; ALAI, Latin American Association of Immunology; FIMSA, Federation of Immunological Societies of Asia-Oceania) with currently 77 member societies and > 60,000 immunologists worldwide (http://www.iuisonline.org). While the overall goals of the IUIS are to promote cooperation and communication between member societies and to contribute to the advancement of immunology in all fields and aspects, most of the implementation of these goals are carried out by the ten committees: Clinical immunology, Education, Gender Equality and Career Development (GEC), Inborn Errors of Immunity, Immunotherapy, Nomenclature, Publication, Quality Assessment and Standardization, Vaccine, and Veterinary Immunology. The task of the Education Committee (EDU) is to promote immunological education and disseminate knowledge to students and young scientists in LICs and LMICs of the world. The EDU Committee is truly international and is currently comprised of 17 members from 16 different countries from around the world, representing the four regional federations and North America (US and Canada) (see **Supplemental Table 1**). In the following sections, we expand on the various activities of the EDU Committee in recent years, including the sponsoring of new courses in LIC/LMICs and providing travel awards for young immunologists from these regions to attend specific well-established training courses. We then focus on the organization of our own brand of immunology courses and describe Immunopaedia (https://www.immunopaedia.org.za/), which is the IUIS endorsed immunology learning site that supports IUIS-EDU courses in LIC/LMICs. For each course, a separate content composed of several modules is generated where relevant topic-related teaching material (reviews, lectures, background information) is collected and made freely available to students. All course participants have free access to the content, not only pertaining to their specific course, but to a rich spectrum of immunology material related to all courses and for an indefinite period.

ACTIVITIES OF THE EDU COMMITTEE

The EDU Committee acknowledges the benefit that young scientists from LIC/LMIC experience when participating in high-level training courses abroad. In cooperation with the American Association of Immunologists (AAI), EDU has selected each year since 2008, three (and now four) students to attend each of the AAI Introductory and Advanced Immunology Courses. In partnership with the Federation of Clinical Immunology Societies (FOCIS), we have also awarded three fellowships per year between 2009 and 2016, for students to participate in the FOCIS Advanced Course in Basic & Clinical Immunology. The IUIS Gender Equality and Career Development Committee (GEC) has helped us financially by sponsoring one student for each AAI course per year and since 2017 has taken over the selection and co-sponsoring of the FOCIS awards. In collaboration with the German Society for Immunology (DGfI), EDU supports three travel awards for candidates selected by DGfI together with those wishing to attend the Ettal Spring School (https://dgfi.org/akademie-fuer-immunologie/spring-school/; see **Table 1**).

These travel fellowships are advertised on IUIS, FAIS, ALAI, FIMSA, AAI, and DGfI websites. For each of these courses, the number of applications by far exceeds the available fellowships, and it is a demanding task for the committees to make a fair candidate selection based on professional competence, gender balance, and region of origin. Depending on fund availability, EDU has contributed financially to several established courses

TABLE 1 | Activities of the IUIS-Education Committee.

A. Ongoing annual activities:

- Since 2008, in collaboration with the American Association of Immunologists (AAI) we have selected annually 3 (now 4) students from the LIC/LIMCs and co-sponsored their participation in the AAI Introductory and Advanced Immunology Courses, respectively. The IUIS-GEC committee provides one of the travel awards
- Since 2011, we have supported annually 3 travel fellowships for students from LIC/LMICs and East-European countries to attend the Ettal Spring School of the German Society for Immunology

B. Previous activities:

- 2009–2016, selection and support of 3 students to attend the FOCIS - Advanced Course in Basic and Clinical Immunology
- 2012–2017, support for the EFIS-EJI South Eastern European Immunology School (SEEIS), in Sarajevo, Bosnia and Herzegovina, Bulgaria, Romania, Montenegro, Albania, and Ukraine, respectively
- Funding for the EFIS-EJI Ruggero Ceppellini Advanced School of Immunology, Milan (2013, 2014); Advanced WHO/TDR Course on Immunology, Vaccinology, and Biotechnology, La Paz, Bolivia (2008), Lausanne (2010); Immunoparasitology Conference, Woods Hole, USA (2010)
- Funding for several FIMSA courses in Queensland, Australia; New Delhi, India; Singapore
- Awards for the Introductory Course in Immunology in Sudan, 2008; Flow Cytometry Schools in Morocco (2013, 2016) and South Africa (2013); Mediterranean Courses of Immunology in Morocco (2007) and Algeria (2010); the ICGEB Training Course in Global Infectious Disease Research 2013, Cape Town, RSA
- Support for John Humphreys Advanced Immunology Courses in Moscow (2007) and Havana (2012)
- Contribution to the International Courses for Clinical Immunology of Infectious Diseases at Suez Canal University (2007, 2008) and the E-training Workshop on Mucosal Immunity/Vaccine in Fayoum University, Egypt, 2009
- Travel awards for students to attend Regional Congresses (FIMSA Singapore 2015; FAIS Durban,RSA, 2012, Nairobi, Kenya 2014, Hammamet, Tunisia, 2017) and International Congresses (Rio de Janeiro, Brazil 2007, Kobe, Japan 2010)
- Funding of multiple ALAI courses: Immunomodulation 2009, Mucosal Immunology, 2010, Immunotherapies, 2010, in Buenos Aires, Argentina; First Argentinean Spring Course in Advanced Immunology, Los Cocos, 2013; Mucosal Immunology and Vaccination, Trinidad, Cuba, 2010; São Paulo Immunology Course, Brazil, 2011; First Meeting about Primary Immunodeficiencies in Latin America, Lima, Peru, 2011

C. Unique activities:

- Organized the BioLegend-IUIS Symposium on "Global Immunology Challenges for Young Investigators" at ICI 2016, Melbourne, Australia
- ISIA Advanced Course of Immunotherapy, Tehran, Iran, 2018

by providing student travel awards. The EFIS-EJI South Eastern European Immunology School (SEEIS), organized annually in a different country, provides an update on immunology and practical exercises in technologies like flow cytometry or diagnostic autoantibody microscopy. EDU and GEC committees both provided travel awards to the Ceppelini EFIS-EJI Ruggero Ceppellini Advanced School of Immunology. **Table 1** illustrates the many courses, workshops and international meetings to which EDU contributed financially since 2007.

Reports from the EDU supported activities can be found on the IUIS-EDU website (http://iuisonline.org/index.php?option=com_content&view=category&id=39&Itemid=81&5a48d87dcdf6fac96a6bc0ffc1b9e64c=6704e3a3cee3647430590629d6d2c3c4).

At the International Congress of Immunology 2016 in Melbourne, Australia, EDU obtained support from BioLegend to organize for the first time a symposium on "Global Immunology Challenges for Young Investigators." BioLegend offered 4 travel awards that allowed the selected students to attend the main conference, share research findings and discuss their challenges with other international students and faculty.

Furthermore, EDU co-organized and co-sponsored (together with the IUIS Clinical Immunology Committee) the ISIA Advanced Course of Immunotherapy, Tehran/Iran in April 2018. Immunology has a long academic tradition in Iran, and this activity again underscores the ambition of the EDU Committee to support "Immunology Education without Borders."

THE CONCEPT OF IUIS-EDU COURSES

Focus on Low and Low-to-Middle Income Countries

Immunology is among the fastest growing disciplines in contemporary biomedical research. Currently, we witness how immune modulating concepts and novel biologics modify and actually replace or complement established therapies at breathtaking pace. Introduction of immune checkpoint inhibitors has revolutionized cancer immunotherapy in recent years (as acknowledged by last year's Nobel Prize in Physiology or Medicine awarded to Drs. James P. Allison and Tasuku Honjo). Furthermore, the approval of cytokine-blocking biologics has helped enormously to ameliorate symptoms in chronic inflammatory diseases. The successful introduction of vaccines can still be considered the most effective preventive measure in medicine worldwide. Notably, however, efficacious vaccines are still in development and not yet available for some of the major infectious diseases (e.g., tuberculosis, malaria, schistosomiasis, HIV) which tend to predominate in LIC/LMICs worldwide. One such example is the outbreak of Ebola in West and Central Africa, reminding us of the urgent need for rapid responses and further research into basic and applied/clinical immunology in order to better understand the complexity of the immune system. This is important for the development of rational immune therapies in the same way this has been done for Ebola vaccination strategies. Given that the prevalence of such tropical and other infectious diseases is disproportionally high in less developed countries, it is mandatory to train the young PhD and clinician scientists in those parts of the world in such a way that they can become future scientific leaders. The ultimate goal is to have in-country immunology leaders who can attract funding and a critical mass of followers to offset the current poor infrastructure and facilities that are found in many LIC/LMICs. The mandate from the IUIS was to increase the numbers of regional courses using our unique brand of blending immunology knowledge with career skills building. This has meant networking and building teaching modules with local immunologists, identifying the most pressing health issues in the area and bringing international faculty to participate in an interactive course. Due to the fact that the EDU budget is very limited, fundraising then becomes an important task for each of the regional courses.

With this in mind, EDU has introduced the concept of "immunology plus," where we aim to promote highly interactive courses that include informal meet-the-speaker sessions, poster presentations, grant writing training, PhD fellowship project writing, and practical sessions on how to prepare a CV and how to verbally interact with colleagues and faculty. The goal is to show students how to become a successful scientist through immunology. One key aspect of a thriving immunologist is the ability to network with peers and more established scientists. Thus, a critical aspect of every IUIS-EDU course is to allow all participants and faculty from around the world to interact and build lasting contacts. Efficient mentoring is most important for the positive establishment of an academic carrier, and we encourage both participants and faculty members to build up lasting mentorship relationships during the courses. We also put an emphasis on specifically encouraging women PhD students and researchers to enter a career in science, despite obvious obstacles in many places. Together with the Gender Equality and Career Development Committee (GEC) we organize sessions on women in science issues, with an inspiring and experienced guest who reflects on her personal career development and advises on gender-related issues. Dr. Olivera Finn, chair of GEC, and Dr. Narinder Mehra, GEC co-chair have organized and chaired several sessions at international meetings, including the FAIS 2014 meeting in Nairobi, Kenya (with guest Dr. Jane Kengeya-Kayondo, Wellcome Trust, Special Adviser for Africa); at ALAI 2015 in Medellin following our Immune-Columbia course (with guest Dr. Nancy Gore Saravia, Scientific Director and Research Leader for Leishmaniasis, CIDEIM); at the International immunology Congress in Melbourse, Australia, in 2016 (with guest Dr. Laurie Glimcher, President and CEO of Dana Farber Cancer Institute); at FAIS 2017 in Hammamet, Tunisia (with guest Dr. Oum Kalthoum Ben Hassine, Founder and Director of the Research Unit of Biology, Ecology and Parasitology of Aquatic Organisms at the University of Tunis); and at ALAI Meeting in Cancun, Mexico, in 2018 (with guest Dr. Clara Gorodezky, Head of the Department of Immunology and Immunogenetics of the Istituto de Diagnóstico y Referencia Epidemiológicos of the General Direction of Epidemiology at the Secretary of Health in Mexico). Dr. Michelle Letarte, past-chair of EDU, has managed several dinner discussion groups including at the Onco-Immunology Mexico Course in San Miguel de Allende in October 2017 and at the Immune-Ethiopia course in Gondar

in March 2017. Dr. Miriam Merad, Mount Sinai Endowed Professor in Cancer Immunology, gave a scientific lecture as well as a career motivation dinner talk at the Morocco course in Fes, in 2018. At the Immuno-Informatics course in Mexico City in April 2019, Dr Selene Fernandez-Valverde, a young Mexican investigator with already an outstanding career at the intersection of bioinformatics and developmental evolutionary biology and who received L'Oreal-UNESCO Research Fellowship For Women in Science Award and International Rising Talents Distinction in 2016 and 2018 respectively, reflected on her personal career development and how it was modulated by family and other gender-based issues. Such exemplary role models can help to motivate young women PhDs to pursue a career in science and to ensure and reassure them that they are not alone.

Application and Selection Procedures

IUIS-EDU Courses are advertised on the websites of IUIS, its Federations and Regional Societies, Immunopaedia, and other relevant networks. Applicants are usually requested to provide a letter of motivation, a short CV (with a publication list, if applicable), a letter of support from their supervisor, and an abstract to be presented as a poster and/or short talk. All applications are reviewed by a scientific committee consisting of members of EDU, the Regional Federation and/or Society, and local scientists. Selection of candidates is based on the respective ranking and additional aspects such as gender balance and country of origin. Generally, students from ten or more countries attend the course and generate an enormous amount of energy and healthy competition. The faculty of all courses is a blend of international and local/regional scientists. Whenever possible, faculty and participants stay at the same hotel to foster informal interactions during breakfast and dinner. Importantly, all the EDU courses use a combination of on-line pre-learning with consolidation of that knowledge during contact time on the course. This "flipped" or blended classroom approach ensures that participants learn or review basic immunology modules on-line prior to contact time. Our adapted approach has been based on several active learning approaches in science, engineering and mathematics (1) as well as innovative teaching in immunology (2). Such an approach has allowed a more interactive and a more discursive 5–7 day course around the theme of the meeting. Evaluation of the course has so far been around the enjoyment and use of Immunopaedia and the ease of learning. Besides holding pre- and post-MCQs to assess short-term knowledge gain, being able to assess whether application and synthesis of immunology knowledge is gained has yet to be made and the IUIS would need to collaborate with immunology education specialists to achieve this goal. Despite this, Immunopaedia is the IUIS endorsed immunology learning site that is used for all our courses in LMICs (see below). The long-term impact of the structured educational program initiated by IUIS-EDU is already visible, e.g., through the formation of networks of young scientists in regions where there had been very little contact before. One example is WAYII, the West African Immunologists' platform launched in 2016 by Léonce Kouakanou and Ulrich Fabien Prodjinotho during the IUIS-FAIS-IMMUNO-GAMBIA course in Banjul/The Gambia. WAYII aims to promote Immunology in Africa by providing an interactive interface for network; to establish and/or reinforce regional collaborations; to enhance transfer of skills and knowledge, and finally to help in organizing meetings, trainings, conferences. More information on WAYII activities is available on the Facebook page: https://www.facebook.com/WestAfricanYoungImmunoInvestigators/. In cooperation with the Federation of African Immunological Societies (FAIS), we have initiated the "Africa Immunology School" concept where on average two courses per year are organized on the continent, rotating between the five regions of Africa. These courses usually accept 40 to 50 participants (PhD students, post-docs, young scientists, and medical doctors) from the host and surrounding countries, with topics adapted to the specific regional needs. In line with the large burden of disease on the Continent, a major topic of courses in Africa focus on the big three: HIV, tuberculosis, and malaria, although there are regional differences in the importance of these. Other significant themes have included Ebola, helminth infections, or infection-associated cancers. A second geographical focus of IUIS-EDU activities is Latin America where courses have been organized in Columbia, Brazil, and Mexico in collaboration with the Latin American Association of Immunology (ALAI) on topics ranging from Vaccines to Immunoregulation and Bioinformatics. Currently we are extending our activities to additional regions: a first course organized in collaboration with the Federation of Immunological Societies of Asia-Oceania (FIMSA) will take place in Jaipur, India. Since the inception of this program in 2015, 11 courses have been organized (Colombia, South Africa [x2], Tunisia, Mexico [x2], Ethiopia, Gambia, Brazil, Morocco, Kenya) and 6 more are being planned (South Africa, India, Benin, Ethiopia, Algeria, Argentina). An overview of topics and locations of IUIS-EDU courses since 2015 is presented in **Table 2**.

The teaching activities of the EDU committee require the voluntary commitment of a dedicated faculty including experts for the various topics from different countries around the globe. Faculty members for IUIS-EDU courses are recruited through the EDU committee but also on the basis of personal interaction of scientists working in closely related fields. We aim to reach a balance between regional and international speakers, and we constantly make efforts to recruit new speakers for our various courses (with a focus on young colleagues). Needless to say that enthusiasm for teaching in an international setting is a "must." If you are interested to teach in one of the future IUIS-EDU courses, we encourage you to contact us by email.

Funding of IUIS-EDU Courses

A major issue of the organization of the EDU courses is how to secure sufficient funding. While all IUIS-EDU courses receive some basic funding from the EDU budget, this seed money is never sufficient to cover all expenses. Some courses have received additional funding from the IUIS Clinical Immunology Committee (CIC). Ideally, we aim to provide full support to accepted participants, which would include accommodation, meals, and transport. Local organizers are asked to seek government, University and private sector funding. In addition,

TABLE 2 | IUIS-Education Committee Courses since 2015.

Year	Course	Topic	Dates	Location
2015	IUIS-ALAI-IMMUNO-COLOMBIA	Immunoregulation in Health and Disease	October 10–13	Medellin, Colombia
2015	IUIS- IDA-SANTHE-FAIS-IMMUNO-SOUTH AFRICA 1	Biomarkers and Correlates of Immune Control of HIV, TB, and Malaria	October 20–24	Cape Town, RSA
2016	IUIS-FAIS IMMUNO-TUNISIA	Tolerance and Autoimmunity	April 4–8	Hammamet, Tunisia
2016	IUIS-ALAI-SMI ONCOIMMUNOLOGY-MEXICO	Oncoimmunology	October 5–8	San Miguel de Allende Guanajuato, Mexico
2016	IUIS-FAIS-IMMUNO-GAMBIA	Immunology of Infectious Diseases	November 19–26	Banjul, The Gambia
2017	IUIS-FAIS-IMMUNO-ETHIOPIA	New Developments in the Immunology, Diagnosis, and Treatment of Leishmaniasis, Schistosomiasis, and Helminth Infections	February 26–March 4	Gondar, Ethiopia
2017	IUIS-IDA-SANTHE-FAIS-IMMUNO-SOUTH AFRICA 2	Immune Tolerance and Evasion Strategies by Pathogens	September 1–6	Gordon Bay, RSA
2017	IUIS-ALAI-IMMUNO-BRAZIL	Advanced Course on Vaccines	December 8–11	São Paulo, Brazil
2018	IUIS-FAIS-SMI-IMMUNO-MOROCCO	Cancer, Inflammation, and Immunotherapy	April 3–7	Fes, Morocco
2018	IUIS-FAIS-IMMUNO-KENYA	How Viruses Hijack Host Immunity Leading to Cancers	September 23–28	Nairobi, Kenya
2019	IUIS-ALAI-SMI- IMMUNO-INFORMATICS	Immuno-Informatics	April 8–10	Mexico City, Mexico
Planned courses:				
2019	IUIS-IDA-SANTHE-FAIS-IMMUNO-SOUTH AFRICA 3	Vaccine Design and Vaccine-induced Immune Responses to HIV, Malaria, and TB	October 7–11	Cape Town, RSA
2019	IUIS-IIS-FIMSA-IMMUNO-INDIA	Basic and Advanced Translational Immunology	October 12–16	Jaipur, India
2019	IUIS-FAIS-IMMUNO-BENIN	Impact of Tropical Infections on Mother and Child Immunity	November 3–10	Ouidah, Benin
2020	IUIS-FAIS-IMMUNO-ETHIOPIA 2	Neglected Tropical Diseases and Malaria Challenges in Sub-Saharan Africa	February 23–29	Bahir Dar, Ethiopia
2020	IUIS-FAIS-IMMUNO-ALGERIA	Allergies and the Immune System	June 24–28	Algiers, Algeria
2020	IUIS-ALAI-IMMUNO-ARGENTINA	Immunological Memory in Infections	tbd	Cordoba, Argentina

members of the EDU Committee undertake substantial efforts to write proposals and recruit additional funds through public and private foundations, industry and other sources. Specifically, the Bill and Melinda Gates Foundation (BMGF), the Volkswagen Foundation (VWF) and the National Institutes of Allergy and Infectious Disease (NIAID), NIH have supported IUIS-EDU courses in Sub-Saharan Africa and Latin America (BMGF: Ethiopia, Brazil;VWF: Gambia, Benin, Ethiopia; NIAID: South Africa).

NOVEL ON-LINE LEARNING: IMMUNOPAEDIA

Immunopaedia (https://www.immunopaedia.org.za/) is the IUIS endorsed immunology learning site used for the purpose of IUIS-EDU courses. It was initiated by one of us (CMG), initially for training South African pediatricians in immunology. Immunopaedia has since developed from its inception in 2005. The original aim was to educate pediatricians on the basics of HIV immunology using clinical case studies to highlight an immunological concept. This was termed the "Trojan Horse" approach (3) and over time, Immunopaedia evolved to encompass a broader spectrum of the discipline. However, still at its core is the use of case studies to highlight the immunological defects leading to clinical abnormalities.

From 2015, we began to use Immunopaedia as an on-line pre-course primer. For each of the IUIS-EDU courses, we develop 6–10 learning modules that provide up to date "core" immunology and relevant topic-related teaching material. Core Immunology Modules include (i) a snapshot of the immune system, (ii) ontogeny of the immune system, (iii) the innate immune system, (iv) MHC and antigen presentation, (v) overview of T cell subsets, (vi) thymic T cell development, (vii) B cell activation and plasma cell differentiation, (viii) antibody structure and classes, and (ix) central and peripheral tolerance, and uses specially written material, interviews and plenty of graphics. Specific themed modules are also developed to support the IUIS-EDU course focus areas. These have included: vaccines, immune regulation, pathogens, cancer and autoimmunity, immunotherapy for example. The modules are compiled at least 2–3 months before each course and then made available to students 6 weeks ahead of the specific course. All faculty members are requested to contribute teaching material related to their specific topic. Students on the other

hand are requested to prepare themselves for the course by studying the on-line material and scoring >75% on set quizzes at the end of each module. These questions are provided by the faculty, although in some cases the Immunopaedia team also devises questions. After the learner finishes each set of Multiple Choice Questions (MCQs) an automated email of their grade is sent with correct and wrong answers, and why the answer is wrong. In 2018, 100% of the 145 registered participants of the various courses completed the pre-courses MCQs.

Immunopaedia also provides on-line evaluation forms to participants after the completion of an IUIS course. The feedback from the participants is very important as a guideline for further improvement. All course participants have free access to the Immunopaedia content, not only of their specific course, but of all Immunopaedia material indefinitely. The Immunopaedia content provides a rich knowledge resource for all fields of basic and clinical immunology. The offering of a pre-course is based on the "flipped" classroom approach which has been applied to other disciplines (4) and where at least one US tertiary institution has done away with lectures to medical students altogether (5). Such a blended learning approach has proved to be successful for some disciplines (1, 4), but questionable for others (6) and success is most likely dependent on course design. Pre-course on-line games for learning innate immunity, in the context of an accredited university course, has proved successful (2). The long term goal of the IUIS-EDU is to develop pre-course materials with a measurable outcome for the short 5–7 days duration.

A further aim of Immunopaedia has been to build a network of scholars from all IUIS-EDU courses by inviting highly active and motivated students who score exceptionally well on quizzes and questions to become Immunopaedia Ambassadors. Each Ambassador is networked via social media and the objective is to create a sustainable learning environment beyond the end of the course and a network of young immunologists. The tasks of the Ambassadors are to promote Immunopaedia in their hosting institution and to provide content, such as "breaking news" or interviews with prominent immunologists in their region. An example of inputs by Ambassadors were video recordings of prominent immunologists who attended the XII Congress of the Latin American Association of Immunology (ALAI) in 2018 (https://www.immunopaedia.org.za/interviews/video-interviews/alaismi-special-video-interviews/). We currently have 60 Ambassadors spanning Africa, Asia, Europe, North America, Oceania and South America and we feature an ambassador monthly. Each young immunologist has a dedicated space on the site and a link to their own website or other on-line presence. We have also partnered with Virtual Keystone Symposia (https://virtual.keystonesymposia.org/ks/) where Amabassadors can be selected to present their immunology research through Sci-Talks. Through this mechanism, the Ambassador platform provides additional networking and career-boosting opportunities.

CONCLUDING REMARKS

As summarized in this article, the activities of the EDU Committee have considerably expanded in recent years. With the initiative in 2015 to organize 3 to 4 structured IUIS courses per year we have substantially helped to promote the education and training of young scientists in LIC/LMICs. Mentoring at various levels beyond pure science through grant and research project writing, sessions on how to prepare a scientific CV and events promoting women in science is an important asset of IUIS courses. We regard this approach as having a sustainable impact on young scientists, as exemplified by the formation of networks of young immunologists in West Africa, or the recruitment of Immunopaedia "Ambassadors" to promote the unlimited potential of the on-line teaching platform. The ultimate aim of EDU activities is to fulfill the IUIS vision of "Immunology Without Borders."

AUTHOR CONTRIBUTIONS

DK, ML, and CG have equally contributed to this manuscript. All authors agree to be accountable for the content of the work.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2019.02012/full#supplementary-material

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Out of the Curricular Shadows: Revolutionizing Undergraduate Immunology Education

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Immunology has its developmental roots in understanding protection of the host from pathogens, leading to the development of vaccines and subsequently identification of soluble and cellular components of the immune system. Thus, immunology education has historically been tightly linked to infectious disease. Decades of research have demonstrated that the complexity and intricacies of the immune system are far greater than perhaps was once imagined. As a system that interfaces with all other organ systems in the body, it plays a key role in both maintaining health and causing life-threatening disease, thereby solidifying its importance in several clinical specialties beyond protective immunity. In the past decade, tremendous advances have taken place in which scientists and physicians have begun to harness the power of the immune system to create immunotherapies to fight cancer, inflammatory syndromes and autoimmune diseases. Thus, the argument can be made that training individuals in the field of immunology is becoming increasingly important. However, immunology is a highly conceptual discipline and understanding how the multiple cellular and soluble components of the immune system work in concert requires knowledge in a number of disciplines, including molecular biology, cell biology, genetics, and biochemistry. Time is needed for students to process, evaluate, and apply this information in meaningful ways. Concomitantly, knowledge in the field of immunology is expanding rapidly, bolstering the need for increased time in the curriculum to facilitate the ability of educators to convey information so that it can be effectively understood and applied. We propose that it is time for a renaissance in immunology education at the undergraduate level to better prepare individuals who will subsequently pursue careers in medicine, related health professions, and research. The purpose of this article is to discuss the current state of undergraduate immunology education with respect to its prevalence and how this compares to other biological disciplines, the need to develop robust immunology curricula at the undergraduate level and the importance of such programs in preparing students for pursuing postgraduate training in the health professions, and research-intensive careers.

Keywords: immunology, education, undergraduate, curriculum, major

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INTRODUCTION

The evolution of discovery in the field of immunology has been immense, highlighting the mechanistic intricacies of the immune system and opening opportunities to develop targeted therapeutic interventions based on understanding the fundamental molecular and cellular processes that regulate the function of the immune system. Education in the field of immunology has traditionally been restricted to graduate-level studies, but has not been widely adopted at the undergraduate level. An evaluation of undergraduate majors and programs that are focused on an immunology-intensive curriculum reveals that there are only a handful of such programs across the country, whereas there has been rapid growth of undergraduate programs in the biomedical field of neuroscience over the past 30 years. The comparison between immunology and neuroscience is particularly relevant because both systems are complex, interact with every other organ system in the body and play critical physiological roles in maintaining health, while at the same time having the potential to cause significant morbidity and mortality when they function abnormally. This raises the question of how and why neuroscience education has flourished at the undergraduate level, whereas immunology education has failed to gain traction. Although it might be logical to predict that this lack of immunology-focused programs may be compensated for by an increase in the number of undergraduate microbiology programs or an increase in the number of degrees conferred in this discipline, which is often associated with immunology, this is not the case. The total number of undergraduate microbiology programs and degrees conferred by such programs has remained relatively stable over the past 30 years.

The rapid expansion of discovery in the field of immunology has increased the demand for individuals who possess an in-depth understanding of the molecular and cellular processes that regulate the normal and pathophysiological function of the immune system, and who can effectively apply this knowledge to promote the health and well-being of individuals throughout the world. Concomitantly, there has been a call for evaluation and reform in the development of biology curricula that emphasizes multidisciplinary integration and the acquisition of competencies that extend beyond discipline-specific knowledge (1). Immunology, by nature, is interdisciplinary, requiring a knowledge of cellular and molecular biology, genetics, biochemistry, physiology, and anatomy. A strong case can be made that an undergraduate immunology major would exemplify the proposed reforms outlined in the Vision and Change report (1). Importantly, the shift to an emphasis on undergraduate training and the presence of robust undergraduate immunology programs could enhance the interest in, and number of students seeking immunology-related careers. We propose that the time has come for a reevaluation of the state of undergraduate immunology education. As a step forward, we have created an interdisciplinary major in immunology that provides both a broad-based curriculum, while at the same time providing a more in-depth focus on understanding the normal and pathophysiological function of the immune system. This major is designed to expose undergraduates to critical foundational and applied concepts in immunology at an earlier point in their educational experience and to prepare students for success at the next level, regardless of whether they choose to pursue a career in the health professions or in research.

Why Immunology

Although it has been patently clear for a long time that the immune system plays a critical role in protecting individuals against infectious diseases based on centuries of research, it is now well-appreciated that the immune system can promote a wide range of debilitating diseases including autoimmunity and inflammatory syndromes that affect every organ in the body. Additionally, when misdirected, the immune system has the ability to cause significant suffering associated with allergies and asthma, which can often be life threatening. In the context of transplantation, the immune response to the transplanted organ presents a tremendous challenge from a clinical standpoint and negatively impacts the ability to provide safe and effective transplants. Thus, identifying ways to selectively block the immune response to a transplanted organ would represent a major advance in the field of transplantation that would dramatically impact the lives of over 100,000 individuals in the US who are waiting for a transplant at any given time (https://www.organdonor.gov/statistics-stories/statistics.html). With the increased use of immunosuppressive drug regimens associated with transplantation, autoimmunity, and cancer therapy, individuals suffer from increased risk of infection by opportunistic pathogens. This problem is accentuated by the fact that there is an ever-increasing risk from drug-resistant microbial pathogens and the emergence of new microbial pathogens in response to numerous technological, sociological and global factors. Finally, recent advances in the field of immunology clearly demonstrate the power of the immune system to fight cancer. Basic knowledge of how the immune system is regulated has led to the identification of checkpoint inhibitors that have been shown to be effective in terms of reactivating the immune system's ability to destroy cancer cells (2–4). Other approaches have taken advantage of the ability of immune cells to specifically identify tumor cells leading to their targeted destruction (5–7). It has only been within the last decade that researchers and clinicians have begun to understand how to harness the power of the immune system in the form of highly targeted and effective immunotherapeutic approaches designed to detect and destroy cancerous cells in the body. Thus, the immune system plays a critical role in both health and disease and there is a robust need for individuals who are focused on all aspects of the discovery and application pipeline from foundational studies to understand how the immune system works, to translation of foundational principles into novel immunotherapies and finally the application of immunotherapies in the clinical setting. Thus, one can make the argument that there is a significant need for individuals who understand how the immune system works and how that knowledge can be applied to improve health.

Although one can make the case that knowledge of how the immune system functions has a high degree of relevance to

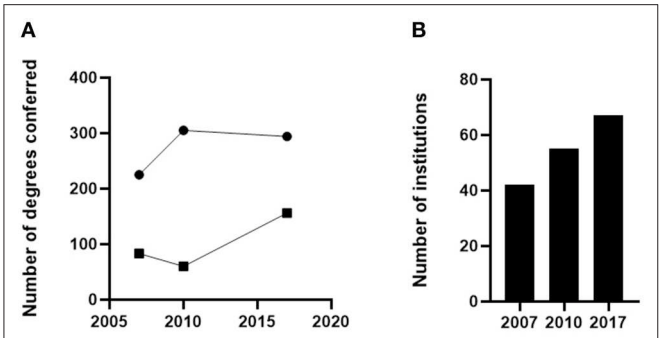

FIGURE 1 | The number of doctoral (•) and master's-level (■) degrees conferred by U. S. institutions **(A)** and the number of U.S. institutions offering doctoral degrees **(B)** described as "Immunology" or "Microbiology and Immunology" or "Microbiological Sciences and Immunology" between 2007 and 2017.

careers in the health professions, biotech/pharma and research, it remains a challenging task to obtain employment data to categorically support the need to train more individuals in the field of immunology, primarily because the vast majority of careers that are most likely to benefit from knowledge of the immune system are not specifically defined by the terms "immunology" or "immunologist." Nevertheless, one can obtain data on postgraduate education in immunology, as well as broad employment sectors in which immunology may be relevant to make the case that there is significant growth in those employment sectors that may be of interest to those individuals with training in immunology. With respect to postgraduate education, data from the National Center for Educational Statistics shows that between 2005 and 2017 there has been a modest increase in the number of MS and PhD degrees conferred by programs with an emphasis on Immunology (**Figure 1A**). In parallel, there has been growth in the number of postgraduate programs that focus on immunology during this same time period (**Figure 1B**). Thus, in contrast to the situation for undergraduate education in immunology, where there is little or no growth, data support the conclusion that postgraduate education in immunology is growing, albeit modestly.

Data from the U.S. Bureau of Labor Statistics also support the conclusion that employment sectors that could be of interest to those with knowledge of the immune are also growing at an above average rate over the next 10 years. The fastest growth sector from 2018 to 2028 is Healthcare and Social Services (8). This sector includes a wide range of occupations that would benefit from knowledge and training in immunology, so this is some indication that earning a degree in immunology may be of value in terms of obtaining a career in this sector. Additionally, there are a wide range of studies and reports from the American Association of Medical Colleges that clearly indicate that the US will face a shortage of approximately 122,000 physicians by the year 2032 (9). Once again, because the immune system plays a critical role in health and disease and has relevance to a wide range of clinical specialties, this suggests that education in immunology may be valuable for those who chose to pursue a career in the health professions. The U.S. Bureau of Labor Statistics predicts that employment in Health Diagnosing and Treating Practitioners that would include an emphasis on immunology will grow by 13% between 2018 and 2028, which is faster than the national average for all career categories (5%) (10). Growth in Medical Scientist careers will similarly increase by 8% between 2018 and 2028 (11). Data for the biotechnology sector from the IBISWorld Industry Report indicates that employment will increase approximately 4.6% between 2019 and 2024, which is slightly above the rate of growth for total employment in the US for that time period (12). Although these data do not specifically identify careers that rely on knowledge and skills in immunology, it can be argued that because of the important role that the immune system plays in health and disease and the increasing emphasis on harnessing the immune system for immunotherapies, that an education, which includes a focus on immunology may be beneficial to those interested in pursuing careers in the health professions, biotech, pharma, and research.

METHODS

Use of College Navigator

Information on the number of institutions offering specific degrees and information on degrees conferred by major and institution in the 2017–2018 academic year was obtained through the National Center for Education Statistics (NCES; nces.ed.gov). College Navigator through NCES was used to identify numbers of institutions offering Bachelor of Science degrees in Neuroscience by searching "Neuroscience," "Neurobiology and Neurosciences, Other;" in Microbiology by searching "Medical Microbiology and Bacteriology," "Microbiology and Immunology," "Microbiology general," "Veterinary Microbiology and Immunobiology;" in Immunology by searching "Immunology," "Microbiological Sciences and Immunology, Other," "Microbiology and Immunology."

Use of IPEDS

An analysis of the number of neuroscience, microbiology, and immunology degrees conferred over time was performed using the Integrated Postsecondary Education Data System (IPEDS) through NCES. Provisional data for all U.S. institutions were searched for "total number" of "first major," "Bachelor," "Master's," or "Doctor's" degree completions (award/degree conferred by CIP). The years 2017 and 2010 used the following degrees and CIP codes "Microbiology, General" and "Medical Microbiology and Bacteriology" (CIP codes 26.0502 and 26.0503) or "Immunology" and "Microbiology and Immunology" and "Microbiological Sciences and Immunology, Other" (CIP codes 26.0507, 26.0508, 26.0599) or "Neurobiology and Neurosciences" (CIP code 26.15). Prior degree categories and codes were slightly different from 2000 to 2009. For the 2007 data the following searches were done "Microbiology, General" and "Medical Microbiology and Bacteriology" (CIP codes 26.0502, 26.0503) or "Immunology" and "Microbiological Sciences and Immunology,

other" (CIP codes 26.0507, 26.0599) or "Neuroscience" (CIP code 30.24).

Literature Searches

Searches in the ERIC database were performed as follows for the indicated discipline.

Immunology, Results = 12

((Immunology AND ("Undergraduate Study" OR "Undergraduate Students")) AND ("College Curriculum" OR "Curriculum Development" OR "Curriculum Design" OR "Curriculum Enrichment" OR "Curriculum Implementation" OR "Instruction" OR "Teaching Assignment*" OR "Teaching Experience*" OR "Language of Instruction" OR "College Instruction" OR "Instructional Development" OR "Courses" OR "Education" OR "Undergraduate Study" OR "Undergraduate Students" OR "major*" OR "program*")).

Neuroscience, Results = 56

((Neurosciences AND ("Undergraduate Study" OR "Undergraduate Students")) AND ("College Curriculum" OR "Curriculum Development" OR "Curriculum Design" OR "Curriculum Enrichment" OR "Curriculum Implementation" OR "Instruction" OR "Teaching Assignment*" OR "Teaching Experience*" OR "Language of Instruction" OR "College Instruction" OR "Instructional Development" OR "Courses" OR "Education" OR "Undergraduate Study" OR "Undergraduate Students" OR "major*" OR "program*")).

Microbiology, Results = 98

((Microbiology AND ("Undergraduate Study" OR "Undergraduate Students")) AND ("College Curriculum" OR "Curriculum Development" OR "Curriculum Design" OR "Curriculum Enrichment" OR "Curriculum Implementation" OR "Instruction" OR "Teaching Assignment*" OR "Teaching Experience*" OR "Language of Instruction" OR "College Instruction" OR "Instructional Development" OR "Courses" OR "Education" OR "Undergraduate Study" OR "Undergraduate Students" OR "major*" OR "program*")).

Searches in the PubMed database were performed as follows for the indicated discipline.

Immunology; Results = 37

((("Students"[Mesh] OR Undergraduate-student*[tiab]) AND Immunology[tiab])) AND (("Curriculum"[Mesh] OR "Competency-Based Education"[Mesh] OR "Education"[Mesh] OR "Learning"[Mesh] OR "Teaching"[Mesh] OR Training-technique*[tiab] OR Pedagog*[tiab] OR Teaching-method*[tiab] OR Educational-technique*[tiab] OR Educational-activit*[tiab] OR Educational-method* OR Short-term-courses[tiab] OR Training-program*[tiab] OR Academic-training[tiab] OR Workshop*[tiab] OR major*[tiab] OR program*[tiab])).

Neuroscience; Results = 130

((("Students"[Mesh] OR Undergraduate-student*[tiab]) AND Neuroscience[tiab])) AND (("Curriculum"[Mesh] OR "Competency-Based Education"[Mesh] OR "Education"[Mesh] OR "Learning"[Mesh] OR "Teaching"[Mesh] OR Training-technique*[tiab] OR Pedagog*[tiab] OR Teaching-method*[tiab] OR Educational-technique*[tiab] OR Educational-activit*[tiab] OR Educational-method* OR Short-term-courses[tiab] OR Training-program*[tiab] OR Academic-training[tiab] OR Workshop*[tiab] OR major*[tiab] OR program*[tiab])).

Microbiology; Results = 103

((("Students"[Mesh] OR Undergraduate-student*[tiab]) AND Microbiology*[tiab])) AND (("Curriculum"[Mesh] OR "Competency-Based Education"[Mesh] OR "Education"[Mesh] OR "Learning"[Mesh] OR "Teaching"[Mesh] OR Training-technique*[tiab] OR Pedagog*[tiab] OR Teaching-method*[tiab] OR Educational-technique*[tiab] OR Educational-activit*[tiab] OR Educational-method* OR Short-term-courses[tiab] OR Training-program*[tiab] OR Academic-training[tiab] OR Workshop*[tiab] OR major*[tiab] OR program*[tiab])).

Searches in the Scopus database were performed as follows for the indicated discipline.

Immunology; Results = 28

("College Curriculum" OR Teaching OR Pedagogy OR major* OR program*) AND ("Undergraduate Students") AND Immunology.

Neurology; Results = 60

("College Curriculum" OR Teaching OR Pedagogy OR major* OR program*) AND ("Undergraduate Students") AND Neuroscience.

Microbiology; Results = 55

("College Curriculum" OR Teaching OR Pedagogy OR major* OR program*) AND ("Undergraduate Students") AND Microbiology.

RESULTS

Immunology Left Behind

The career path decisions of students are influenced by a variety of factors (13). Chief among these factors are personal interest and academic ability, self-confidence (14) and importantly, for women or those from underrepresented groups, the availability of appropriate role models (15–17). Although conscious factors such as personal interest and academic ability contribute to student choices, learning experiences can subconsciously influence student perceptions of academic fields and subsequent career choices. Students who enter college with a strong sense of science identity, that is supported by a positive academic experience and perceived competence, tend to maintain a science identify and persist in a science career following graduation (18, 19). This raises the question of how and when to expose students to concepts in a given scientific field to enhance their positive perceptions of, and interest in that field. Traditionally, education in the field of immunology is not a major focus of science curricula at the high school or undergraduate college level. As a result, students are not exposed to the concepts in

immunology in a meaningful way until they enter postgraduate educational programs.

In an effort to better appreciate the status of immunology education at the undergraduate level, we performed a number of comparisons to assess the number of undergraduate programs in immunology, the number of undergraduate degrees granted, and the extent to which immunology education is discussed in the literature. For these analyses, immunology was compared to two other disciplines; microbiology and neuroscience. Microbiology was chosen because historically, immunology has been associated with this discipline and in many instances, if immunology is taught, it is in the context of a microbiology undergraduate major, although curricula specific to immunology are often very limited and do not constitute a major emphasis in the vast majority of undergraduate microbiology majors. Secondly, neuroscience was chosen because from a biological and physiological perspective, neuroscience has a number of characteristics in common with immunology. The nervous system and the immune system are the only systems in the body that are comprised of a dispersed network of organs, tissues, cells, and soluble mediators that work in concert to regulate the function of that system. Moreover, both the nervous and immune systems interface with every other organ in the body, as well as each other. Thus, these systems are both highly complex entities that play a critical role in diverse aspects of health and disease. Both the nervous system and the immune system require students to understand conceptually how the system works as a whole, while at the same time appreciating the mechanistic interrelationships between the specific components that regulate the normal and pathophysiological function of the respective system. Both neuroscience and immunology have significant relevance in medicine and have the potential for significant technological and therapeutic breakthroughs that will impact the health of individuals throughout the world. For these reasons, the analyses conducted focused on comparing the status of undergraduate education in immunology to these two benchmark undergraduate majors.

Information on the number of institutions offering specific degrees was obtained through the National Center for Education Statistics (NCES; nces.ed.gov). It has been previously reported that undergraduate programs in neuroscience have grown rapidly over the past three decades (20). In 1986, only seven institutions reported having an undergraduate neuroscience program (major). This number more than tripled within a decade and tripled again by 2006 (25 institutions in 1996 and 90 institutions by 2006). Since 2006, the number of institutions offering undergraduate programs in neuroscience has continued to increase at a rapid pace, such that as of the 2017–2018 academic year, 210 institutions offered a Bachelor of Science degree in neuroscience (**Figure 2**). In contrast, there were 106 institutions that offered a Bachelor of Science degree in Microbiology, and only 10 institutions identified as offering an "immunology-related" major during the same academic year (**Figure 2**). The "immunology-related" majors were identified by including "Microbiological Sciences and Immunology, Other" and "Microbiology and Immunology." Using only the search term "Immunology" yielded zero results. Furthermore, searching for a Bachelor of Science using "Immunology" as a keyword in internet-based college-finder software programs such as princetonreview.com and collegeboard.com yielded zero results.

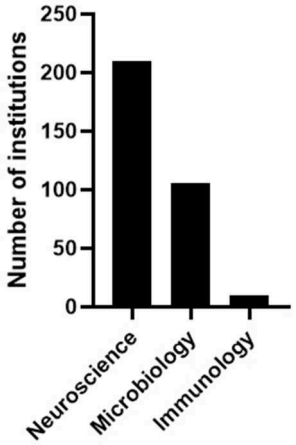

FIGURE 2 | Comparison of the number of institutions offering Bachelor of Science degrees in the fields of Neuroscience (210), Microbiology (106), and Immunology (10) as of the 2017–2018 academic year. Data were collected from all U.S. institutions listed in the IPEDS data center.

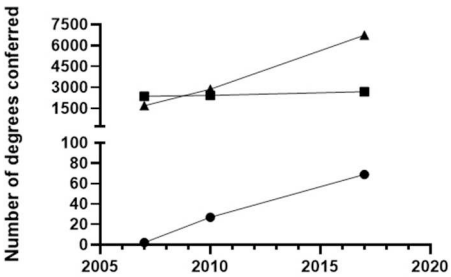

FIGURE 3 | The number of Bachelor of Science Degrees in Immunology (•), Microbiology (■), and Neuroscience (▲) conferred by all U.S. Institutions listed in the IPEDS data center between 2007 and 2017.

An analysis of the number of neuroscience, microbiology, and immunology degrees conferred over time was performed using the Integrated Postsecondary Education Data System (IPEDS) through NCES. Similar to the number of neuroscience programs, the number of neuroscience degrees conferred since 2007 has rapidly increased (**Figure 3**). In comparison, the number of microbiology degrees conferred has remained relatively constant between 2000 and 2500 annually. The first immunology degrees conferred were in 2007. The number of immunology degrees conferred since then have been drastically fewer in number than the number of microbiology or neuroscience degrees.

Importantly, as mentioned above, a search for institutions with an "immunology major" yielded zero results. Thus, identifying "immunology-intensive" degree-granting programs,

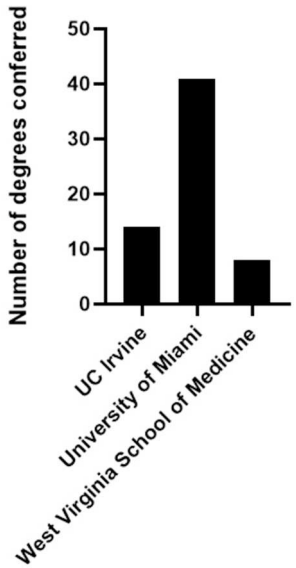

FIGURE 4 | The number of Bachelor of Science Degrees in Microbiology and Immunology emphasizing immunology content conferred by U.S. accredited institutions in the 2017–2018 academic year.

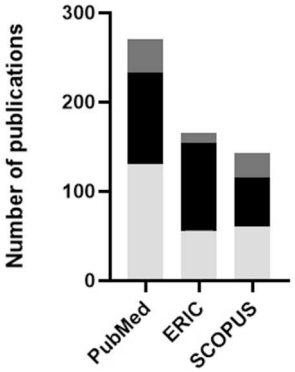

FIGURE 5 | Education-related publications in the fields of immunology (dark gray), microbiology (black), and neuroscience (light gray) identified following searches of the PubMed, ERIC and Scopus databases. The search was performed on July 29th, 2019 and included all publications up to that date that met the search criteria.

specifically, required further review of the Bachelor of Science course requirements for the 10 Microbiology and Immunology programs listed in College Navigator. This analysis revealed that the emphasis on immunology content was highly varied. Of the 10 programs identified by College Navigator in 2017, only three programs specifically offered a Bachelor of Science in Microbiology and Immunology that required three or more immunology courses to fulfill the degree requirements. In the 2017–2018 academic year, 69 degrees (B.S. in Microbiology and Immunology) between three institutions were conferred (**Figure 4**). All other programs listed were either majors in microbiology offering a maximum of two courses in immunology, concentrations available under other degrees that offered a maximum of two courses in immunology, or programs available only for graduate studies that were likely listed in error. It should be acknowledged that these numbers are approximate, as majors may exist that are not identified in IPEDS or College Navigator, such as the Immunology and Infectious Disease Major at Pennsylvania State University (https://vbs.psu.edu/majors/iid). Furthermore, we cannot account for programs that may offer concentrations in immunology that are optional and not required for the major. Regardless, the data obtained demonstrate that vast differences exist in the emphasis on undergraduate training in the fields of neuroscience, microbiology, and immunology.

In addition to the large offering of neuroscience and microbiology undergraduate programs, both the neuroscience and microbiology fields have education-focused journals (Journal of Undergraduate Neuroscience Education and the Journal of Microbiology and Biology Education, respectively) that support the development and dissemination of educational innovations. Furthermore, the Faculty for Undergraduate Neuroscience (FUN) held their first meeting in 1995 and created a set of guidelines for the development of undergraduate neuroscience programs, which are regularly reviewed and updated, and have served as a "blueprint" for the creation of new undergraduate majors by many institutions (21). Publications in neuroscience education have sought to identify the number and types of neuroscience programs and characteristics of the institutions offering them (20), how neuroscience is being taught at the undergraduate level (22, 23), and how best to assess undergraduate neuroscience programs (24, 25). Similarly, in an effort to support and initiate reform in undergraduate microbiology education, the American Society for Microbiology has created curriculum guidelines (https://www.asm.org/Guideline/ASM-Curriculum-Guidelines-for-Undergraduate-Microb) and also provides professional development resources (26). Similar efforts to promote undergraduate education in immunology at the national level are currently lacking, with perhaps the one exception being the American Association of Immunologists (AAI). AAI sponsors an Education Committee that broadly promotes immunology education, it hosts a special session at its annual meeting that focuses on immunology education, including curricular and pedagogical interventions in undergraduate, graduate, and medical education, the society has a resource page on its website (https://www.aai.org/Education/Teaching-Resources), and it has launched a new series "Teaching Tools" in its bi-monthly newsletter.

Finally, a literature search was performed to map the current state of undergraduate education in the fields of immunology, neuroscience, and microbiology. The databases PubMed, Scopus, and ERIC were searched using the terms, "Immunology," "Neuroscience," and "Microbiology" as these fields relate to "Undergraduate Education" and "Curriculum" (**Figure 5**). Searches were broadened with appropriate synonyms specific to the individual databases, and reference lists for relevant articles were also searched. The purpose of this literature review was to determine the extent to which the field of undergraduate

immunology education is represented in the literature and how this compares to microbiology and neuroscience. Although the results do not account for duplicate publications across databases, a total of 479 results were retrieved from the three databases. Approximately 20% of the citations retrieved focused on immunology, revealing a paucity of literature in this area compared to neuroscience and microbiology.

Based on these different analyses, it is readily apparent that undergraduate immunology education lags far behind neuroscience and microbiology. Microbiology programs have existed at the undergraduate level for decades and there has been only modest growth in the number of programs or in the number of degrees conferred during the past 30 years. In contrast, undergraduate neuroscience education has experienced robust growth in the same timeframe. At present, there are only a handful of programs that focus intensively on immunology education. It is possible that this is due to a lack of infrastructure to support such programs within the immunology community in the form of faculty groups and publications focused on undergraduate immunology education. It is possible that there are simply too few faculty who are trained to teach immunology and that undergraduate institutions do not have the necessary infrastructure to create new academic programs in this field. However, the fact that both microbiology and neuroscience are taught at a large number of undergraduate institutions, many of which are not directly affiliated with a school of medicine, tend to argue against this possibility. Finally, it is possible that the lack of growth in undergraduate immunology education may be due to a lack of awareness of the general public about immunology and its role in health and disease, which means that there is a lack of demand for such programs on the part of the "consumer" (i.e., the student). However, once again, one has to question how and why there appears to be a significant demand on the part of students to participate in microbiology and neuroscience programs, but not in the case of immunology.

DISCUSSION

A New Path Forward

As demonstrated by the information discussed above, immunology, as a discipline, has made little headway in developing undergraduate programs and educational curricula as compared to its content counterpart, microbiology and the equally complex field of neuroscience. Student training in the field has been almost solely focused at the graduate and professional school level. We and others (27), propose a change from student training focused at the graduate and professional level to the development of educational curricula and training at the undergraduate level. As the pace of discovery in immunology accelerates and as novel immunotherapeutic interventions are developed, it can be argued that there is an increasing need for individuals who are trained in immunology and who will enter the workforce at multiple points in the pipeline, including those who are engaged in research-intensive careers, those who have the skills and knowledge to translate foundational discoveries into novel therapeutic interventions and finally, those individuals who are able to harness knowledge of the immune system and associated immunotherapies in the clinical setting (28). At most undergraduate institutions, courses in immunology are limited in number and scope. Traditionally, departments/programs in biology may offer one or two courses in immunology or host-pathogen interactions. Even at institutions with microbiology or microbiology and immunology departments/programs, immunology usually consists of one or two courses that are offered, with the exception of a few notable programs. The result is that the vast majority of students are exposed to immunology at most in one or two courses. Even then, the number of students entering graduate school or professional schools who have had an immunology course is in the 25–30% range. This raises several issues, including the fact that students are not likely to be able to fully appreciate how the overall immune system works from a conceptual perspective after a single overview or survey course, much less to understand how the system is regulated on a cellular and molecular basis, how the immune system is responsible for mediating serious disease processes, or finally, how it can be harnessed to fight disease. Because there is a clear lack of emphasis on immunology education at the undergraduate level, this significantly diminishes the number of individuals who are exposed to this discipline in an in-depth manner earlier in their educational experience and this may in turn impact the number of individuals who go on to pursue immunology-related careers.

At the University of Alabama at Birmingham (UAB), we have recently developed an undergraduate immunology major, the Undergraduate Immunology Program (UIP), which offers a Bachelor of Science degree, and is jointly sponsored by the Department of Microbiology in the School of Medicine and the Department of Biology in the College of Arts and Sciences. This major was purposefully developed not only to engage undergraduate students in the field of immunology but to promote the development of the core competencies outlined in The *Vision and Change in Undergraduate Biology Education* final report (1) and articulated by the National Postdoctoral Association (https://www.nationalpostdoc.org/page/CoreCompetencies). In addition to learning immunology content in the core courses of this major, students will develop transferable skills, including professionalism, communication, ethics, teamwork, and leadership. Through an intensive focus on undergraduate research, which is a requirement of the major, students will also develop critical thinking, problem solving, and analytical skills.

An outline of the 4 year curriculum is provided in **Table 1**. It is important to note that the UIP provides students with the opportunity to pursue a broad curriculum that includes the humanities and social sciences as well as core requirements in the sciences, including biology, chemistry, physics, and mathematics to meet the requirements for entry into professional schools. Course requirements for the major are listed in **Table 2**. In the first year of the major, students will focus on completing the university and science core requirements while taking an introductory seminar on current topics in immunology. Freshmen are introduced to several conceptual frameworks in this course that are carried on throughout their 4 year curriculum. These include the medically-relevant concepts

TABLE 1 | Undergraduate immunology program four-year curriculum.

First term	Second term
Freshman	
English	*Current Topics in Immunology (MIC 150)*
Math	Science core
Science core	Science core
University core	University core
Elective	Elective
Sophomore	
Seminars in Immunology (MIC 250)	*Introduction to the Immune System (MIC 275)*
Science core	Science core
Science core	Science core
University core	University core
Elective	
Junior	
The Innate Immune System (MIC 401)	*The Adaptive Immune System (MIC 402)*
Research in Immunology (MIC 398)	*Research in Immunology (MIC 398)*
Science core	Science core
Science core	Science core
University core	University core
Senior	
Pathogen-Immune System Interactions (MIC 403)	*Immune-mediate Diseases (MIC 404)*
Research in Immunology (MIC 398)	*Research Seminar in Immunology (MIC 492)*
Science core or Statistics	Science core
Science core	Science core
University core	

TABLE 2 | Course requirements for the immunology major.

Requirements	Hours
Biology	
Introductory biology I	4
Introductory biology II	4
Genetics	3
Biology of microorganisms	4
Chemistry	
General chemistry I/general chemistry I laboratory	4
General chemistry II/general chemistry II laboratory	4
Organic chemistry I/organic chemistry I laboratory	4
Organic chemistry II/organic chemistry II laboratory	4
Fundamentals of biochemistry	3
Physics	
General physics I: mechanics	4
General physics II: electricity & magnetism	4
Mathematics	
Calculus I	4
Introduction to statistics or biostatistics	3
Immunology	
Current topics in immunology	1
Seminars in immunology	1
Introduction to the immune system	3
Foundations in immunology: the innate immune system	3
Foundations in immunology: the adaptive immune system	3
Foundations in immunology: microbial pathogen-immune system interaction	3
Foundations in immunology: immunologically-mediated diseases	3
Undergraduate research (minimum of 6 h are required)	
Undergraduate research in immunology & host defense	3
Undergraduate research seminar in immunology and host defense	3
Total hours	72

of how immunology relates to vaccines, emerging infectious diseases, autoimmunity, allergy, transplantation, cancer, and immunotherapy. The goal is to provide context to help students understand how and why studying the immune system is relevant to health and disease.

The second year allows students to continue working on core science courses and in the second semester students take the first course in the immunology core series, Introduction to the Immune System (MIC 275). This is an overview course designed to introduce students to basic concepts pertaining to the innate and adaptive arms of the immune response. This course provides the foundation upon which subsequent Foundations in Immunology 400-level courses, of which there are 5, will build. MIC 401-MIC 404 are required courses, whereas MIC 400, The Microbiome in Health and Disease, is optional.

In the third year, students take MIC 401, The Innate Immune System, followed by MIC 402, The Adaptive Immune System. These courses expand on the topics that were discussed in the Introduction to the Immune System course in order to develop the students' depth and breadth of content knowledge pertaining to the normal function of the immune system. Additionally, spanning the first three core courses (MIC 275, 401, and 402), is an embedded information literacy project. In MIC 275, students are introduced to databases, literature searches, and the concept of acquiring information from sources other than textbooks. Lectures and learning activities in MIC 401 require students to perform effective literature searches and foster the development of skills necessary for identifying and extracting relevant information and communicating information to peers. In MIC 402, students will be able to apply the skills they have developed through the completion of a presentation project. Throughout their sophomore and junior years, students in the UIP are expected to develop their written and oral communication skills through a series of individual and team-based activities. Examples of such activities include, writing articles to communicate to the lay public how immunology relates to disease (MIC 250), team-based presentations on techniques or therapies (e.g., vaccine development, flow cytometry, and monoclonal antibodies) that play a critical role in immunological research and treatment of diseases (MIC 275), team-based journal article presentations

(MIC 401), and individual presentations covering "immunology in the news" topics (MIC 402).

In the fourth year, students will take the two remaining 400-level Foundations in Immunology courses; Microbial Pathogen-Immune System Interactions (MIC 403) and Immunologically-Mediated Diseases (MIC 404). In these courses, students will apply immunology concepts to understanding the interplay between microbial pathogens and the immune system as well as the importance of immune homeostasis in health and disease. These courses will reinforce the normal and pathophysiological principles pertaining to the immune system in a manner that is similar to what students might experience in medical school, thereby preparing them for the transition into that educational space. Going forward, it will be critical to incorporate additional content into the curriculum in MIC 404 that is focused on harnessing the immune system for the development of immunotherapies, as this is a rapidly growing area both in research and medicine. As mentioned above for the core courses taught in the sophomore and junior years, students will continue to be exposed to activities that reinforce their information literacy and communication skills. These educational themes will culminate in MIC 404, which is the Capstone course for the UIP, in which seniors will be expected to write a thesis and present their work orally.

Given the benefits students gain from research experience as an undergraduate (29, 30) and its influence on their attitude toward science and career choice (31), undergraduate research is a major component of the UIP. Students are expected to take a minimum of 6 credit hours of undergraduate research. In their sophomore year, students take the Seminars in Immunology course (MIC 250) in which they are introduced to research topics being pursued by faculty in the School of Medicine. This course is designed to reinforce many of the health-related themes that are built into the major and to encourage students to investigate research labs and meet with investigators in order to identify a lab with a suitable research project. Because this course is offered early in the sophomore year, we recognize that students may not have an in-depth appreciation of the immune system, much less concepts in research, including technical approaches. For this reason, we have modified the format of the Seminars in Immunology class recently to provide students with more opportunities to prepare for lectures from faculty. We have decreased the number of faculty lectures, and increased the number of lectures that talk about the specific areas of research that will be covered, as well as the techniques that are used. In this manner, students are given additional information to help them appreciate the stories that are presented to them by faculty. Additionally, we provide faculty with a rubric to ensure that they formulate a lecture that is primarily focused on the relevance of their research to health and disease, as opposed to being focused on technical details of the research itself.

Students in the UIP have the ability to choose from among over 100 faculty who are members of the Program in Immunology at UAB for research opportunities and are expected to join a laboratory no later than the beginning of their junior year. Starting in the fall of 2020, all freshmen in the UIP will be required to take a 1 credit hour course designed to introduce them to the principles of research. This course will be offered online and will cover the ethical conduct of research, safety training, the use of animals in research and human studies. Students will also learn what is expected of them in the research setting including, professionalism, record keeping, rigor and reproducibility, and other essential skills. Students are able to choose either undergraduate research or honors-level undergraduate research. In either case, students are encouraged to present their work at local, regional or national scientific meetings. For honors-level research, students are expected to write and defend a research thesis.

CONCLUSION

Based on an analysis of the number of immunology programs/majors, the number of degrees conferred by such programs, the prevalence of articles in the literature that discuss curricular or pedagogical interventions in immunology, or the infrastructure available in the form of organized faculty groups, journals or other resources to support education in immunology, education in immunology does not appear to constitute a major focus at the undergraduate level. As a result, individuals are not readily able to gain an in-depth appreciation of principles in immunology or how those principles are applied to health and disease prior to entering graduate or professional school. This in turn may negatively impact the number of individuals who pursue immunology-related careers. This reality is in stark contrast to the state of undergraduate education in neuroscience, or microbiology. This realization begs the question; is it time for the immunology community to reevaluate the state of undergraduate education in immunology and to undertake a concerted effort to develop resources and programs to expose undergraduate students to this field more broadly? Hannum et al. have called for greater communication between undergraduate, graduate, and even professional level educators who teach immunology to start a dialogue regarding best practices for developing evidence-based learning outcomes to inform efforts to teach immunology at the undergraduate level. Moreover, it has been argued that immunology is truly an interdisciplinary field that inherently benefits from the cross fertilization of ideas and techniques from other areas in STEM (32, 33). A case in point is the fact that all sciences are now beginning to rely more heavily on informatics approaches, and immunology is no exception (33). This raises the potential for not only creating robust educational experiences in immunology, but interfacing those experiences with other STEM fields to create a truly interdisciplinary experience that prepares students to have greater flexibility to pursue a wide range of careers. The workforce demand for students with interdisciplinary degrees and the need for more individuals specifically trained in immunology (28) make a strong case for the immunology community to initiate a

unified effort to develop robust undergraduate immunology programs. To date, only a handful of programs have been created that have an in-depth emphasis on immunology as a requirement. The UIP at UAB and other programs, including those at Penn State University, the University of Miami, West Virginia University, and the University of California, Irvine are such examples. These programs, in addition to the efforts of many other educators who oversee undergraduate courses in immunology offered through biology, microbiology or other science majors, provide a foundation upon which the immunology community can begin a serious dialogue to ask whether there is a need to drastically rethink how and when we should provide educational opportunities for students to expose them in an in-depth manner to the foundational and applied concepts of immunology. It is time to examine the need for a revolution in undergraduate education in immunology.

DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://nces.ed.gov/.

AUTHOR CONTRIBUTIONS

Each individual named as an author made substantial contributions to the manuscript. LJ and HB wrote the manuscript and generated all figures. JD created and performed all literature searches. All authors approved the final version of the manuscript to be submitted.

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PERSPECTIVE
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Demystifying Cancer Immunotherapy for Lay Audiences

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Immunotherapy is now mainstream. Advertisements are ubiquitous in print and visual media for immune based-therapies for various conditions and diseases. Smaller companies that develop novel immunotherapies are often quickly acquired by larger companies. More and more clinical trials are open for immune-based therapies, particularly for immune checkpoint blockades. As such, immunologists need to engage the public in conversations about the strengths and limitations of immunotherapy, and the necessity of research in propelling the field further. In this article, we discuss approaches we have taken to convey key concepts in immunology and cancer immunotherapy to non-scientists and health care professionals without expertise in immunology. Although the devil is always in the details, basic concepts in immunology and immunotherapy can be readily conveyed using stories and analogies, some of which we present here.

Keywords: cancer, community, engagement, immunotherapy, outreach

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INTRODUCTION

The need to inform the public about immunotherapy is more important than ever, as immunotherapy is now a key driver of cancer care and precision health. Here we describe community outreach approaches in immunology and cancer immunotherapy we developed for the Masonic Cancer Center (MCC), an NCI-designated comprehensive cancer center at the University of Minnesota.

KNOW YOUR TARGET AUDIENCE

Time is precious. Don't waste it by giving the audience a "one size fits all" rote presentation or one you would give your peers. Identify topics that are likely of greatest interest to your audience by asking representatives beforehand what their most important issues or questions are. Meld your expertise with the needs and background of your audience and tailor the presentation specifically to them. The audience should leave with actionable knowledge and the belief that their time was well spent.

Our discussions of immunology basics don't differ much between disparate ethnic groups but our discussions of how to apply immunology do. These are tailored to the needs of the group. For example, cervical cancer rates are higher for American Indian, African American, Hmong, and Hispanic women in Minnesota than for others (1–3). In meeting with these groups, we often focus on how vaccines work, how vaccination against human papillomavirus (HPV) reduces the risk of cervical cancer, and the need to increase cervical cancer screening for early detection and a subsequent reduction in cancer mortality (1).

Be aware of the audience's range of knowledge in science and medicine. If you are updating health care workers on checkpoint blockade therapy or chimeric antigen receptor-transduced T-cells, you can assume a baseline knowledge of the immune system and focus on the specific strengths and limitations of these therapies. If you are speaking to a broad audience, assume an eighth-grade average reading level and a cursory knowledge of immunology and cancer (4). We developed a series of animated videos that includes Cancer 101; this describes cells, how cancers can form, and how to minimize risks (5). Because this video is appropriate for both adult and youth audiences, we find it useful to show at the outset of presentations.

Maximize visuals and graphics on slides while minimizing text. Use analogies, simple language, and avoid jargon whenever possible. When it is not possible to avoid a technical term, define, and explain it clearly before weaving it into your story. Know the physical layout of the venue in which you will speak. This includes its audio and visual equipment, lighting, and acoustics.

ENGAGE THE AUDIENCE

Consider using experiential activities accessible to broad audiences. This will provide participants who learn by visual, auditory, and kinesthetic methods opportunities to access and retain the information. We invested in wireless polling devices that allow the audience to respond to questions posed by the presenter in real time. This permits the presenter to gauge the audience's readiness to move on to the next section. Because these data measure impact and collect information anonymously in a non-threatening way, we derive information from communities less inclined to respond to surveys.

What follows is the story we typically tell adult, lay audiences about cancer immunotherapy. This is not meant to be an inclusive review; rather it is one example of how to explain immunology and cancer immunotherapy. We focus on recent advances in T-cell based immunotherapy because these are more topical than well-established monoclonal antibody-based therapies such as Herceptin for breast cancer and Rituximab for B-cell lymphomas (6, 7).

IMMUNE ACTIVATION

We begin by describing how molecules, cells, tissues, and organs in the body work coordinately in systems to achieve particular functions. Most everyone is aware of the digestive system, so we begin there by saying the digestive system processes food and absorbs nutrients and water. People are generally less aware of how the immune system functions, so we start by saying the immune system maintains homeostasis throughout the body. When that balance is perturbed by injury, infection, or disease, the immune system is activated. Under normal physiological conditions in a healthy individual, an activated immune system restores homeostasis by eliminating the infection, healing the injuring, or eradicating the disease; the immune system then itself returns to homeostasis. What flows naturally from this introduction are discussions of what turns on and off immune responses.

We show pictures of red and white blood cells and note that white blood cells are part of the immune system. White blood cells become activated and start an immune response when their receptors signal that an infection/injury/disease has occurred. At this point we define a receptor. We show an animated slide that likens receptors and the signals they deliver to the electromagnetic waves received by home satellite dishes and the resultant images they relay to monitors. The external signal received by the receptor/satellite dish is conveyed to the cell/living room via an internal signal cascade/cable network. Physiologically, receipt of this internal signal leads to a change in the white blood cell's activity and the beginning of an immune response. Questions that logically follow this description include: what are these immune-activating signals, where do they come from, how are they recognized, and how do they mediate changes in cell function?

We next note that signals indicative of an infection typically come from the pathogen itself and so are externally-derived. Before going further, we define pathogen as a disease-causing entity. Collectively pathogen-associated molecules that induce immune responses are called stranger signals and include molecules we cannot make ourselves. In contrast, danger signals are internally-derived molecules our bodies make in response to tissue injury or disease. Danger signals are not normally accessible to the immune system but are released when a cell is damaged or ruptured or stressed. Stranger and danger signals typically indicate something deleterious has occurred that requires an activated immune system to resolve. The receptors on immune cells that recognize stranger and danger signals have coevolved with the cells' abilities to contain or eliminate physiological insults (8).

The immune system has a spectrum of molecular and cellular mechanisms that maintain homeostasis. Innate immune responses reside at one end of the spectrum and acquired immune responses at the other. Innate immune responses are elicited by stranger and danger signals, cause inflammation, and recruit leukocytes that can non-specifically eradicate pathogens. That is, innate responses can eliminate groups of pathogens but do not distinguish between individual pathogens within the group. Innate immune responses also trigger acquired immunity; these responses take longer to resolve infections because pathogen-specific immune cells are initially present at low frequencies ($\leq 10^{-5}$) and take time to expand to sufficient numbers to control the disease (9). Acquired responses are specific to molecules unique to the disease-causing organism. The advantages of acquired immune responses include this specificity and long-lived memory responses to prevent recurrent infections of the same pathogen. The net result is that activated white blood cells can destroy invading bacteria, kill virally infected cells before viruses are released, and eliminate nascent tumors.

IMMUNE SURVEILLANCE

Immune surveillance refers to the immune-mediated elimination of nascent malignancies before they become clinically apparent. This occurs constantly and perhaps is the last barrier a cell must breach before becoming malignant (10, 11). By definition, cancers have escaped immune surveillance. And this stymied the

field of cancer immunotherapy for over a century. Immunologists long recognized the immune system could be exploited to treat cancer because of four key characteristics: specificity, potency, memory, and adaptability. Specificity is the holy grail of cancer therapy because it widens the therapeutic window by reducing off-target toxicity. Potency permits relatively small numbers of cells to mediate curative responses. Memory minimizes the potential for recurrence. And adaptability counters the genetic instability of many tumors; tumor cells that express altered proteins (neoantigens) arising from ongoing mutations can be recognized as foreign and eliminated immunologically. Before we can discuss how malignant tumors evade immune surveillance, though, we must consider how tumors arise in the first place.

THE ODDS ARE NOT IN OUR FAVOR

Let's do the math. For one cell to become two, it must copy all of its contents. These include proteins, lipids, carbohydrates, and nucleic acids. Nucleic acids are DNA and RNA and are the genetic storage, retrieval, and information transfer systems of the cell. All of the information encoded by a cell's DNA is called its genome. The genome is akin to a cookbook filled with recipes cells follow to function properly. There are only four different letters in a cell's cookbook, but each cookbook contains 12.8 billion total letters (6.4 billion base pairs per human diploid genome × 2 nucleotides/base pair). It is estimated that the average human adult has about 37 trillion cells (12). If we assume a daily turnover rate of about 0.5% (200 billion cells), then about 2.5 trillion billion (10^{21}) nucleotides must be copied every day. To put this differently, the DNA in a single human cell is about 2.2 m long (340 pm/base pair × 6.4 billion base pairs/human diploid genome). The length of DNA copied every day is therefore approximately 440 billion meters, which is almost three times the distance from the earth to the sun. Copying errors are inevitable with such large numbers, and these copying errors can alter the recipes in the cookbooks and lead to cancer.

WHAT IS CANCER AND HOW DO WE GET IT

Cancer is defined as a population of cells that grow uncontrollably and invade local or distant tissues. Cancer arises from changes in DNA itself (genetic) or changes in how and when different regions of DNA are accessed (epigenetic). To carry the cookbook analogy further, the addition of the letter "b" to "tsp" increases the amount of an ingredient added from a teaspoon (tsp) to a tablespoon (tbsp). Single letter changes (i.e., point mutations) could have no, slight, or profound consequences, depending on the ingredient and recipe. Changes on a larger scale would be like tearing off the bottom half of one recipe and replacing it with the bottom half of a recipe from a different chapter (i.e., a translocation). Alternatively, the cell might inappropriately use one recipe (e.g., for crème brûlée) when it should have used another (e.g., sautéed liver and onions). This is called an epigenetic error ("epi" means above). The genetic material itself has not changed but the way it is used has. Epigenetic changes could have deleterious consequences for the host (e.g., if guests were promised crème brûlée for dessert but instead were given sautéed liver and onions).

Cellular mechanisms have evolved to minimize genetic mistakes, to correct mistakes once they are made, to provide redundancies to counterbalance loss-of-function mutations, to induce cell death if a cell acquires too many genetic lesions to copy its DNA successfully, and to eliminate nascent malignant cells via immune surveillance. Cancers ultimately evade all of these barriers typically by accumulating mutations and genetic lesions sequentially over decades (11, 13).

With this information we can now distill how someone gets cancer down to three ways. (*1) Old age.* Cancer is like a biological clock. The longer an individual is alive, the more s/he can acquire deleterious mutations from DNA copying errors or exposure to carcinogens (DNA-damaging agents) that can lead to cancer. (*2) Bad luck.* An individual can inherit mutated genes that predispose them to cancer, or they can be unintentionally exposed to sufficient doses of carcinogens to cause cancer. (*3) Lifestyle choices.* Cancer prevention and regular screening are likely the best ways to reduce one's risk for cancer. Prevention includes minimizing exposure to known carcinogens, being vaccinated against pathogens known to cause cancer, and eating foods rich in anti-oxidants and other known chemopreventive agents. Regular screening (e.g., colonoscopies) can detect cancer at earlier, more treatable stages. It is worth stressing that among old age, bad luck, and lifestyle choice, the only one we can control is our choice of lifestyles.

CANCER IMMUNOTHERAPY

Cancers co-opt normal biological processes to escape immune surveillance. We present these processes collectively as a wall between the malignant tumor and anti-tumor immune cells (**Figure 1A**). It has only been in the past 10–20 years that immunologists have begun to understand how cancers erect these walls: what the bricks and mortar are. Although this knowledge has led to many immune-based approaches for cancer therapy, most rely on one of two strategies.

The first is figuratively to reduce the height of the wall or compromise its integrity (**Figure 1B**). This permits tumor-infiltrating lymphocytes and other *in situ* immune effector cells to avoid suppression and eliminate malignant cells. Immunological approaches that fall into this class include checkpoint inhibitors. Checkpoints such as CTLA-4 and PD-1 suppress activated immune cells and allow them to return to homeostasis (14, 15). Some cancers engage these checkpoints and escape immune surveillance; monoclonal antibody-mediated inhibition of checkpoint signaling permits immune-mediated tumor cell death (16, 17). FDA-approved checkpoint inhibitors such as Yervoy (ipilimumab; anti-CTLA-4) and Keytruda (pembrolizumab; anti-PD-1) can profoundly increase survival for some patients with cancers such as melanoma and metastatic non-small cell lung cancer (18).

The second strategy is to induce such a strong immune response that it figuratively crashes over the wall, much like a tsunami breaching a seawall (**Figure 1C**). This approach relies on mass action: the number of immune effectors exceeds the number of immune inhibitors. This immune tsunami is typically

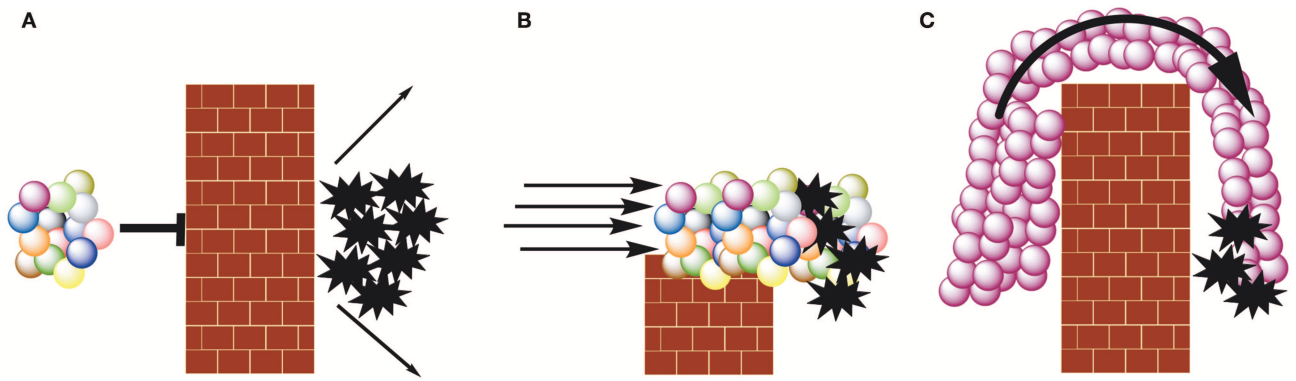

FIGURE 1 | The spheres represent cells of the acquired immune system, with each color representing a different specificity. The brick walls represent tumor-induced immune suppression. The black, 10 point stars represent tumor cells. **(A)** Escape from immune surveillance. Malignant cells suppress immune effector cells. **(B)** Checkpoint blockade therapy. Inhibiting cancer-induced immune suppression via checkpoint inhibition permits tumor infiltrating lymphocytes to kill malignant cells. **(C)** CAR T-cell therapy. Autologous white blood cells (typically T- or NK-cells) are transduced with a CAR-encoding construct, rendering all the transduced cells specific for the same antigen. These cells are expanded to large numbers *ex vivo* and then infused into the patient.

created in three ways. The first is to use a therapeutic vaccine to elicit an anti-tumor response in the patient (19). This approach has had limited success primarily because the patient's immune system is systemically suppressed by disease and prior therapies. Figuratively this creates a hole in front of the wall making the barrier that much higher.

Discussions of cancer vaccines with lay audiences must address persistent misconceptions about the safety of vaccines. We suggest a multi-pronged approach. State that vaccines are among the biggest success stories in modern medicine. Show pictures of individuals infected with smallpox and pediatric polio victims in iron lungs; these images are likely to have the greatest impact. Show data regarding the dramatic declines in mortality due to vaccination and the eradication of smallpox in 1980 (20). Briefly describe how vaccines elicit pathogen-specific immune responses in the absence of disease; these responses then prevent disease by quickly eliminating the pathogen should it infect again. Note the 1998 publication that fueled the anti-vax movement has been discredited and retracted (21). This paper claimed that the measles/mumps/rubella vaccine was linked to autism in children. However, the data were irreproducible, and the lead author did not reveal that some of his research was funded by lawyers suing vaccine manufacturers. Acknowledge that while vaccinations often cause common local reactions (e.g., pain, swelling, and redness at the injection site), these are minor and transient and simply indicate recruitment of immune cells that subsequently will protect against infection from the pathogen targeted by the vaccine. Conclude that vaccines are a boon to humanity and that herd immunity protects children and immune-compromised individuals.

The second approach to create an efficacious anti-tumor response is to remove tumor-specific cells from the patient, grow them to large numbers in the laboratory, outside of the immune-suppressive environment of the patient's body, and then return them to the patient. This has had more success than the vaccine approach, but it is hampered by the difficulty in identifying truly tumor-specific immune cells in the patient (22).

The third approach takes some of the patient's healthy white blood cells and genetically reprograms them to recognize and kill tumor cells, regardless of what the immune cells were born to recognize. The engineered autologous cells are expanded *ex vivo* and then infused in the patient. This approach has been a game changer for certain B-cell leukemias and lymphomas as patients with otherwise incurable diseases are alive today (23). These genetically modified cells are called CAR cells, where the acronym CAR stands for chimeric antigen receptor.

While cancer immunotherapy has enormous potential, we need to caution that providing false hope can be an unintended consequence of presentations like those we just described. The presenter has a moral and ethical obligation to note that many patients still do not respond favorably to cancer immunotherapy, and that it has other drawbacks. These include acute and chronic immune-related adverse effects, cost, and access. More research is needed to overcome these limitations.

CONCLUSIONS

In many cultures, storytelling is the traditional method of teaching. In the Hmong culture, skills, customs, historical knowledge, and traditions are passed orally from generation to generation via rote learning, memorizing, and storytelling (24). Because humans are attuned to story-telling, we tell stories based on immunology and cancer immunotherapy that weave in facts with easily recognizable analogies. We typically begin talks on cancer immunotherapy with a picture taken in 2010 of five-year old Emily Whitehead, the first pediatric patient treated with CD19-specific CAR T-cells (23). The Whitehead family has allowed Emily's story to be told publicly to promote immunotherapy. We say that in 1960, Emily would have had a 10% chance of survival given her diagnosis of pre-B-cell acute lymphoblastic leukemia. But thanks to 50 years of research, her prognosis in 2010 was much better as her chances of long-term survival were 85–90%. Unfortunately, she relapsed following standard therapy and was near death with resistant disease in

2012. We then state we will return to Emily at the end of the talk, which we do after presenting the above material starting with immune activation and ending with cancer immunotherapy. At the end of our presentation we close the story loop by showing a picture of a healthy teenage Emily taken in 2019. At this point we present the limitations of immunotherapy, particularly CAR T-cell immunotherapy, and note that only more research will lead to improved outcomes with reduced off-tumor effects. We then have an open question and answer period followed by informal interactions with the attendees.

We routinely provide our slide decks to the attendees electronically and give them printed materials with contact information for MCC specifically and cancer immunotherapy in general. We have pamphlets printed in English, Hmong, Somali, and Spanish to reflect the demographics of our community. These outreach efforts are almost always well-received and leave attendees with the belief that their time was well spent.

AUTHOR CONTRIBUTIONS

KE and CP developed various community outreach activities related to cancer prevention and immunotherapy, and together outlined and wrote this article.

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Using Inquiry-Based Learning to Enhance Immunology Laboratory Skills

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A challenge in teaching immunology in the undergraduate laboratory is to encompass the many varied skills that need to be applied when performing an investigative study of such a complex area. It requires background knowledge, data analysis skills, critical thinking, and design capacities to include relevant controls and applications of particular techniques to answer a research question. It also requires strong technical skills. One such approach is to use inquiry-based learning which allows students a more proactive and integrative role in their learning. In one of our final year immunology units we have incorporated an inquiry-based exercise that runs across four 5-hour sessions. Students are given two cornerstone immunology techniques (ELISA and a flow cytometry-based cytokine bead array), which they use to formulate a study investigating inflammation. Stage one is to design the experiment with some guidance from teaching staff, stage two is to perform the experiment, and then finally students are required to analyze the data, apply appropriate statistics, and write a report outlining their findings. This approach provides students ownership of the process and allows them the opportunity to investigate a real-world problem rather than just attempting to obtain the expected "correct answer." Feedback from both students and staff has been positive with strong engagement and high quality reports produced.

Keywords: inflammation, undergraduate student, pedagogy, inquiry-based learning, active learning and teaching methodologies, laboratory skills

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INTRODUCTION

As a discipline, immunology is considered a difficult area to master by many undergraduate students (1, 2). Using traditional undergraduate teaching strategies students learn many of the basic techniques fundamental to immunology. However, to create innovative learners, it is necessary to move from the recipe-based approach that is common in laboratory classes to a more creative mode of teaching. We use a mix of traditional, recipe-based laboratory classes, and open-inquiry based approaches to enhance creativity and scientific knowledge in our students.

By their very nature, practical classes are active learning environments. Active-learning approaches encompass many different teaching activities, but are designed to have students actively engaged in their own learning. One style of active learning is inquiry-based learning. Active learning in general, and inquiry-based learning in particular, has been reported to improve student scientific literacy (3), improve student retention (4), and reduce failure rates (5). A difficulty in assessing the effectiveness of inquiry-based learning is that there is no clear definition, and different researchers use the same terminology for different activities (6).

Generally, inquiry-based learning approaches are student-centered learning activities that require student immersion in the learning process. Banchi and Bell (7), as well as others (6, 8) describe an "inquiry-continuum," from highly structured with a large amount of input and direction from facilitators (sometimes known as confirmation inquiry) to open-inquiry, whereby students develop a question for testing, a method or procedure to address the question, and develop a solution to the question. Here we focus on research that has used genuine inquiry, whereby students are expected to search for an answer to a problem and construct their own knowledge, rather than other problem-based learning approaches where students are often seeking the "right" answer.

Inquiry-based learning is difficult to implement, particularly at the university-level and in large classes, but Summerlee and Murray (9) used a longitudinal study to determine the longer-term advantages of inquiry-based learning techniques. In this study, students from diverse university courses were followed over the length of their studies. Students with the lowest grades on entering university and who engaged in inquiry-based learning in their first year showed the greatest improvement in their final year marks compared to the highest-achieving students, suggesting the inquiry-based learning approach assisted students to become more engaged in learning, and more confident in accessing research resources to assist their learning. In a study by Spronken-Smith and Walker (10), investigating different levels of inquiry-based learning, classes that used the most open inquiry level tasks had the best outcomes in terms of students understanding the scientific process within the particular discipline being studied. In another study, by Lord and Orkwiszewski (11), students completed laboratory classes in either a traditional directed or inquiry-based manner. Students in the inquiry based group not only demonstrated increased understanding of discipline knowledge, they also enhanced their scientific thinking skills and appreciation of the scientific process.

Inquiry-based learning does place a strain on students, requiring a high-cognitive load, and some educators believe that this approach is a less efficient and less effective form of instruction (12). However, the skills that science students can learn from this approach include scientific thinking and research processes. Not every practical class should be based around inquiry-based learning, as the basic skills taught in more traditional laboratory classes underpin necessary skills for the inquiry-based tasks (13), and using just inquiry-based methods can create frustrations for students (3). However, the higher level thinking that inquiry requires means that incorporating it at some stage of the curriculum can help students develop skills that are transferable to discipline-based research (3, 14).

There are few examples in the literature on methods to successfully integrate inquiry based learning for teaching immunology laboratory practical skills in undergraduate laboratories. Manzoni-De-Almeida et al. (15) describe a guided-inquiry approach to develop immunology-specific knowledge in undergraduate and graduate laboratories. They found, even using a quite structured approach to inquiry, that students improved their scientific processes knowledge and improved the current (or future) links between students and researchers. Another paper, from Gunn et al. (16), describes the design of a module for level 2 inquiry-based learning (structured) looking at the molecular outcomes of a range of mediators of inflammation. This module was aimed at students earlier in their course progression than what has been implemented for our course. Finally, Berkes and Chan (17) describe an undergraduate immunology project that includes inquiry-based tasks to develop hypotheses and test the effect of a range of anti-inflammatories on macrophage cytokine production. Despite these inquiry-based tasks only forming part of the wider project, upon completion students still demonstrated enhanced confidence and awareness of both the scientific process and also immunology-specific laboratory skills. Here, we describe one example of a more open level of inquiry for students further progressed in their degree and closer to starting employment or a postgraduate degree; the described activity has not been formally evaluated, and is offered as an example activity that others may replicate in their teaching. We have drawn on the described published insights that inquiry-based learning can be beneficial in the right context and applied these when developing this exercise. The unit in which this exercise is performed is practical-based, that also has other more traditional style practical classes covering aspects of immunology such as allergy, diagnostic techniques for rheumatic diseases and influenza testing to strike a balance between delivery methods. The exercise also builds on previously learnt knowledge in the degree as level 2 immunology is a pre-requisite.

IMPLEMENTING AN INQUIRY-BASED PRACTICAL INTO THE CURRICULUM

We feel that incorporating a genuine inquiry-based practical as part of our curriculum is an important pedagogical approach that helps students to develop relevant general scientific and research-discipline specific skills, as well as achieving key graduate attributes of becoming critical and creative scholars (18). In our curriculum, inquiry-based learning is defined by a student-designed experimental approach with a genuine creation of new knowledge. Students, and therefore educators, aren't seeking the "right" result, rather they are developing and applying scientific thinking and principles to their work.

Students that complete an immunology major at our university complete two level 2 units and four level 3 units. At level three students have a choice of two theory units, and three practical units to fulfill the requirement of the four units. At the completion of the major, students are expected to have high-level immunology knowledge as well as demonstrate a deep understanding of the scientific process and how to design and evaluate methods to investigate immunological problems. These units use a variety of teaching and learning approaches, with numerous opportunities to be actively engaged in the generation of knowledge. In one of our immunology level 3 practical units, we use an inquiry-based learning technique. Students develop a research question, design a methodology to address the question, and then write a report on their work. Students test their own saliva samples (at two time points) for the presence of a number of inflammatory (and anti-inflammatory) markers

through the use of a competitive ELISA (to test levels of LTB4) and cytokine bead array (CBA; to test for IL-1β, IL-6, IL-8, IL-10, IL-12p70, and TNF). These two techniques cover a range of pro- and anti-inflammatory molecules, allowing for a more realistic and detailed analysis of the inflammatory response to the chosen stimuli. Students approached this assessment in four major steps; background research, research design, conducting the experiment, and reporting.

In the first stage, students are introduced to the idea of testing their saliva for the presence of inflammatory markers and techniques used for detection and quantification (competitive ELISA and CBA). Student groups then brainstorm ideas that may impact inflammation; they are encouraged to reflect on their knowledge from previous units to identify relevant ideas, and additionally draw on ideas that are presented in the popular media, or from cultural backgrounds. Ideas range from consuming green tea or turmeric lattes, to undertaking vigorous exercise; generally groups brainstorm 20–25 topics. Within each group, students are assigned a few topics to research in more depth; students are reminded to use databases such as PubMed to ascertain the availability, or lack, of current evidence regarding the role of their proposed idea in influencing inflammation, as well as other at factors that impact any influence (e.g., dose or timing). This initial reading and investigation supports skills and graduate attributes in accessing and evaluating appropriate resources.

Following their background research, students discuss their literature findings in the next session with their teaching associate (TA) and student group. Students then choose an intervention, discuss, and agree on a design including appropriate data analysis. Most chosen interventions are based on consuming either a particular food or drink (e.g., eating boiled peanuts daily for 1 week, with saliva samples collected on day 0 and 7; drinking one shot of tequila, with saliva samples collected before alcohol consumption and 30 min after consumption), although engaging in exercise has also proven popular. This stage of the inquiry-based design encourages and supports scientific thinking, including generating a hypothesis, and data analysis. Students are also supported to identify potentially confounding variables, appropriate controls, and discuss ethics. For example, the group of students who chose to investigate the proposed anti-inflammatory effects of tequila needed to discuss the ethics of consuming alcohol before class and how they could alleviate the effects, deciding on consuming a meal. Here, students opted to consume a pre-determined, healthy meal, to mitigate the confounding effects of food on the inflammatory response.

Following the design stage, student groups (n = 8–12) perform their chosen intervention, collect their saliva samples and then perform their competitive ELISA and CBA. These techniques, while using quite advanced skills, still use a traditional recipe-based approach; students use the same kits, and therefore instructions, as any researcher using these kits in a research laboratory. These two techniques are also cornerstone techniques in immunology being ELISA and flow cytometry for the CBA, supporting the development of student's technical skills. Once data has been collected, it is analyzed accordingly using appropriate statistical measures; all students have completed, as part of their degree, at least one unit that teaches statistics.

An important aspect of inquiry-based learning is reporting, which helps to develop a deeper understanding of the topic. A major benefit of inquiry-based learning is that it develops authentic skills, those that researchers use in their own science, and so the learning and assessment tasks associated with this learning activity are meaningful to a "real-life" laboratory situation.

Each student produces an individual practical report based on the collective data from their group, consisting of a title, an introduction, methods section, results, discussion, and reference section. Proponents of inquiry-based learning maintain that reporting is a critical aspect to learning in an inquiry-based task. Reporting has obvious educational and assessment benefits; students need to assess their data, interpret it meaningfully, and contextualize it within the current scientific literature. These aspects underlie effective scientific communication and are key components of inquiry-based writing (19). As mentioned, part of constructing this report, requires students to implement appropriate statistics in their data analysis. There is supporting evidence that integrating statistics into inquiry-based activities in the life sciences undergraduate laboratory, contributes to retention of knowledge gained and also an increase in understanding of the applications (20). Furthermore, students are encouraged to publish their work in undergraduate research journals, such as *Reinvention*, giving them scope to improve their employability, and their attractiveness as a research student.

As students are assessing multiple inflammatory markers using two different methods, it enables a more holistic understanding of an inflammatory response, which is more reflective of investigations undertaken in a research laboratory. It allows students to create a narrative and also consider the cause of any perceived incongruent results, such as an increase in the anti-inflammatory cytokine IL-10 accompanied by an increase in IL-6 which they may have only encountered in a pro-inflammatory context. They need to consider if all of their results are supported by current knowledge in the field of immunology, and if not, why this might be. It draws on their previously learned knowledge and stretches them to consider possibilities of how the immune system is reacting without resorting to the concept that they need to find a specific answer. It also reinforces the importance of the technical aspects of a study as it illustrates how accuracy, proper controls and keeping track of samples can enormously effect how well-acquired data can answer the proposed research question.

STUDENT AND STAFF PERSPECTIVES ON BENEFITS AND DRAWBACKS OF AN INQUIRY-BASED TASK

As described, there are multiple educational benefits to an inquiry-based teaching approach. One such benefit is the genuine engagement and excitement that students and TAs demonstrate. Students are much more focused on discovering the answer to their question rather than finding out the "right" answer. TAs are co-learners in this exercise, and are equally interested in the

results that their students obtain, as they also do not know the outcome. Students are involved in the authentic generation of new knowledge creating a true feeling of excitement. Students report they feel like "real scientists," and TAs report the classes are more enjoyable, and student groups are more engaged and demonstrate better teamwork.

While engaging, it is also difficult to implement inquiry-based approaches into the curriculum. Teaching associates need good training in advance, and it requires trust to "let go" and allow students to design their intervention. Our TAs are either post-doctoral researchers or post graduate students with previous teaching experience. TAs with less teaching experience often want to be involved in the experimental design, however we encourage them to stand aside, allowing students to make mistakes, and step in at only certain stages to provide guidance. This is not to suggest that the task is not well-scaffolded, however we do encourage students to take the lead in the design of the experiment, with the TA asking pointed questions to guide students where necessary. This approach is also time-consuming, requiring more class time than a traditional laboratory class, meaning other techniques may be left out. However, we believe the skills gained in research are well worth the sacrifice of learning a new technique.

Inquiry-based learning can be intellectually draining, requiring a high cognitive load. Scholars have argued that this decreases the effectiveness of the approach (12); our approach however is highly supported through the guidance provided by TAs reducing some of the problems associated with cognitive overload. TAs provide guidance at specific stages, including at the planning and design, implementation, and analysis stages. Used in moderation, we feel inquiry-based tasks can only enhance student engagement and learning. It challenges students to apply the type of higher order thinking which is transferable to their working life, gives them a sense of the processes involved in conducting research, and therefore develops key skills required to pursue a research career. Inquiry-based learning also fosters the curiosity and creativity of our students and gives them the opportunity to experience that possibility of making new discoveries which is so integral to the scientific method and can sometimes be diminished in the more recipe-based practical classes.

Students do find the exercise challenging, but also rewarding. Anonymous student feedback about their experience include "While challenging … the inflammation prac … helped [us] work on some really useful skills, particularly for those of us looking to go into research" and another student reported that it was "the first taste of real-world science." "It allowed for us to gain a deeper understanding of the reality of research and how much planning and thought goes into designing a study." Staff feedback report that it allows students to develop their critical thinking skills, be creative, think about experimental design and feasibility, understand research, and helps them in future assessments that require creativity and critical thinking. While previous research has indicated that, due to the increased difficulty and cognitive-load required by the inquiry-based approach, students are quite resistant to the introduction of such tasks (3), an alternate study found that students were overwhelmingly positive about their experience (11). Similar to the latter study, we found student satisfaction in the unit being maintained since the introduction of this, and other, inquiry-based tasks, through formal student evaluations of the unit. Students report that they apply their deeper understanding in tasks that require a more in-depth appreciation of immunology and the scientific process, such as a research proposal and scientific poster which are later assessments in this, and other, immunology units.

FINAL THOUGHTS

Inquiry-based learning is a challenging teaching tool in undergraduate teaching laboratories; it requires more time than a more traditional approach, it requires TAs to be trained differently, and to approach their teaching differently, and places a large cognitive strain on students. However, the benefits of higher student engagement and increased understanding of scientific processes outweighs the negatives. Students have a greater understanding of experimental design, the importance of controls, confounding effects, and statistics. Applying previously acquired theoretical knowledge to a genuine problem engages both students and staff, and consolidates learning. While students recognize the higher-level thinking required, and acknowledge that this is more demanding than more traditional exercises that they have completed, their high levels of engagement mean that, rather than resenting the increased difficulty, they embrace the challenge and feel more at ease in their understanding of immunology and the scientific process.

AUTHOR CONTRIBUTIONS

MD and KM contributed to the concept and design of the manuscript. KM and AB designed and implemented the pedagogical approach outlined herein. MD, AB, and KM contributed to the writing and editing of the manuscript.

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MINI REVIEW
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Team-Based Learning for Immunology Courses in Allied Health Programs

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Immunology is now a major component of studies in human biology, with many diseases having immune system involvement. Because so many areas of study include aspects of immunological knowledge, how to teach and incorporate immunology must be evaluated and assessed at all levels of education including K-12, undergraduate, graduate, medical, and professional programs. Traditional teaching methods such as lecture have significant shortcomings which make them less appealing to students today who are more digitally inclined and demand more active and engaging learning environments. Herein, we describe and propose the use of the active learning model of Team-Based Learning (TBL) to incorporate immunology into medical and professional programs. TBL is defined as an evidence based collaborative learning strategy taught in a three-step cycle: pre-class preparation, in-class readiness assurance testing (RAT), and application-focused exercises. In TBL, students are assigned to 6–7 member teams. Students complete the in-class RAT individually followed by taking the RAT as a team (T-RAT). Following the RAT and T-RAT, the instructor can then provide immediate feedback on concepts that proved especially difficult. The remainder of class time is then spent with teams working case studies and applications relative to the instructional topic or disease. Teams decide the best outcome or answer for a given application and report their answers simultaneously in class, followed by a discussion facilitated by the instructor. Research indicates that students involved in active learning classes, such as those using TBL have significantly increased levels of student engagement and high performance on examinations. This review will highlight how to implement TBL into a professional program (medical, dental, nursing, or pharmacy), how to assess student performance and provide real world examples of case studies and applications.

Keywords: Team-Based Learning, active learning, TBL, flipped class, pharmacy

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INTRODUCTION

Collectively, the biological sciences have a general reputation of being difficult academic subjects. The reasons for this are varied and may include the "language of immunology" which has new key words (e.g., Cytokines, complement, various types of immune specific cells) that are not discussed in other biological fields.

The immune system can be characterized as an expansive network of tissues, cells, cytokines, and signaling processes which support the function of all other body systems. Consequently, failings of

the immune system can have far reaching effects throughout the body. For example, autoimmune diseases such as Multiple Sclerosis present with neurological symptoms and patients are treated by experts in neurology. But it cannot be ignored that MS is an aberration of immune regulation involving T and B cells, among others. The transition of macrophages into foam cells during the development of heart failure is another example of where an aspect of the immune system overlaps with another disease state and body system. More obvious examples include the role of the immune system in fighting off various types of infectious diseases and cancers, as well as in its governance of immunization and organ transplantation outcomes.

Because of its foundational role in human health and pertinence across an array of disease states, it is imperative that students of the health sciences develop a strong appreciation for immunology and a robust understanding of immune function. A key question is how to best deliver immunology education. It has been well-documented that lecturing is a passive, and perhaps outdated, educational pedagogy. Students in lecture courses often report boredom and loss of interest after approximately 15 min of lecture. This means that for a 60-min class, only 25% of the material is truly delivered to the student. Furthermore, the delivery of material via lecture can often limit question and answer opportunities and decrease student engagement. Thus, in this review we propose Team-Based Learning (TBL) as a method to deliver immunology material with a particular emphasis on optimizing health professions education.

ACTIVE LEARNING USING TBL

Active learning techniques have been celebrated for decades as promising solutions to the commonly perceived problems of student engagement and subject matter retention. Multiple reviews have covered the evidence base for the use of such paradigms in STEM (Science, Technology, Engineering, and Mathematics) education, with a focus on those methodologies which incorporate cooperative student groups engaged in problem solving exercises that require some degree of mastery of the pertinent subject matter (1–3). Such pedagogies can be described as *constructivist* in that they champion the notion of learners building knowledge for themselves, an approach that stands in stark contrast to the classic lecture model in which information is transmitted passively to students with expectations of memorization and little hope of integration (4). These constructivist strategies have been demonstrated, with varying success and significance, to improve student engagement, critical thinking, exam scores, pass rates, and retention rates in a variety of settings (3).

In 1992, Larry Michaelsen published the description of a novel approach to small group teaching which was intended to capitalize upon the strengths and address the shortcomings of other active learning strategies (5). This highly structured and intentional approach was ultimately branded as "Team-Based Learning" (TBL) and has subsequently been successfully employed across multiple STEM fields. More particularly, TBL is exquisitely suited to education in the allied health professions as it allows for an efficient treatment of meaningful, multivariate, and complex clinical situations through peer guided case assessment and active problem solving (6). This was demonstrated in a study by Burgess et al. (6) in which TBL was compared to Problem-based learning (PBL) in a cohort of medical students. Students utilized both PBL and TBL methodology to study musculoskeletal, cardiovascular, and respiratory units. At the end of the term students completed questionnaires regarding the strengths and weaknesses of each method in relation to their learning. Students favored the TBL format over the PBL and reported the decreased group size, pre-reading assignments, and assessment activities contributed to improved learning and better understanding of the material. Students also noted the immediate feedback from experts and relevant applications led to better engagement with the material and understanding.

In accordance with several recognized critical attributes of effective learning methods, TBL is a constructivist process which focuses on the acquisition of procedural knowledge and capitalizes on the ability of groups to learn more efficiently than individuals while relying on student ability to articulate explanations and defend group reasoning as part of the assessment of subject mastery (2). Haidet et al. have carried out an exhaustive review of the TBL literature and found that students in TBL courses reported (on average) higher levels of engagement and satisfaction (7). Additionally, those that were initially on the bottom of the curve reported improved individual outcomes. Furthermore, the TBL paradigm allows for the traverse of multiple tiers of Bloom's taxonomy via a three-phase process which capitalizes on peer interactions to build upon, and ultimately result in, the individual's competency and personal responsibility for learning (8). The example at the end of this review is a typical application that requires students to have read and learned basic immunological terms and concepts such as the various types of immune cells and their function, the process of inflammation and the role of some specific cytokines and pattern recognition receptors. TBL has successfully been employed as a pedagogy for the delivery of immunology course materials and has likewise enjoyed broad application and generated positive outcomes in a variety of related fields in both the basic and clinical sciences (9–13). Our purpose here is to present an example of a TBL application and assessments specific to the immunology content of coursework in the allied health professions.

STRUCTURE AND STUDENT ASSESSMENT IN TBL CLASSES

Knowledge and basic comprehension are developed in phase one of the TBL process through individual preparation exercises which commonly take the form of pre-class readings guided

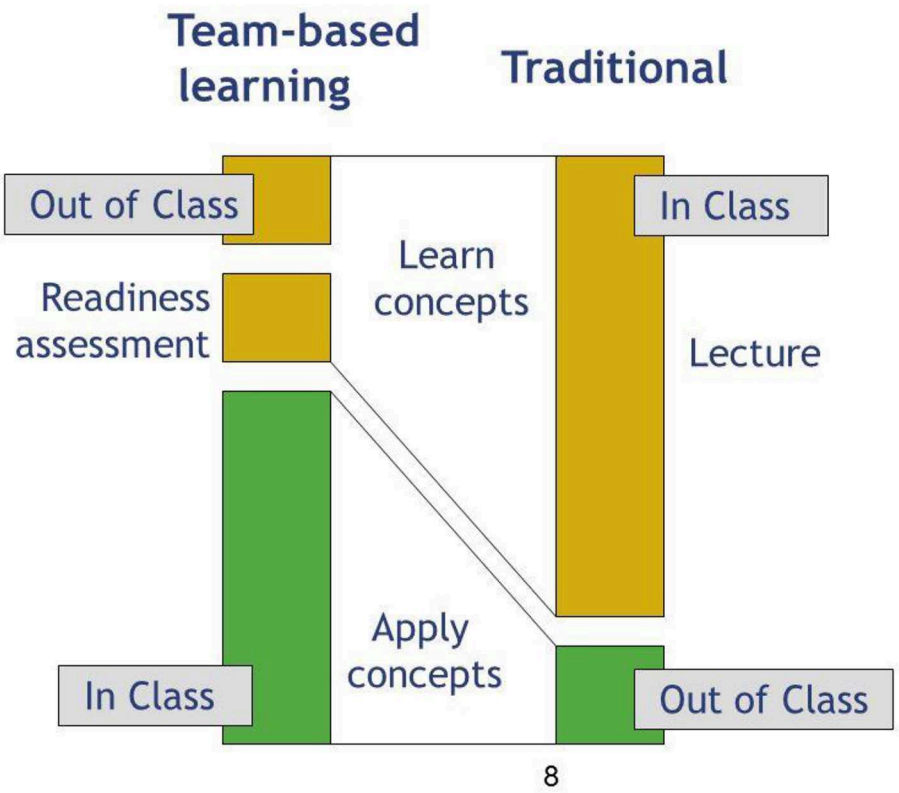

FIGURE 1 | TBL utilizes a flipped classroom model, in which students are responsible for reading and reviewing material prior to class time, so the majority of class time is spent practicing applications and case studies with instructor guidance. This is in comparison to traditional lecture methods in which students would be introduced to material during a lecture.

by a list of specific learning objectives. This serves to enhance classroom efficiency by placing the onus of achieving lower levels of Bloom's Taxonomy on the learner (i.e., self-directed learning). That is, no class time need be spent on basic concepts, definitions, or terminology which the learner is expected to read and review ahead of time (**Figure 1**). In the example used at the end of this review, students will have read a primary literature article and been given supplemental information (in the form of textbook chapters, videos) on basic concepts in innate immunity. Students will also have completed a required microbiology course.

In phase two, individual and team readiness assurance tests (iRATs and tRATs, respectively) not only incentivize the completion of pre-class preparations, but also serve to clarify concepts and reinforce comprehension (14). After each student completes the 10–20 question iRAT on their own, they immediately reconvene with their team (4–6 other students) to work on the same assessment as a group. The tRAT is scored using a scratch-off card (Immediate Feedback Assessment Technique®, or IF-AT, card). IF-AT cards are similar to lottery tickets in that each team responds to tRAT items by scratching off their agreed-upon answer to reveal a star if they have chosen correctly. If an incorrect answer has been chosen, the team continues discussion and scratches off their second choice, repeating the process until the correct answer is identified. Full or partial credit (4 points, 2 points, 1 point, 0 points) is awarded based on the number of attempts needed to answer correctly.

The tRAT with IF-AT scoring supports learning in multiple ways and renders a superior feedback mechanism when compared to traditional assessments which require that students actively check numerical grades after-the-fact to determine what their knowledge deficits are. IF-AT cards provide immediate feedback to confirm knowledge and build student confidence while eliciting germane questions and correcting errors in thinking through team discussion in real time. Furthermore, the promise of partial credit serves to stimulate these continued discussions and fosters participation in iterative rounds of peer-to-peer teaching which reinforce and improve student understanding of material. In addition to these benefits associated with the immediate feedback afforded by IF-AT cards, the iRAT process can be further capitalized upon when coupled with a computer-based testing program which gives faculty immediate access to psychometric data and item performance. Such reports serve to identify items that are still unclear to a substantial number of students, thus affording the instructor the opportunity to address specific areas of confusion via moderated class discussion or mini-lecture.

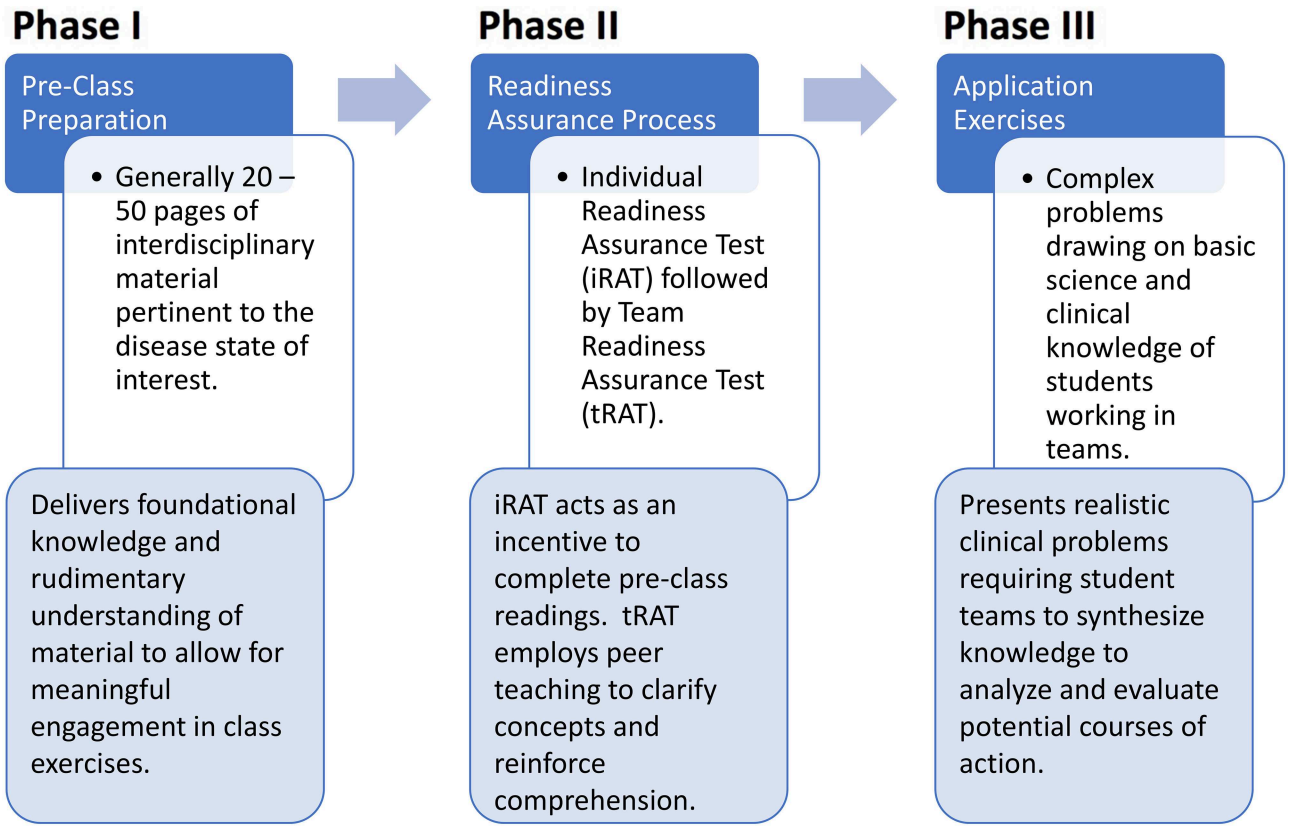

FIGURE 2 | TBL uses 3 distinct phases: Prior to class students spend time independently reading and reviewing material assigned by the instructor. This is followed by completing a readiness assessment process (typically a quiz) to insure they are prepared for class. The final phase is completed during class time, and involves using the knowledge gained during phase I and II to evaluate and draw conclusions on practical applications or case studies.

After RATs are complete and knowledge deficits are addressed, the majority of class time can be spent on phase three, in which more complicated case studies and often confusing concepts can be covered through significant Application Exercises (AEs) aimed at achieving mastery of higher levels of Bloom's Taxonomy. AEs are solved at the team level and allow students to work together to apply the basic concepts learned in phases one and two. Faculty facilitation of AEs occurs at the class level and involves oral reports which require individuals to articulate and defend their team's rationale for answer selections/non-selections. Team-to-team discussions often ensue with instructor oversight, providing a rich environment for rigorous study of course material. As indicated in the application example, the instructor can use the questions to further engage students in a conversation regarding immunological processes and topics. The AE process is designed with the ultimate goal of empowering students to apply their knowledge toward the analysis and evaluation of potential courses of action in the context of realistic clinical problems. Multiple examples exist in the literature highlighting not only the ability of TBL to achieve these outcomes, but its further value in promoting professionalism, improved communication skills, and teamwork (15–17) (**Figure 2**).

To further encourage active engagement in class activities, students have the opportunity to assess their team-members in a round-robin peer evaluation process that covers a wide range of topics including inter-professional communication, contributions during class, and professionalism. Finally, an overarching assessment of student learning is achieved through individual midterm and final exams. Course grades are calculated as a weighted composite of individual performance (iRATs and examinations), team performance (tRATs and AEs), and peer evaluation scores. It is worth noting that the weighting of individual and team grade components deserves thoughtful treatment in order to avoid undesired outcomes such as excessive grade inflation, loafing, or individual students being "saved" by team performance, as team grades tend to be substantially higher than those achieved by individuals. One useful approach to guarding against the progression of dubiously qualified students is to base progression solely on the individual performance grade such that no student can progress without demonstrating competence. Using such a model, a threshold grade (e.g., 70%) must be achieved on exams, iRATs, and/or the combination of the two in order to pass the course, with team points being awarded to calculate the final grade once the pass/fail criteria has been met.

CHALLENGES ASSOCIATED WITH TBL

TBL presents a number of challenges for both students and faculty. Students have typically spent many years learning passively with transfer of knowledge from faculty to student in lecture settings. TBL requires active engagement on the part of students as they take responsibility as life-long learners. The conversion from passive to active learning can take time and requires programmatic support of students making the transition. We have previously presented at the American Society of Health Pharmacists that students in a TBL program demonstrate improved problem-solving and critical thinking skills as well as improved study behaviors characterized by less cramming. In addition, students cite increased respect for the value of teams and the opinions of other team members along with an increased likelihood to share opinions with other team members, similar to observations reported by Luong et al. (18).

Challenges for faculty include pre-class preparation. In addition to researching, gathering, and writing pre-class preparation materials, RATs must be created and application exercises crafted to be of sufficient difficulty that they require a higher level of thinking on the part of the student. One way to accomplish this, particularly relevant for the health professions, is to utilize case studies. De-identified patient cases drawn from the personal experience of the facilitator often make for ideal AEs, though examples drawn from the literature can be effectively developed by faculty with minimal clinical experience and there are ample opportunities to deliver non-clinical basic science content through TBL (see example below). Finally, facilitation of TBL RATs and AEs requires faculty development in areas distinct from the ability to provide lectures. Faculty may initially be challenged in a TBL environment where student participation may often direct the course of discussions to elicit unforeseen questions and tangential explorations.

AN EXAMPLE TBL APPLICATION

The application below is an example of how a study from the literature may be adapted to a TBL application exercise in an introductory pharmaceutical science class. This class topic was urinary tract infections, and students had previously studied sexually transmitted infections. Prior to class, students were required to read "Overdiagnosis of Urinary Tract Infection and Underdiagnosis of Sexually Transmitted Infection in Adult Women Presenting to an Emergency Department" by ME Tomas, which was published in *J Clin Microbiol* in 2015. This paper was a nice example to turn into an application as it is relevant to the class topic, provides engaging and relevant information for future health professionals, and gives the instructor the opportunity ask higher level Bloom's taxonomy questions regarding how the immune system responds to infections. The class was then given application questions:

1) Which immune cell would first respond to a UTI?

   a. Macrophage
   b. Neutrophil
   c. Eosinophil
   d. NK cell

The correct answer is B, neutrophils. Upon team reporting the instructor can use this opportunity to probe further as to how neutrophils are recruited to the site of an infection, what their role is in innate immunity.

2) Would you expect the same cell type chosen in question 1 to be the first line defense in an infection with Herpes Simplex Virus-2?

   a. Yes
   b. No

The correct answer would be no. This question is more open ended and provides the instructor to discuss differences in immune responses to bacteria vs. viruses.

3) Which of the following plays the MOST important role in the innate response in bladder epithelial cells upon initial infection?

   a. TLR4
   b. cAMP
   c. TRPML3
   d. Caspase-8

The correct answer should be A. This question helps the students understand the process of intracellular signaling and pattern recognition receptors such as TLR4 and the cascade of events which follows their engagement.

4) A common STI is human papilloma virus, the most common cause of a UTI is *E. coli*. Since it is important not to delay therapy in either case, could you treat both of these bacteria with the same antibiotic?

   a. Yes
   b. No

The correct answer is no, because we do not treat viruses with an antibiotic. This question provides the instructor a nice opportunity to query students in differences of immune responses to viruses or bacteria.

Following each question the facilitator discusses common symptoms and pathology, differences in presentation of different types of UTIs and importance of treatment. The third question also gives an opportunity to discuss differences in the types of bacteria that cause each disease, the mechanism of action of various antibiotic which may be used to treat.

CONCLUSIONS

As our breadth of immunological knowledge expands, our approaches to education must also change. As mentioned, lecturing is now recognized as a passive form of education for the student that is not as effective at developing critical thinking skills as newer, active learning methods. As the

development of active learning styles are evolving, TBL has emerged as an evidence based methodology that fosters improved critical thinking, better retention, and also has the advantage of developing "soft skills" among students including listening and communication skills. Such skills are particularly relevant for the health care professions, where providers must not only be experts in their field but must also be able to communicate effectively to their patients.

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SJ conceived the idea for this paper, wrote, and edited. PC and MM wrote a significant part of this paper.

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Inoculating a New Generation: Immunology in Medical Education

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Educating the next generation of physicians is a key means of communicating and disseminating impactful immunologic scientific knowledge, and its practical application to human disease. We present our perspective, using as our model a first-year medical school course entitled Host Defense. As the name suggests, immunology is the overarching principle that links the multiple subjects in the course. We address a range of immunologically relevant topics, including innate and adaptive immunity, vaccines, inflammation, allergy, tumor immunotherapy, transplantation, and autoimmunity. These topics are integrated with the fields of infectious diseases, pathology, clinical laboratory testing, and public health, to illustrate how the basic science discoveries in immunology are relevant to clinical practice. The course objectives are not only to deliver "first principles" and molecular mechanisms, but also to connect these principles with the clinical world of diagnosis and therapy. We detail the different methodologies used to achieve these objectives and to reach today's medical students. This provides a framework for course structure and execution designed to engage both the novice and the more "immunologically experienced" learner. The framework includes classical didactic components and personalized instructor access, aligned with current approaches to self-directed learning and using digital media. We also address some of the challenges of assembling a course like Host Defense in the context of an academic medical center with multiple scientific, educational, and clinical missions. This perspective is not meant be proscriptive, but rather to outline our experiences on the strategies tried, while describing their advantages and drawbacks in teaching immunology.

Keywords: immunology, medical, education, digital, clinical

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INTRODUCTION

Connecting the concepts of immunology to the clinic is a challenge for medical students (1, 2). To quote a clinician/educator at our institution, "Of all the science topics covered in medical school, immunology was one of the hardest to wrap my head around." Achieving this goal is not trivial for either learner or instructor. The learner can be daunted by the ever expanding "alphabet soup" constituting the language of immunology; cytokines, chemokines, effector molecules, cell types, cell surface receptors. The instructor cannot elucidate immunology's basic concepts without extensive use of terminology. Furthermore, effective teaching of immunological concepts requires integration of basic knowledge from multiple disciplines in the context of clinical observations and laboratory findings (3, 4).

We describe strategies for teaching immunology to first year medical students. In a course entitled Host Defense, we integrate immunological topics with the fields of infectious diseases,

pathology and laboratory testing to explore the impact of the immune response on human health. The course is designed to deliver "first principles," and to connect these principles with the clinical world of diagnosis and therapy. Herein, we address the following questions:

- What are the main challenges of course organization?
- How can we integrate digital media into education?
- How does one connect basic science to the clinical world in a way that is both educational and meaningful?
- What are some emerging trends in immunology education?

In this Perspective, we describe strategies that worked well for us, and some that did not. We also provide specific examples in the hope that others might adapt these strategies in their unique medical education and immunology teaching settings.

LOGISTICS

Logistics, "the detailed coordination of a complex operation involving many people, facilities, or supplies" is an underappreciated, yet crucial, part of any course. The importance of logistics has long been appreciated by the military.

> "Amateurs talk about tactics, but professionals study logistics." –Gen Robert H. Barrow, USMC, as well as others.
> "My logisticians are a humorless lot … they know if my campaign fails, they are the first ones I will slay." –Alexander the Great.

Running a course that involves multiple lecturers, spans several disciplines and includes activities outside of lecture, presents a logistical challenge. Importantly, from the faculty standpoint, the quote from Alexander is relevant—if there are problems with delivery of the material, or performance of medical students on standardized tests such as USMLE Step 1, it is the director of the course who pays the price! Thus, the logistics of the course matters; determining the number of hours of didactic instruction, organizing specific topics to optimize the flow of ideas, scheduling, and recruiting lecturers as well as facilitators for Problem Based Learning (PBL) groups are just some of the hurdles.

We must now also grapple with the challenge of integrating the digital world into a course in ways that engage students, provides current, accurate information, and enhances learning. **Table 1** summarizes the advantages and disadvantages of e-resources we utilized in Host Defense. To bridge the traditional and digital worlds, we advocate a hybrid strategy where selected content can be delivered using a self-study, electronic format (5), so that in-person lecture can be used to integrate key concepts in the context of health and disease (6). A full description of our course structure, learning objectives and lecture materials is provided in **Table S1**. The next several sections describe our experiences, and challenges we faced in organizing the course and its content.

TRANSITION TO DIGITAL CONTENT

Many features of digital content delivery appeal to today's students. Links embedded in a document, and the ability to look up unfamiliar terms or find digital images instantly, enrich the learning experience (7). These advantages led many medical schools, including our own in 2012, to use electronic tablets (in our case, iPads) to deliver didactic content. Using electronic content freed us from printing a 650-page syllabus weeks in advance, allowing editing of the content closer to lecture. Over time, we moved from syllabus replacement to using the iPad to deliver new material linked to lecture content. With the invaluable help of our institution's instructional design expert, we introduced on-line modules to explore diagnostic laboratory microbiology (8, 9). Modules on bacteriology and virology were contained in five iBooks linked to clinical cases (www.idimages.org), each followed by a computer-based self-assessment of knowledge related to the diagnostic tests (**Table 1**).

We did face challenges in using iPads for content delivery. To quote Marshall McLuhan, "The medium is the message" (10). We found there were unanticipated consequences to introducing new technology that changes the inter-personal dynamics between instructor and learner. During lecture, students focusing on the iPad, and not the lecturer, detracted from the ability of the lecturer to "read" the audience and gauge the effectiveness of their delivery. Unfortunately, this parallels the filing of electronic medical records while interviewing a patient, to the dismay of patients and physicians alike. The interaction between the student and the lecturer is further compromised if the student succumbs to the temptation to use the tablet or laptop for activities unrelated to lecture, e.g., shopping, messaging with friends, etc., as their attention wanders (11).

THE PERILS AND PITFALLS OF E-LEARNING TOOLS

While the iBooks used to explore diagnostic microbiology were viewed favorably, we cite two experiences where introducing electronic learning tools into Host Defense did not proceed as smoothly as hoped.

Learning vocabulary remains an essential step in immunology and, indeed, all of medicine. Clinicians use this vocabulary daily, and remark that medical vocabulary is the major part of the first 2 years of medical school. Although many students view memorization of terminology pejoratively, there is no more rapid means to shred professional credibility than to mangle the vocabulary. Defaulting to "However you say it …" is no longer acceptable.

In consultation with both students and our instructional design team, we prepared an extensive set of e-flashcards with application *Study*© for the vocabulary of immunology and infectious diseases to be used in a self-study format. The application was purchased by our institution, provided to each student and formal instruction offered. Along with text, incorporating audio allowed us to add the proper pronunciation for a given term. Despite expending considerable effort to create

TABLE 1 | Activities and resources used in host defense: advantages and disadvantages.

Activity/Modality	Advantages	Drawback/Disadvantage
In-class demonstrations by presenter using props and models.	Potential to engage and involve students: serve as a "memory peg" for learning. Provides a break allowing students to re-focus.	Students may remember the demonstration but not the immunological concept. Time consuming.
Small group exercises in class. Pose a question and discuss.	Enhances peer-to-peer engagement. Presenter can quickly assess if students are progressing and can discuss answers in real time.	Time consuming. Instructor must keep a relatively firm hand on organization or it can become chaotic.
iPad for content delivery.	Ability to store large amounts of information, searchable, can annotate files, and look things up in real time. Can view textbooks, slides, and lecture notes in class.	May be a distraction; e.g., shopping, messaging with friends. Annotating notes can detract from classroom awareness.
E-flash cards for vocabulary.	Self-directed and self-paced learning. Will accommodate images, audio, and video links and text. Can provide pre-made cards or have students build their own sets.	Preparation is work-intensive. Only a portion of the class may use them. If you select one specific application, it can become obsolete and/or unpopular.
Audience e-response tools.	Rapid feedback to students. Increases student engagement. Can quickly determine if they are absorbing concept.	Must commit to the technique and the specific tool. If system falters, student attention quickly diminishes.
iBooks for teaching clinical laboratory.	Provides opportunities for interactivity not available in a PDF format.	Work-intensive to assemble. Once assembled, cumbersome to edit.
Case studies in infectious diseases sponsored by the Infectious Diseases Society of America.	Clinical cases compiled by experts in infectious diseases and presented in an interactive, expository format. Many cases annotated for medical students.	Not an encyclopedic collection, but growing. Found at idimages.org.
Interactive white board application for iPad.	Fosters collaborative interaction in real time in digital realm. Useful as a study tool for a group and to generate interactive "mind maps."	Slow response time of Wi-Fi network, and alternative personal preferences, led to its rapid demise.
Visual Dx.com	Electronic dermatology image database of an extensive array of diseases, with examples across the range of human skin pigmentation. Addresses lack of diversity.	Institutional access requires a subscription.
Twitter peer-to-peer and student-to-faculty communication	Followed by entire class in real time. Can easily retweet relevant articles linked to breaking immunology topics. Many students use Twitter.	Need to use consistently, can only use for certain tasks; limited by length of content; requires some digital skill.

the e-flashcards, it did not translate into widespread utilization by students. One colleague quipped, "If *you* build it, they *won't* come." Course surveys revealed only ∼25% of the class found the e-flashcards "very useful." In contrast, a professional, visually based program employing "memory pegs" (12) and animation, *SketchyMicro*©, was considerably more popular, with ∼75% finding it "very useful." Illustrating the gap between students and faculty, we were initially unaware of the degree to which *SketchyMicro*© was adopted, even though the more popular application was relatively expensive and available only for rent.

In a second instance, we observed students using an interactive computer whiteboard to share content in real time over the Internet and create concept maps (13, 14) as a study tool. With the help of these students and our instructional design expert, we introduced and demonstrated a free, interactive whiteboard iPad application to the entire class during a lecture. We tasked all students to use the application in their respective Problem Based Learning (PBL) group to replace the conventional classroom whiteboard. Our goal was to make it easier to share learning objectives and concept maps of Host Defense PBL cases with the class. Disappointingly, our "top-down" approach quickly crashed, and the students stopped using it after 1–2 sessions. Students stated that the response time of the network was too slow to keep pace with the group's discussion. It was faster to simply write on the board and take a picture on their phone. Furthermore, many students had already been using other platforms, such as Google Docs, and were unwilling to switch. We learned the hard lesson that students often outpace faculty in identifying and adopting new digital applications. Moreover, their popularity can change rapidly through peer-to-peer communication to which faculty are often not privy.

COPYRIGHT AND FAIR USE

The advent of digital content delivery raises the question: How does one use textbooks, particularly in the context of lectures? Does one create all one's own figures (a time consuming and daunting task) or use existing material? In the latter case, there are numerous immunology textbooks, with excellent, professionally designed figures. However, with the steady decline in the purchase of textbooks by students, copyright issues rise to the fore.

Issues surrounding Fair Use of copyrighted material depend upon the precise circumstances when they are used (15–18). Instructors have long used published figures to supplement their lectures, and this has generally been deemed permissible. However, if the course materials are posted on-line, ease of re-distribution can pose copyright problems. If the library buys a site license for a course text, this issue can be mitigated to some extent. However, as we have experienced, if the library buys a

site license and later discontinues it, you may need to redo the digital content for your entire course. Posting class materials on portals with access restricted to registered students, such as Blackboard, may serve as an important barrier to potential copyright infringement. Nevertheless, if copyright infringement is alleged, the instructors are usually left to fend for themselves (15). Your institution's library staff is a good resource for Fair Use guidelines to help navigate these issues.

MAKING CONNECTIONS BETWEEN DISCIPLINES

Understanding immunological concepts requires the expert integration of multiple disciplines and concepts. Can you teach someone to be an expert in immunology in a medical school class? Obviously, not; becoming an expert takes years of intense effort and dedication. However, it is possible to illustrate how experts *think* by using examples to make connections between topics students perceive as disparate (19). To illustrate passive immunity, we described the delivery of anti-toxin by the sled dog Balto for the treatment of an outbreak of diphtheria in the Inuit population of Nome, Alaska (20). This was used to segue into serum sickness, Lupus, Rh disease, rattlesnake bite therapy, monoclonal antibodies, and tumor immunotherapy (**Figure 1A**). We have also used concept mapping (13, 14) to connect the fields of infectious disease, inflammation and adaptive immunity. In a lecture "From Bacterial Capsules to Vaccines," we start with classic studies from the 1920's on infection caused by *Streptococcus pneumoniae* to describe how a bacterial structure, polysaccharide capsule, results in evasion of phagocytosis, leading to lung inflammation and consequent pneumonia (**Figure 1B**). We then transition to the bacterial capsule as an immunogen to explore the concepts of antibodies as opsonins, pneumococcal serotypes, conjugate vaccine design, and immune evasion using the same concept mapping approach.

CONNECTING TO THE CLINIC

Medical students recall immunological concepts most effectively when they are placed in a clinical context (6, 21–23). We make clinical correlations by incorporating cutting-edge immunology topics in the news and examining mishaps that occur in medicine, such as transplanting a mismatched kidney. We can review not only the immunology involved, but also encourage discussions on medical ethics. To strengthen the link between basic and clinical immunology (24), we conduct in-class small group exercises to measuring immune responses, with emphasis on the uses of antibodies. Further, we have a series of PBL sessions based on clinical cases emphasizing basic science that, with the help of a facilitator, students work through as a team.

We incorporate physicians into the course; as lecturers in their area of expertise to connect basic science to clinical care, but also to communicate how they think about patients (25). We have a clinical immunologist deliver lectures on inflammation, hypersensitivity, asthma, and autoimmunity, and the roles of monoclonal antibodies and other biologics in the therapy of immunologic diseases. We then reinforce and expand these concepts by recruiting a dermatologist to lecture on cutaneous manifestations of adverse drug reactions. We also have two in-class sessions on clinical decision-making in infectious diseases. Clinicians describe their own cases and the decisions they made in terms of diagnosis, therapy and follow-up; emphasizing the evolution of their thinking over time. While clinical vignettes can never fully replicate the experience of a physician connecting with an individual patient for whom they are responsible, they can demonstrate how an expert physician integrates basic science into clinical medicine. The physicians inter-weave all aspects of patient history with basic and clinical science, while communicating their sense of responsibility for the patient's well-being.

The clinical lectures by physicians also serve as an important bridge between the basic science and clinical spheres, and illustrate how basic science information is applied. For example, as shown in **Figure 1**, we explore the role of the antibody and complement in promoting phagocytosis of encapsulated bacteria. Complement and immune complexes are reintroduced in the context of serum sickness resulting from the passive immunization against diphtheria toxin using horse serum (see Balto, **Figure 1**), and later in the context of immune complex diseases such as systemic lupus erythematosus (SLE). Complement comes up yet again in a discussion of immunodeficiencies, exemplified by increased susceptibility to infection by the bacterium *Neisseria meningitidis,* as well as increased frequency of autoimmune diseases. The spaced repetition of the complement system in different contexts is not only an excellent learning tool (26), but also helps to integrate the multidisciplinary field of immunology.

Integrating clinicians into a course poses challenges. First, the lecturer often over-estimates the students' clinical knowledge. Consequently, students often feel overwhelmed by their presentations. It is also hard to schedule clinicians to fit within the flow of the course, as their patient care responsibilities always come first. Finally, the clinicians usually do not have the time to examine the course content in detail. A common expression uttered, which never fails to cause considerable consternation among students (and the directing faculty), is "I don't know if you've had this yet, but…," giving the unfortunate perception that the course is disorganized and lecturers do not communicate with each other. We coach the lecturers to not use that phrase (not always successfully) by emphasizing where we are in the lecture series and the relative level of audience expertise.

OFFERING THE BEST OF BOTH WORLDS

We embrace the utility of digital resources and understand their appeal (see **Table 1** for details of resources and activities used in Host Defense, along with pros and cons). However, we feel strongly that the most important component of our course is a traditional one; direct interaction with students, in person. Students frequently request that lectures be video recorded; this is problematic from several standpoints. Viewing a video of a good lecture cannot adequately replace the dynamic of *attending*

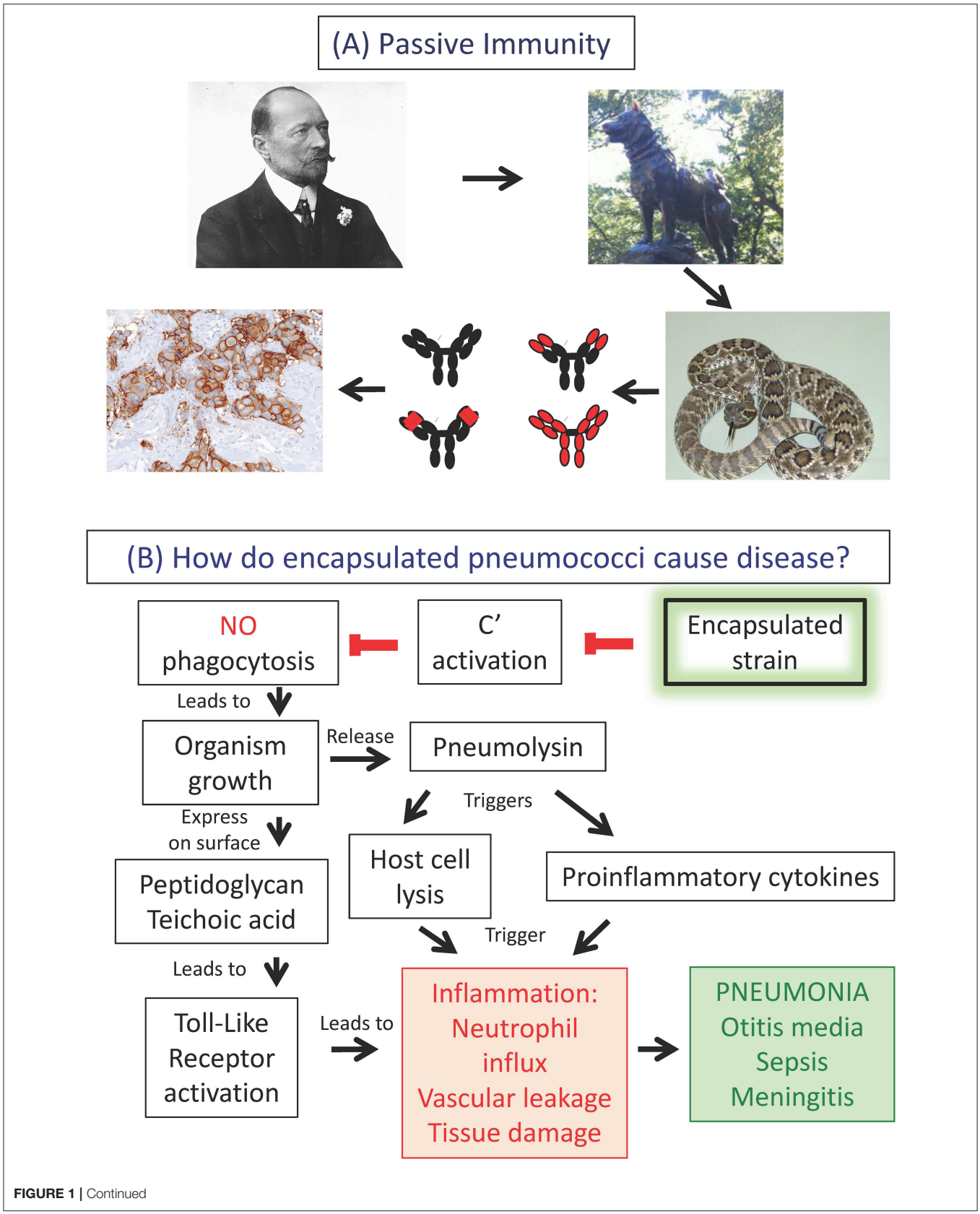

FIGURE 1 | Continued

FIGURE 1 | Making connections between disciplines. **(A)** Antibodies in immunity, disease and therapy. **(A)** Illustrates one example used in didactic lectures to make connections in immunology. This slide design is used in lecture to create "memory pegs" between material covered in the course and to demonstrate how many of the same basic principles can be applied to several clinically relevant situations. Here we show a picture of the Nobel prize winner von Behring who developed diphtheria antitoxin. This form of passive immunity was memorably applied in the delivery of antitoxin by the sled dog Balto and his owner Gunnar Kaasen for the treatment of an outbreak of diphtheria in Nome, Alaska. From here one can segue into the role of antibodies in treating snakebites, the structure of antibodies to minimize immune complex disease, the modern use of passive immunization using humanized monoclonal antibodies such as Herceptin® (trastuzumab) for tumor immunotherapy, and other related topics such as Rh disease. Links to additional slides and other educational resources for teaching Immunology can be found at the American Association of Immunologists (AAI) website (https://www.aai.org/Education/Teaching-Resources). **(B)** Connecting infectious disease, inflammation and adaptive immunity with concept mapping using the bacterium *Streptococcus pneumoniae*, the pneumococcus, as an example. How do encapsulated pneumococci cause disease? Inhaled encapsulated strains fail to activate complement, thereby evading phagocytosis by alveolar macrophages followed by outgrowth of the organism. Bacterial cell walls, containing peptidoglycan and teichoic acid, activate Toll-like receptors, inducing inflammation. Concomitantly, the bacterium releases the protein pneumolysin, lysing lung cells and inducing proinflammatory cytokines, thereby exacerbating inflammation. Neutrophil influx, vascular leakage and tissue damage manifest as pneumonia, with potential dissemination of infection to extra-pulmonary sites.

a good lecture, with the opportunity to view the spectrum of instructor-student interactions, questions, and comments. Video recording of lectures also inevitably leads to a decrease in attendance, resulting in less interaction with instructors and with peers (27).

Effective interaction with a large class requires moving beyond standing at the podium, holding forth for an hour and then exiting the room. We use several approaches to facilitate that interaction, summarized in **Table 1**. For example, to restore waning student attention during lectures, students are routinely called upon to participate in demonstrations in front of the class that illustrate major teaching points. We also intersperse lectures with small group activities to both make teaching points and help foster teamwork. The instruction team must also find a balance between course objectives and the time students need to master the material. We provide in-class time to perform computer-based exercises to provide personalized instruction, if needed. The course director attends all lectures, and is available to consult with students in the lecture hall when no formal lectures are scheduled, a time we have termed Questions and Answers (Q and A).

Like many institutions, we use similar multiple choice questions to those on Step 1 USMLE as one of our assessment mechanisms. However, it is challenging to construct questions that truly assess students' grasp of conceptual knowledge or their ability to synthesize and apply concepts in immunology. To address this issue, we have tried several types of writing exercises that also provide feedback to instructors as to gaps in the student's knowledge. Our current approach, favored by students and instructors alike, is a small-group exercise performed outside of class explaining the underlying immunology involved in an article or video from a popular media source. This reflected the increasing frequency of immunology-based treatments, or clinical scenarios involving immunology, described in commercial or social media, with the expectation that their future patients will want explanations of these new treatments. The group could either choose an article or pick from a list provided. For example, one article titled "HIV used to cure 'bubble boy' disease" instead described using gene therapy to cure severe combined immunodeficiency disease. Each group was tasked with explaining the immunologic mechanisms of the treatment, its advantages over previous approaches, potential drawbacks, or adverse consequences, cost considerations, and any biomedical errors perceived in the article. Their report was limited to two pages, including a picture or diagram of the immunologic mechanisms involved and a description of the issues just described. All students were expected to read the reports of the other groups. Students valued the opportunity to be creative, work as a team, and to take an active role in directing their learning process.

In all these exercises, logistics, in terms of planning, timing in the lecture and smooth execution, are critical. Faculty time, commitment and direct in-person guidance are essential to maintain their organization and assure communication of the outcomes of the activities to the entire class. Since the initiation of significant course re-modeling in 2012, student surveys demonstrated an increase in the quality of teaching and the quality of the course overall. We used a Likert-like rating scale from 1 to 5 with the following categories: 1. "Needs much improvement," 2. "Needs some improvement," 3. "Satisfactory," 4. "Good" and 5. "Excellent." Ratings for the course overall improved steadily from slightly below "Satisfactory" in 2011, with an average score of 2.80, to scores consistently in the "Good" to "Excellent" category in 2015 through 2018, with averages ranging from 4.29 to 4.41. Concomitantly, the ratings for overall quality of teaching in 2015–2018 were also in the "Good" to "Excellent" category, with averages ranging from 4.36 to 4.47.

DISCUSSION

We advocate a self-study, electronic format to deliver specific content (5) that affords lecture time to integrate key concepts in the context of health and disease (6). Appreciating that learning may be enhanced by complementing didactic lectures with interactive activities (2, 7, 28, 29), lecture can be supplemented with brief, small group activities during lecture, and in more detailed PBL sessions spanning several days. This hybrid approach is extremely flexible. Recognizing that digital technologies and innovations are constantly being developed, one can blend and experiment with digital advances, while maintaining the best of traditional methods.

The experiences we have described are with medical education in the U.S. We have also utilized the hybrid approach in our basic science courses in microbiology and

immunology for undergraduates and graduate students. Moreover, we believe that these lessons will also be valuable to educators outside of the U.S. because many of the challenges faced, particularly on how to incorporate the ever-expanding modes of delivering information, are shared concerns. These educational issues include the balance of traditional methods such as lectures with electronic resources, the increasing adoption and preferences of students for digital modalities, and the role of broad electronic platforms such as internet web sites and social media. These issues are common to educational endeavors wherever one teaches. This shared experience is reflected in studies from outside the U.S. cited herein, including those on student interest in immunology (Australia) (1), use of electronic tablets (United Kingdom) (3) and e-resources (Brazil, Germany, Switzerland) (2, 28, 29) in teaching, and connecting basic science to the clinical world (Canada) (3, 23, 25). Furthermore, it is increasingly recognized that educational strategies must be developed for teaching immunology in the resource-constrained regions of the developing world (30). Open access to internet-based, digital resources (2), such as those listed in Faggioni et al. (31), will facilitate closing the gaps between under-served regions and developed areas of the world. In addition, through their respective Education Committees, the International Union of Immunological Societies (iuisonline.org, in association with immunopaedia.org) and the American Association of Immunologists (aai.org/Education/Teaching-Resources) are committed to providing and disseminating quality digital educational resources, as well as organizing meetings and courses, to fill this need. We hope that the strategies we propose herein will help guide the use of these electronic resources effectively.

Looking to the future, we see three emerging technological trends that we anticipate will make major impacts in teaching immunology and related disciplines. They include:

1. A multi-institution collaboration to develop a "shared medical school curricular ecosystem" has been proposed (32, 33) using online videos to deliver core content to preclinical students, thereby affording faculty more class time to facilitate personalized, interactive learning experiences.
2. The increased incorporation of social media (34) including blogging (35) and Twitter (36–38), to facilitate student-student and student-faculty communication.
3. The integrated analysis of the human immune response and systems immunology (39), which require concomitant development of both basic immunological literacy and information literacy skills (40–42) early in medical training.

Whatever the future holds, one can be certain that Immunology will impact nearly every aspect of a physician's practice (24). The sophisticated technological approaches that will become "normal" for today's students as they move into medical practice will be deprived of their potential promise without fostering life-long learning and interest in immunology early in their training. However, we are cognizant of a time-tested quote:

"The only thing constant is change" –Heraclitus.

In that light, we advocate a blend of methods to teach the concepts and applications of immunology, but one that affords the flexibility to adapt to changing times. Immunologists, of course, excel at adapting!

AUTHOR CONTRIBUTIONS

CH and JF contributed equally to the concept, organization and writing of this manuscript.

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The image of the snake is found at https://commons.wikimedia.org/wiki/File:Crotalus_scutulatus_02.JPG.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2019.02548/full#supplementary-material

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PERSPECTIVE
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Leveraging Micro-Stories to Build Engagement, Inclusion, and Neural Networking in Immunology Education

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Storytelling is a highly effective strategy for delivering course content. It can provide real-world contexts and the relevance students desire. Through personal connections to the narrative details, anecdotes facilitate the incorporation of content into pre-existing knowledge and neural networks that enhances retention. In addition, stories can honor students' diverse backgrounds, which builds a sense of belonging and community. In turn, these aspects can drive intrinsic motivation to learn and increase students' alertness in class and overall engagement in the course. Despite the educational power of stories, there often is not enough time to integrate them into curricula. To address this dilemma, faculty can condense stories into micro-stories that require relatively minimal class time. Many aspects of stories that enhance learning can be leveraged in just a few sentences by focusing on narrative details that engage a variety of cognitive and emotional processes. In particular, the inclusion of multiple sensory descriptions and small details, like locations and names, can provide sufficient context to maintain the value stories provide. Micro-stories can function independently or extend a single theme throughout a course. Presented in this Perspective are examples of micro-stories for concepts in immunology and strategies for developing them. Proposals are made for leveraging micro-stories to enhance student engagement and course community, content retention and retrieval, and satisfaction with immunology courses of all sizes and levels.

Keywords: immunology education, storytelling, neural networking, retention, diversity, inclusion

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INTRODUCTION

On a chilly Fall afternoon, a student asked for class to be composed solely of stories about immunology. His classmates laughed and agreed they would not return if there were no stories the rest of the term. Although in jest, the comments underscore that many students find stories about science more enjoyable and easier to understand than dense textbooks and lecturing (1–3). Fortunately, leveraging stories to convey science content also can enhance academic outcomes (3–6).

Stories are one of the frameworks human beings use to process experiences and understand the world (7). They provide a familiar paradigm for learning complex and interwoven material while eliciting strong engagement from many students. The engagement is often driven both through a natural desire to uncover a story's conclusion and varied affective (emotional) motivations (8, 9).

Robust social-emotional associations with course material, educators, and the course community can lead to increases in attentiveness in class and personal motivation, which can promote deeper levels of learning synergistically (8–10). In turn, deeper learning enhances the formation of memory and recall of information.

Memory can be viewed as hubs of interconnected records of one's experiences and the information that one has learned. These networks provide a scaffold to which new information can be incorporated by association. The more associations that connect new information to existing neural networks, the more easily the information can be recalled (11). In addition, the more associations that are activated when retrieving information, the more strongly the information will be maintained (12). Thus, the contextual details of stories can enhance retention of immunology concepts by connecting the concepts to memory networks containing information beyond science. Strong sensory descriptors can stimulate mental imagery and reactivate the sensory and motor cortices which initially processed the sensations (11, 13). In both cases, the associations between content and real or visualized experiences can increase the ability to retain and recall specific information (14–16). Cuevas and Dawson demonstrated that university students who invoked visual imagery while hearing statements recalled two-fold more than students in the auditory-only cohorts in the short term, regardless of learning style preferences (81.9 and 40.2% correct answers, respectfully).

Despite storytelling's power as an educational tool, faculty face a conundrum regarding its implementation. How can one balance the use of this effective strategy beloved by many students with the time needed to cover necessary content? Even with calls to reduce content to incorporate social learning strategies and relevant applications of science, it is difficult to pare down the material to create time to leverage storytelling (17, 18). Employing micro-stories can address this issue. Micro-stories are terse narratives that focus on specific sensory and contextual details to harness the affective and cognitive benefits of storytelling in minimal amounts of time.

This Perspective shares strategies to develop and infuse course materials and class time with micro-stories that can increase student learning outcomes by succinctly (1) invoking associations among content and students' existing neural networks, (2) enhancing students' intrinsic motivation by strengthening course communities, and (3) reinforcing content retention through distributed recall. Overall, the goal is to empower educators to incorporate new strategies or extend current ones that enhance student performance and enjoyment of immunology.

DEVELOPING MICRO-STORIES TO ENHANCE LEARNING AND MEMORY

When constructing micro-stories, it is helpful to incorporate some of the features that make case studies appealing to students: characters with whom students feel empathy, an interest-arousing focus like social conflict, drama or adventure, and personal relevance (19, 20). Providing first names and using female and male protagonists fosters affinity for the characters. Details about the setting can help transport students into micro-stories and stimulate imagery (perceiving in "the mind's eye"). These features can be specific geographic locations, like New York City, or general ones, like the campus' library or a room of a home. Adventure can be introduced by setting the micro-story in the midst of an exciting activity, distant city or foreign country. Social issues at the community, national, and global levels, like requirements for vaccination, can be extremely engaging and need an inclusive approach (21). Elements of micro-stories that relate to the five senses and engender empathy are especially critical because they facilitate students' engagement with the narratives and build connections to students' personal experiences. This can link the course material to varied neural networks which can enhance retention and retrieval of the immunology concepts, even if a story's details don't exemplify an immunologic concept. The following example conjures a familiar setting for many students with relatable visual, auditory, and tactile components. Some students will empathize with Cody being a weaker student and some with Yolanda as the stronger one. "The campus center was noisier and more packed than usual when Cody arrived to study with Yolanda. He was grateful to get out of the rain and for Yolanda's help preparing for their immunology midterm. However, Cody was nervous about being in a crowded area because he has chronic granulomatous disease (CGD). Although his case is relatively mild, he is susceptible to respiratory infections and worries about pneumonia due to antibiotic resistant *S. aureus*." After disclosing the aliment, the instructor can interrupt the story so students can hypothesize about Cody's disease and symptoms.

The next example directly ties the micro-story to a role of IgE. Faculty could spend just 60 additional seconds capturing students' attention and imagination with a micro-story like: "Olivia moved to Alaska to explore its wilderness during time off. After a day of fly-fishing, she stuffed a salmon she caught with garlic cloves and sprinkled it with salt and pepper. It smelled delicious as it blackened rapidly over the campfire. But, the fish didn't cook completely. Unfortunately, Olivia contracted a tapeworm. Hopefully, she will produce IgE antibodies specific for the parasite." The details quickly create adventure and, hopefully, empathy for Olivia. Although most students probably have not traveled to Alaska, the details make the micro-story accessible. Students may have experience camping or be able to imagine the tastes and smells of the fish. Many students may have had an experience with raw or undercooked meat, seafood, or fish. The goal is to aid students' recall of the concept by coupling it to established memories. In addition, asking students to reflect for a moment on a related personal experience constructs bridges between micro-stories and their memory networks.

If writing micro-stories seems daunting, they can be created by condensing stories from a variety of sources. Newspaper articles (for example, about anti-PD-1 cancer treatments)

and single-paragraph highlights in *Nature* and *Science* (for example, concerning patients who appear HIV-free following stem cell therapy) demonstrate direct application of concepts of immunology (22, 23). Micro-stories can also be distilled from historical anecdotes. For example, Charles Richet and Paul Portier's attempts to develop antivenom to the stings of Portuguese man o' war lend themselves to describing the smell and taste of salty sea air, the swaying of the vessels and/or the pain of the stings. Such a micro-story could conjure adventure and empathy, activate multiple sensory networks, and create personal connections, even if students recall an insect sting instead of a hydrozoan sting. Ultimately, there are countless micro-stories faculty could develop to meet the needs of their specific student populations (**Figure 1** and **Supplementary Table 1**).

MICRO-STORIES CULTIVATE COMMUNITY VIA SHARED EXPERIENCES

A strong sense of course community increases student engagement and performance (24, 25). Robust instructor immediacy (students' feelings of closeness to their educator) considerably strengthens the course community (26). When instructor immediacy is high, students' attention, motivation, effort, and willingness to ask questions increase (27, 28). In turn, the perception of having learned, actual learning, and student performance all increase as well (29, 30). Sharing personal experiences, humor, and one's mistakes demonstrates to students that educators are human and enhances instructor immediacy (31). Even in large-enrollment courses, the safety such behaviors instill can encourage students to forge relationships with each other and seek help outside of class (27).

When discussing barriers, innate responses, or integrated immune responses, an educator could share about an accident or infection: "My first summer of graduate school, I went mountain biking. The woods smelled like the pine air fresheners used in cars. I took a turn too quickly, hit a tree and broke a few fingers. The cuts burned and were full of debris. What do you think got into my hand? How do you think my immune system responded?" The sensory details can assist students in relating to the anecdote even if they haven't been mountain biking. Colds, food poisoning, and hypersensitivities are other compelling topics for micro-stories because they are experiences about which students probably can commiserate with each other and faculty.

A sense of belonging among students can be fostered when students share their own, relevant micro-stories. This provides opportunities for weaker students to contribute to class as experts because their experiences exemplify immunology. It is critical to emphasize that it is ok to share; however, sharing is not requested or required, nor will it impact grades. Students should not feel pressured to share personal information. In the author's courses, students have been eager to discuss being resuscitated after a reaction to peanuts, battling vitiligo, being on the autism spectrum and more common topics.

Micro-Stories	Weekly Topics	Other Tools
• My mountain biking accident	Introduction, Data supporting active learning	• Cells of the immune system CM HW
• Should I take allergy medicine when my hand is infected?	Innate immunity	• Innate immunity CM
• Olivia's tapeworm from raw salmon	Immunoglobulins (Ig)	• Ig Venn diagram HW
• XLA Case Study (Bill)	Ig genes, B cell development	• Hands on V(D)J recombination strips
• Preeda wonders about MHC with her 3rd cold	MHC, Antigen processing	• Antigen processing, presentation flowchart
• X-SCID Case Study (Martin); No mom, T cell "shots" won't help	TCR, T cell development	• Flipped class, BM to T cell flowchart
• Olivia's tapeworm from raw salmon II	T cell activation, Differentiation, Cytotoxic cells	• Comparative table for T cells
• Create your own histograms for Bill and Martin HW	Humoral immunity The big picture	• Physical CM on classroom walls
• Deja worries her grandma will get influenza	Midterm, Immune evasion	
• Bill's new belt caused a rash; Martin's mom recalls his BMT	Hypersensitivity, Transplantation	• Hypersensitivities table
• No thanks on the aloe, it's lupus, not sunburn	Autoimmunity	• Breaking tolerance CM HW
• How can you be afraid of eggs Benedict, Bill?	Mucosal immunity	• Mucosal vs systemic immunity CM HW
• Imani and Mateo debate BMT for HIV	HIV, Immunodeficiencies	• Who's sicker? discussion
• FDR's tricks for hiding paralysis; Can Bill or Martin be vaccinated?	Vaccines	• Discuss a vaccine-preventable outbreak
• Stefanie Joho's story in the Washington Post	Tumor immunology	• 2018 Nobel Prize: Removing repression
• Bill, Martin question	Final Exam	

FIGURE 1 | Micro-story topics and other learning tools used in a 16-week immunology course. The topics covered each week are indicated in the center. The themes of micro-stories told with each topic are on the left. Other learning tools and homework assignments are indicated on the right. Several of the homework assignments are started in class. The case studies are discussed in full. The micro-stories and examples of their implementation are provided in **Supplementary Table 1**. BMT, bone marrow transplant; CM, concept map; FDR, franklin delano roosevelt; HW, homework; Ig, immunoglobulin.

DIVERSITY IN MICRO-STORIES BUILDS INCLUSIVITY

With the expanding diversity of student populations, cultivating a sense of inclusion of all students in course communities is essential. Thus, micro-stories need to represent varied ethnic, racial, geographic, gender, and economic backgrounds as well as first-generation students. This recognition fosters a sense of belonging in the class and institution, which can increase interactions with faculty, engagement, motivation, development of cognitive skills, retention at the institution, and overall outcomes (25, 32, 33).

A simple way to incorporate diversity in micro-stories is using global settings and culturally diverse, but not stereotypical, names. Names with multiple origins increase self-identifying with them. Amana and Tam are East African and Middle Eastern names, with Tam also being Pan-Asian and Scottish. Lina and Kai are equally diverse and, with Isabella, Jasmine, Martin, Micah, and Tyler, span other populations of the United States. Diversity can also be introduced with examples that are relevant to student demographics like levels of MHC diversity (34). Micro-stories that compare relationships among the old friends hypothesis, allergy, autoimmunity, and genetic predispositions could use examples from rural vs. urban areas and similar incidences of type 1 diabetes in youth in Algeria and the United Kingdom (35). In addition, a micro-story about vaccination could focus on the early use of variolation in India, Asia, and/or the Ottoman Empire instead of Edward Jenner's overshadowing experiment.

Forms of diversity that are less obvious in the classroom also require consideration. For example, a plot might involve Kiara explaining to her wife, Beth, why she can't be a bone marrow donor for their nephew. Zayd might share his excitement about his summer research position and his concerns about finding another job in the Fall. With all micro-stories, it is very important to highlight positive qualities and avoid negative associations to prevent stereotype threat. Stereotype threat is a fear of conforming to a negative stereotype about one's social group. Anxiety from stereotype threat prevents students from focusing on course work and reduces academic performance (36).

NEVER-ENDING STORIES DRIVE RETRIEVAL AND RETENTION

Case studies are excellent vehicles for increasing critical thinking skills, comprehension, and retention; however, they can take time to work through. By combining a case study with a series of micro-stories about the case's protagonist, the tools synergize. A short case study can be the anchor to which information in micro-stories is related throughout a course. If students know the protagonist and his or her situation well, it requires minimal class time to review the immunologic condition and ask students about the impact of a new concept. As students continually revisit the protagonist's situation, they solidify concepts via increased networking and distributed retrieval (repeatedly recalling information at intervals, **Figure 1** and **Supplementary Table 1**). When learning from science texts, including biology, 84% of students using retrieval practice performed better on short answer questions than students using elaborative studying with concept maps [means of proportion correct were 0.73 and 0.54, respectively (37)].

The strategy used by the author introduces two short case studies early in the term about agammaglobulinemia (XLA) and X-linked severe combined immunodeficiency (SCID); however, one is sufficient (38). A variety of free, peer-reviewed immunology cases is available at the National Center for Case Study Teaching in Science (39). For brevity, focus here is on the XLA patient Bill. The case itself addresses the roles of antibodies in immune responses, B cell development, signaling processes downstream of the B cell receptor, and flow cytometry. Students learn Bill's name and condition by discussing these topics. By extending Bill's narrative through micro-stories, the immunologic principles above can be recalled frequently. Similarly, new concepts related to Bill's health and immunodeficiency can be incorporated through the term. For example, a micro-story about Bill's transition to college bolsters discussions of vaccine types (**Supplementary Table 1**). Bill's skin reaction to a belt his girlfriend gave him can enliven the exploration of the types of hypersensitivities. Bill's frustration at not being able to donate blood for a campus drive can remind students about the half-lives of immunoglobulins and passive immunity.

Micro-stories related to a single protagonist facilitate interleaving of course material. Interleaving is a strategy of reviewing related, but different concepts instead of focusing on a single concept at a time (40). The approach presses the brain to differentiate concepts and focus on details instead of being lulled into a false sense of knowing the information. With the example above, students' familiarity with Bill's situation allows faculty to re-visit multiple principles of immunology in quick succession. The power of this never-ending story is exemplified by a student's email months after his immunology course concluded (Jorge Dominguez, personal communication April 17, 2019):

> "Dear Dr. Katja and Lukin
> I saw this in the news and instantly was reminded of your case studies with Bill and Martin … https://www.google.com/amp/s/amp.cnn.com/cnn/2019/04/17/health/bubble-boy-disease-cure-study/index.html
> Jorge"

DISCUSSION

Immunology is a continually expanding field in which complex and interwoven concepts are abundant. In part, this results in many students struggling with and not enjoying the coursework. Instructional storytelling is a powerful education tool that students find pleasurable and engaging (3, 5). However, it can consume class time needed to cover content. The "six-word story" genre attributed to Ernst Hemingway demonstrates that stories need not be lengthy to capture attention (For sale: Baby shoes. Never worn). This paper suggests that terse micro-stories can promote engagement and associative learning. By constricting narratives to key contextual details, micro-stories can be told in <2 min or presented in a few sentences. Consequently, these anecdotes can be incorporated into class

discussions and assessment items and interwoven with other learning tools frequently (**Figure 1**).

Micro-stories have the potential to connect principles of immunology to memories of common sensory perceptions, personal experiences, and newly created imagery of scenarios. Linking the principles to memory networks and imagery can facilitate learning and subsequent retrieval (14, 16). As recollections focus the networks to which the information is linked, memory of the material is more rapid (12). By employing micro-stories about themselves and to recognize diversity in the class community, educators can enhance instructor immediacy and students' perceptions of belonging, which can augment the development of cognitive skills and overall success (25, 27, 33). Moreover, the core aspects of micro-stories align with andragogy (the teaching of adult learners). Thus, micro-stories can help faculty support the needs of this growing population across all levels of post-secondary education in the United States (32, 41).

The examples presented here are based on experiences with diverse, urban student populations. Since student demographics vary greatly among institutions, the suggestions about unifying factors in the micro-stories will need to be adapted to each student population. The flexibility of the contextual details facilitates this. While micro-stories can be effective for classes of any size enrollment, collecting data about students' interests to tailor micro-stories may be challenging with high-enrollment courses.

To reduce barriers to adopting micro-stories, faculty are encouraged to integrate the tool incrementally. Educators can focus first on a few key concepts with which students often struggle. If sharing personal experiences is uncomfortable, avoid them. Students may perceive them as false intimacy, false intimacy, which could produce negative feelings. Enhancing available resources, like examples in end of chapter practice questions, can expediate the development of micro-stories. Also, the tool is not restricted to in-class discussion. Micro-stories can be incorporated into practice and assessment questions to elevate students' focus and enthusiasm for the tasks. Similarly, the development of micro-stories as homework or group work allows students to express their creativity (**Supplementary Table 1**). High-quality submissions can be leveraged in subsequent courses. Despite their potential benefits, it is likely that not all students will enjoy micro-stories. This can be addressed when educators explain their teaching styles each term.

This Perspective suggests that the incorporation of micro-stories into immunology curricula can enhance student engagement, motivation, satisfaction, and academic outcomes. However, a significant limitation is the lack of assessment of the tool. Future studies are required to evaluate the impact of micro-stories on the affective and cognitive dimensions of student performance. It will be important to assess these independently and to determine their interdependence. In addition, dissecting the impacts of micro-stories on different types of course assessments will be valuable. Together, this analysis will inform educators on how to leverage the tool to support students most effectively.

AUTHOR CONTRIBUTIONS

The ideas in this Perspective article were developed by the author. The author is the sole contributor to this manuscript and approves the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2019.02682/full#supplementary-material

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Targeting the Achievement Gap: Strategies Toward Removing Inequities in Undergraduate Immunology Education

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A diverse student body enriches the classroom with lived experiences, varied skillsets, community and cultural knowledge, resiliency, and altruistic interests, all critical attributes that benefit both the classroom and the STEM field at large. However, a persistent disparity in academic and educational attainment exists between under-represented minority (URM) and non-URM students in STEM fields. This achievement gap discourages talented URM students from entering STEM professions, threatening the potential, expertise, and perspective of these professions. Here we describe the factors that contribute to the achievement gap and present strategies, utilized in our Immunology classrooms, for combating each factor. We discuss project-based learning pedagogy to give students increased agency and feelings of empowerment. We also highlight concrete practices to foster students' science identities and sense of community, factors that highly promote STEM retention. The dynamic subject of Immunology provides myriad opportunities to implement a curriculum committed to equity, as we outline below.

Keywords: URM, project-based learning, groupwork, science-identity, inflammation

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INTRODUCTION

Lack of access to and discrimination in higher education has nurtured unacceptable achievement gaps between under-represented minorities (URM) and non-URM white and Asian students across STEM fields, threatening the expertise, breadth, and perspective of future STEM professions, and limiting social mobility for URMs interested in STEM (1, 2). A URM identity often intersects with First-Generation (FG) college-student status and low-income status, two other factors that can threaten student retention in higher education (3). A variety of factors contribute to the achievement gap, including stereotype threat, missed opportunities to affirm diverse values, lack of community, and a too-rigid roadmap to success. Therefore, to run equitable courses, it is imperative to minimize these roadblocks. Here, we describe practices that we have successfully utilized to break down barriers to equitable achievement in our Immunology classrooms at public Hispanic-Serving Institutions (HSIs) in New York City and Southern California.

STEREOTYPE THREAT

The lack of diversity at the top tiers of STEM can create isolating environments for URMs and also perpetuate the insidious and inaccurate perception that non-URM white and Asian men

have superior STEM abilities, thus contributing to decreased achievement of women and URMs in STEM (4, 5). Stereotype threat can be countered by highlighting the contributions of "non-stereotypical" scientists (6–8). For example, we have had success with showing diverse faces of the scientists who contributed to discovery of course content on slides (whether first author, last author, or entire labs) to portray a more accurate picture of the individuals driving the field forward. We feel it is important not to limit our "personification" of Immunology to seminal findings, but to incorporate current studies, thus leveraging the increasing diversity of the field to help offset harmful stereotypes (8). Increased representation in the classroom also helps to counter stereotype threat, as students learn from their diverse peers; thus reinforcing the importance of retaining all of our students in their Immunology coursework and in STEM curricula. Having a "non-stereotypical" instructor can trigger "stereotype inoculation" (9), demonstrating the urgency to diversify faculty; however, even a non-URM instructor can contribute to breaking down academic spaces that trigger stereotype threat by sharing personal anecdotes about content they personally struggled with, difficulties balancing academic achievement with other obligations, and strategies for overcoming these challenges. Bringing in URM guest-lecturers and encouraging students to attend seminars given by URM scientists is another tool to highlight diverse role models and minimize stereotype threat.

VALUES

Many URMs that leave STEM report that they felt the majors failed to prove interesting or useful to their overall education (10). To help students affirm the value of Immunology to their lives, communities, and intended careers, we have found it crucial to incorporate a personal element into the course. This begins on the first day of class, when we invite our students to take a survey in which they reflect on why they are in the class, how taking the class fits in to their future goals, and which aspects of Immunology they care most about and why. This serves as a "utility-values" intervention, in which students personally reflect on why course material is important to them, and has been shown to foster increased motivation and to lower the achievement gap between FG-URM students and others by 61% (11). Related to this, URM students on average may be more motivated by altruistic values (12). Therefore, highlighting and giving students the opportunity to reflect on the medical or socioeconomic impact that Immunological paradigms have can be especially motivating to a group of students that is particularly interested in bridging classroom knowledge into impactful ways to support their communities (12). In parallel, giving validity to the diverse interests and insight shared by students also contributes to an inclusive classroom and helps recruit new and diverse contributors to the Immunology field. We try to mention topics or applications that students listed on their surveys as they relate to material in a lecture. Indeed, values affirmation has also been shown to decrease achievement gaps in Biology classes (13). We also use survey responses as one criterion to form groups for the final class project, so that students with similar interests can work together to develop them, as described below.

We feel that an element of self-directed and self-chosen application of Immunology class material is essential to provide space for every student in the room to affirm the value of Immunology to their particular interests and goals. This is one of the reasons why we allow students to choose the topics of their final research projects, in which they choose a disease and research the Immunological mechanisms at play during the disease. As Immunology topics vary widely from pathogen clearance to immunopathology, research projects indeed help students both master and expand course content as they delve further into mechanistic research for their presentations. Importantly, our students often choose topics relevant to themselves, their communities, and their values, such as Diabetes (disproportionately affects Latinx and Black Americans), autoimmune diseases such as Lupus erythematosus and multiple sclerosis (disproportionately affect Latinx, Asian, and African descendants), STDs (disproportionately affect Queer communities and Black Americans), and Neglected Tropical Diseases (disproportionately affect developing countries and America's poor and ethnic minorities). Self-directed learning also occurs as students work hard to master and practice utilizing their Immunological vocabulary, and as they further explore concepts to build a more robust understanding of a topic they care about. Allowing students to work on their final project in groups can increase values affirmation as described above, and also decrease grading time. We also suggest directing students to create video presentations to post on a course YouTube page, to save on precious in-class time.

CLEAR AND EQUITABLE PATHS TO ACHIEVEMENT

Another factor contributing to the achievement gap is a too-rigid roadmap to success, with a perceived unnecessarily demanding pace (10). Students with more demanding lives and diverse priorities may often feel that missing one deadline or doing poorly on one exam damns them to failure in the course and may lose motivation. For this reason, we feel that having multiple opportunities for success in the class with myriad ways to earn points allows students to see a path to success even if they struggle with one particular aspect of the class. Similarly, outlining all course deadlines and milestones for success on day-1 and sticking to them, so that students can plan their work schedules, childcare arrangements, and other commitments around these dates and milestones is crucial for supporting all students equitably. Students that were not brought up in the "culture of college," or that are not as well-networked within their Universities may also have a less clear understanding about expectations for assignments and exams. Therefore, we have found that transparency about expectations is especially critical to promote student equity. Designing clear and measurable learning outcomes is also important to provide students with a study guide for the class. In addition, posting rubrics detailing how assignments will be graded is also crucial in "lifting the

veil" so that all students can easily see a clear pathway to success in the course. In some cases, providing examples of work that was previously deemed outstanding can bolster students' appreciation of their own ideas and be highly motivating. We have also found that clear and fair expectations help to establish trust of the instructor, a valuable indicator of student motivation and achievement (14).

Inclusion of low stakes, formative assessments that test in-class learning in addition to the traditional and heavier grade-weighted summative (cumulative) assessments is also beneficial for equitable achievement (15). Formative assessments are beneficial for two reasons. First, they allow students to test their knowledge, an act that has been shown to increase student learning (16). Secondly, querying student learning throughout class time also provides the instructor an avenue to gauge the level of learning in real-time and an opportunity to identify student misconceptions and clarify them on the spot. For example, when first introducing the different immune cells, a student was concerned that two cells had a similar phagocytic property. This allowed the instructor to highlight that although we categorize immune-cells into different types, two cells can express the same or similar proteins to carry out similar cell activities-highlighting the broader biological concept of structure-function. This moment also allowed the instructor to break down some of the rigidity of existing Immunology concepts (which are currently being revised with recent research findings), providing an important segue to a discussion about how we are still in the process of uncovering how different cell properties arise and currently still discovering new immune-cell functions.

IMMUNOLOGY AS A FOREIGN LANGUAGE: ENHANCING LANGUAGE EQUITY

Many URM students who excel in other science curricula often find that they struggle with Immunology, as it has a daunting and complex language of its own that can be difficult to master (17, 18). Thus, many otherwise-confident URM and/or FG students experience difficulty when faced with demonstrating their knowledge of Immunology in a classroom setting or during formal examinations. In particular, English-Language-Learners (ELL) often feel that they lack the skills they need to communicate in the field's language and consequently perceive they will be ill-equipped to succeed in the course and in the Immunology field at large.

There are a number of ways in which we have strived to make the language of Immunology more accessible. First, we provide students with additional resources to help them link terminology with memorable visuals and conceptual clues. One of us has found it successful to include an interactive video game, ImmuneQuest, in our curriculum, as this allows students to actively engage with the material (17). We also incorporate mnemonic devices into the lecture material to boost concept retention and memory, which is particularly useful for ELL (19). In addition, given that many students experience anxiety when confronted with essay questions on exams, we allow students to choose whether they will answer essay questions on exams in paragraph format, or by concept mapping with terms (see Stranford et al., this issue) or illustrations. To grade these questions fairly, we formulate a detailed grading rubric to

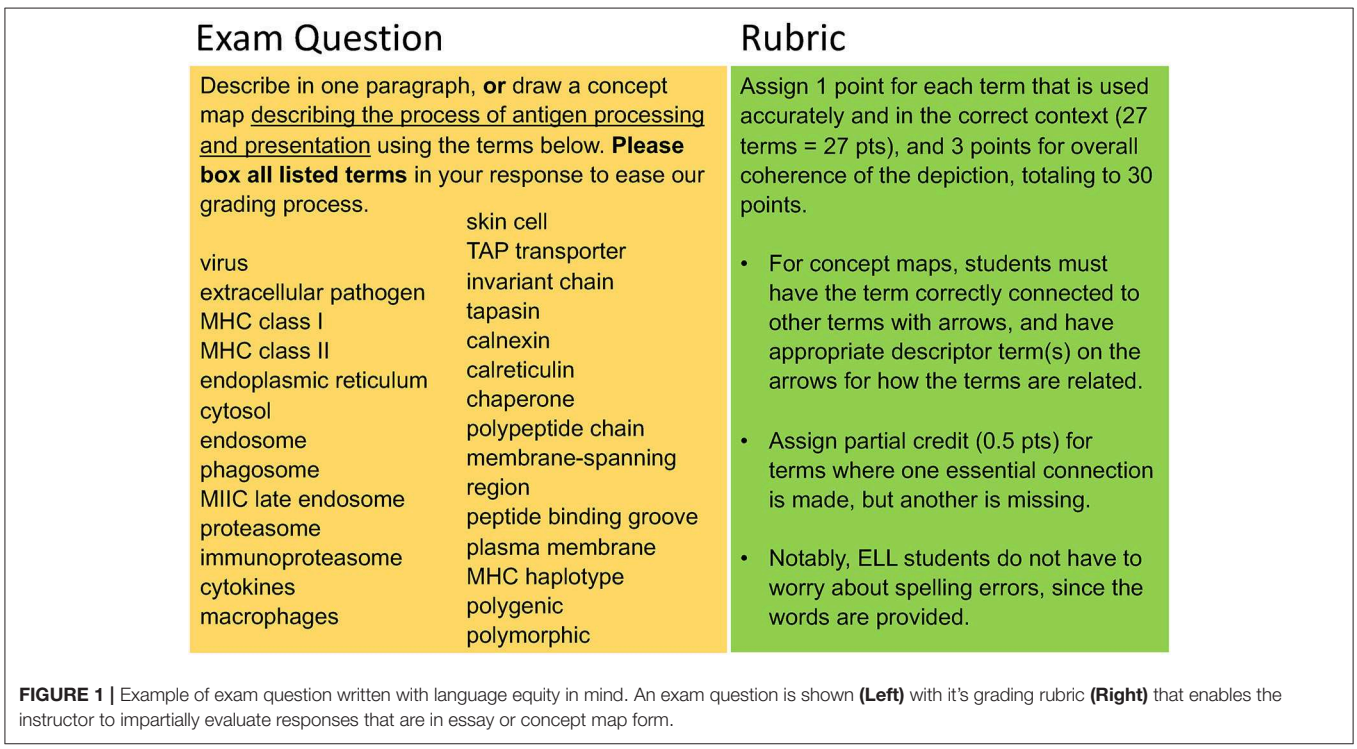

FIGURE 1 | Example of exam question written with language equity in mind. An exam question is shown **(Left)** with it's grading rubric **(Right)** that enables the instructor to impartially evaluate responses that are in essay or concept map form.

accommodate both written and pictorial responses, emphasizing the accurate depiction of and connection among key terms. As example is shown in **Figure 1**. Indeed, encouraging students to construct and explain their knowledge through models is a powerful tool in understanding complex STEM topics and has been recognized as an authentic form of science assessment (20). The efficacy of model-building in higher education and as a practice in promoting STEM equity is currently being investigated by National Science Foundation-funded groups.

Devoting class time to "thought exercises" in which students are asked to link key concepts in Immunology has proved indispensable in building confidence among those that are apprehensive about mastering the field's technical language. Students are divided into small groups and are asked to brainstorm responses to questions that demand a connection among multiple topics in Immunology, such as "You cut yourself with a sharp knife while cooking and bacteria gets into your skin. Describe the immune response that ensues." Thought exercises like these serve several distinct purposes. First, students are able to grasp the everyday relevance of concepts that may have previously seemed esoteric. Second, they are able to practice using Immunology's vocabulary in a non-threatening setting. Third, they are able to see how multiple concepts connect to one another. All three of these actions are critical for maximizing student learning (21) and also allow students to draw on the knowledge of their peers while simultaneously observing their own intellectual contributions to the assignment. Indeed, many studies suggest that active-learning methods enhance student performance when compared with lectures (Stranford et al., this issue) (22–24).

Additionally, we recommend ending class with an activity where students record on a piece of paper/notecard something that they have learned during that class and a "muddiest point" in which the students list something that is still unclear to them, they found difficult to understand, or on which they need additional clarification. This will allow the instructor to monitor whether they are covering the intended learning outcomes in the method and depth they intended, as well as identify areas where students experienced difficulty. In this manner, all students can seek out help and it may help to quell stereotype threat by providing an avenue for students to anonymously identify difficult concepts. By addressing these topics with the whole class, it will also reveal to the students that they were not the sole person that struggled with an aspect of the material, but rather it was a commonly challenging topic. The latter would also signal to the instructor that the topic merits further instruction time or they need to provide another instructional resource to help clarify the subject.

BELONGING, COMMUNITY, AND THE SCIENCE IDENTITY

Many College environments can also foster feelings of a "lack-of-belonging" for FG, transfer, veteran, and URM students, which can hinder academic success (25). Many of the active learning activities outlined in this issue (Stranford et al., this issue) help foster a sense of belonging in a learning-community as long as they are conducted in an inclusive environment. However, group work can be one of the most powerful experiences to promote a sense of belonging in college, providing students an opportunity to develop friendships and build their future professional network (26). Group work also allows students to organize their knowledge, building conceptual frameworks (21, 27). While many students bemoan group work, we have found that the following strategies promote successful group work dynamics, attested by positive student feedback. We implement purposeful group formation by giving students a survey to assess student interests and time availabilities, and also allow students to suggest peers that they would like to work with (see section Values). In addition, we ensure that groups are balanced with introverts and extroverts to aid in cohesion (28) and try to "scaffold performance" in group formation, for example not putting 2 "A" students with 2 "D" students. Group makeup is also balanced by gender and URM composition to minimize inadvertently triggering feelings of stereotype threat, and as instructors, we emphasize how the sharing diverse perspectives is an important scientific practice. To model tolerant and constructive communication, we take class-time to discuss constructive vs. destructive group work behaviors and allow students to designate the role that they will play in the group (28). Half of the grade for the group project is then assigned based on the entire group's performance and the other half is awarded to each individual in the group for the strength of their contribution and commitment to their delegated part. Students also perform "peer evaluations" of their group-members at the end of the semester, using a rubric that is posted online on the first day of class, so that students are aware of how to be good group members throughout the course. To further enhance exposure to diverse perspectives and give students increased networking chances, groups can also be "scrambled" for smaller assignments throughout the course. By facilitating productive and positive group experiences, a student's overall sense of academic and social belonging will be bolstered, contributing to student persistence and success (29).

Laboratory portions of Immunology coursework have myriad powerful virtues discussed in this issue (30, 31), including establishing a sense of community and helping students build a science identity. In working together to formulate and test hypotheses, students are able to take an active role in the scientific process. To this end, we have found great success in incorporating *true unknowns* into otherwise-controlled experiments. Allowing students to participate in generating novel data enables them to build a science identity and appreciate their increasing science-efficacy, major factors contributing to STEM retention (7, 32, 33). Additionally, mastery of techniques that are widely used in basic and clinical Immunology laboratories underscores the ongoing relevance and importance of Immunology and allows URM students to see that they have the potential to advance the Immunology field.

The last aspect of encouraging science identity is to help students envision how their gained skillsets and newfound knowledge can be utilized on their continued path to success. To achieve this, we expose students to primary literature in

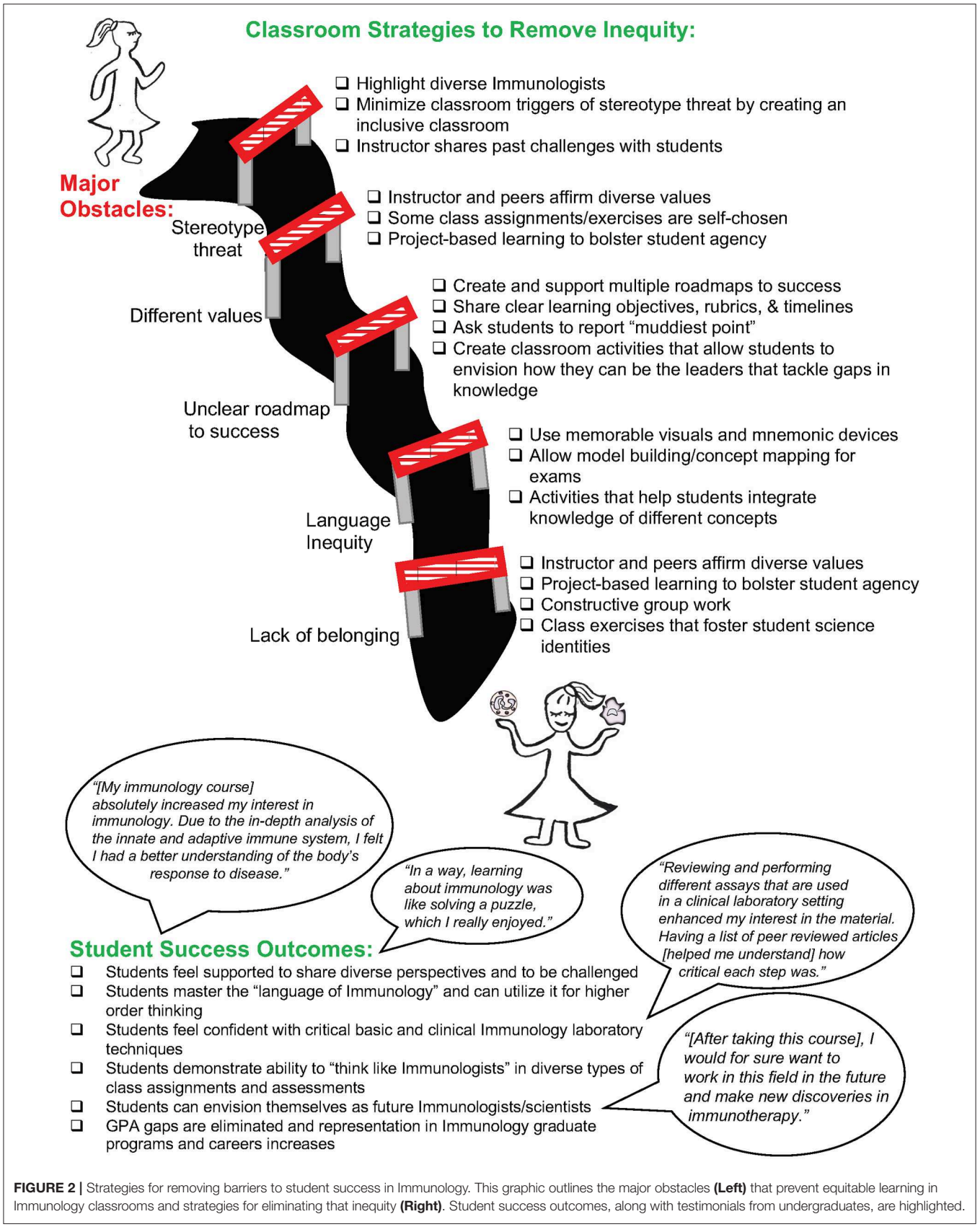

FIGURE 2 | Strategies for removing barriers to student success in Immunology. This graphic outlines the major obstacles **(Left)** that prevent equitable learning in Immunology classrooms and strategies for eliminating that inequity **(Right)**. Student success outcomes, along with testimonials from undergraduates, are highlighted.

the classroom setting. Through reading and dissecting primary literature, students engage in higher-order thinking as they practice interpreting immunology research findings and integrate their immunology knowledge with research techniques. After discussions, one of us asks the students to formulate new hypotheses and share with the class. Powerfully, we then present examples of research laboratories and pharmaceutical companies that are pursuing similar projects to the ones students proposed. Students recognize that they are capable of thinking like scientists and future pharmaceutical company leaders. Thus, these types of exercises also affirm a student's science identity and increase science-efficacy, positively contributing to URM persistence in STEM (7, 32, 34). Importantly, students also appreciate gaps in knowledge that remain in the Immunology field and the instructor can enthusiastically highlight how students can be the ones to lead future Immunology discoveries or help deliver the latest immunological therapies. Additional in-depth discussions of using primary literature in undergraduate Immunology class (35) and focus on emerging applications (36) are included elsewhere in this issue.

DISCUSSION

Learning communities, active learning, and other student-centered pedagogical strategies presented here, as well as creating an inclusive classroom, are all important components of the STEM persistence framework (32). Importantly, this framework helps to uplift students from *all* backgrounds, including URM, FG, low-income, and students with disabilities. Thus, a proactive approach to removing all barriers in the classroom (**Figure 2**) and to foster learning communities may significantly impact all students well-past their Immunology course, contributing to long-term retention in STEM and overall persistence of URMs in STEM and higher education (34, 37). Creative activities that integrate and celebrate a student's science identity, their other intersecting identities, and their diverse values are a unique contributor to URM persistence and success in STEM (38). Thus, we have presented examples of their successful implementation in our Immunology classrooms and laboratories (**Figure 2**). We believe that equitable teaching mirrors and leverages the diverse nature of the current Immunology field, and in turn will drive Immunology's inclusive expansion and intersections with other STEM disciplines and applications. Looking forward, we advocate for data collection on GPA gaps in specific courses so that instructors can confront and address any gaps that exist. Moreover, long-term measures of success include increased retention in the major and students pursuing advanced degrees and professions in Immunology and the biomedical sciences.

AUTHOR'S NOTE

The perspective presented is based on our collective classroom experiences.

AUTHOR CONTRIBUTIONS

AR, AM, and FM wrote and edited the manuscript.

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Analysis of Student Perceptions of Just-In-Time Teaching Pedagogy in PharmD Microbiology and Immunology Courses

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Madiraju C, Tellez-Corrales E, Hua H, Stec J, Nauli AM and Brown DM (2020) Analysis of Student Perceptions of Just-In-Time Teaching Pedagogy in PharmD Microbiology and Immunology Courses. Front. Immunol. 11:351. doi: 10.3389/fimmu.2020.00351

Just-In-Time Teaching (JiTT) active learning pedagogy is utilized by various disciplines, but its value in a professional pharmacy curriculum has not yet been demonstrated. The purpose of our research study is to implement and evaluate JiTT in a Doctor of Pharmacy (PharmD) program. The impetus in implementing JiTT into a PharmD curriculum was to provide students with an out-of-classroom learning opportunity to enhance knowledge-based skills. The current study summarizes the implementation of JiTT in four distinct instances: two iterations of the required courses "Integrated Microbiology and Virology" (Fall 2016 and Fall 2017) and "Integrated Immunology" (Winter 2016–2017 and Winter 2017–2018). JiTT included knowledge-based questions in multiple-choice format, integrated case studies, and student responses prior to the actual lecture session. After the conclusion of each course, students were asked to provide feedback on the utilization of JiTT by way of an anonymous survey. Following the Fall 2016 iteration of the Microbiology & Virology course, students found the integrated case studies to be beneficial (mean = 3.27 out of a maximum of 4, *SD* = 0.62), and their overall endorsement of JiTT was high (mean = 3.61 out of 4, *SD* = 0.50). For the other three courses included in this study, the primary dependent variable was the student's average rating of JiTT, rated on a five-point scale. Aggregating the scores from the Fall 2017 iteration of the Integrated Microbiology & Virology course and both instances of the Immunology course, students rated JiTT very favorably (mean = 4.17 out of a maximum of 5, *SD* = 0.77). Students' performances in JiTT-based courses were compared against non-JiTT-based courses. Analysis of assessment data for student's performance on knowledge-based questions showed JiTT was helpful for student learning and JiTT-based courses had more consistent exam scores compared to non-JiTT-based courses. The current results are a promising initial step in validating the usefulness of JiTT in a pharmacy program and lays the foundation for future studies aimed at a direct comparison between a traditional lecture style and JiTT pedagogy implemented into PharmD curricula.

Keywords: just-in-time teaching (JiTT), Integrated Microbiology & Virology, Integrated Immunology, PharmD curriculum, instructional pedagogy

INTRODUCTION

Just-in-Time Teaching (JITT) is an active learning pedagogy aimed toward improving student learning skills and educational outcomes (1). JiTT technique essentially involves a feedback loop between the outside-of-class learning environments and the face-to-face classroom sessions (1). JiTT active learning strategy provides students with an opportunity to self-reflect on their level of understanding of the lecture material and on the prior knowledge they have on each lecture topic. The basis of JiTT active learning strategy requires students to work on individual assignments often referred to as "warm-ups" (2).

In JiTT technique, students are provided with an opportunity to work on an assignment (or assignments), based upon an upcoming lecture topic, before coming to an actual class session (1). Before each lecture session, the course instructor gathers student responses to the assignment, and obtains a fairly good impression of the following: (1) student's foundational knowledge relevant to the required reading material for the upcoming class, (2) concepts within the assigned reading material for the upcoming lecture topic that students find them are new and challenging, and (3) student's perception of the course material and subject matter. Student responses to a given JiTT assignment provide an opportunity for faculty to tailor the classroom lecture session "just-in-time" (1). Classroom session can then be utilized effectively to discuss JiTT assignments, address misconceptions, and troubleshoot a problem within a case study while discussing course content (3).

The usefulness of JiTT has been demonstrated across various disciplines (4). Results from assessment of JiTT approach implemented for biomechanics education indicated significantly higher learning gains and better understanding of a concept-based JiTT course, relative to a non-JiTT course (5). JiTT methodology effectively enhanced knowledge-based skills required for comprehensive understanding of topics including core health-care professional curricula (2, 6–10). Medical residency programs identified JiTT as an effective approach that helped residents in their interactive learning of clinical modules, increased learner participation during core sessions in the curriculum and enhanced retention of JiTT course content (7, 8). More recently, JiTT using video-based lectures (VBLs) was incorporated and was very well-perceived by students enrolled into a neurology clerkship program (9). Besides, it was successfully incorporated into neuroeducation study as a reinforcement-based learning tool to help establish the foundational knowledge of neuroanatomy in novice learners (10).

Analogous to JiTT, just-in-time (JiT) training strategy is a simulation-based training (11, 12). JiT training undertaken at a Pediatric Emergency Department was found to significantly improve medical students' and resident trainees' procedural skills, procedure-related knowledge, and comfort level of trainees to perform a given procedure (11, 12). Similarly, JiT training strategy was found to markedly improve knowledge of nursing training staff that brought prior JiT training information to the bedside educational discussions (13). JiT training tool was used to validate minimum competency of bedside nursing staff managing high-risk low-volume therapies in order to ensure patient safety (14). A recent literature report also suggested that JiT active learning of evidence-based healthcare curricula created an opportunity for students to engage with facilitators and peers, enhance knowledge-based skills, and increase their chances of reinforcing and retaining their curricular knowledge (15). It is established that active learning teaching practice benefits small class sizes to a greater extent while showing an overall gain in student performance in undergraduate science, technology, engineering, and mathematics (STEM) courses compared to a traditional lecturing approach (16). Active learning fosters opportunities for students to come prepared, stay engaged and develop specific process skills that help in integrating knowledge during their learning of the material (17, 18).

JiTT as an active learning tool was implemented previously in an upper-level undergraduate Immunology course (19, 20). Results from students' survey analysis indicated JiTT to have a positive impact on student learning of the Immunology course material. JiTT pedagogy was well-received by students enrolled into Immunology course and students perceived JiTT to be especially beneficial during problem-solving of the case studies (19, 20). The latter is very important because when it comes to health care professional courses like Immunology or Infectious Diseases, it is easier for students to recall basic science concepts as applicable to problem scenarios or clinical cases (21, 22). Hence, a sound knowledge of basic science concepts and recalling of the concepts is essential to initiate a thought-provoking discussion and problem-solving of clinical case studies; in this regard, JiTT pedagogical approach implemented for undergraduate Immunology course has been perceived to be beneficial (19, 20). Learner-centered active pedagogy and flipped classroom model approaches, implemented into integrated basic science curricular framework, were shown to not only facilitate student engagement during in-class discussion but also help with their understanding, retention and application of basic science curricular concepts (23, 24).

Unlike medical education programs, JiTT was not implemented into any Doctor of Pharmacy (PharmD) curricula. Depending on curricular innovation needs, several other active learning techniques have been implemented into Pharmacy curriculum, including: audience response system, interactive web-based learning, visual aids-based learning, team-based learning (TBL), problem-based learning (PBL), process-oriented guided inquiry learning (POGIL), patient simulation and also blended approach of embedding active learning instructional tools within traditional lectures (25–29). Based on these reports it is widely accepted that in pharmacy health professions field, compared to traditional instructor-centered teaching approaches, student-centered active learning pedagogies serve as essential tools that help students understand and apply core conceptual knowledge to clinical practice. There is a report on JiT training strategy incorporated into a simulated influenza vaccination clinic that had an objective to train student pharmacists in just-in-time format (compared to traditional training approach) for administering emergency pediatric influenza vaccine (30). This training of student pharmacists in a simulated influenza vaccine clinic elicited significantly positive outcomes in students,

including: competency, confidence and comfort to administer emergency pediatric influenza vaccine (30).

The purpose of our research study is to implement and evaluate JiTT in a Doctor of Pharmacy (PharmD) educational program (31, 32). JiTT was developed and implemented for P1-PharmD Class 2020 and P1-PharmD Class 2021 Integrated Microbiology & Virology and Integrated Immunology courses offered during Fall and Winter quarters (31, 32). A survey was administered at the end of each quarter that provided an opportunity for students to assess their perceptions of JiTT. A comparison was made between students' performances on knowledge-based exam questions in JiTT- vs. non-JiTT- based courses in order to assess the helpfulness of JiTT.

The overarching goal of implementing JiTT into PharmD curriculum is to provide graduates with the best possible knowledge during the course of the curriculum. The hypothesis is that JiTT pedagogy is beneficial to the active learning of PharmD course material. The primary objective of implementing JiTT is to structure out-of-class time and equip students with the best possible resources that help students develop effective study skills during their learning careers (1). Toward this end, research questions included: (1) How did students perceive JiTT pedagogy implemented for Integrated Microbiology & Virology and Integrated Immunology courses? (2) Was JiTT pedagogy beneficial to student learning of the course material? (3) Was there any difference in student learning outcomes in JiTT-based courses compared to non-JiTT courses?

MATERIALS AND METHODS

JiTT Pedagogy

JiTT education sessions consisted of assignments including required reading material (self-directed slide presentations), multiple-choice questions, and integrated case studies that were developed as part of the active learning teaching pedagogy. There were an average of 20 multiple-choice questions included into each JiTT assignment and an average of two case studies per topic. Prior to each class meeting, students were asked to read the required course material posted to the course website (Moodle) and complete out-of-classroom assignments including the aforementioned multiple-choice questions and/or integrated case study assessments. Integrated clinical case study assignments relevant to each lecture topic were designed and administered in group-based assessment format to improve learner participation. Students were assessed for competency with just-in-time learning skills through various forms of assessment (pertinent to JiTT assignments and required reading material) including daily graded in-class individual quizzes, graded in-class exams, problem-solving of case studies, and participation during lecture sessions. The instructor used students' responses to tailor each class session to clarify difficult concepts and address any misconceptions on a given topic during the class time. In-class active learning group exercises and discussion of integrated case studies further reinforced concepts outlined in JiTT assignments. JiTT was applied in two courses for multiple cohorts of students at Marshall B. Ketchum University College of Pharmacy. The first course was "Integrated Microbiology & Virology," which is offered during the Fall quarter of the first year of pharmacy school. The second course was "Integrated Immunology," which is offered during the Winter quarter of the first year of professional pharmacy curriculum.

JiTT Implementation Approach

The intention of JiTT is to provide an opportunity for students to participate in an out-of-classroom learning environment. Therefore, JiTT assignments pertaining to a given class session were posted on Moodle a week prior to that particular class session. Students are encouraged to ask questions to the course instructor and discuss with their peers, and are provided the opportunity to utilize office hours, electronic communication and engage in a discussion on topics that are difficult to comprehend. Course instructors note down student's responses prior to each class session. JiTT assignments prepared students for a closed-book quiz on ExamSoft prior to the class session. Students are not allowed to use their notes or assignment readings when taking the quiz. Instructors check the quiz performance and make a note of the percent response for each question, make notes on topic areas where students are having difficulty, and merge them with student responses obtained during out-of-classroom learning format such as one-one discussion or electronic communication with instructors. Instructors tailor their classroom environment to emphasize topic areas where students had difficulty. A flow chart depicting JiTT implementation approach for PharmD Microbiology and Immunology courses is shown in **Figure 1**. Various approaches including schematic models and flow charts are utilized to reiterate concepts from JiTT assignments that students identified as crucial gaps or missing links in their learning of key concepts.

Even though integrated case studies were developed separately, implementation procedure for case studies was similar to course material pertaining to conceptual knowledge (**Figure 1**). Case studies were implemented by correlating basic science concepts underlying Microbiology and Immunology with clinical information. Topics were selected depending on the relevance and frequency at which students encounter infectious diseases or immunological disorders in clinical practice. Some case studies were developed by the course instructors and some obtained from required textbooks or relevant literature. Cases were dispersed throughout the course and were posted on Moodle the week before class to provide an opportunity for students to participate in an out-of-classroom learning environment. Integrated case study assignments required students to work with their assigned team members. Students were encouraged to share their responses and ask questions to the course instructors during out-of-classroom learning prior to guided classroom discussions. Students analyzed the cases in team-based format and shared their responses either *via* one-to-one discussion with the instructor or electronic communication. Faculty made amendments in a JiTT format to tailor the class session to case studies where students had hard time applying their knowledge-based skills to clinical practice. Students had an opportunity to summarize the answers to the case studies in team-based format during in-class session in order to ensure correct understanding of the case studies.

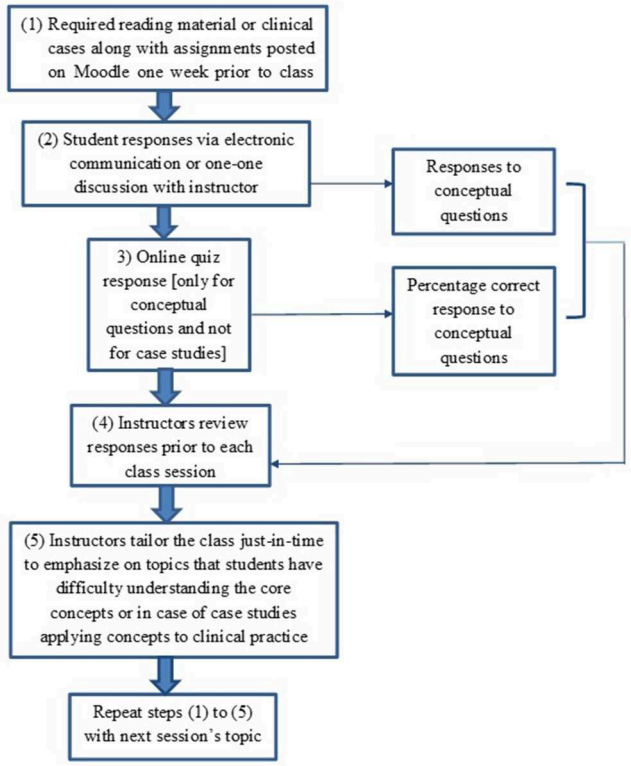

FIGURE 1 | Flow Chart of just-in-time teaching pedagogy. Flow chart of just-in-time teaching pedagogy implemented for PharmD Microbiology and Immunology Courses.

JiTT consisted of assignments that included multiple-choice questions, integrated case studies and feedback obtained from students prior to actual lecture session. JiTT assignments were designed first to help students build a thorough understanding of the conceptual knowledge pertinent to Microbiology, Virology, and Immunology. Integrated case studies pertaining to a lecture topic were administered in JiTT format to help students translate basic conceptual knowledge into pharmacy practice. Students worked on JiTT assignments that encompassed conceptual knowledge related to the upcoming lectures and/or integrated case studies pertinent to the lecture topics, before coming to class sessions. At the beginning of the lecture sessions, course instructors tailored the respective session content to students' learning needs based on information gathered "just-in-time" from student responses to the individual assignments and topics that students had difficulty understanding. A survey was administered at the end of each quarter that provided an opportunity for students to assess their perceptions of JiTT. Participants of the survey included students form the two cohorts, PharmD Class 2020 and PharmD Class 2021 (see **Table 1**). Comparison was made between students' performances on knowledge-based exam questions in JiTT- vs. non-JiTT- based courses in order to assess the helpfulness of JiTT. **Table 2** has the list of JiTT and non-JiTT courses offered to PharmD Class 2020 and PharmD Class 2021 cohorts.

Study Participants

Demographic information of the study participants from the two cohorts (PharmD Class 2020 and PharmD Class 2021) is included in **Table 1**. The first cohort to take the JiTT and non-JiTT courses was the PharmD Class of 2020 (see **Table 2** for the list of JiTT and non-JiTT courses offered for PharmD Class 2020 cohort of students). This cohort took a survey to rate their perceptions of JiTT after their Integrated Microbiology & Virology class concluded in Fall 2016, and all students enrolled in the class ($n = 43$) took the survey. This cohort then filled out a survey about their perception of JiTT after their Integrated Immunology course concluded in Winter 2016/2017; 38 students filled out this survey ($n = 38$).

The second cohort to take the JiTT and non-JiTT courses was the PharmD Class of 2021 (see **Table 2** for the list of JiTT and non-JiTT courses offered for PharmD Class 2021 cohort of students). These students ($n = 53$) filled out the survey on perceptions about JiTT after finishing Integrated Microbiology & Virology class in Fall 2017. This cohort ($n = 43$) also filled out JiTT perception survey upon completion of the Integrated Immunology class during Winter 2017/2018.

Table 1 contains demographic information about the PharmD Classes of 2020 and 2021. Because the surveys were anonymous, it was impossible to discern which students opted not to participate. These statistics describe the totality of the respective cohorts.

Survey Materials

At the end of the Fall 2016 iteration of the Integrated Microbiology & Virology course, students were provided a voluntary, anonymous survey containing 21 statements about the helpfulness of JiTT and the integrated case studies. All the 21 items listed as statements in the survey #1 are shown in **Supplementary Table 1**. The absence of JiTT literature in the health professions field made the use of an existing validated instrument ready for use difficult. Thus, the overall survey is a compilation of newly developed questions by the authors combined with questions modified from an existing survey on formative assessments in Biology education (33, 34). Cronbach-alpha was obtained to assess internal consistency and reliability. Students rated each statement on a 4-point scale ranging from *1 (I strongly disagree)* to *4 (I strongly agree)*. Each question had an option to indicate *I have no opinion,* which was treated as missing data. All items were positively phrased, e.g., "JiTT questions help me understand what it takes to be successful in this course." The arithmetic mean of responses to these questions was computed for an aggregate measure of student perception of JiTT. Among these 21 statements, 13 statements asked students to evaluate the integrated case studies, such as "Integrated clinical cases helped me make connections across basic science and medicine"; the average score of these 13 items were averaged into a subscale of students' perception of the integrated case studies. The other eight questions asked about overall perception of JiTT. The average score of the entire survey had strong interrater reliability, Cronbach's Alpha 0.94. The survey had an open-ended

TABLE 1 | Student demographics.

PharmD class year	Academic quarter	Gender		Ethnicity					BS/BA degree	Total
		Female	Male	Asian	Black	White	Hispanic	2 or more		
2020	Fall 2016	26	17	27	4	10	1	1	37	43
	Winter 2016–2017	25	17	26	4	10	1	1	37	42
	Spring 2017	25	16	26	4	9	1	1	37	41
	Winter 2018–2019	23	15	24	4	8	1	1	37	38
2021	Fall 2017	34	22	33	3	15	2	3	52	56
	Winter 2017–2018	31	21	32	3	12	2	3	51	52
	Spring 2018	31	21	32	3	12	2	3	51	52

Student demographics for PharmD Classes 2020 and 2021. Gender and ethnicity of students enrolled into each academic quarter are shown above. The academic degrees of students before joining PharmD program and the total number of students enrolled in each academic quarter are also shown. Demographic information shows a diverse group of students from PharmD Classes of 2020 and 2021 that participated in the survey.

TABLE 2 | List of JiTT and Non-JiTT courses.

PharmD class cohort (year)	Academic quarter	JiTT courses	Non-JiTT courses
2020		Course Title	Course Title
	Fall 2016 P1 Year	Integrated Microbiology & Virology	Pharmaceutical Biochemistry Foundations of Human Body & Disease – I
	Winter 2016–2017 P1 Year	Integrated Immunology	Foundations of Human Body & Disease – II
	Spring 2017 P1 Year	-	Foundations of Human Body & Disease – III
	Winter 2018–2019 P3 Year	Biotechnology, Pharmacogenomics & Precision Medicine	Biotechnology, Pharmacogenomics & Precision Medicine
2021	Fall 2017 P1 Year	Integrated Microbiology & Virology	Pharmaceutical Biochemistry Foundations of Human Body & Disease – I
	Winter 2017–2018 P1 Year	Integrated Immunology	Foundations of Human Body & Disease – II
	Spring 2018 P1 Year	-	Foundations of Human Body & Disease – III

List of JiTT and non-JiTT courses utilized for comparison of student's performance in knowledge-based questions derived from individual assessments.

question that asked how JiTT influenced students' learning of the course material.

Factor analysis on the first survey, for Fall 2016 Microbiology& Virology course, identified two distinct dimensions to our questions. Questions 1–13 were recognized as mostly belonging to one dimension, and these were the questions on case studies (explaining 47.55% of the variance). Questions 15–22 were recognized as mostly belonging to another dimension, and these were the questions about the overall perception of JiTT (explaining 24.37% of the variance). These two categories of questions cumulatively explained 71.92% of the variance. See **Supplementary Table 3** for full results of factor analysis.

When the students were asked to rate their perception of JiTT in the Winter 2016/2017 iteration of the Immunology class, the survey was revised to (1) discard redundant questions, (2) increase the number of questions about different aspects of JiTT, (3) reduce the number of questions about the integrated case studies, (4) introduce several reverse-coded negatively phrased items as an attention check, and (5) be used in multiple courses that utilized JiTT pedagogy. The revised survey contained 22 items. All the 22 Items listed as statements in the revised survey #2 are shown in **Supplementary Table 2**. Five items were negatively-phrased, e.g., "JiTT questions made the course more difficult," and 17 items were positively phrased, e.g., "JiTT provided structured opportunity for students to actively construct new knowledge of relevance to the lecture material." Among these 22 items were two items that specifically asked students about integrated case studies: "JiTT case studies helped me reflect upon a topic that has already been covered in class," and, "JiTT case studies helped me integrate basic science concepts with clinical case scenarios"; the average score on these two items created a subscale for students' perception of JiTT case studies.

For the revised survey, all items were rated on a 5-point scale in which *1* indicated *"Strongly disagree"* and *5* indicated *"Strongly agree."* The survey eliminated the answer choice of *"I have no opinion,"* in order to compel respondents into providing feedback. All 22 items of this revised survey were utilized to

compute an aggregate JiTT perception score. First, we computed the reverse score for the negatively-phrased items so that, for example, a score of 1 out of 5 was recoded as 5 out of 5. Scores were not transformed for the positively-phrased items. Then, an average score was computed using the scores for the positively-phrased items and the reversed scores for the negatively-phrased items such that higher scores reflect more-favorable perception of JiTT.

From this point forward, all surveys evaluating JiTT utilized the revised survey that was introduced to the Immunology class beginning with Winter 2016/2017. Factor analysis revealed that each iteration of this survey contained either three or four major categories of questions. However, in all instances, the top two categories which explained the most variance were perfectly mapped to the positively-phrased questions and negatively-phrased questions. For Winter 2016/2017 Immunology, the positively-phrased items explained 58.61% of the variance, and the negatively-phrased items explained 10.04% of the variance, with these top two dimensions cumulatively accounting for 68.65% of the variance. The survey for the Fall 2017 Microbiology & Virology class had 62.66% of the variance explained by the top two dimensions of questions: the positively-phrased items explained 50.26%, and the negatively-phrased questions explained an additional 12.40% of the variance. And, 73.86% of the variance was accounted for by the top two dimensions of the survey given to the Winter 2017/2018 Immunology class: 61.74% of the variance was accounted for by the positively-phrased items, and 12.12% of the variance was accounted for by the negatively-phrased items. See **Supplementary Table 3** for full results of factor analysis.

In summary, factor analysis on the updated survey for Winter 2016-2017, Fall 2017, and Winter 2017-2018, found either three or four dimensions to the survey questions. In all three of these surveys, however, Dimensions 1 and 2 explained the most variance. In all instances, the "Dimension 1" questions perfectly mapped onto our positively-phrased questions, and the "Dimension 2" questions perfectly mapped onto our negatively-phrased questions. With the factor analysis confirming that the positively- and negatively-phrased questions achieved their intended effect, we believe it was appropriate to compute an aggregate JiTT score using all 22 items after reversing the scores for the negatively-phrased items. Interrater reliability of the aggregate JiTT score was very high; Cronbach's Alpha for Winter 2016/2017 Immunology, Fall 2017 Microbiology & Virology, and Winter 2017/2018 Immunology classes were, respectively, 0.96, 0.92, and 0.96. Therefore, comparisons about these three classes utilized the aggregate JiTT perception score as the dependent variable instead of the components of the scale (e.g., positively- or negatively-phrased items).

Assessment of JiTT Pedagogy

Student's performance on knowledge-based questions in JiTT- vs. non-JiTT-based assessments were compared. **Table 2** summarizes information about JiTT vs. non-JiTT courses, administered for PharmD Class 2020 and PharmD Class 2021 cohort of students, assessment data from which is included for comparison.

Three courses that did not rely on JiTT pedagogy approach are referred to as non-JiTT courses and these included the following: Pharmaceutical Biochemistry, offered in Fall Quarter; Foundations of Human Body & Disease I, II & III, offered in Fall, Winter and Spring Quarters, respectively; and Biotechnology, Pharmacogenomics and Precision Medicine, offered in Winter Quarter. While Pharmaceutical Biochemistry and Foundations of Human Body & Disease I, II & III were offered to Class 2020 and 2021 cohorts during their P1 Year of the curriculum, the Biotechnology, Pharmacogenomics and Precision Medicine course was offered until now only to Class 2020 cohort when they were enrolled into P3 Year. Class 2021 cohort is currently enrolled into Biotechnology, Pharmacogenomics and Precision Medicine course; hence, data presented for this course is only from Class 2020 cohort. Additionally, Biotechnology, Pharmacogenomics and Precision Medicine course is one course wherein a portion of the course had JiTT pedagogy implemented into it and another portion of the course that did not rely on JiTT pedagogy. The list of JiTT and non-JiTT courses that students from the two cohorts were enrolled into, is shown in **Table 2**.

The mean Kuder-Richardson Formula 20 (KR-20) values were used to assess consistent student performance on knowledge-based questions in individual assessments derived from JiTT vs. non-JiTT courses. We also compared the percentage of knowledge-based questions correctly answered for questions derived from JiTT-based vs. non-JiTT-based assessments. We compared two other objective measures, Discrimination Index (DISC) and Point Biserial (PB), for JiTT-based vs. non-JiTT-based assessments. DISC measures item quality and PB is a good discriminator between high-scoring and low-scoring students. Descriptive statistics for objective measures used for assessing knowledge-based learning outcomes are listed in **Supplementary Table 4**. Majority of the questions from JiTT or non-JiTT assessments were primarily knowledge-based. Every question in each assessment is mapped to one of the levels within Bloom's taxonomy. While all exams in JiTT vs. non-JiTT courses had knowledge-based questions, not all exams had higher order questions from Bloom's taxonomy included in them. A few exam questions were mapped to Bloom's taxonomy of "application" but these were not analyzed because they were very few of them. Therefore, we focused on knowledge-based questions.

Data Analysis

SPSS Statistics for Windows, version 25 (SPSS Inc., Chicago, Ill., USA) was used for all data analysis. All analyses utilized two-tailed statistical significance at the $p = 0.05$ alpha level.

RESULTS

Perception of JiTT

Demographic information presented in **Table 1** suggests a diverse group of students from PharmD Classes of 2020 and 2021 that participated in the survey.

The first JiTT survey was administered to first-year pharmacy students (Class of 2020) after the conclusion of the Integrated Microbiology & Virology class during Fall 2016. Items included in the first survey are listed in **Supplementary Table 1**. Thirteen

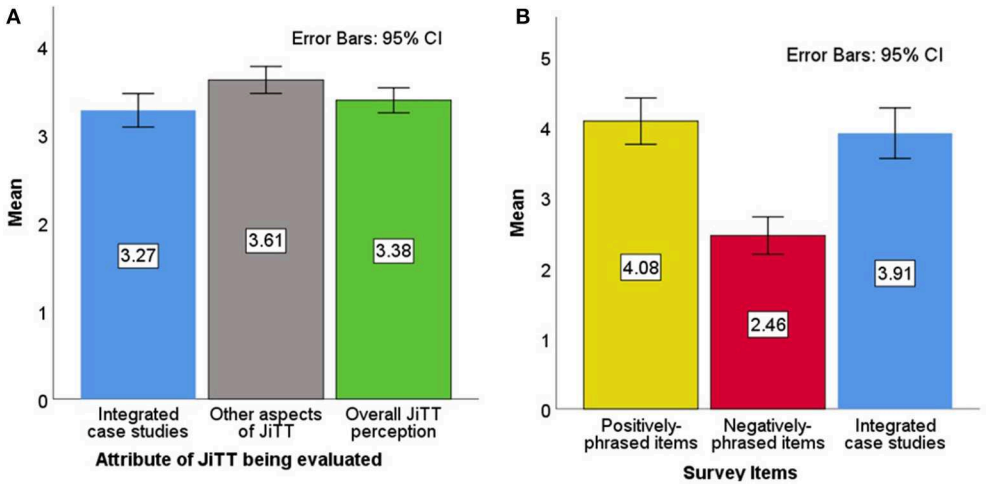

FIGURE 2 | Class of 2020 perception of JiTT. Mean scores of three different attributes of JiTT evaluated for Fall 2016 Microbiology & Virology Class (**A,** left). Thirteen statements in the survey on integrated case studies were endorsed by students with an average score of 3.27 ($SD = 0.62$) out of a maximum of 4 points [blue bar]; eight positively-phrased items on other aspects of JiTT in the survey were endorsed by students with an average score of 3.61 ($SD = 0.50$) out of 4 points [gray bar]; all 21 items in the survey that reflected the overall JiTT perception score were endorsed by students with an average of 3.38 ($SD = 0.46$) out of 4 points [green bar]. Mean scores of items in JiTT survey evaluated for Winter 2016/2017 Immunology Class (**B**, right). Positively-phrased statements in the survey were endorsed by students with an average score of 4.08 ($SD = 1.00$) out of a maximum of 5 points [yellow bar]; negatively-phrased items in the survey were endorsed by students with an average score of 2.46 ($SD = 0.80$) out of 5 points [red bar]; integrated case studies were endorsed with an average of 3.91 ($SD = 1.09$) out of 5 points [blue bar].

items asked students for their endorsement (rated 1 through 4) of various positively-phrased statements specific to the integrated case studies that were utilized within the JiTT framework, and average endorsement was 3.27 ($SD = 0.62$) out of a maximum of 4 points; see **Figure 2A**. Eight items asked students for their endorsement on various statements related to the other aspects of JiTT, and average endorsement was 3.61 ($SD = 0.50$) out of 4 points. Scores on all 21 items of this survey were averaged into an overall JiTT perception score of 3.38 ($SD = 0.46$) out of 4 points. The Fall 2016 iteration of the Microbiology & Virology class was the only time when this version of the survey was used.

All subsequent coursework evaluated JiTT using the revised version of the survey in which possible scores ranged from *1* to *5*. Items included in the second revised survey are listed in **Supplementary Table 2**. The dependent variable for this survey was the aggregate JiTT perception score, i.e., the arithmetic mean of the positively-phrased items and the reversed scores of the negatively-phrased items. The Class of 2020 filled out this survey after the Winter 2016/2017 Immunology class, and aggregate JiTT perception was 3.96 out of 5 ($SD = 0.87$). Endorsement of the positively-phrased items had an average score of 4.08 ($SD = 1.00$) out of a maximum of 5 points; see **Figure 2B**. For the negatively-phrased items, the average raw endorsement was at 2.46 ($SD = 0.80$) out of 5 points; the relatively low score indicates that students typically disagreed with the statements that found faults with JiTT. For the subset of questions that asked students to evaluate the case studies, the average score was 3.91 ($SD = 1.09$) out of 5 points.

The next cohort to experience these two JiTT classes was the Class of 2021. These students took the Microbiology & Virology course during Fall 2017. The aggregate JiTT perception was 4.34 out of 5 ($SD = 0.58$). Average endorsement of the positively-phrased items was quite high, 4.56 ($SD = 0.57$) out of 5 points; see **Figure 3**. Raw endorsement for the negatively-phrased items had an average of 2.41 ($SD = 1.07$) out of 5 points. And, students found the case studies quite helpful, with an average score of 4.34 ($SD = 0.75$) out of 5 points on the items asking about JiTT case studies.

The final class in this study was the Winter 2017/2018 Immunology class, which had an aggregate JiTT perception score of 4.14 ($SD = 0.84$). Student endorsement of the positively-phrased survey items was 4.29 ($SD = 0.94$) out of 5 points, and their raw endorsement of the negatively-phrased items had an average of 2.35 ($SD = 0.76$) out of 5 points; see **Figure 3**. The average score on the questions asking about case studies was 4.01 ($SD = 1.15$) out of 5 points.

The aggregate JiTT perception scores for the Winter 2016/2017 Immunology class, the Fall 2017 Microbiology & Virology class, and the Winter 2017/2018 Immunology class were compared in an analysis of variance (ANOVA) model (see **Figure 4** for the scores being compared). This ANOVA analysis omitted the survey from the Fall 2016 survey of the "Integrated Microbiology & Virology" class because its responses were on a four-point scale whereas the latter three surveys were on a five-point scale and the two surveys did not use the same items. Results from the ANOVA model on aggregate JiTT perception suggest that JiTT was comparably well-received across these classes, $F(2, 131) = 2.94$, $p = 0.057$, $R^2 = 0.43$. A Tukey's HSD *post-hoc* test found that the Winter 2016/2017 Immunology class was less-favorably rated than the Fall 2017 Microbiology & Virology class, $p = 0.046$ All other pairwise comparisons were not statistically significant, all p-values > 0.4.

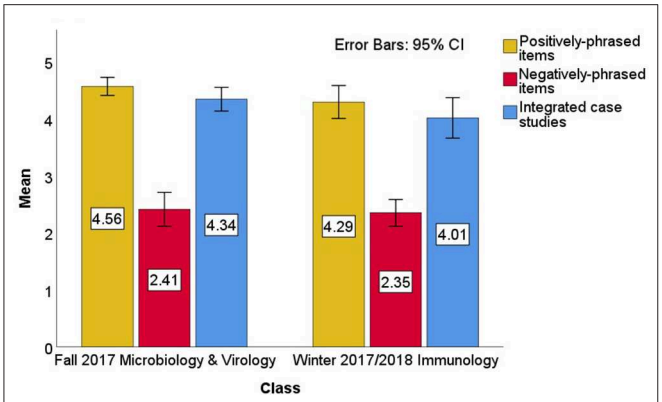

FIGURE 3 | Class of 2021 Perception of JiTT. Mean scores of items in JiTT survey evaluated for Fall 2017 Microbiology & Virology Class. Positively-phrased statements in the survey were endorsed by students with an average score of 4.56 ($SD = 0.57$) out of a maximum of 5 points [yellow bar]; negatively-phrased items in the survey were endorsed by students with an average score of 2.41 ($SD = 1.07$) out of 5 points [red bar]; integrated case studies were endorsed with an average of 4.34 ($SD = 0.75$) out of 5 points [blue bar]. Mean scores of items in JiTT survey evaluated for Winter 2017/2018 Immunology Class. Positively-phrased statements in the survey were endorsed by students with an average score of 4.29 ($SD = 0.94$) out of a maximum of 5 points [yellow bar]; negatively-phrased items in the survey were endorsed by students with an average score of 2.35 ($SD = 0.76$) out of 5 points [red bar]; integrated case studies were endorsed with an average of 4.01 ($SD = 1.15$) out of 5 points [blue bar].

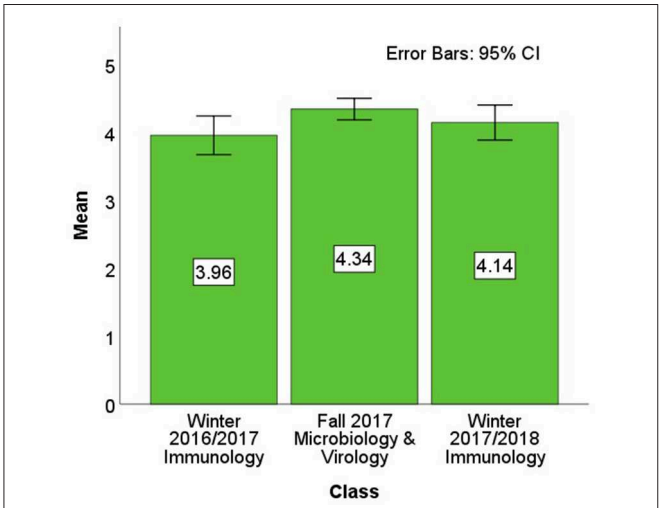

FIGURE 4 | Aggregate perception of JiTT. Aggregate mean overall JiTT perception score was calculated from the mean values derived from the positively-phrased items and the reversed responses from the negatively-phrased items. The aggregate JiTT perception score for the Winter 2016/2017 Immunology class of 2020 cohort was 3.96 ($SD = 0.87$) out of 5, for the Fall 2017 Microbiology & Virology class of 2021 cohort was 4.34 ($SD = 0.58$) out of 5, and for the Winter 2017/2018 Immunology class of 2021 cohort was 4.14 ($SD = 0.84$) out of 5.

Despite statistical significance in *post-hoc* testing, however, the scores were quite high overall and the ANOVA accounted for very little variance, and so a larger picture of students' perception of JiTT was warranted by combining all the JiTT perception ratings. After aggregating the scores from the Fall 2017 Microbiology & Virology course and both instances of the Immunology course, students' grand mean JiTT perception score was quite favorable, 4.17 ($SD = 0.77$) out of 5.

Objective Comparisons Between JiTT vs. Non-JiTT Assessments

We conducted analyses on whether objective measures would have significant differences based on whether or not JiTT was utilized in teaching the material. This data presented in **Figures 5**, **6** reflects consistency and learning outcomes in knowledge-based questions. **Table 2** has a list of JiTT and non-JiTT courses, administered for PharmD Class 2020 and PharmD Class 2021 cohort of students, assessment data from which was used for comparison. One analysis focused on objective student performance, which we defined as the percentage of students who correctly answered each knowledge-based question on an exam. Each unit of observation was one knowledge-based question from an exam, and the sample was every exam from a set of courses that utilized JiTT (Fall 2016 Microbiology & Virology, Winter 2016/2017 Immunology, Fall 2017 Microbiology & Virology, and Winter 2017/2018 Immunology, and Winter 2018/2019 Biotechnology, Pharmacogenomics & Precision Medicine) and a set of courses—taken by the same students—that did not utilize JiTT (Fall 2016 and Fall 2017 Pharmaceutical Biochemistry, Fall 2016 and Fall 2017 Foundations of Human Body & Disease I, Winter 2016/2017 and Winter 2017/2018 Foundations of Human Body & Disease II, Spring 2017 and Spring 2018 Foundations of Human Body & Disease III, and Winter 2018/2019 Biotechnology, Pharmacogenomics & Precision Medicine). From these classes, 684 distinct knowledge-based questions were identified.

On average, exam questions from courses that utilized JiTT were answered correctly by 85.87% of the students ($SD = 14.37\%$). Exam questions from classes that did not utilize JiTT had an average of 82.35% performance ($SD = 15.20\%$). This difference was statistically significant, $t_{(682)} = 3.05$, $p = 0.002$, which suggests JiTT is helpful for student learning (**Figure 5**). See **Supplementary Table 4** for item statistics data.

KR-20 scores were analyzed as another objective measure. Because KR-20 scores apply to the consistency of an entire exam, the unit of observation in this analysis was each distinct exam. From the courses listed above, 29 distinct exams were identified: 15 exams on topics that were not taught with JiTT and 14 exams on topics taught with JiTT. For courses that utilized JiTT, the mean KR-20 score for exams was 0.70, $SD = 0.11$. Exams from courses that did not utilize JiTT had mean KR-20 score of 0.50, $SD = 0.21$. The difference was statistically significant, $t_{(27)} = 3.17$, $p = 0.004$, indicating that JiTT-based courses had more-consistent exams (**Figure 6**). See **Supplementary Table 4** for item statistics data. The other two objective measures analyzed, Discrimination Index (DISC that measures item quality) and Point Biserial (PB, a good discriminator between high-scoring and low-scoring students) were not statistically significant between JiTT-based vs. non-JiTT-based courses, $t_{(682)} = 0.306$, $p = 0.759$ and $t_{(682)} = 0.825$,

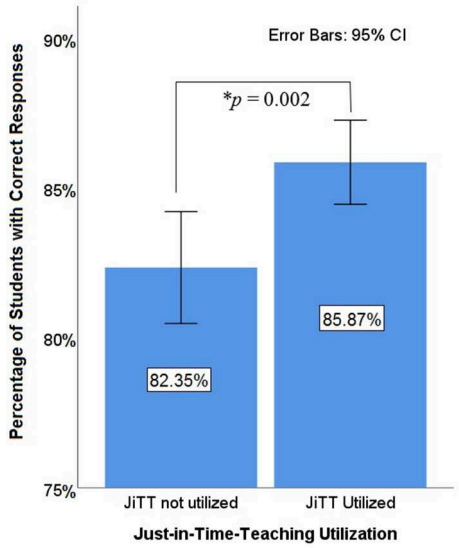

FIGURE 5 | Student performance on individual exam items. Student learning outcomes were assessed by the average performance on individual test questions. Student's performance was compared on individual exam questions that asked about topics taught with JiTT and topics without JiTT. Knowledge-based questions were only analyzed. Each exam question was one observation. For questions on topics that utilized JiTT, 85.87% of students got the questions correct. For questions on topics not utilizing JiTT, 82.35% of the students got the questions correct. The difference is statistically significant, $t_{(682)} = 3.05$, $p = 0.002$.

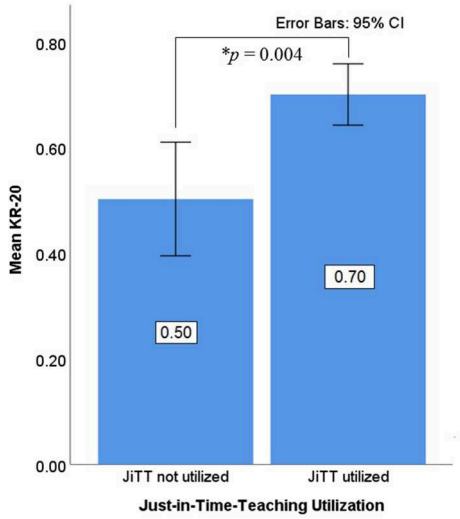

FIGURE 6 | Exam-Level Consistency. The Kuder-Richardson Formula 20 (KR-20) values were used to assess consistent student performance in JiTT vs. non-JiTT courses. Mean KR-20 values for knowledge-based questions were extracted from individual assessments pertaining to JiTT and non-JiTT courses. There were 15 exams on topics that were not taught with JiTT (JiTT not utilized). With each exam as one observation, the average KR-20 score was 0.50, $SD = 0.21$. There were 14 exams on topics taught with JiTT (JiTT utilized). With each exam as one observation, the average KR-20 score was 0.70, $SD = 0.11$. This difference between JiTT vs. non-JiTT exams is statistically significant, $t_{(27)} = 3.17$, $p = 0.004$.

$p = 0.410$, respectively (see **Supplementary Table 4** for item statistics data). This suggests items from all the assessments were equally reliable.

Survey analysis showed that students perceived JiTT was beneficial to their active learning of the course material and helped them keep track of the course content. Students' performance data comparing JiTT- vs. non-JiTT- based courses indicated that JiTT was beneficial for student learning. JiTT pedagogy was conducive for enhancing knowledge-based skills and this is based on assessment of student learning outcomes in JiTT-based courses vs. non-JiTT-based courses.

DISCUSSION

JiTT is an active learning pedagogy that was successfully implemented across various scientific disciplines (1, 4). However, the usage of JiTT has not been reported in a PharmD curriculum. Our goal toward implementation of JiTT as a meaningful learning tool was to enhance conceptual knowledge of core topics within Integrated Microbiology & Virology and Integrated Immunology courses. The idea of implementing JiTT active learning technique in a flipped classroom model is to divert students from sheer memorization of the required course material prior to any major assessments. Hence, JiTT active learning pedagogy was implemented for both courses that are part of the Biomedical Sciences curriculum offered to PharmD students during the first year of their program (31, 32). Preparation of JiTT assignments and case studies were an integral part of PharmD Integrated Microbiology & Virology and Integrated Immunology courses.

Results from both the surveys demonstrated that the overall perception of JiTT in PharmD Integrated Microbiology & Virology and Integrated Immunology curricula offered during Fall Quarter 2016 through Winter Quarter 2018 was favorable. The aggregate mean score for overall perception of JiTT, from survey analysis of JiTT implemented in two courses for two different cohorts of students, was quite high, indicating the positive influence of JiTT on students' learning of the course materials. These observations are in agreement with the previously reported student's perception of JiTT-based teaching approach for an undergraduate-level Immunology course (19, 20). Responses to an open-ended query on how JiTT influenced learning of the course material indicated that students perceived integrated case studies administered in JiTT format to be thought-provoking that helped identify their areas of improvement in certain areas of basic sciences. Students also felt participation in JiTT assignments markedly improved their understanding of the relevant course topics, helped participate in discussions involving case studies, be on track with the course material while helping them prepare for exams and retain information better. This is consistent with what was observed earlier that JiTT augmented learning of key points, increased learner participation, and enhanced learner retention of core concepts (7, 19, 20). Student-centered active learning pedagogies implemented into

integrated basic science curricula facilitate student engagement during in-class discussions and help students understand, retain and apply basic science concepts to clinical practice (19–24).

To summarize students' responses from positively-phrased items in the survey, JiTT was beneficial, helped students enhance their knowledge-based skills and JiTT created an interactive active learning environment. This aligns with what was reported earlier that significantly favorable perception of JiTT may have been because JiTT educational experience matched with the evolving needs of millennial learners, which included: interactive learning, self-directed teaching and use of novel digital teaching technological methods (8, 21). Statistical analysis showed significantly favorable overall perception of JiTT when Integrated Immunology courses were compared. Our data is in agreement with reported literature that JiTT serves as an effective learning tool that helps novice learners to recognize, understand, and retain the jargon before engaging in deeper learning of Immunology concepts including integrated case studies (10, 19, 20). The consistently low scores for the negatively-phrased items indicate that students disagreed with disfavorable statements about JiTT instructional pedagogy.

Comparison of student performance on knowledge-based questions between JiTT vs. non-JiTT courses from major assessments indicated that JiTT was helpful in student's learning of knowledge-based concepts. This is in agreement with previously reported observation that JiTT methodology effectively enhanced knowledge-based skills required for understanding of core health-care professional curricular topics (2, 6–10, 15). Additionally, analysis of mean KR-20 values from each assessment also showed that courses with JiTT pedagogy had consistent exam performance compared to non-JiTT courses offered to the same cohorts. This data suggests that teaching a concept with JiTT is correlated with better outcomes and more-consistent exams when compared to non-JiTT approaches. The current data is a promising initial step in validating the usefulness of JiTT in a pharmacy program.

One limitation of the study was the usage of anonymous surveys. The rationale behind anonymity was to provide students the comfort and freedom to express their opinion of the quality of teaching. Without any ability to link the students to their responses, all observations were treated as independent in the analyses, and a time-series analysis was impossible. Another limitation of the study was the usage of two different surveys. The Microbiology & Virology course made extensive use of integrated case studies, and the Fall 2016 iteration of the class was the first time this class was offered at this particular university. Therefore, the JiTT survey was catered to that particular course, and many items focused on the integrated case studies. When the time came to assess students' perception of JiTT in the next course, a survey was created that could be used for any course that utilized JiTT pedagogy. Because data was collected after an academic quarter of applied use of JiTT, these findings should reflect valid student perceptions. Another limitation was that JiTT utilization was confounded by instructors and by courses—each course only had one instructor, JiTT was utilized in certain courses but not others, and it is possible that the courses varied in difficulty, thus necessitating the analyses on item reliability. Although a fully-factorial design would eliminate this confounder, doing so was impossible due to the limited number of faculty assigned to courses at the time the courses were taught.

Current study demonstrated that JiTT was advantageous to students in that it compelled students to read and be better prepared for the course material posted online for an upcoming lecture topic. In agreement with Novak et al. JiTT helped course instructors adapt to student's learning needs (1). Course instructors waded into the task of tailoring and fine tuning each class session, based on learning gaps identified *via* student responses to JiTT assignments, instead of taking the traditional approach of one size fits all. Consistent with previous observation on usefulness of JiTT in an undergraduate Immunology course (19, 20), it was also observed during class sessions that students demonstrated competency with JiT learning skills through increased student participation and greater student engagement. Our results suggest that JiTT assessments were linked with higher student performance and consistency.

CONCLUSIONS

Based on results from both the surveys, students perceived JiTT was beneficial to their active learning of the course material and helped them keep track of the course content. Students' performance data comparing JiTT- vs. non-JiTT- based courses indicated that JiTT was helpful for student learning and JiTT pedagogy was conducive for enhancing knowledge-based skills. The current data is a promising step in validating the usefulness of JiTT in a pharmacy program and lays the foundation for a direct comparison between a traditional lecture style and JiTT active learning pedagogy implemented into PharmD curricula.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Institutional Review Board of Marshall B. Ketchum University. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CM developed JiTT pedagogy for the two courses, implemented JiTT while being a Course Coordinator and/or Course Instructor for three courses, participated in writing and facilitating case studies, participated in JiTT survey design, and wrote the manuscript. ET-C implemented JiTT while being a Course Coordinator and/or Course Instructor for three courses,

participated in writing and facilitating case studies, participated in JiTT survey design and wrote the manuscript. HH participated in JiTT survey design, created revised version of the JiTT survey, performed data analysis, and wrote the manuscript. JS was the Course Coordinator for a non-JiTT Pharmaceutical Biochemistry course and contributed to writing the manuscript. AN was the Course Coordinator for a non-JiTT Foundations of Human Body & Disease I, II, and III course series and contributed to writing the manuscript. DB originally implemented JiTT for an undergraduate Immunology course, participated in survey design, and contributed to writing the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2020.00351/full#supplementary-material

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Broadening and Strengthening Underrepresented Group Inclusion in Immunological Research

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Promoting diversity across biomedical fields is crucial for building comprehensive and innovative research programs, as well as providing trainees from underrepresented groups (URGs) the ability to establish agency and develop skills in a culturally and structurally supportive environment. Despite this awareness, there is still a lack of students from URGs being trained for independent research careers. The Immunology, Microbiology, and Virology (IMV) graduate program at the University of Rochester School of Medicine and Dentistry (URSMD) has been working for the last 13 years to increase diversity through an NIH funded Post-baccalaureate Research Education Program (PREP). Historically, our program has trained URG scholars in Immunology, but as we have progressed we have embraced the understanding that both the scholars and the institution benefit from expanding the interdisciplinary nature of our program. Over the last 3 years, we have integrated a broader and highly collaborative faculty mentor pool, including representation from Immunology, Microbiology, Virology, Neuroscience, Genetics, Biochemistry, Biophysics, Toxicology, and Biomedical Engineering. This expansion, coupled with changes in our education program, including skill building workshops and cross campus integration with our student diversity groups and the Office of Diversity and Inclusion, has strengthened the competitiveness and success of our cohorts. These improvements are enhancing the diversity of our graduate school, creating a research environment that retains students from URGs in biomedical research. We attribute our success to the interdisciplinary and team-building nature of our pipeline program, as well as the URSMD's initiatives to be a more inclusive and equitable institution.

Keywords: educational program, Diversity & Inclusion, graduate program, career developement, training & development

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INTRODUCTION

It is increasingly recognized that a wide range of scientific disciplines across biomedical fields is crucial for building comprehensive, innovative, and diverse research programs (1–3). Perhaps less obvious, the opportunity to choose among a broad area of research specialties is also important to provide individuals from underrepresented groups (URGs) the ability to establish independent research in a culturally and structurally supportive environment (4, 5). However,

to date, this aspect of training is insufficiently developed for URG scholars (URGs) (5). This is further evidenced by the paucity of URGs at the faculty level who are conducting biomedical research (6, 7). We present here how the University of Rochester School of Medicine and Dentistry (URSMD) is successfully diversifying and enriching a long-standing Immunology based program designed for post-baccalaureate URGs. We discuss how we restructured our pipeline research education program to be more inclusive of our scholars' scientific interests centered around immunological research and to foster a research environment that increases trainee retention in biomedical research.

UR-PREP HISTORY AND SUCCESS—INSTITUTIONAL AND WORKFORCE DIVERSITY ENHANCEMENT

The URSMD Post-baccalaureate Research Education Program (UR-PREP) was designed to prepare promising URGs to successfully advance in their pursuit of biomedical research toward immunology and infectious diseases. Over the 16-year course of our program (established in 2003 by Stephen Dewhurst, PhD, and succeeded by Edith Lord, PhD) we have successfully trained, or are currently training, 112 scholars. Importantly, 82 (73.2%) scholars entered PhD or dual MD/PhD programs, and 79.2% of these scholars have either graduated with a PhD or are still enrolled in their doctoral training programs (**Figure 1**). Notably, among all scholars, 74.1% have endeavored to pursue research related careers (**Table 1**). These data indicate that UR-PREP has been overall successful in its mission to provide URGs the opportunity to develop research and academic skills that will afford them the competencies necessary for graduate school and impactful scientific careers.

While we have witnessed much success, we have come to better understand and appreciate the changing landscape of research interests and that it is imperative to diversify our program. UR-PREP has been rooted in the Department of Microbiology and Immunology, but in 2016 we decided to extend our programming and research experiences across our whole institution, concurrent with implementing a new leadership and organizational strategy. The specific goals were to enhance the research experiences and education of our scholars toward their career goals, to enrich their professional development, and ensure an effective and inclusive mentoring. Data from the literature demonstrate that it is necessary for URGs to develop their skills in a culturally and structurally supportive environment with community support and effective mentoring (4, 8). It is also critical to introduce URGs to the career opportunities afforded to them upon receiving their doctorates (1, 8, 9). Described below are the innovative approaches we have undertaken in the last 3 years of UR-PREP to meet this need, as well as preliminary evidence of our success thus far.

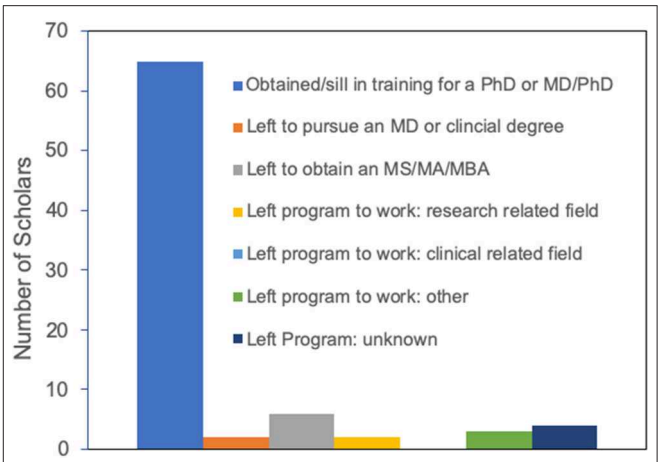


FIGURE 1 | Status of all UR-PREP scholars who entered doctoral training programs (2003–2019).

TABLE 1 | Career/training status of all UR-PREP scholars (2003–2019).

Current status in biomedical training	Percent scholars (%)
Research Related—Academia	49.1
Research Related—Industry	15.2
Research Related—Government	2.7
Currently applying to Ph.D. Programs	7.1
Clinical	14.3
Other	4.5
Unknown	7.1

APPROACHES TO ENHANCE URGS INCLUSION IN IMMUNOLOGY BIOMEDICAL RESEARCH

To better adapt our UR-PREP scholars to the changing immunology landscape, we have markedly restructured our program. First and foremost, we have diversified opportunities to train in immunologically extended disciplines involving a wider range of mentors. This is complemented by a more integrated educational curriculum strongly relying on team spirit and building within the UR-PREP family-like group and across the institution. A synergistic co-director and team leadership approach consolidates the cohesiveness and coordination of this educational program. Notably, our team-based leadership provides UR-PREP scholars easier availability to meet with co-directors, members of the steering committee, or counselors, which enhances sensitivity to any issues they may encounter. In turn, this permits the leadership to better adapt curriculum options and professional development opportunities toward the scholars' needs. This model creates a more attractive research environment, which helps to retain URGs in biomedical research and build a sense of belonging in our URSMD community.

EXTENDING RESEARCH OPPORTUNITIES FROM THE IMMUNOLOGY HUB

Diversifying Mentor Involvement

Immunology is a research field with broad reach and high potential for fostering collaboration and scientific innovation. The URSMD recognizes that our learner populations seek opportunities to bridge these immunological reaches and encourages interdisciplinary research, which allow our learners to explore and apply their research perspectives. As such, UR-PREP has extended its available research training opportunities to our URGs beyond the Department of Microbiology and Immunology. Via communicating directly with Chairpersons from all of our research departments and centers across the URSMD, we have identified researchers with sufficient mentoring and training history to include in our UR-PREP mentor pool. We specifically include motivated junior faculty who bring fresh perspectives to our program. We were also mindful of addressing diversity with regards to gender equality and race/ethnicity. This outreach led us to extend our scientific research fields from Microbiology/Immunology (inclusive of ∼25 mentors) to as many as 15 scientific fields including ∼60 mentors (**Figure 2**). Our faculty mentors now encompass a range of research disciplines that can connect with immunology including cancer, cardiovascular disease, HIV/AIDS, respiratory diseases, stem cell biology, neurodegenerative diseases, toxicology, and RNA biology. Furthermore, these training opportunities comprise both fundamental and clinical research areas that are related to health disparities (e.g., HIV/AIDS), which are likely of interest to our scholars. The attractiveness of these options is evidenced by the wide range of academic appointments and affiliations to research departments and centers of mentors who have trained our UR-PREP scholars over the past 3 years (2016–2019; **Figure 3A**). For purposes of comparison, **Figure 3B** shows that from 2003–2019, 80% of our scholars trained with faculty who had primary appointments in Immunology compared to only 20% in other research fields. In the last three recruited cohorts, however, there has been a more even distribution of scholars between Immunology faculty (53%) and other disciplines (43%). This branching from the Immunology hub is important as it extends the research network of collaborators and fosters interaction between our scholars and faculty beyond their mentors (**Figure 3C**).

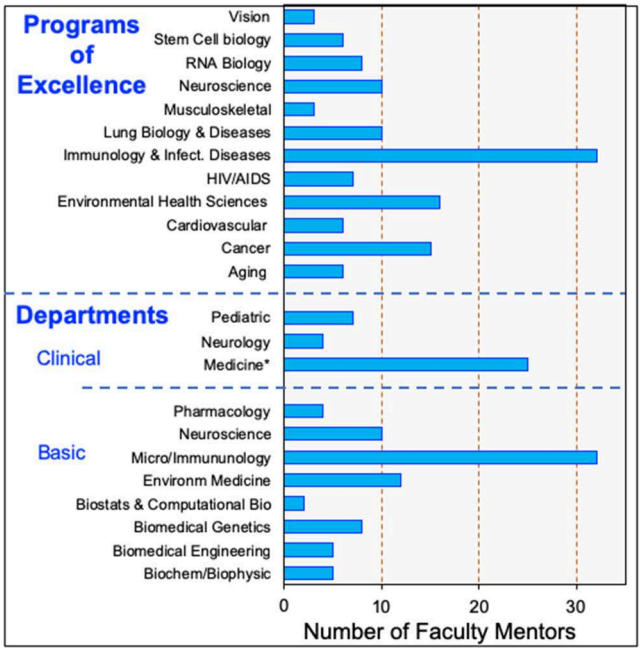
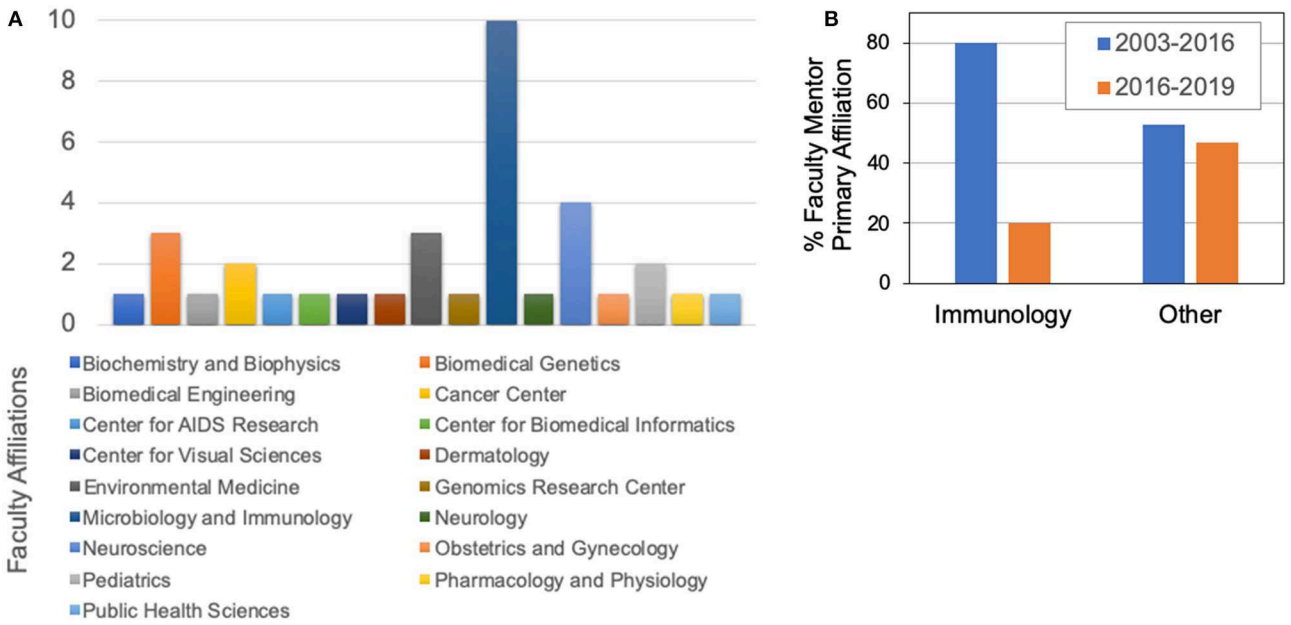


FIGURE 2 | Research Expertise and Interconnectivity of UR-PREP Training Faculty. Number of faculty with research projects within 13 of the 14 URSMD Programs of Excellence, and with departmental primary/secondary appointments. *Medicine includes multiple departments, only Neurology and Pediatric with more than 1 training faculty are mentioned.

Diversifying Our URSMD Graduate Programs

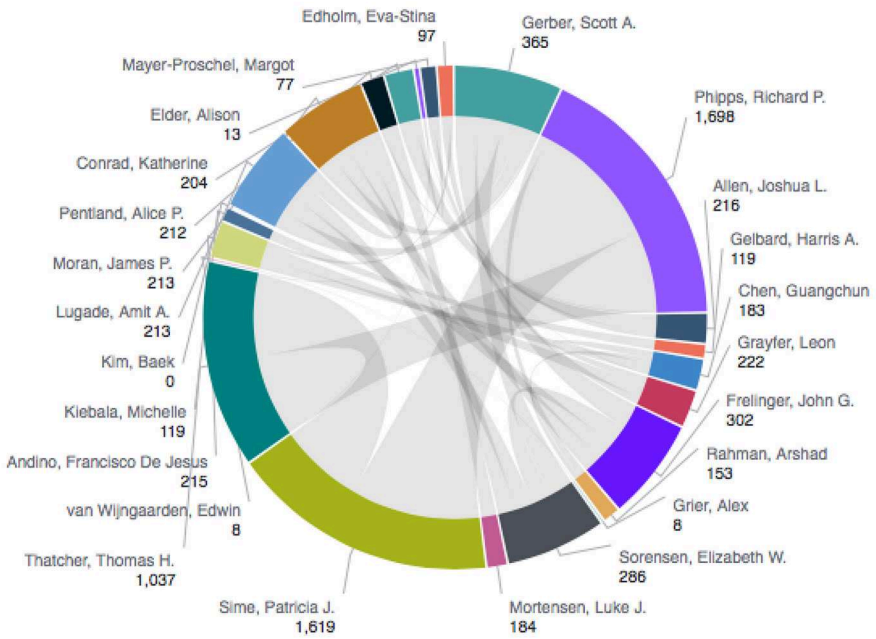
It is noteworthy that as a result of broadening our research areas we witnessed an unintended but positive effect on retaining PREP scholars in our graduate programs. Prior to extending beyond immunology, our UR-PREP scholars were competing with each other for the same graduate student placements in the Immunology graduate program at the URSMD. Many of our scholars were also competing for placement at other graduate schools within the same immunology focused training programs. By broadening our UR-PREP training opportunities, our scholars are now applying to more diverse programs at the URSMD. Indeed, in the past 3 years UR-PREP scholars have applied to Immunology, Cell Biology of Disease, Toxicology, Translational Biomedical Sciences, Neuroscience, and Biomedical Genetics. Consequently, our UR-PREP scholars are remaining at the URSMD for their graduate studies, which has contributed to an overall increase in the number of URG graduate trainees at the URSMD from 10.6% in 2016 to 17.8% in 2019. Importantly, UR-PREP scholars constitute the majority (∼10%) of this increase in URG graduate trainees. Interestingly, among the URGs matriculated into our graduate school, 27.5% (a substantial increase from 13.3% in 2016) have been awarded training fellowships and/or individual fellowships/awards, including some of our UR-PREP scholars. Collectively, this is evidence that our pipeline program critically contributes to diversifying our student population.

Table 2 shows the graduate programs into which 7 former UR-PREP scholars have matriculated and are currently still training at the URSMD. This also provides a snapshot of research areas pursued by each scholar as part of their training. In line with our goal to broaden research disciplines, none of the current students listed in **Table 2** are in the Immunology graduate program, although 6 out of the 7 are conducting research that includes immunology aspects and involves mentorship within the Department of Microbiology and Immunology. We surveyed these students to inquire why they choose URSMD for their training. The following are representative testimonials of their responses:



C

New Tilincite collaboration network for UR-PREP mentors 2016-2019e collaboration network



Indicators: Times Cited. **Affiliated Organization:** University Of Rochester. **Collaborates With ID Type Group:** Name. **Collaborates With ID Type:** Fullname. **Collaborations with People:** Wright, Terry W., Pavelka, Martin S., Robert, Jacques, Proschel, Christoph, Maggirwar, Sanjay B., Dewhurst, Stephen, Lord, Edith M., Murphy, Shawn P., Susiarjo, Martha, Gill, Steven R., Noble, Mark D., Fazal, Fabeha, Delouise, Lisa A., Lawrence, Paige, Foxe, John J., Freedman, Edward G., Cory-slechta, Deborah A., Munger, Joshua C..

FIGURE 3 | UR-PREP Interdisciplinary Network **(A)**. Graphical representation of faculty appointments of our UR-PREP mentors who have trained or are currently training scholars (2016–2019). **(B)** Graphical representation of our UR-PREP scholars who trained with faculty mentors holding primary appointments in Immunology compared to primary affiliations in other research fields from 2003 to 2016 and 2016 to 2019. **(C)** Interdisciplinary network of our UR-PREP mentors. Shown is a visual representation of the expanded collaborations of our mentors over the last 3 years. The middle gray area is the centralized hub of the mentors with a web of affiliated collaborators and co-authors (Data collected using Web of Science and ORCID identifiers at the URSMD).

TABLE 2 | Currently matriculated UR-PREP scholars in URSMD.

Scholar year	URSMD graduate program	Research project summary
2015–2016	Cell Biology of Disease	Elucidating a potential mechanism of action of Bacillus Calmette-Guérin (BCG) immunotherapy for non-muscle invasive bladder cancer
2016–2017	Translational Biomedical Sciences	Applied immunology and microbiology in the clinical setting, including atopic and inflammatory diseases
2016–2017	Translational Biomedical Sciences	High-throughput approach to profiling the differences in antigen presentation between young and older adults to define drug repurposing targets for improving vaccine efficacy
2016–2017	Translational Biomedical Sciences	Prenatal immunological and stress factors associated with childhood development
2017–2018	Neuroscience	Molecular and Signaling Mechanisms of Synaptic Plasticity in Memory Formation and Mental Health
2018–2019	Translational Biomedical Sciences	The impact that the oral microbiome has on the outcome of disease. Specifically, how different environmental factors play a role in influencing microbiome composition and how this can be used as a tool to predict or prevent disease outcomes
2018–2019	Cell Biology of Disease	Understand the co-evolutionary relationships between the structure of selected molecules and their functions in innate and adaptive immunity against tumors and viruses using the frog *Xenopus laevis* as animal model

"Welcoming environment"
"Collaborative opportunities"
"[Translational Biomedical Sciences graduate program] provided a unique way to combine bench and clinical science."
"[I] had a great experience in lab/PREP, the mentorship I received gave me confidence that the type of support needed in a PhD program would be available."

Thus, the matriculation of our UR-PREP scholars into programs beyond immunology is significantly contributing to increasing diversity across the institution and reducing the biases that have long been associated with the ability of minority biomedical researchers to be successful (10–12).

Curriculum Modifications

We recognize the necessity of modifying our educational curriculum to supplement the broadened research experiences of our program. Therefore, we have taken several steps in the past 3 years to enhance our educational programming. These steps, described herein, are designed to provide high quality laboratory-based research education, are have been adjusted to the specific needs of URGs.

Evidence has shown that learners from URGs have unique experiences and attitudes regarding access to research, academic, and professional development opportunities (12–15). Thus, URGs do not necessarily enter graduate school with the same academic and skill proficiencies as their non-URG counterparts (5). These decreased proficiencies are often the primary factor in determining a scholar's success in academic programs (16). UR-PREP addresses these concerns by providing URGs an opportunity to develop research and academic skills as well as provide better psychological and professional support.

Immediate Readiness and Team-Building—Basic Skill Workshop

In 2016 we implemented an intensive 2-week basic laboratory and soft skills workshop at the beginning of the UR-PREP year in conjunction with the URSMD Life Sciences Learning Center co-directed by Dina Markowitz, PhD, and Danielle Alcena, PhD, who is a former UR-PREP scholar. This workshop is designed to introduce common laboratory principles and techniques (e.g., molarity, pH, dilution, cell culture, statistics, etc.) and soft skills (e.g., oral presentation, abstract writing, conflict management, etc.). We also seek to identify potential challenges by administering short quizzes and more extensive take-home exercises, allowing us to assess progress and areas where additional training is needed. Importantly, this 2-week experience fosters a group dynamic and builds a team spirit that has been tremendously helpful for our PREP scholars during the challenging training period. Since our scholars disseminate into labs across the URSMD from our Immunology hub, we have to ensure that they are prepared to enter their research niches with confidence and a sense of belonging. While only in its third year, we have received positive feedback about our workshop with regards to the scholars' ability to quickly integrate into their laboratory settings and begin active research projects (selected testimonials below).

"The workshops put everyone on an even playing field and assures that they at least have the fundamental techniques down before beginning work on their independent research projects." (*2017–2018 scholar and current URSMD Neuroscience graduate student*)
"[I] think having a period at the beginning where PREP students can become accustomed to the school and each other is very useful." (*2018–2019 scholar and current URSMD Translational Biomedical Sciences graduate student*)
"[The student workshop leader] was great! Overall, the training was a good review before getting started in the lab." *(2019–2020 current scholar)*

Academic Autonomy

All of our UR-PREP scholars are required to take a graduate level course, Ethics and Professional Integrity, and a student research seminar to prepare them for the academic rigors of graduate school. Given the history of our academic and research roots in Immunology, our UR-PREP cohorts have primarily enrolled in the basic Immunology course and related student seminar. However, with the broadening of

our research program, our scholars can now select courses that are relevant to their research goals. Recent enrollment is as diverse as: Cell Biology of Human Disease; Cellular Neuroscience; Foundations in Modern Biology; Genomics and Systems Biology; Microbial Pathogenesis; Neurons, Circuits and Systems. Student seminars have included: Current Topics in Experimental Pathology, Genetics, Microbiology, Immunology, and Neuroscience. By gaining academic enrichment outside of Immunology, our UR-PREP scholars are interfacing with more faculty and students, as all of our courses are typically team taught by faculty with expertise in certain subject areas with the help of PhD student and postdoctoral teaching assistants. Thus, our scholars are benefitting from selecting courses that are best for their growth, as well as gaining new academic knowledge that will be beneficial to their scientific careers.

Importantly, aside from taking course related to their research interests, our optimized program also requires our UR-PREP scholars to take a professional development course or attend URSMD sponsored workshops to supplement their training. There is evidence to support that coaching URGs in how best to reach their goals outside of laboratory skill development is integral to their success (8, 14, 17). As such, our scholars are advised to select from many courses and workshops offered by the URMSD, Center for Professional Development, and UR Broadening Experiences in Scientific Training that suit their professional growth. Within the past 3 years our scholars have enrolled in Leadership and Management for Scientists, Scientific Communication for Broad Audiences, Scientific Writing in Research, and Drug Discovery, and have attended workshops including Resume and Curriculum Vitae (CV) Writing, Interviewing, Grant Writing, and Manuscript Writing. Furthermore, our scholars met with our Director of Career Services within their first 2 months of the UR-PREP year to build their CVs, establish a professional LinkedIn social media presence, and begin their Individual Development Plans.

Team Approach to Broadening Leadership Perspectives Beyond Immunology

Another key aspect of our extended URG training program is its team leadership concept. We have implemented a co-director team leadership approach grounded in complementary expertise by two directors: Research Development (Jacques Robert, PhD) and Professional and Academic Mentorship (Elaine Smolock, PhD). While the research development director more specifically oversees research components of the training (e.g., workshop organization, interface with research mentors, scientific contents of scholar projects, conference attendance), the professional/academic director focuses on communication skills and professional preparation (e.g., writing, communication, scholarship, academic progress, course advising). This dual and integrated leadership is enriched by a team-based environment providing advice and feedback from an Advisory Committee, Steering Committee, and Professional Development Group. This model is specifically designed to include faculty, students, postdoctoral appointees, counselors, and professionals from many scientific disciplines, expertise, and backgrounds (**Figure 4**). This insures a system of guidance, assistance, and support that is broad in perspective and appropriate to our UR-PREP scholars' research and career goals. This cohesive team-based program is directly beneficial to the scholars in that they have ample options to feel individual ownership of their research experience by meeting with any of the team members, allowing them to feel highly connected to the larger URSMD community.

Heightening Scholar-Community Integration and Outreach

A crucial aspect to the success of UR-PREP is fostering a strong sense of community and inclusiveness among our scholars within the URSMD. Indeed, learners from URGs can struggle with finding their academic identify (4). Admittedly, the long-standing Immunology centricity of our UR-PREP was successful in building unity and cohesiveness among our UR-PREP cohorts; however, that model was less successful in integrating our scholars within the greater student body. With the recent broadening of UR-PREP beyond immunology, we have taken key steps to better integrate our scholars and retain the cohesiveness of the group, with the goal of fostering a research identity and a sense of belonging.

PREP Council

We initiated a PREP Council in 2016. This organization includes the current UR-PREP scholars, a postdoctoral fellow, and/or senior PhD student who is from a URG with interest in education. This is a critical aspect of our training program, as there is evidence that near-peer URG mentors build inclusivity and awareness of the unique needs of trainees from URGs (8). It is also an opportunity for our current graduate students and postdoctoral appointees to develop their own cultural agency (18).

The council hosts an annual symposium featuring previous UR-PREP scholars who return to the URSMD to discuss their post UR-PREP research and career experiences in both academic and non-academic environments (e.g., industry, government). In addition, the council organizes an annual seminar given by a renowned extramural guest speaker. The scholars are encouraged to invite speakers in the scientific disciplines of their interests to promote an extended view beyond immunology and provide perspective about scientific careers. The Council recently connected with the URSMD Alliance for Diversity in Science and Engineering (ADSE) group that hosted Avery August, PhD (HHMI Professor of Microbiology and Immunology at Cornell University) who spoke about his experiences as a URG biomedical researcher. These events are widely advertised across the institution to raise attention regarding the involvement of our URG learners.

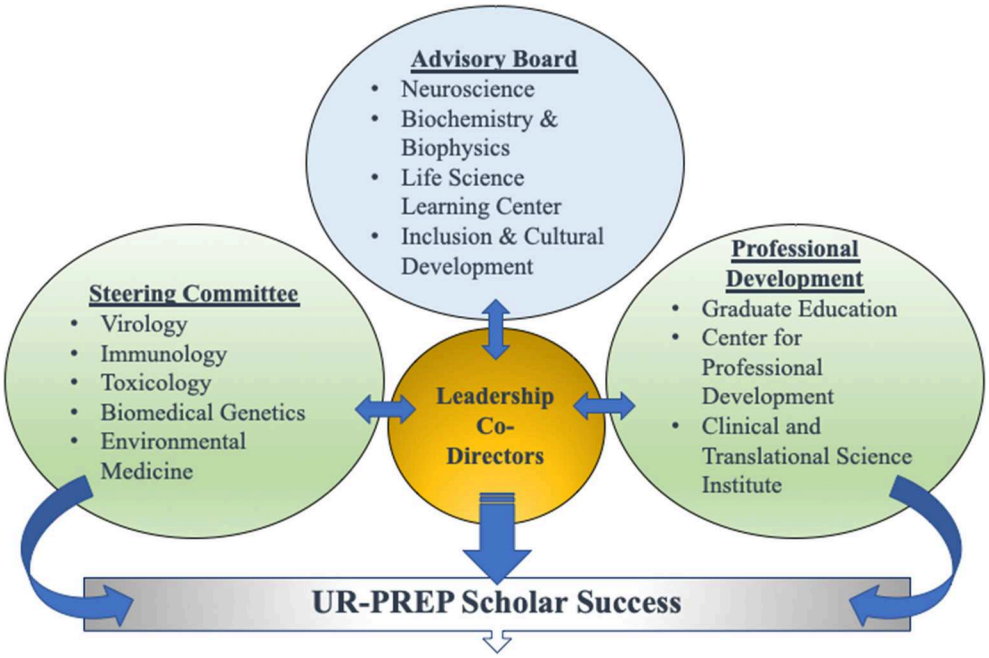


FIGURE 4 | Team Leadership of UR-PREP. The Co-Directors are informed by a large group of faculty, students, and postdoctoral trainees who reside in a vast array of scientific and professional disciplines, all designed to promote UR-PREP scholar success.

Cultural Capital, Awareness, and Advocacy

As mentioned above, establishing cultural capital among students from URGs is crucial for their success (4, 19). Notably, this capital increases graduate school readiness (16). We have recently made efforts to better help our scholars establish identity and integrate into the larger scientific community at our institution. We have taken steps to connect the scholars with the URSMD Office of Diversity and Inclusion. Specifically, our UR-PREP scholars meet at least three times per year with our Diversity Officer (John Cullen, PhD). These meetings happen in the absence of the co-directors to allow the UR-PREP scholars opportunities to advocate for themselves and freely discuss any concerns. This innovative approach has been instituted to promote better understanding of our UR-PREP scholar needs and teach them how to discuss the value of their diverse perspectives in academia and biomedical research broadly.

DISCUSSION

The implementation of our UR-PREP to include a more diversified biomedical research experience extending beyond immunology and a more integrated team- and inclusion-based leadership approach has only been ongoing for 3 years. However, there is tangible evidence of success exemplified by the percentage of UR-PREP scholars entering graduate school in areas beyond Immunology, as well as a change in attitude and perception toward URGs within the institution. Faculty members and students from the different departments and centers now have increased opportunities to interact with our UR-PREP scholars, which has beneficial effects in easing misconceptions and minimizing unconscious bias toward URGs.

Given the relative short time (3 years/3 cohorts), our data are preliminary, but suggest steady increase in success (e.g., broadening of research opportunities, scholar matriculation into graduate school, inclusivity, etc.). Our analysis has also revealed a few areas that would merit further modification. A first concern is that broadening the research opportunities away from the Immunology hub could potentially reduce a sense of cohort. To thwart this, we have developed weekly UR-PREP courses where we promote group-based discussions and preparation for graduate school. These regular meeting are a good setting to evaluate progress and unexpected challenges or difficulties encountered by a particular scholar or by the whole group. Our active UR-PREP Council should also counteract potential isolation of our scholars in different areas of our institution. Likewise, together with our Office of Diversity and Inclusion and the ADSE student group, we are actively promoting social outings and outreach opportunities that are intended for team-building. As an example, a recent partnership with the Graduate Women in Science leadership, Catherine Ovitt, PhD, our UR-PREP scholars visited a local Rochester public school and discussed their experiences in STEM. Subsequently, our UR-PREP Council organized and hosted an on-site visit of high school students who are interested in pursuing STEM.

A second potential challenge in our training model is that the broadening of courses offered to our scholars may lessen ability for study groups, with the risk for some scholars to be

insufficiently prepared and ultimately fail a class. To address this, we established a tight communication system with the course directors so that we can rapidly be aware of any scholar who is struggling, find tutors to supplement in-class learning, and/or provide additional study sessions when necessary.

In summary, we are successfully diversifying and enriching the experiences of URGs by extending beyond basic Immunology training. Our restructured and broadening of our UR-PREP pipeline is now more inclusive of our scholars' interests and unique academic and professional goals. However, there is still a paucity of URGs in faculty positions at academic institutions and a need to provide checkpoints to insure continued success (6). Furthermore, data of the National Institutes of Health tracked from 2009 to 2016 reveal a need to prioritize funding investments and support of URG early-stage and new investigators (7). Together these findings emphasize the importance of pipeline programs such as PREP. As a future direction of our UR-PREP, we will be mindful of the challenges and circumstances that continue to face our PREP scholars after they matriculate and pursue careers in biomedical research. In line with NIH-funded National Research Mentoring Network models (20), we are currently planning long-term mentoring plans to provide support throughout career development. The goal is to improve retention of our scholars in biomedical research so that there is better representation of URGs at the faculty level, hopefully someday minimizing the need for these pipelines programs.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

AUTHOR CONTRIBUTIONS

ES and JR have been involved equally in the conception and writing this article.

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Active Learning and Technology Approaches for Teaching Immunology to Undergraduate Students

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Immunology is a fascinating and extremely complex field, with natural connections to many disciplines both within STEM and beyond. Teaching an undergraduate course in immunology therefore provides both opportunities and challenges. Significant challenges to student learning include mastering the volume of new vocabulary and figuring out how to think coherently about a physiological system that is so anatomically disseminated. More importantly, teaching immunology can be complicated because it requires students to integrate knowledge derived from prior introductory courses in a range of fields, including cell biology, biochemistry, anatomy and genetics. However, this also provides an opportunity to use the study of the immune system as a platform on which students can assemble and integrate foundational STEM knowledge, while also learning about a new and exciting field. Pedagogical theory has taught us that students learn best by engaging with complicated questions and by thinking metacognitively about how to approach solutions. Building this skill set in today's students, who now hail from a broad demographic and who are accustomed to acquiring their knowledge from a variety of different media, requires a new set of teaching tools. Using perspectives from four different immunology educators, we describe a range of student-centered, active learning approaches that have been field-tested in a number of different immunology classrooms and that are geared to a variety of learning styles. In this paper, we explore the hypothesis that active learning approaches to immunology improve comprehension and retention by increasing student engagement in class and their subsequent mastery of complex topics.

Keywords: active learning, concept maps, immunology education, just-in-time teaching, student-centered learning, technology in education, undergraduate

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INTRODUCTION

Not so long ago, immunology was regarded as a medical sub-specialty, taught exclusively to medical or graduate students and rarely offered at the undergraduate level. In contrast, today's undergraduate biology curricula frequently include one or more elective courses in immunology. Collectively, the co-authors of this article have taught immunology to undergraduates for more

than 90 years. In the process, we have endeavored to keep pace as our field has matured to a discipline ripe with opportunities to integrate and contextualize many of the core concepts that students encounter in a standard biology curriculum. Simultaneously, pedagogical advances have encouraged us to expand the range of tools that we use to cultivate and assess student learning. This article will describe some of the ways in which we have employed active learning strategies to help students understand how the immune system works; a topic they report to be as challenging as it is fascinating.

Students enjoy studying immunology in part because it teaches them about their own bodies; indeed, it is often the first medically-relevant course they experience in college. In addition, they take delight in the subject as an integrative discipline that asks them to apply information learned in other courses (e.g., biochemistry, genetics, cell biology, anatomy, physiology, etc.), to the study of an organism-wide system. They also learn to appreciate that immunology is a dynamic field in which important conceptual advances are still emerging.

However, our students frequently struggle with the discipline's specialized and often arcane vocabulary. Just like learning a foreign language, a course in immunology requires students to learn the meaning of new words, and then rapidly apply that new vocabulary to build a knowledge base and answer complex questions. It is therefore not surprising that some students flounder or become discouraged in the early weeks. We have found that a flexible approach to the subject with use of creative learning strategies can help students overcome these initial hurdles.

In this paper, as four seasoned teachers, we share some of the approaches that have worked for each of us in the undergraduate immunology classroom. We acknowledge that immunology courses are content-heavy and as such, must include extensive reading assignments as well as some conventional lecture components. However, a considerable body of pedagogical research has shown that, if we want students to retain the material they are exposed to, apply it to future situations, and in particular, appreciate the connections between different sections of this course and between this course and others, we need them to engage in "*active learning*" (1).

What is "active learning"? A frequently cited paper by Bonwell and Eison (2) suggests that students participating in active learning "must do more than just listen: They must read, write, discuss or be engaged in solving problems. Most important, to be actively involved, students must engage in such higher-order thinking tasks as analysis, synthesis and evaluation." They continue: "Within this context, it is proposed that strategies promoting active learning be defined as instructional activities involving students in *doing* things and *thinking about* what they are doing" (emphases ours). Thus, most active learning approaches are also student-centered, positioning the student as the architect of their own knowledge and building metacognitive skills. Active learning strategies can vary greatly, from short group discussions to more complex single- or multi-day engagements, and the effectiveness of particular approaches should be carefully and frequently assessed, with adjustments made as necessary (3). However, the use of active learning in the classroom has been clearly demonstrated to improve student understanding across all STEM disciplines (4). Importantly, the pedagogical literature further suggests that, although *all* students gain from the use of active learning strategies, those students from non-college preparatory backgrounds or who fail to thrive in standard lecture-based settings derive particular benefits. Thus, active learning approaches can be instrumental for leveling the playing field, and are therefore viewed as vital for effective and equitable teaching (5).

Current students have been born into an information-saturated environment; answers to even the most obscure question can be ascertained within seconds via any search engine. Therefore, instructors in the modern classroom must thoughtfully teach students how to distinguish between verifiable information supported by reliable evidence and random "search results" devoid of scientific support (6). Today's faculty are also increasingly challenged to work with a student population that tends toward impatience in accessing information and adheres to a "faster is better" philosophy (7). Many of the strategies discussed below attempt to address this issue, using critical analysis, reflective discussion and contextual placement of information, interleaving technology that feels natural to today's student.

Active learning involves moving the focus away from the instructor and toward student engagement, both inside and outside the classroom. The use of technology and electronic devices can provide important conduits to foster this engagement, especially in large classes. However, questions regarding the appropriate use of electronic devices in the classroom are bound to arise. Research has documented the potential for distraction when such devices are unregulated (8) and experiments have shown that students who take class notes in longhand show better retention than those who use a keyboard (9). Nonetheless, tablets and other electronic devices can be powerful tools to facilitate learning, especially given their ubiquitous presence in our lives. Approaches for the effective use of these devices in the classroom will be discussed.

In this article we describe a variety of interactive exercises that have been field-tested and found to work in our immunology courses. These include concept maps, "Just-in-Time" Teaching strategies, classroom games, formative writing assignments, reenactments of cellular events, written, video or audio material, as well as the use of tablets in the classroom. Throughout, we discuss the use of technology in ways that help draw students in rather than intimidate them, and we provide examples that can be used by interested instructors. We recognize that there are many potential active learning approaches that are not covered by this article. For example, immunology-based labs and the use of primary literature are not presented here, but instead are addressed by other articles in this volume (10–12). Likewise, the important discussion of how these approaches, and others, can help reduce learning inequities in the U.S. (13) and beyond (14) appears elsewhere in this issue.

We believe that our classroom experiences support the hypothesis that active learning approaches greatly assist students in understanding the complex and interdisciplinary discipline of immunology. We have found that, by teaching immunology with these techniques, our students demonstrate retention of material from module-to-module and critical thinking. We have taken a "before, during and after" approach to our description of the techniques. We begin by discussing some strategies that we have found help students to arrive in the classroom prepared to engage, such as Just-in-Time Teaching and video or audio preparation. We next address the involvement of students in classroom activities, including clicker questions, reenactments, strip sequencing, short presentations, and concept maps. With our discussion of the different kinds of concept maps and their varied use, we bridge into providing examples of work that students may begin in class but complete outside of the classroom, and then move into a description of some non-examination writing assignments. We finish with a discussion of novel uses of iPad devices in the teaching of immunology, both inside and outside the classroom.

PRE-CLASS PREPARATION AND JUST-IN-TIME TEACHING

Learning immunology requires engagement with new vocabulary and some paradigm-breaking biological concepts. We have found that immunology students who regularly spend time before class grappling with new words and concepts come to class more prepared to ask good questions, practice their skills, and apply this new knowledge in higher-level thinking endeavors. In our experience, if students participate in well-designed, pre-class preparation exercises, the in-class time with the instructor is demonstrably more productive. Furthermore, our students report that the additional workload imposed by these pre-class exercises is worthwhile, because it aids in their understanding through reinforcement of pre-class material in class, and helps to entrain an incremental work ethic as opposed to cramming.

We have found the method of Just-in-Time Teaching (JiTT) to be an excellent strategy for organizing and implementing pre-class immunology-based learning (15). Basically, JiTT is a form of homework reimagined or a semi-flipped classroom (before its time), employing regular pre-class exercises called "warm-ups" or "pre-class questions," to motivate and direct student preparation shortly before class meetings (16). Students are asked to read, listen to a podcast, or watch an online video in preparation for answering questions shortly before class. They then submit answers to these pre-class questions online, between 1 and 24 h prior to the class meeting. Student responses are used by the instructor to provide whole-class feedback and to better focus the in-class plan on the collective needs of the students, transforming the classroom from instructor-dominated to student-centered (17). In this way, feedback in both directions occurs "just in time" to appropriately address the material at hand. Ideally, this creates a feedback loop where in-class and outside-of-class work is highly connected, where the instructor is consistently apprised of the level of student understanding and where students can identify faculty expectations for mastery. An added benefit for the instructor is that there is nothing better than walking into a class where students are already hotly engaged in a debate over their thoughts on questions related to that day's topic!

TABLE 1 | Examples of pre-class questions for just-in-time-teaching.

Topic: primary vs. secondary responses and innate vs. adaptive immunity
1. (True/False) Primary lymphoid organs are where lymphocytes develop and become activated. Please provide a brief rationale for your choice.
2. (True/False) Innate immunity involves soluble products and is a part of humoral immunity, while adaptive immunity involves the work of B and T cells, or cell-mediated immunity. Please provide a brief rationale for your choice.
3. (Essay) Is adaptive immunity engaged during both a primary and a secondary immune response? What about innate immunity? In other words, what is the relationship, if any, between the innate/adaptive and primary/secondary immune response?
4. (Optional) Do you have any questions from this part of the reading/viewing preparation for class? Please be as specific as possible.
Topic: innate responses and pattern recognition receptors
1. (Multiple Choice) Which of the following type/s of PRR/s are responsible for detecting foreign antigens in the cytosol of an infected cell? Please select all that apply. A. TLRs B. CLRs C. NLRs D. RLRs E. ALRs
2. (Multiple Choice) Based on shared vs. unique properties, which two categories of pathogen do you think might be treated most *differently* by the immune response? Please provide a brief rationale for your choice. A. viruses and intracellular bacteria B. viruses and extracellular parasites C. extracellular bacteria and extracellular parasites D. fungi and extracellular parasites
3. (Essay) There are only a small number of different ligands, or different "types" of ligands, for TLRs (see Table X in your textbook). What patterns or common features do these ligands share? Thinking of evolution and natural selection, why do you think these types of ligands make "good choices" in terms of recognition structures for the immune system?
4. (Optional) Do you have any questions from this part of the reading/viewing preparation for class? Please be as specific as possible.

The structure of JiTT pre-class exercises or assignments can vary, from questions that probe basic vocabulary or the application of concepts, to real-world dilemmas or queries about an assigned journal article. Questions that highlight common confusions and misconceptions are ideal. We have found that a combination of recall or fact questions (especially early in the semester), along with some higher-level questions that require open-ended responses, provides a good mixture of positive reinforcement and challenge. Examples of pre-class questions related to two topics are shown in **Table 1**. Optimally, at least one open-ended question and an opportunity for students to ask the instructor their own questions are included

in each assignment. Responses to open-ended questions, in particular, provide valuable, low-stakes opportunities for students to articulate their understanding of topics in their own words, using their newly-acquired vocabulary. Likewise, by adding "with rationale" to True-False or Multiple-Choice questions, students are given an opportunity to briefly explain their thinking.

We suggest that most, if not all, of the credit for these pre-class exercises should be awarded for good-faith attempts to answer questions, or for a clear articulation, using immunologically accurate terminology, of any areas of confusion. The use of pre-class questions allows the instructor to come into class with a distinct sense of the parts of a topic that are causing students the most difficulty, as well as the overall level of student understanding. More importantly, the questions provide students with valuable opportunities to think through complex information in their own time. Some instructors award a fraction of available points for accuracy. In our experience this can be counter-productive, as it can lead to a focus on the one right answer over an explanation of reasoning that, even when flawed, may illuminate misconceptions and roadblocks to learning. At its most effective, JiTT affords instructors an opportunity to peek inside the heads of their students right before class.

JiTT can also be valuable as a term-long system for organizing the assignments and workflow for both faculty and students. This method has been shown to help spread the work of studying more evenly throughout the term and makes it much harder for students to fall behind without the instructor's knowledge (15). In 20 years of using this technique to teach immunology, students routinely report that weekly pre-class questions are one of their favorite parts of the structure of the course. Almost one half of students in a recent undergraduate course said that the questions ensure that they always know what they "need to know" and where to focus their attention while reading, and that this activity forces them to keep up with the material, minimizing the need to cram before exams.

This pedagogical strategy works best when the thinking students do before class is closely aligned with that day's material, and students are given immediate opportunities to either demonstrate mastery or identify their areas of uncertainty. Likewise, follow-up questions that arise during class can be included in the next set of pre-class assignments, setting up a nice learning feedback loop. While the design of good questions can be time-consuming at first, effective questions can become the material for the day, making planning for class time relatively easy. Finally, in our experience, the JiTT strategy is especially helpful for non-traditional or first-generation students and others who thrive in highly organized academic settings, where outside-of-class expectations are laid out clearly and where there are regular opportunities for low-stakes, formative assessment (13). It is worth noting that significantly more students from sections set aside for students from resource limited backgrounds (with no other course modifications) made favorable comments on the use of JITT than those in traditional course sections. We believe that techniques like this, where outside-of-class expectations are laid out clearly and there are regular opportunities for low-stakes, formative assessment, can help to level the playing field (13).

VIDEO AND AUDIO SUPPLEMENTS

Technology enables the use of audio and visual tools for powerfully conveying information. Today's students are used to acquiring information from videos or by listening on their phones and other devices. While strategic reading and note-taking are invaluable exercises that allow students to integrate knowledge and develop their own interpretation of a topic, supplementing reading assignments with video or audio material is particularly useful when students are learning complex topics or reviewing background material. For example, transfer students may not have had a molecular and cellular biology course for several years. Reviewing the central concepts of cell and molecular biology will be essential for understanding certain immunological topics. We have found that high quality videos provide an excellent way for students to get up to speed before class.

Videos can also be used to introduce and illustrate new topics. "Seeing" complex pathways of cell interaction or protein cascades in action can help students better understand them. **Table 2** lists some of the videos that we have found to be most useful. For example, several Khan Academy and Crash Course videos are particularly useful for both review and learning new material. Kurzgesagt–In a Nutshell provides entertaining cartoon animations that students enjoy. Videos from Nature, iBiology, HHMI, and the Walter and Eliza Hall Institute, are all high quality and highly illustrative, as are some of the short videos or animations offered as Supplementary Materials with various textbooks, research papers or on the websites of faculty active in particular fields or research[1]. Videos can be paired with worksheets or pre-class questions (see JiTT section) to ensure students focus on the concepts that the instructor will later reinforce in the classroom.

Another useful resource is the expanding array of science-related podcasts. Podcasts range from general interest to specialized presentations of new findings and important papers. However, it is important to choose podcasts that are accessible to undergraduates, piquing their interest rather than overwhelming them. A list of the podcasts we currently find most useful can be found in **Table 3**. The American Society of Microbiology (ASM) podcasts describe many pathogens and their interactions with the immune system, and also include a dedicated "Immune" podcast devoted to current topics in immunology. The ASM podcasts are particularly useful in that they allow filtering for criteria such as the target audience (undergraduates are one option). As these weekly podcasts consist of discussions and critical analysis of the latest cutting-edge research, we have also found them to be an excellent commute-time resource to keep ourselves up-to-speed in selecting new research to cover in class. The American Association of Immunologists (AAI) also produces an immunology podcast, although these are directed more toward graduate and medical students, or professional immunologists. Podcasts often include interviews with the authors of the study

[1] For examples, see: https://www.cimr.cam.ac.uk/research/principal-investigators/principal-investigators-a-h/griffiths and https://www.vet.upenn.edu/research/research-laboratories/research-laboratory/hunter-laboratory.

TABLE 2 | A list of immunology video supplements.

Video	Home: youtube or website	Sample video
Crash course	https://www.youtube.com/channel/UCX6b17PVsYBQ0ip5gyeme-Q	https://www.youtube.com/watch?v=GIJK3dwCWCw&t=436s
HHMI biointeractive	https://www.biointeractive.org	https://www.biointeractive.org/classroom-resources/targeting-infected-cells-immune-defense
iBiology	https://www.ibiology.org	https://www.ibiology.org/online-biology-courses/immunology-flipped-course/
Khan academy	https://www.khanacademy.org/	https://www.khanacademy.org/science/biology/human-biology/immunology/v/role-of-phagocytes-in-innate-or-nonspecific-immunity
Kurzgesagt–in a nutshell	https://www.youtube.com/channel/UCsXVk37bltHxD1rDPwtNM8Q	https://www.youtube.com/watch?v=zQGOcOUBi6s&t=15s
Nature	https://www.youtube.com/user/NatureVideoChannel/featured	https://www.youtube.com/watch?v=5AXApBbj1ps&t=6s
Nature immunology	https://www.nature.com/ni/video	https://www.youtube.com/watch?time_continue=2&v=CXz6FVqPqHw
Walter and Eliza Hall Institute	https://www.wehi.edu.au/wehi-tv/animation	https://www.wehi.edu.au/wehi-tv/immune-system

TABLE 3 | Examples of immunology podcasts.

Podcast and comments	Link
Bite size bio (https://bitesizebio.com/) has a listing of some top science podcasts; not all immunology but all are interesting	https://bitesizebio.com/24598/our-12-favorite-science-podcasts/
American Society of Microbiology; several different series, can filter for level of audience, some in Spanish	http://www.microbe.tv/immune/
Audioimmunity; informal, low key, likely to appeal to undergraduates	https://player.fm/series/audiommunity
Journal of Immunology; too specialized for most undergraduates	https://player.fm/series/the-journal-of-immunology-immunocasts
Nature; a wide variety of science podcasts of general interest	https://www.nature.com/nature/articles?type=nature-podcast
"Talkin Immunology with BioLegend;" a high quality production from BioLegend	https://www.biolegend.com/podcast

being discussed, increasing student's direct access to scientists. This can be particularly beneficial when these scientists come from non-stereotypical backgrounds, expanding students' visions of who scientists are, as well as what they look and sound like. If a paper chosen for a class discussion is discussed in a podcast, the podcast can be a helpful supplement.

Whether using videos or podcasts, it is important to remember that multimedia content is in constant flux. Links must be checked and searches conducted regularly, as new material is released frequently. In fact, students enjoy being enlisted in the effort to maintain up-to-date digital resources and indeed, one useful class activity is to have the students search for new videos or podcasts and report on which ones they think are most useful and why. As part of the exercise in finding new online material, they can be encouraged to update links to existing videos and podcasts.

We have also found that students enjoy using audio books on topics related to the class material. The book *Get Well Soon: History's Worst Plagues and the Heroes Who Fought Them* by Jennifer Wright (18) has proven to be a popular choice for student listening, and the chapters on smallpox, polio, and HIV are particularly relevant to an immunology course. The audio recording of the book is excellent, and the author's popular culture references make it particularly relevant and entertaining for undergraduates. Students can either listen to or read assigned chapters (they are required to listen to the first chapter) and then write a short reflection paper. In one case, students were asked whether they preferred reading or listening to the material, forcing them to think about how they best acquire and absorb information and providing them, and the instructor, with important metacognitive feedback. Not surprisingly, the students had a variety of preferences: reading only, listening only, or reading while listening.

CLICKER QUESTIONS

Interactive response systems, more commonly referred to as "clickers," have been used in educational settings for over a decade, as a way to engage students and encourage active class participation (19). During lecture, a question, most commonly multiple-choice, is posted by the instructor and students respond using a dedicated device (typically termed clickers) or via Wi-Fi on their own phone, tablet, or computer. Many students prefer to use their own Wi-Fi devices, which can save time and money (20). However, even when required to purchase an eClicker, our students consistently rank Clicker questions and follow up discussions as a favorite element of the course in helping them to assess and focus their learning.

While most clicker questions are framed as multiple-choice questions, the options can be expanded. Poll Everywhere, a web-based response system, includes word clouds, Q & A, clickable images, surveys, open-ended and even competition questions. Even when Clicker questions simply probe lower-order Bloom's skills like immunology vocabulary retention, the use of these questions at the beginning of each lecture provides students with the motivation to review the previous class before the subsequent one, which our students also report to bolster their incremental study habits. They also work

well during lecture, first to review the terms or complicated concepts just introduced, then as higher-level questions that challenge students to build upon what they just learned. Textbook test banks, as well as instructor's homework and exams from previous courses, provide a good source when starting to use clicker questions.

The anonymity of clickers enables participation from students who might otherwise hesitate to verbally answer questions in class. Thus, clicker questions can provide a powerful tool for engaging students who are typically less confident about raising their voices in class, a group that frequently includes students of color, women, and those who may feel hesitant about their knowledge of the material (21, 22). By awarding points for *participation* in answering clicker questions, rather than for *arriving at the correct answer*, students are encouraged to answer questions when they are unsure and to take risks with their responses, providing valuable low-stakes assessment. Using a musical theme (such as the Jeopardy theme) as a timer adds an element of fun.

If the distribution of answers shows that many students are confused, we then utilize a Think-Pair-Share approach (23). In the case of clicker questions, the "Think" step corresponds to the students' original response to the question. Students then "Pair" with their neighbor, discuss the topic for a minute or two, and then "Share" by answering the question again or by participating in a whole class discussion. This approach is generally well-received by students and usually results in a notable improvement in comprehension. The discussion time can either be pre-set or left to the judgment of instructor. Students quickly learn that when the projected answers show significant variability, it's time to turn to their neighbor and discuss it. As instructors, we have learned that in the rare cases where we don't observe improvement after the "Think-Pair-Share," we need to re-approach how we explain the topic. Clickers therefore serve as an excellent formative assessment for faculty to reflect on their teaching effectiveness.

A related fun activity that is also useful as a study tool is to create a Jeopardy game. One site, Factile[2], allows instructors or class members to easily build Jeopardy style games. In addition, there are a number of games created by other instructors, which can be accessed by searching for "immunology" on the Factile website. Downloaded questions can be used by groups in class, employed individually as flash cards or as a memory game, or used by peer mentors during study sessions.

SIMULATIONS, REENACTMENTS, AND OTHER INTERACTIVE IN-CLASS ACTIVITIES

Nothing makes a learning environment more active than when students get up out of their seats and move around. We have found that some elements of immunology learning are particularly amenable to simulations, reenactments or other interactive in-class activities. Students who struggle with auditory, visual or written modes of learning particularly benefit from activities that include kinesthetic elements. Most of these approaches also work well in study groups outside of class or during peer mentor sessions, and students frequently request access to the props outside of class. Below we briefly describe four examples of such activities. Most will require at least 30–45 min to complete, although timing can be varied by supplying more or less directed guidance and by adding discussion afterwards.

Table-Top or Whiteboard Simulation of Somatic Recombination

V(D)J recombination is frequently cited as one of the most difficult concepts for immunology students to grasp; the structure-function elements involved in antigen-specific receptor generation and maturation as well as the use of multiple gene segments to create a single receptor chain are common sources of confusion for students. Paper or other props, including yarn "DNA," can be used to depict the genomic arrangement of gene segments and their behavior during somatic recombination.

Groups receive packets containing V, D, and J gene segments, with multiple gene segments of each type. First they organize the segments as they would appear in a non-immune somatic cell. Next, students begin the process of recombination. Different colors are used for V, D, and J segments, and students are given multiple, numbered segments of each type/color, allowing groups to generate different receptors. The goal is to produce an arrangement of gene segments that encodes a TCR or BCR locus. Finally, students attempt to draw out their BCR or TCR as a protein on the cell surface, using colored markers linked to the colors of the paper gene segments to depict locations of the V, D, J, and C gene segments. This is a nice reminder of important gene structure-function relationships and can lead to discussions of somatic hypermutation and affinity maturation in B cells. If there is time remaining, students can walk around the room to see what other groups have produced, an activity that often leads to interesting discussions.

MHC Diversity Illustration Using Simulated Genotypes and Phenotypes

When students and faculty are asked which aspects of immunology they find to be the most challenging, the MHC often comes out on top. For this reason, we continue to explore creative ways to present this particular topic. The following activity aims to help students grasp the difference between polygeny and polymorphism, as well as highlight how codominant expression allows unique class II allotypes to be expressed. Finally, this exercise illustrates the power of diversity at the MHC, and how this is manifested at the population-as compared to the individual-level.

For this activity, colored paper props are used to depict alleles of MHC genes. Gene names are written on each strip of paper (e.g., "Aα" if using human, or "Kα" if using mouse, Class I nomenclature). The same is done for the class II region, with alpha and beta chains represented by separate strips of colored paper. See **Figure 1** for a visual illustration of the props. The final product represents the theoretical diversity of MHC alleles in

[2]https://www.playfactile.com/

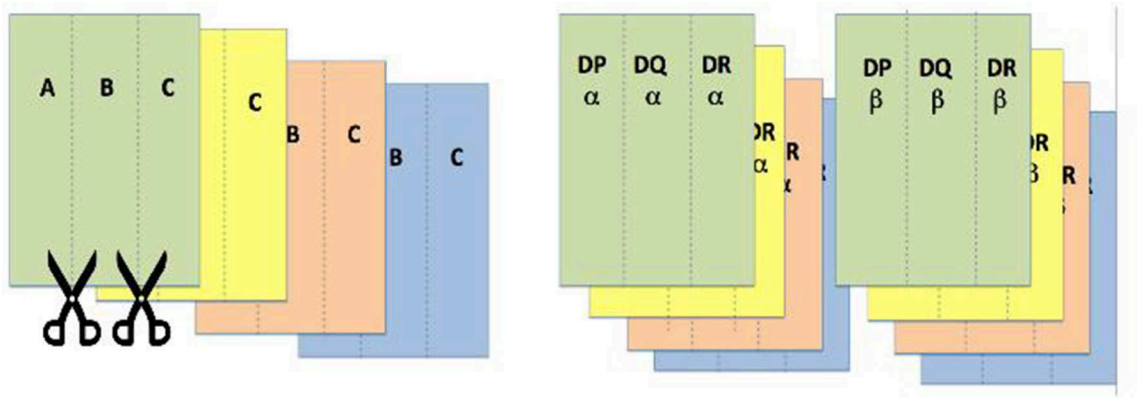

FIGURE 1 | MHC Diversity Activity. Examples of the paper cut outs used to generate a "gene bank" for the MHC diversity activity. We usually make many copies of the same gene in the same color to represent common alleles, and one or a few unique colors for each gene to demonstrate rare alleles.

a given population. In class, students work in groups to create an individual genotype. This can be done either by providing each group with a packet containing all the genes needed for one individual (so, two copies of each gene) or by asking a representative from each group to collect from a "gene bank" what they need to depict the MHC genotype of one individual. At some point, students need to grapple with the presence of two copies of each gene due to maternal and paternal contributions and the presence of multiple genes of the same class. Non-classical, non-polymorphic MHC genes such as CD1 and MR1 can be included, with only one option for the strip colors, to provide a complete overview of the MHC locus.

Once their colorful paper genotypes have been laid out, students use them to create MHC molecules, and call an instructor over to check their work. Next, each group is asked to assume these slips of paper are protein chains and hold up in the air all the Class I molecules that would be expressed on the surface of this individual's cells. This usually leads to some questions regarding codominant expression. By looking around the room, we get a quick glimpse of individual diversity (e.g., some "individuals" have six colors of Class I molecules and others have only three) and population level diversity (a rainbow of Class I molecules in the room). This gets even more complicated when they are asked to do the same for all the Class II molecules expressed by their "individual," as they deal with combinatorial association and questions of which chains can and cannot pair. Students can also be asked to hold up all those molecules expressed by different cell types, a question that asks them to recall the difference in expression between Class I and Class II MHC genes.

Groups are next asked to create the MHC genotype of a gamete for their individual. Groups hold up a single set of MHC genes for their gamete and then select another group to "mate" with. Pairs of groups now create the diploid MHC genotype of their "new individual" or progeny, at which point each group is asked to display the virtual MHC genotype/phenotype of their new individuals. Questions about whether new Class II molecules can arise from unique combinations of the alpha and beta chains originating from different parents provide important and productive opportunities for correcting misconceptions. Again, a glance around the room provides students with a sense of individual and population level diversity. An optional final segment of this activity involves posing questions about what happens when there are allelic associations with disease susceptibility or resistance connected to specific alleles (colors, in this case). This physical demonstration of the difficult concepts of polygeny and polymorphism in the MHC is consistently highly rated by students.

Strip Sequence Activity to Practice Cell-Cell Interactions During an Immune Response

The many steps and players in the various cell-cell engagements that occur during a given immune response are notoriously difficult for students to master. Strip sequences or other types of poster materials are an excellent teaching tool in these instances. For example, the instructor can create a set of paper strips, each outlining an individual event, surface marker, intracellular component or signaling event; instructors can tailor the number of these "immune players" to the complexity of what they expect students to learn. Each student team is given a complete set of these paper strips, each of which also contains a number for tracking purposes (out of order, of course). The instructor provides one challenge question to the whole class, such as the following; "Map out the events that occur after a naïve T cell encounters cognate viral antigen, ending with an activated CTL." The students use the paper strips containing immune players and events to create an appropriate sequence.

In one recent variation on this technique, students were asked to make a poster that described all the steps in an immune response from recognition of an antigen by a dendritic cell to the production of antibodies. Strips and cutouts included paper shapes representing cells, molecules and organs, not all of which were relevant, so students had to decide which cutouts to use and which to discard. Each group of four or

five students received a large sheet of paper, tape, scissors, construction paper, markers and strips. The instructor circulated among the groups and answered questions. Students enjoyed the "big picture" aspect of this class and interesting questions asked by one group were shared with their colleagues. Some of the posters were visually stunning, but most importantly, this exercise allowed students to integrate a great deal of material in a very short period of time. In one recent class, 36% of the students highlighted the poster exercise as particularly useful in helping to synthesize the content of multiple lectures. Thirteen percent of the students were not enamored of this project.

We find that discussions of differing opinions can be very fruitful. For this reason, allowing time for a whole class discussion is quite valuable. By creating a really comprehensive set of strips and cutouts, instructors can reuse the same set and pose different challenge questions. This is also a great activity for outside-of-class review and mentor sessions, where the instructor supplies a list of challenge questions and a matching numerical sequence key for each.

Reenactment Activities of T Cell Activation and B Cell Affinity Maturation

Reenactments of immune events using student volunteers and props are always a crowd-pleaser. Students who do not volunteer to come to the front of the room can still be engaged to direct the actions of others, so that everyone is involved. For large classes or to encourage discussion by more reluctant students, this direction can be provided using student audience teams. One example of this activity is a reenactment of T cell clonal selection in a secondary lymphoid organ. The instructor prepares by bringing required props and labels. We like to use candy (e.g., Hershey's Kisses) for the antigen, chairs, and tables to depict particular microenvironments (e.g., follicle or a follicular dendritic cell), and student volunteers to act as specific cellular players. These volunteers wear signs around their neck declaring their cell types (e.g., dendritic cell, B cell, T Helper cell, etc.). The instructor can also provide multiple clip-on or pin-on buttons for relevant surface markers (e.g., CD28, B7, CD40, etc.), asking the students to determine when and where these are needed. MHC molecules can be labeled plastic cups, which hold peptide fragments. Decoy surface markers make a nice challenge and help identify important misconceptions.

Students in the audience are asked to direct the action by providing the student "cell-type volunteers" with instructions regarding what to do and where they need to go at each step. In this example, the action might begin as the dendritic cell encounters antigen in the periphery or in a secondary lymphoid organ. Students in the audience tell the cellular players which buttons they will need (e.g., maybe a particular pattern recognition receptor), when they need to acquire these and how interactions with other cells should proceed. For example, the "dendritic cell" student might use a pattern-recognition receptor button to acquire antigen (e.g., Hershey's Kisses). The antigen must then be processed (make sure this volunteer likes chocolate!) and "presented" as a fragment (the Hershey Kiss label works well for this), along with an MHC class II molecule (labeled plastic cup holding the Hershey Kiss label). This MHC-antigen fragment is presented to the student acting as the T cell, along with a B7 button in the other. The T cell student volunteer is told to respond using one hand as the TCR and holding the CD28 button in the other hand. And so on.

For the affinity maturation enactment, T-B cell cooperation and sequential rounds of somatic hypermutation can be simulated using additional student "cell" volunteers. The process by which T and B cells recognizing the same antigen can join forces, even when recognizing different epitopes, soon becomes apparent–a topic that is notoriously challenging for students to grasp. Affinity maturation can be simulated using additional students acting as B cell progeny, with higher or lower affinity receptors, following rounds of somatic hypermutation. To depict the evolving process of changes in BCR affinity, the "progeny" selects from a deck of cards labeled "higher affinity," "lower affinity" or "same affinity." The higher affinity B cell player gets to use all five fingers and both hands to pick up as much candy as possible from the table (a follicular dendritic cell). The player with the "same affinity" card is told to use only thumb and one finger of each hand, while the "lower affinity" B cell player is further handicapped in some way from grasping candy, simulating affinity maturation. We then count the candy acquired by each B cell player and discuss what happens next in interactions with T helper cells or as antigen becomes limiting. The final discussions of this activity can be done as a whole class, by engaging table groups or as an after-class assignment if time runs short. This activity can take most of a class period but is one of the more effective ways we have found for driving home this process, complicated by multiple cell types, surface molecules, events and locales.

IN-CLASS SHORT PRESENTATIONS AND POSTERS

In information-dense courses like the average undergraduate immunology class, students rapidly come to appreciate a respite from listening to their instructor and gazing at PowerPoint slides, no matter how accomplished the professor or how appealing the images. One technique that has proven useful has been to divide the course or the lecture day into sections, with the faculty member sharing some in-class presenting time with students. For example, the instructor might set the stage for a topic and then have groups of students deliver some of the material. Sometimes, the faculty member will need to return to emphasize the main points that have been made and offer a summary of the conclusions. Alternatively, students can be charged with presenting on a topic of interest to them, as it relates to immunology.

This approach is particularly useful when the subject involves presenting information in the form of a list of similar, but slightly different molecules, cells or even topics. When student groups are responsible for different parts of the lecture the perceived "sameness" of the material is broken up, helping the students to

associate particular molecules with different people, and acting as an *aide memoire*.

In one example, the instructor introduced the overall concept of innate immune receptors and then delved into a discussion of members of the TLR family. Student groups then took up the story of innate immune receptors, with groups of three or four students presenting the other innate receptor families, while a separate group tackled the inflammasome. The structure and function of different cytokine receptor families is another topic that works well in this approach. Designing and delivering these mini-lectures gives the students (usually much needed) additional experience and confidence in presenting to a group.

Another popular student-led classroom activity is a variation on the classic paper presentation. A more detailed discussion of how research articles and reviews can enhance the immunology classroom is to be found elsewhere in this volume (12). All the students in the class are given a paper to read, but a subgroup of those students is asked to prepare a set of questions about the paper for their peers. The questions are shared with the instructor ahead of time, who works with the subgroup to refine the questions and then to select two or three of the most interesting for class discussion. This activity typically takes 20–30 min of the class period. Moving away from a rote presentation that lists all the figures and tables in turn, but instead asking specific questions that students must address, ensures a deeper level of engagement on everyone's part and better models the scientific process.

In some courses, a segment of the semester, usually near the end, is dedicated to short student presentations. Since many of our students enroll in immunology with specific interests or connections to immunologic disorders, allergies or immune therapies, saving time for students to engage in self-directed learning can be rewarding for all. This gives the students a chance to practice their vocabulary and concept comprehension, plus some ownership over their learning. Since the instructor is released from class preparation during this time, they can meet with individuals or small groups to discuss content, structure and presentation style, improving the experience for all. Likewise, a requirement that students include some data from the primary literature in their presentations gives them a chance to practice reading about, interpreting and presenting scientific results. To lower stress levels and increase overall performance, clear guidelines and a grading rubric published well in advance are vital. In fact, these rubrics can be adapted for fast, real-time grading and feedback, making assessment less onerous.

Finally, in-class student presentations can be converted into poster sessions, especially helpful when class sizes are large. Posters can be generated by small groups or individual students, and can cover specified topics or areas of student interest. Again, clear guidelines and grading rubrics are important. Students can hang their posters and the class can enjoy a "gallery walk" around the classroom to learn about what other students investigated, with or without formal evaluation. Grading can also be done by scheduling meeting times with individuals or small groups of students, where they "present" their poster for Q&A and evaluation outside the usual class meeting time with the instructor. Downtime during associated laboratory sessions can work well for this purpose.

CONCEPT MAPS

When studying any discipline for the first time students lack cognitive "hooks" on which to hang the new facts and ideas they encounter. Lacking a framework within which to organize their new knowledge, students can become overwhelmed and feel like they are swimming in a sea of unrelated factoids. Students of cognitive psychology will be familiar with the work of David Ausubel who showed how important a student's prior knowledge is to the acquisition and processing of new, related information (24). Building on Ausubel's theories, Novak and his research team developed the methodology of concept mapping as a means by which science students at all levels could position newly-acquired information in a pre-existing knowledge structure (25). We have found that our students are very polarized in their assessment of concept maps on course evaluations; however, enough students report finding them extremely helpful in synthesizing and modeling their recently gained knowledge to merit their continued use in our classes.

A concept map typically represents each idea, experimental result, organ, cell or molecule as a shape, joined to other shapes by lines that indicate the conceptual connection between them. These lines can be labeled with phrases that are used to describe the relationship between the linked shapes. In a classical concept map, such relationships might be, for example, "causes," "requires," "combined with," "is part of," "occurs simultaneously with" or "occurs within" (see **Figure 2**).

We have found that this technique is particularly well-suited for teaching immunology, as students must master an impressive number of new words and concepts in a short period of time in most introductory courses in the discipline. However, like learning a foreign language through immersion, words and concepts are learned better when placed into their natural context and not simply memorized from index cards. We have had considerable success assigning concept maps after studying chapters that are particularly jargon-heavy. Concept maps work well as in-class group and individual activities, as well as take home study tools. Assigning students to work on creating concept maps in groups of three or four decreases the grading burden, allowing the instructor to give more thoughtful feedback to students; it also allows students the benefits of discussing with each other what belongs where, and why. Thus, in the process of making the map, the students are highly engaged in peer-instruction and metacognition.

Concept maps are most effective when there are multiple descriptor words on each arrow, and when many connections are made from a single node (26). Accordingly, we often find that the "messier" the concept maps appear, the better! Furthermore, the maps provide the instructor with a great assessment tool to identify where misconceptions lie or where connections were not made (27).

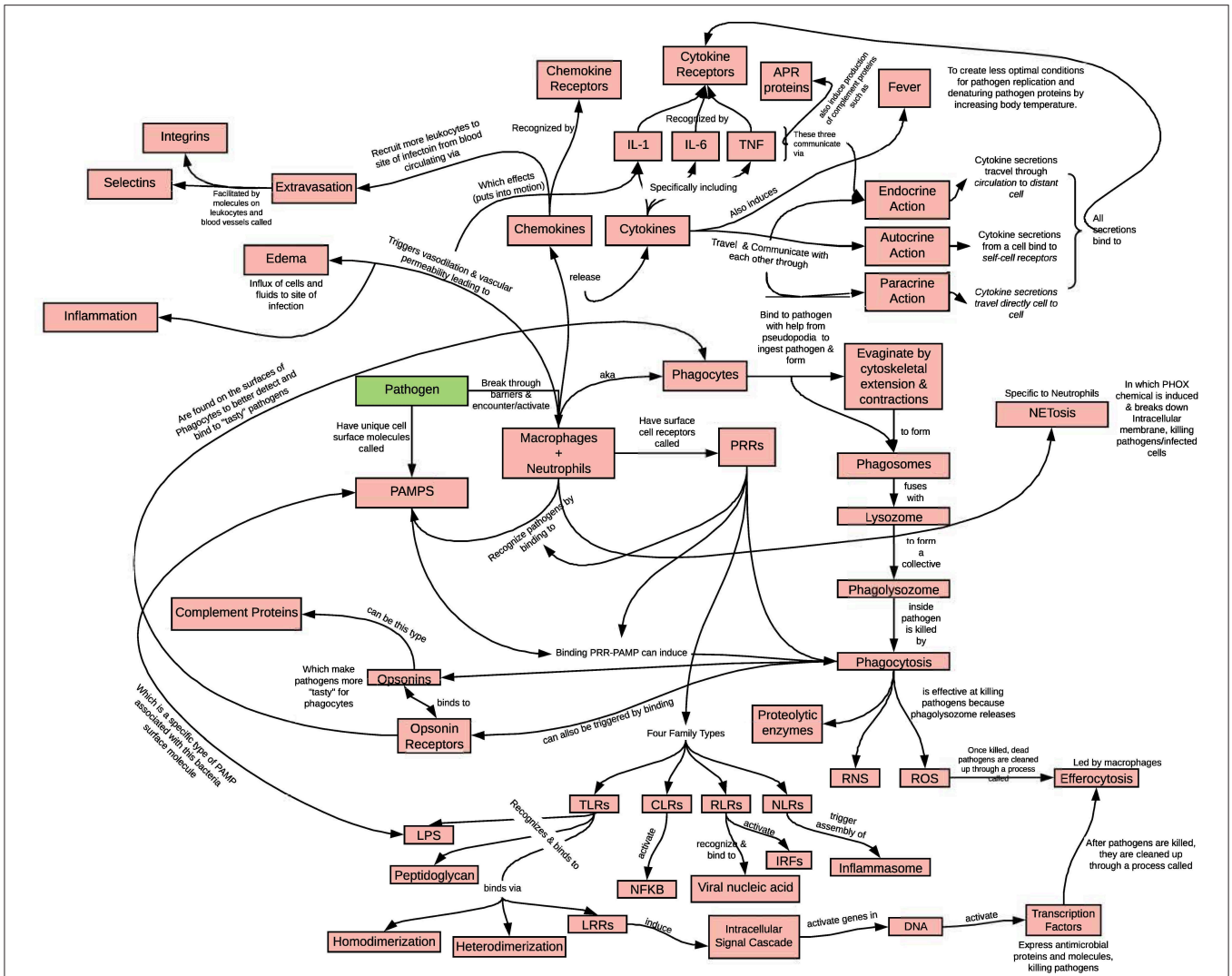

FIGURE 2 | Example of a group generated concept map. An example of a student concept map of innate immunity and inflammation, using the terms listed in **Table 5**. At the end of each week of class, the instructor assigns a list of important terms from that week for students to concept map, working in groups. One such concept map developed by four students working outside of class is shown. Each boxed term was on the list of assigned terms. The instructor grades the map for accuracy and completion. Students generated this concept map using the Lucidchart program, which has free educational access and allows real-time collaboration between students.

Concept maps make an excellent in-class activity, and have the advantage that they can easily be photographed and uploaded for assessment. These maps, whether handwritten or electronically-generated, can be saved as photograph or image files and later uploaded for grading. Especially when generated by hand, these maps can be quite creative, allowing students to express their artistic skills. **Figure 2** shows a concept map generated with the Lucidchart program, which has free educational access and allows real-time collaboration between students. **Table 4** lists the terms used for the complex concept map shown in **Figure 2**, while **Table 5** lists terms useful for an in-class exercise. Individual concept-mapping exercises require students to organize the information on their own, which can be helpful for students who find speaking up in a group to be challenging. Making or studying previously-made concept maps can be an excellent review tool for certain types of learners.

Assigning concept maps for group work outside of class brings students together to discuss the material and facilitates the formation of study groups. However, finding time to spend on group work each week can be particularly challenging on commuter campuses. In this case, students have utilized creative strategies such as skyping with cameras aimed at whiteboards, or completing the maps individually followed by a group meeting to share and critique each other's maps, and then develop one to submit as a group. An advantage of this layered process is that, as students notice aspects of the maps generated by their colleagues that are different from their own maps and discuss how to insert the new content into the master map they are actively synthesizing ideas and making new connections.

TABLE 4 | Terms for the concept map shown in **Figure 2**.

Terms to be used in your innate immunity and inflammation concept map	
Pathogen	Inflammation
Integrins	Phagocytes
Selectins	Cytoskeletal extension and contraction
Extravasation	NETosis
Chemokine receptors	PRRs
Cytokine receptors	Macrophage
APR proteins	Neutrophil
IL-1, IL-6, and TNF	PAMPs
Fever	Complement
Endocrine	Opsonin
Paracrine	Opsonin receptor
Autocrine	Proteolytic enzyme
Cytokine	RNS
Chemokine	ROS
Edema	TLR
Heterodimer	CLR
LRRs	RLR
NFkB	NLR
Viral nucleic acid	LPS
Intracellular signaling cascade	Peptidoglycan
DNA	Homodimer
Transcription factor	IRFs
Efferocytosis	

TABLE 5 | Sample concept map terms for an in class exercise.

Terms to be used in your BCR-TCR concept map	
Lymphocyte antigen receptors	Ig domain
B cells	Igα
T cells	Igβ
APCs	CD79α
MHC Class I	CD79β
MHC Class II	TCRα
BCR	TCRβ
TCR	CD21
Antigen	CD19
Antigen peptides	CD81
Variable regions	CD3γ
Constant regions	CDδ
Heavy chains	CDε
Light chains	CDζ
λ light chain	ITAMs
κ light chain	CD28
CDRs	CD80 or 86

Another use for concept maps is to help students better visualize and connect the sequencing of steps in pathways that occur on different conceptual levels. For example, students usually learn about the genetics of V(D)J recombination and B cell development in different lectures and with reference to different textbook chapters. A concept map done as a physical exercise after students have learned about the two processes can provide a useful tool to line up the two sets of ideas to create a picture of what is happening when and where, as shown in **Figure 3**.

In this example, students are provided with, or prepare themselves, two sets of paper strips, each set in a different color. One set contains the steps in V(D)J recombination, e.g., D-J_H joining; activation of TdT; V_L-J_L joining; cell-surface expression of pre-B cell receptor; etc. The other set contains descriptions of stages of B cell development, e.g., pro-B cell stage, small pre-B cell stage etc. Students arrange the colored notes in two vertical columns, with one column showing the sequence of gene rearrangements and the other, the sequential development of B cell precursors. Students then draw lines between the two columns to show the correct relationships. This exercise is easier if the paper strips are sticky notes, as they can be arranged on a white board or poster, so that students can easily compare their maps. For a further challenge, an additional set of paper strips can be included that lists surface molecules such as CD79, CD19, pre-B cell receptor, etc. (not shown in **Figure 3**).

This mapping exercise allows students to develop for themselves a picture of what is happening at each stage of B cell development. If half of the class works on T cell development and half on B cell development, a comparative discussion can follow. Yet another variation would be to ask students to add a third column describing the place in the body and/or within the immune organs where the relevant cells are found.

WRITING PROJECTS IN IMMUNOLOGY

John Bean's masterful book, "Engaging Ideas" (28), stresses the importance of carefully-designed writing assignments to the development of students' critical thinking skills. In her foreword to this book, Maryellen Weimer emphasizes that: "Writing forces the clarification of ideas, attention to details, and the logical assembly of reasons." In this section, we offer some examples of writing assignments that we have used successfully in our classrooms. Since each assignment requires students to perform some level of independent library research, students may benefit from interacting with library staff early in the course of each project, possibly during a class or lab period, so that they can master a range of specialized scientific search methodologies.

Of course, building up the skill of scientific critique takes some practice, especially when students are new to the primary literature. Attention to this before assigning writing projects can therefore be beneficial. One appealing example of a short writing exercise that aims to build critical thinking and break students of their reliance on the conclusions made by others, involves providing them with a "naked paper"–fragments of a research article, usually just the tables, figures and legends, plus any details or abbreviations they need to understand the data as

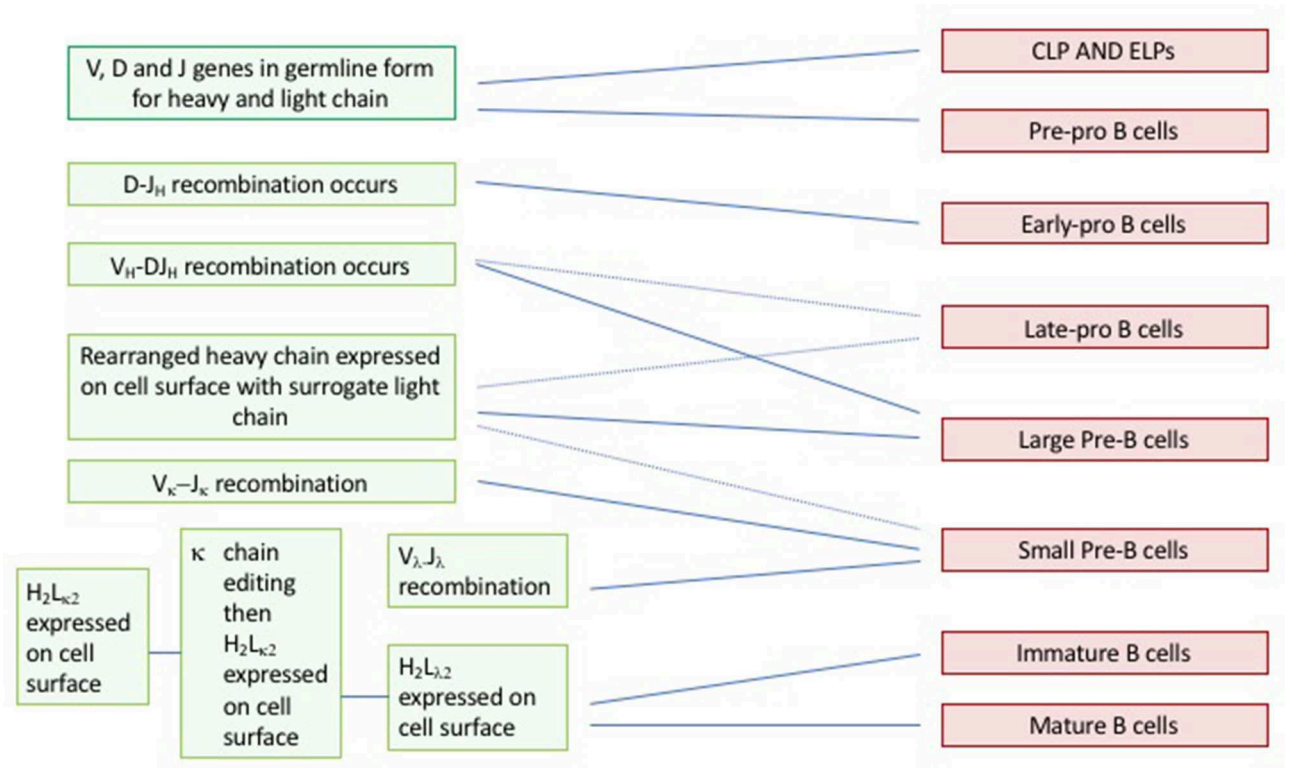

FIGURE 3 | Student-generated B cell development concept map. B cell development concept map. Working in groups of two to four, students arrange the sticky notes on a poster chart in two vertical lines, representing the chronological sequences of events or differentiation states. Next, they draw the horizontal lines that connect the stage of gene rearrangement with the stage of B cell development.

presented. The students are then asked to write a short abstract and a proposed title for these data (on their honor not to try to just look this up!) outside of class. The instructor then shares the real paper, for comparison, along with anonymous student abstracts, maybe with a vote for the winner who came closest. After that, it's valuable to spend some in-class time discussing what story the students believe the data actually told, how the authors choose to interpret their data, and whether sufficient results were presented for the conclusions the authors made. Of course, it's important to select the paper for this assignment carefully. We've found that short research articles requiring only moderate background, especially those that lend themselves to alternative conclusions, can help students to build this critiquing skill and lead to excellent discussions.

Treasure Trail / Biography of an Experiment

In the simplest form of this assignment, the Treasure Trail, students working in small groups select a seminal paper in the field and begin by learning about the original rationale for the experiment. Why was the question important? What was already known at the time the paper was written? What was the hypothesis/hypotheses being tested and what was the major advance described in this paper? Students are asked to explore the methodology of the experiment in depth so that they fully understand how the data were generated. They look up anything they don't understand about the experimental techniques, data presentation and analysis, and critically evaluate the conclusions.

Members of the group then pool their knowledge to develop a series of questions designed to lead a beginning student through the important points of the paper, and write the answer key. Asking the students to write a guide to the research paper in a question-and-answer format requires them to achieve a high level of clarity in their understanding of the paper, and working in a group context helps to ensure that students are not frustrated in isolation by the complexities they encounter. Details about this assignment are provided at the beginning of the course and they are given a considerable amount of time in which to complete it, in order to minimize time pressure and maximize opportunities for critical thinking, group work and for submission of revisions for grading. All students in a group receive the same grade.

The Biography of an Experiment assignment is a more complex variation of the Treasure Trail, and is particularly effective when used with senior students in small classes. (Development of "The Biography of the Experiment" concept owes much to the pioneering work of Profs. Jenni Punt and Iruka Okeke, both formerly of Haverford College). Students again are assigned a paper and perform the same type of research regarding its rationale, the experimental protocols that were used, the methods of analysis and data presentation, and the conclusion. The difference between the two types of assignment is that, in the Biography of the Experiment, students annotate the pdf of

the paper to provide explanations of rationale, methodology, results, implications, critique and information about the authors as clickable links on the article itself. Where possible, students are encouraged to interview the senior author, either in person, or via phone or video link, and the annotated paper and interview are published together on the course website, along with a commentary by the student. The opportunity to communicate directly with a scientist who made a major contribution to the field has proven to be a particularly inspiring aspect of this project. This project can also be performed as a stand-alone independent study for an upper-level student.

Boxes

Most biology textbooks now include "Boxes," or discrete sections of text that are narratively separate from the main part of a particular chapter, but address related subject matter. In the textbook co-written by two of the authors of this article (SS and JO), boxes are classified into four categories: the evolution of some aspect of the immune system, significant advance, related clinical issue, or classical experiment. The key to this assignment is that a good box provides succinct, interesting and useful information about an immunologically-relevant concept that is of particular interest to the student. A typical box assignment will have an explanatory title, might be 800–1,000 words long, and includes at least one figure which may be derived from an original article or review paper, plus figure legends and attribution [see **Kuby, 8th edition** for examples of the different types of Boxes (29)]. Figures may be used as published or modified by the student to better suit their purposes (again, with appropriate attribution). Figure legends must be written by the student and show how the figure is related to the text.

Students typically enjoy Box assignments because they appreciate the opportunity to select a topic they are interested in and explore it in depth, developing their research and writing skills in the process. In our experience, many students use the chance to study a clinical application of an immunological topic, but of interest is that, as climate change becomes a more important part of a biologist's curriculum, plant immunology recurs more frequently among student topic choices, something that we encountered only rarely in years past. Faculty should take every opportunity in class to point out topics that they think might make suitable boxes, so that students develop a good sense of the range of options compatible with this assignment.

The Mechanism of Action of a Drug That Acts on the Immune System

Many of our students plan to pursue a career in the medical or public health fields. Time constraints during a typical undergraduate course often preclude delving deeply into clinical aspects of the subject, and a written assignment that asks the student to explore a medically-relevant topic is often received with enthusiasm. There are many drugs that affect the immune system, as well as a range of pharmaceuticals derived from monoclonal antibodies, cytokines etc., that are designed to treat various malignancies and other disorders, such as hepatitis. In this assignment, students work in groups to ascertain the biochemical nature of the drug, its target and mechanism of action, and the disease that it is designed to treat. The results of the group's research can be expressed either in a short paper with appropriate figures and citations, or as a poster or PowerPoint presentation to be shared with the class. Almost all students highly rate this project, citing their enjoyment of the freedom to explore immunological mechanisms in a clinical context and the stimulation of working together as a group on a single paper. Those who did not enjoy the project often cited the difficulty of writing as a group and creating a cogent whole.

Research Paper

Another approach is a research paper assignment that builds on the skills students acquire while learning to read complicated journal articles. Students identify three recent (published in the past 3 years) journal articles from different labs on a topic of their choice. These topics are often clinically related and need not all share the same conclusions. In their paper they introduce the topic, then analyze and critique each paper in turn. Next, they synthesize the findings of these papers, build a model explaining the results, and propose future experiments. Alternatively, students can elect to investigate research papers from 2 to 3 different decades in our evolution of understanding on a particular subject (e.g., tolerance) or a sequence of papers from the same lab describing a progression of ideas on a specific topic (e.g., regulatory T cells).

Students write this paper in stages, first getting their topic and papers approved. They then submit their first draft for peer editing by two other students. The peer editing consists of both written feedback and in-class discussion. For the in-class discussion, students meet in groups of three, with two students discussing the third student's paper for about 15 min. The written comments can be shared as a hard copy or uploaded to a class Google Drive. Peer reviewers are expected to go beyond editing comments, and critique the scientific content and clarity of the paper. This face-to-face peer review is very effective, and provides another opportunity for improving communication skills.

The paper can be a major assignment in the class, with the majority of the points given for the final product, although students receive some points for their first draft (to ensure that it is complete) and for the quality of their peer editing. Originally the first drafts were also edited by the instructor but students tended to address the instructor's points and ignore the peer review. However, students are encouraged to meet with the instructor to discuss their articles, and almost all do so.

Critical Analysis of Social Media Posts

The hot topic of immunology appears often on social media posts, where much of the population gets its news. For many instructors, fostering the ability of students to critically evaluate immunology as it appears in the world around them is a major learning objective. As students progress in their learning and acquire the skills to read immunology articles, they are well-positioned to read social media reports and immunology news stories with this critical eye. For this activity,

students are directed to pay attention to science-related social media feeds throughout the term, choose a post related to immunology that they find interesting, and then research the accuracy of the post, using primary literature. The student then writes a paper summarizing what the primary literature shows about the topic, comparing it to what is reported or conveyed in the social media post, and then evaluating whether the social media post was accurate and responsible. This exercise gets at higher-order Bloom's taxonomy skills (evaluation and critical thinking) while utilizing a space in which many students spend much of their time, on social media, further reinforcing the real-life relevance of course content. It also encourages students to become peer-educators, commenting on each other's posts.

iPADS AS A TOOL FOR ACTIVE LEARNING

While electronic devices are often seen as an unwanted usurper of student attention in the classroom, we believe this equipment can be used to promote active learning. In particular, iPads are being increasingly used in classes at many levels (30–32) although they are not a ubiquitous feature in the classroom. The most often reported uses in undergraduate science classes are for Anatomy and Physiology, which tend to be particularly image-intensive (33, 34). Given that today's students are digital natives and use electronic devices as a regular part of their daily lives, tablets such as the iPad are comfortable and intuitive for them to use.

One of us (RP) has successfully incorporated iPads into teaching immunology (31). Each student in the course is issued an iPad for the semester, which is used in multiple ways throughout the class. Providing iPads to the entire class ensures that all students, regardless of financial need, have access to this technology. Students are expected to determine which of the available iPad tools and apps work best for them, requiring reflection on their own learning styles, and to adopt the approaches that best help them learn the material, building their metacognitive intuition.

What advantages do iPads offer over a laptop or paper and pen? The devices are portable and lightweight, the touch screen allows easy manual manipulation, and there are many apps that offer fun new features not available with more conventional tools. As students increasingly prefer to submit work electronically, the ability to complete and immediately upload forms, worksheets, etc. on the iPad, either written by hand or typed, is also highly attractive.

Likewise, using iPads in class allows students to project their work to the class or as part of a class presentation, and to submit this for assessment. The camera feature is also useful, to copy complicated illustrations that are drawn on the board by the professor or other students, and to document hands-on work done in class. As students increasingly rely on videos as learning tools, iPads also provide a convenient vehicle for this. In our hands, distraction during class has not proven to be a problem with this approach, especially since students generally would have laptops or smartphones in class anyway. Plus, an iPad allows students to organize the material for their class, and takes much less space in a backpack than accumulated handouts, a notebook, laptop, and textbook.

TABLE 6 | iPad apps useful in immunology classes.

App	Purpose
Notability	Note-taking, writing, drawing
Poll everywhere	Clicker questions, with multiple types of questions
Google drive	Shared file access
Dropbox	Shared file access
RCSB protein data bank	Visualizing proteins of the immune system
BioLegend	Provides useful information and tools
Inspiration	Concept mapping

iPads can also provide specialized help for many students with disabilities, who use design features built in for individuals with vision or hearing disabilities (35). One student with a movement disorder found the iPad to be particularly helpful, and subsequently purchased one to help her in her graduate studies in neurobiology. Lectures can be recorded and linked to a PowerPoint (see the Notability app below), which is useful for students who normally need note-takers or record lectures with other devices. The ability to enlarge what is on the screen, whether text or images, as well as record lectures and synchronize the recording to notes, are useful for all students, but especially for those with learning differences.

Certain iPad apps are particularly useful in academic settings and the ones we use most are listed in **Table 6**. One such app is Notability[3]. The most common use is for notetaking; lectures (PowerPoint or other formats), journal articles, or other materials can be uploaded as pdfs, and notes taken directly on the pdfs. A fiber mesh stylus or Apple pencil allows for the most fluid writing. Notability is particularly useful for lectures, as the record function links with the handwritten notes, allowing students to go back and review what was being said with a particular slide. In our experience, virtually all students utilize the record function. (The responsible use of the record function does need to be covered when the iPads and Notability are introduced to the students). There are numerous color options and line widths for writing, highlighting and typing, allowing students to organize their work using color and emphasis. The automatic saving function and easy sharing of notes are another big plus. Students can also use the Notability app to take photos during lecture of drawings on the board, which are then seamlessly incorporated into their lecture notes. This app is the most extensively used one in the course, and the one that students are most likely to use in other classes.

Discussions of original journal articles are an essential component of most immunology classes, and Notability can be valuable tool here as well. Students often comment that Notability allowed them to easily mark passages or add comments in articles or other students' papers for later discussion, and that learning to read and understand the primary immunology literature is one of the most important and useful things they learn in the class.

[3]https://www.gingerlabs.com/

The app can be set to automatically back up work on a cloud service. Students tell us that they use Notability to read the papers because they can read them in color, enlarge figures to see them better, and easily mark up the papers and write comments. When explaining a point about a paper figure in class, it can be projected onto a screen from the iPad, and the instructor can mark up the figure in response to student questions. While many students use hard copies during the first paper discussion, we have found that, before the end of the class, most of the students are working from their iPads.

iPads are also useful for interactive group work, including concept maps, drawing of detailed pathways, and group presentations. Most students find that Notability works well for concept mapping and allows them to creatively link concepts. The maps, drawings, or other work done in the group can then be projected while the students present their work to the class.

iPads are superbly adapted for use in the lab, as lab manuals are easily accessed, and the results of experiments can be directly entered into the iPad (36) Students frequently use the camera to document results (observations on their mice, ELISA plate results, tissue culture contamination) which they can share with the instructor to ask questions or use in their final lab reports. Electronic lab notebooks are also improving in quality and increasing in use. Not without downsides, they do also offer many advantages, including providing the instructor with remote access to student data on a real-time basis.

When using iPads (or laptops) in the lab, students must have a prior safety briefing, for example, to ensure they don't bring laboratory contaminants home. When needed, protective sleeves, designed to protect iPads in the kitchen, can be provided for protection from powders and liquids. Additionally, we use iPads in the lab to discuss how to analyze and graph data. After students do their first ELISAs, they graph their results and upload them to the class Google Drive or the Learning Management System (Blackboard, Moodle, etc.) as pdfs. As the graphs are projected, the instructor can ask the class for feedback and write comments and suggested revisions directly on the graph or figure. This results in greatly improved figures.

One of the most important outcomes from using iPads in courses is that students become comfortable experimenting with different approaches to learning the material. This reinforces the point that acquiring information is an ongoing, constantly evolving process. The class winds up being a collaborative exercise between the students and the instructor throughout the term, as both experiment with new approaches, revising (or dropping) them as they go.

The cost of iPads is a critical consideration when in-class iPad use is being mandated. While a typical iPad costs less than most smartphones or laptops, their purchase price is nonetheless non-trivial for a college student, especially given the relatively short half-life of the device. When we first began providing iPads for students enrolled in the Immunology class, half of the students later purchased iPads for academic use, and the percent of students obtaining iPads continues to rise. This raises a difficult issue; students who might benefit from having an iPad for their academic studies, but cannot afford them, can be further disadvantaged. This is an ongoing issue, with no easy solutions, although providing low-cost or subsidized rental equipment for students with need offers one potential solution.

Overall, iPads can greatly enhance the teaching of immunology and facilitate active learning approaches. However, some faculty are not as comfortable with these devices as their students. Given the many ways to teach (and learn) immunology, iPads should be viewed as one of many exciting options in the toolbox to assist students on the challenging journey of learning about the immune system.

DISCUSSION

Teaching immunology to undergraduates offers unique rewards and challenges. In terms of rewards, the subject matter is engaging and easily connected to everyday life. Since the topic is usually offered as an elective, it tends to draw students with a keen interest and motivation to learn. Discussions of the immune response naturally lend themselves to review of basic areas of biological understanding and can help students to hone their facility with these areas of study. Likewise, connections of the discipline to medical, ethical and social issues are endless. Working with undergraduates offers an unparalleled opportunity to tap into the wonder that students at this level experience the first time they are faced with the beauty and complexity of the immune system. Their thinking is flexible, and because everything is new, nothing feels out of the ordinary. We have watched undergraduates effortlessly absorb concepts that we ourselves found difficult, simply because they lacked knowledge of earlier, engrained paradigms or preconceived notions of how things "should" work.

One of the main challenges we face as teachers is the diversity of scientific backgrounds that students bring to the course, which is highly dependent on prior coursework and experiential learning opportunities. Even when they have taken the foundational courses, concepts and terminology from associated fields are still quite new and therefore easily confused. It can be hard to know where to start with teaching immunology, and the mountain of new terminology does not help with this. Therefore, faculty must resist the temptation to try to cram too much into the course without attention to what the students need at this stage and are able to appreciate.

In this article, we have described a number of student-centered, active learning strategies that we have employed in our classrooms to enhance student motivation, comprehension and retention. Our hypothesis is that these strategies, which are time-consuming and take real effort to implement, enhance student comprehension and retention to a degree that makes the extra time and effort on the instructor's part demonstrably worthwhile. We are not aware of studies by teachers of immunology that compare student outcomes following courses that engage in active vs. passive learning. The "data" that we do have to share derives from student course evaluations and from many years of talking with alumni/ae regarding their perception of how their experiences in our courses prepared them for their future careers.

Those of us who have taught for many years have seen a change in the ways in which our students best learn, and have striven to adapt our own teaching styles to the needs of our students. In a recent course, students were asked: "Tell me how useful (or not) you found the active learning exercises and which ones, if any, you found particularly useful." Ninety percent of the students in this class found one or more of the exercises useful or very useful and a frequent comment in student responses was that the opportunity to take a moment in class to talk in a small group about difficult questions that were addressed by the learning exercise was helpful. As teachers, we have all seen how students who are too shy or intimidated to talk aloud within the class as a whole can come alive when small group exercises are offered. Notably, the few students who failed to find the exercises useful were either indifferent or left the answer blank, indicating that they did not feel that the exercises were a poor idea.

Two common themes arise in our collective teaching experiences; a need to prepare students before they enter the classroom and the desire to help students *do* rather than merely *view* immunology. These principles are at the core of our current understanding of best practices in undergraduate STEM teaching, and therefore hold true in any classroom setting.

We have by no means attempted to be comprehensive in this review, and we are certain that many other excellent examples of active learning applied to the immunology classroom exist. Two of the most common and successful active learning approaches, class discussions of the primary literature and laboratory experiences, are topics of other papers in this issue (10–12). A third active learning approach, Just-in-Time-Teaching (JiTT), is only briefly addressed here but covered in more depth in other papers in this issue (15).

These ideas are offered as one might present a smorgasbord; no one teacher can use all of these strategies in any one class, and the selection of activities must be carefully matched to the subtopic and to the student population. A lively group of sophomores may learn best if they are encouraged to move around the classroom, whereas a smaller group of graduate-school bound seniors might benefit more from group writing assignments. The experienced teacher knows the student population and their challenges, and will adjust accordingly.

Importantly, as we apply these ideas to the classroom, it is worth considering current student populations and present-day issues. Active learning approaches and mixed assessment methods have been shown to reduce achievement gaps, increase retention, and improve comprehension for all students, but especially in groups currently underrepresented in the sciences (4, 13, 37). However, one size does not fit all, and some student-centered or active learning approaches may not work for certain students or in specific settings. For example, anxiety is an increasing problem among high school and college-aged students. A study by Cooper and colleagues (38) found that some active learning approaches in a large classroom (e.g., cold or random call) elevated anxiety levels in students, as compared to conventional, lecture-based approaches. Clicker questions and group work have similarly been found to have the potential to either increase or decrease anxiety, depending on how they were administered. Cooper and colleagues outline several valuable strategies for reducing anxiety while employing specific active learning methods (38). The addition of active learning, like any new pedagogical approach, requires thoughtful implementation and regular assessment if we hope to enhance student learning and level the playing field. In fact, if we want to make these changes in our classrooms, building trust among and between students and their teachers may be crucial first steps (39).

In closing, this article presents implementation of a few pedagogical advances made in the last several decades, applied to the teaching of undergraduate immunology. However, we recognize that the field of STEM education is currently moving as quickly as the science it seeks to communicate, and we eagerly await new breakthroughs. As immunologists, we look forward to the opportunity to apply best practices from these rigorously evaluated methods to "infect" the next generation of undergraduates with the joy of learning about the immune system.

AUTHOR CONTRIBUTIONS

RP: conceived and organized the project. JO and SS: wrote the first drafts of the abstract, introduction, and discussion. All authors wrote sections of the manuscript and edited others, and focusing on the approaches used in their classrooms. SS: JiTT. FM and RP: video and audio supplements. FM and RP: clicker questions. SS: simulations, reenactments, and interactive in-class activities. JO, RP, and SS: in-class short presentations. FM, JO, and RP: concept maps. FM, JO, RP, and SS: writing projects. RP: iPads. The authors all contributed to manuscript revision, read and approved the submitted version. This paper was a deeply collaborative effort by all authors.

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Designing Cases for Case-Based Immunology Teaching in Large Medical School Classes

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Case-based, interactive sessions for small groups (in a large medical school class of 150 students) reinforces basic immunology concepts by including clinical scenarios that stimulate student learning and consolidate critical concepts. Careful design of cases (designing backwards from the key concepts) leads students through successively more complicated and linked group-work questions. This paper details why cases are effective learning tools, how to design an effective case, how to ask appropriate questions and how to help students apply basic immunology concepts to a case. Each group work session is facilitated and followed by a question and answer presentation by faculty, where student groups are directly asked to answer the questions and also challenged with "bonus questions" not presented with the original case. This allows students to "put together" immunology information into a "story" that they can tell and prevents student frustration by summarizing the results at the end of each case. Case design is carefully discussed including clinical relevancy and accuracy, how to write questions that do not give away the answers, how to emphasize mechanistic questions that allow students to "clinically explain as a physician" the immunological basis for the answers. Additionally, students better understand the role of immunity in both normal and disease states. A case-based approach promotes student learning by re-emphasizing basic concepts in the context of the case and promotes better students understanding of critical immunological concepts.

Keywords: immunology education, case-based learning, medical school education, team-based learning, key concepts, active learning, integrated curriculum

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INTRODUCTION

Previous studies have shown that problem-based learning can be effective in large medical school classrooms (1). A meta-analysis of active learning studies (2) in undergraduates showed an advantage for student learning and satisfaction for specific active learning activities over traditional lectures in the sciences. However, the literature on active learning may also have some publication bias (3), but the evidence in the literature still strongly indicates the value of interactive learning activities and the overall effectiveness of problem-, team- and case-based learning.

Medical schools are tending to increase active learning in the curriculum and also to integrate basic science information with clinical cases across disciplines (4). In addition, medical

educators have proposed using Entrustable Professional Activities (EPAs) for undergraduate medical education, similar to how these are used in Graduate medical education (5). Case-based learning is especially appropriate for pre-clinical training in undergraduate medical education. A randomized study looked at case-based learning and found it comparable to problem-based learning with better student satisfaction (6). Burgess et al. (7) examined team-based learning (TBL), that uses fewer faculty than the problem-based learning (and therefore may be easier to implement for many medical schools) and found that TBL fostered more competitiveness and desire to learn, but that PBL yielded increased clinical reasoning. The authors concluded that some hybrid of these two approaches might yield the best results. A subsequent study showed that students preferred the team based approach to problem based learning, but student preference is not always indicative of actual student learning (7).

Medical cases stimulate students to be more active in their learning and to not just memorize facts, but to attempt to learn critical concepts. Chonkar et al. (8) have hypothesized that students who participate in case-based learning gain deeper and more long lasting knowledge than students who seek to mostly memorize (but not apply) critical scientific facts. Case based learning has been shown to motivate students to learn more deeply in a number of studies (9). Turk et al. (10) showed a significant improvement in practical knowledge application (OSCE scores) for case based learning over the traditional approach. Given the widespread use of case studies, the evidence for increases in student motivation, the opportunities for deeper and more long-lasting learning and the increased ability to apply case based concepts to practical applications, this paper attempts to describe a method for designing better cases that are more applicable to medical student needs.

In order to better incorporate active, case-based learning into the curriculum, medical school educators need cases that ask carefully designed questions that challenge but do not frustrate students. Problem based learning (on which case based learning is based) helps stimulate student inquisitiveness, but one of the possible drawbacks is student frustration. Cases need be designed to emphasize critical learning objectives, to be medically relevant and to not easily give away the answer to promote differential diagnosis skills. Also, using the "backward" design approach for medical school cases (11) helps to insure that the learning objectives are covered in the case. The steps for designing a medical school case are outlined below, using an actual case and the questions for the case as examples to help illustrate medical school case-based design and implementation.

Specifically, for immunology education in medical school, using team-based learning has been shown to be an effective method (12). While our approach for case based learning uses some of the team based approaches (such as pre-class learning modules (combined lecture and self-guided learning, with learning objectives embedded in the learning materials), there was no readiness assurance testing. Instead, students were motivated to learn because they knew their group could be called on to explain their answers.

MEDICAL SCHOOL CLASSROOM SET-UP FOR CASE-BASED LEARNING

These cases are designed for students working in groups of 4–6 students in a large classroom (one class of 150 students, or two sessions of 75 students each). Groups size was 4–5 students from the literature for the effectiveness of small groups and because our medical school had preassigned groups of four to five students (13). About 3–5 faculty "advisors," who have been prepped on the case and have an answer key, circulate in the room (it can be a large lecture hall, but a smaller room with moveable desks works better) to ask questions and guide, but they do not directly answer question or explain (Student: What is the answer to this question? Faculty: What do you think the lab result from the case shows and why is it important?). The students have access to the case (with the questions) at least 3–5 days in advance of class and are required to answer a few very basic questions individually on the case before the class session (What is the case about? What is your differential diagnosis?). Students can use any available resources to answer the basic questions or the more detailed questions in class and are encouraged to use material from lecture, from pre-recorded lectures of from faculty directed studies and readings. Lecture material and reading material all have learning objectives to help guide students in their preparation for the in-person classroom activity. Student groups get an allotted time in class to answer the questions, and then the class reconvenes and faculty ask questions of the groups. The groups are called on randomly to answer the questions in the case and faculty can ask additional "bonus" questions, designed to test knowledge of concepts that are NOT on the case the students are given. One advantage of allowing students to use any resources, including the internet, is that students will quickly gravitate to more reliable resources, if they know they have to defend their answers. For an incorrect answer, a faculty facilitator can ask where the student obtained that information, in order to understand whether the misinformation came from a source or from the student not understanding the question or the material. If a group has an incorrect answer or cannot come up with an answer, the faculty facilitator can ask some leading questions or ask if another group can offer assistance or call on another group to help out. If students are still struggling with a particular question, further leading questions can be asked of the entire class. Usually, the simpler questions are asked first and the more difficult questions come at the end of a case. About three to five cases with questions can be covered in a 2 h block with a quiz at the end. The quiz is often based on some of the key learning objectives covered in the case-based session.

BACKWARDS DESIGN OF A MEDICAL SCHOOL CASE

For backwards design of a case, it is important to start with the learning objectives and core competencies that we want the students to have (14). This helps insure that the case covers the critical learning concepts we want the students to encounter. We also deliberately integrate a number of topics (for this case,

TABLE 1 | Immunology Concept Mapping Chart.

Core immunology concept	Learning objective	Question on case:
PAMP and DAMP activation of innate immunity	Describe the TLRs that recognize specific PAMPs and DAMPs.	What Toll-like receptors (TLRs) are likely to be activated by this infection?
TLR activation and signaling	Explain how TLR activation/signaling primes the innate immune response	What cytokines would you expect to be elevated in the blood in this patient after this infection?
Actions of mediators of acute inflammation	Describe the actions of mediators acute inflammation (IL-1/TNF-alpha	Why is the white count elevated? What cell type is most likely to be elevated? Why are the band cells increased? What is the molecular mechanism for the increase on neutrophils and band cells
Physiological and effects of acute inflammation.	Describe the physiological effects of elevated IL-1, TNF-alpha and IL-6.	What is the significance of the increasing fever and the presence of bacteria in the blood? What is the molecular mechanism for the fever increase and why does this concern you?
Pathological effects of acute inflammation.	Describe the pathological effects of elevated IL-1, TNF-alpha and IL-6.	Why is the blood pressure dropping in this patient? Why is does he have systemic edema? What are the molecular mechanisms for the drop in blood pressure?

immunology, microbiology, pathology, pharmacology, physical exam results, and lab medicine are integrated) in order to have students apply prior knowledge and make the case more realistic.

For this pre-clinical medical school case, the learning objectives were the following:

1. Describe the local and systemic effects of gram-negative bacterial sepsis including expected physical exam and lab results.

2. Explain the molecular mechanisms of how gram negative bacterial infection and septic shock causes elevated body temperature, chills, elevated CRP (C-reactive protein), elevated white cell count, neutrophilia, increased band cells, and hypotension.

3. Explain why high doses of the appropriate anti-bacterial agents can cause increased shock symptoms and possible death in septic shock.

In this example, the learning objectives help set up the case. The case has to be a gram negative septic shock case. The physical exam, lab results, CBC and other tests should reflect a patient in gram negative sepsis. Before starting the case, however, it is helpful to design some of the open-ended questions to ask. The questions start off simply from basic concepts and help to lead the students through the basic concepts without giving away too much and then get to the more difficult applications of these concepts (see **Table 1**).

Other helpful ways to design and write a case include modeling the case after a real case, following the SOAP note format (Subjective, Objective, Assessment, Plan (and leaving OUT the Plan from the case), and setting up the case in a specified manner:

1. Age, gender how, and where the patient presents.

2. Subjective: Chief complaint, relevant history (how long have the symptoms been present, any other relevant history, travel, operations, medical history).

3. Objective (where relevant): Vital signs, physical exam results, lab tests results, relevant drugs the patient is taking.

4. Assessment: Do NOT give a diagnosis, let the students do this, but ask the questions.

5. Plan: leave the plan out of the case, but ask the students questions about the plan or treatments.

6. Check the case for accuracy when done, consult with a clinical colleague with expertise. Are there any other explanations for the case that could lead the students to alternative explanations? Sometimes the case can be intentionally vague, and we can ask for further tests to help distinguish between possible diagnoses.

7. Avoid Zebra cases: Zebra cases are cases with rare genetic defects (many of the currently available immunology cases are zebra cases) and these cases often will not be seen by most students and represent a small specific area of immunology. Feedback from clinical site preceptors has indicated that students need additional basic science applications in more common cases. Medical boards also ask questions on these rare cases. Designing more common cases makes it more clinically relevant for the students and we make charts for the more rare genetic defects in immunology for use in board studying.

8. Keep the vignette (case) short and to the point.

9. Instead of creating an entirely new case, it sometimes is effective to change one or more test results to point the case toward a different diagnosis. The question can then be asked: If the test results are now Y instead of X, what is the explanation?

Sample case (student version):

A 62-years old male initially presents with fever (38.5°C), elevated C-reactive protein (CRP) levels and ESR (erythrocyte sedimentation rate), hypotension (BP 100/70), white count (12,500 and 15% bands), hyperglycemia (blood glucose, 140), and lower right flank pain. He has had a previous history of benign prostatic hyperplasia and a urinary bladder catheterization (but no history of diabetes). Two days after the last catheter insertion, he developed a fever and now on the third day he is mildly disoriented, and on examination has tenderness in the lower right quadrant. His urine culture yields over 102 gram negative rods. Twenty-four hours later, the patient's condition has deteriorated. His blood pressure has dropped to 85/65 (is requiring a crystalline blood infusion), his blood glucose is 150, he has systemic tissue swelling, his CRP has increased, and his temperature is now increased to 39°C. All three blood samples currently yield multiple colonies of gram negative bacteria on culture.

DESIGNING THE QUESTIONS FOR CASE

When designing the questions for a medical school case, it is important to let the students do the differential diagnosis. Another key to designing the questions is to start with the simpler questions, to help lead the group toward the more complex explanations. Also, asking questions about the molecular mechanisms is particularly important for understanding the immunological basis for the response. For the case above, here are some sample questions and the rationale for the questions. Students get the questions in italics along with the case. Bonus questions are not included in the preview that the students get, but are asked of the group during the class by faculty facilitators:

1. What Toll-like receptors (TLRs) are likely to be activated by this infection? What cytokines would you expect to be elevated in the blood in this patient after this infection?

These questions start with the initial mechanism of gram negative bacterial infections, how they trigger TLR2 and TLR4 activation. The student should recognize that TLR4 is specific for LPS and gram negative bacteria. Also, the goal is to have students groups start with the bacterial infection, go to the TLRs, then the cytokines and then the local and systemic effects. So the first question is simple and leading question designed to set up the subsequent questions and help the students groups think in a linear progression.

2. Initially, this patient has local tenderness and flank pain. Explain what cells you expect to be increased locally (in the bladder and kidney) in the first 24 h? What is the molecular mechanism for these cells migrating to the initial site of infection? This question focuses the student groups on the molecular mechanisms for the induction of neutrophil and leukocyte rolling (Selectins) and tight binding (chemokine inside-out signaling and high affinity integrin binding) and migration. The student should recognize that neutrophils will be the first immune cells to migrate to an area of inflammation, followed by macrophages and then lymphocytes and should be able to elucidate the stepwise mechanism of leukocyte migration described above.

Bonus questions (Not on the student copy): If a patient has a defect in neutrophil migration, would that increase susceptibility to infectious agents and what specific agents?

This bonus question addresses the role of neutrophils in protecting from bacterial infections. Lack of neutrophils at the site of an infections would decrease the response to bacterial infections and particularly to infections with Staphylococcus or Streptococcus on the skin.

3. What is the significance of the increasing fever and the presence of bacteria in the blood? What is the molecular mechanism for the fever increase and why does this concern you?

This question focuses the students groups on explaining the physical exam results and the role of inflammatory cytokines (pyrogens) in fever. Also, it helps students trace the course of sepsis and to understand the clinical effects and danger to the patient. The student should be able to start with TLRs, go to increased cytokines (IL-1 and TNF-alpha, increased prostaglandins in the hypothalamus and then to increased temperature set point. An increasing fever indicates the infection is getting worse, not better (point out that the temperature should be taken at a similar time since body temperature can vary with circadian rhythms).

4. Why is the white count elevated? What cell type is most likely to be elevated? Why are the band cells increased? What is the molecular mechanism for the increase on neutrophils and band cells? What do increases C-reactive protein and ESR (Erythrocyte Sedimentation Rate) mean and why are they increased?

These questions address the specific laboratory and physical exam results that indicate sepsis. Student groups should be focused on the molecular mechanisms for the CBC, leukocytosis, neutrophilia and the increase in band cells results in the case. Students should be able to describe the increase in inflammatory cytokines (IL-1, TNF-alpha, IL-6) the increase is CRP (from the liver), the increase in G-CSF and GM-CSF that will increase band cells (immature neutrophil) production and release from the bone marrow.

Bonus question: In a patient undergoing chemotherapy for cancer who has neutropenia, what drug could be given to increase the absolute neutrophil count?

This bonus question is designed to help the student groups think about the role of G-CSF and GM-CSF in responding to infections. Usually G-CSF (peg-filgrastim, Neupogen©, or a similar drug) is given to increase neutrophils. It enhances both neutrophil production and release. GM-CSF is also effective but is used less often.

5. *Why is the blood pressure dropping in this patient? Why is does he have systemic edema? What are the molecular mechanisms for the drop in blood pressure?* These questions help to focus the student on the clinical situation of septic shock and to understand the underlying immunological mechanisms for the clinical effects. Blood pressure drops because fluid (exudate) leaks out permeable blood vessels in shock (high levels of IL-1 and TNF-alpha). Additionally, cardiac output is diminished. Systemic edema is due to the systemic IL-1 and TNF-alpha, the increased permeability throughout the circulatory system and the formation of exudate in the extracellular space.

Bonus question: What is a possible danger of giving a high dose of antimicrobial therapy in this case?

Why do a bonus question? The bonus question is designed to keep the after group-work questioning "fresh," since the students know that may get MORE questions than just what are specified on the question sheet and to help students think "on the spot" more.

This bonus question is designed to help the student groups understand the molecular mechanism of LPS-induced septic shock and to understand the possible role of antimicrobials in releasing more LPS (due to bacterial killing) and making shock worse. It aligns with the learning objectives from the pre-class material.

Sometimes, these questions may call for a differential diagnosis and while these are first or second year medical students, it is meant to help them practice this skill in a low stakes environment. Also, the review helps to model the thinking used for a differential diagnosis.

SUMMARY

Using cases in a group, active learning context to highlight the basic science concepts in immunology is a useful tool for engaging medical students and for consolidating their knowledge in immunology. Careful design of cases helps prepare students for clinical preceptorships in their third and fourth years. Additionally, these cases can help integrate a number of subject areas including immunology, microbiology, pathology, lab medicine and internal medicine. The sample case presented above is an example of a possible way to design cases. The "backwards" engineering of the case from learning objectives and the clinical relevance of the case helps to make this case-based learning more effective for the students.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Teaching Immunology as a Liberal Art

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A complex, rapidly evolving biomedical field that is of critical relevance to human health and well-being, immunology provides important and substantive opportunities to practice and teach the central tenets of a liberal arts curriculum.

Keywords: immunology education, undergraduate, liberal arts, storytelling, metaphor

GALLERY DAY

It's one of those "end of semester" days in December—I am looking forward to wrapping up the term, the familiar mix of exhaustion and anticipation in my bones. The junior and senior biology majors in my immunology survey course at an undergraduate liberal arts college in the Midwest are setting up their immunology-themed art presentations. A pile of "plushies"—giant stuffed fabric white blood cells decorated with their known surface markers invites tactile exploration, and an impromptu game of toss. An immune cell synapse wired with LEDs lights up in series as "activation" switches are flicked on. Students flock to the edible displays. A towering croquembouche "lymph node" of choux pastries invites them to pull out individual ones to taste—flavored with different fillings, the pastries represent the different cells in a lymph node. As the puffs get eaten, the spun sugar matrix of the tower loses shape, much as a lymph node matrix would without resident cells. The hematopoiesis cookie table is a hit. The student who set it up explains how a basic set of ingredients is flexibly transformed into different kinds of cookies—at which points commitments to certain final products occur and when and how steps become irreversible; class-mates sample some of the finished products and take turns building cookies of different "lineages" with nuts, fruit, chocolate chips, bits of candy sparking a spontaneous discussion about food allergies, routes of exposure and safe handling practices. A student clears their throat and the hum of chatter subsides. A self-described "non-artist," they have chosen instead to deliver a "testimony to Congress" to advocate for robust funding for immunological research inspired by the advocacy of members of the American Association of Immunologists (1). As stand-in lawmakers, we listen attentively to the evidence-based arguments for the importance of basic immunology research for a healthy society. There are tough but respectful questions on animal research ethics, a plausible timeline for a universal flu vaccine and the structural inequities of access to cutting edge cancer therapies such as CAR-T cells. After the Q&A, students read each other's artist's statements, take turns trying to sit on the fold-out monocyte chair without falling, and play with the stick and string co-stimulation maze which can only be solved with 3 manipulations in the correct sequence!

THE PERFECT LIBERAL ART

Over 20 years ago, I was an undergraduate in an immunology class, irresistibly drawn to the discipline despite the confounding maze of nomenclatures, the alphabet soup of transgenic TCR names and the flood of cell types and molecules that went over my head. Through graduate and post-doctoral work, my love for the field endured and I realized that I wanted an undergraduate liberal arts curriculum to be the canvas for my immunology teaching and research. I don't think that, at the time, I could have foreseen a class period quite like the one I just described: students making the material their own in inventive and surprising ways, going confidently into the heart

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of foundational and cutting-edge concepts and using their intellectual and practical engagement with the material to connect their study of immunology with their lives. Teaching and learning immunology as a liberal art together with my students has been transformative for all of us.

Macalester College is an urban small undergraduate liberal arts college with ∼2,000 students−30% students of color, 14% international, and 16% first-generation. Biology is one of the top 5 majors. I teach an immunology survey course with laboratory for undergraduates who have taken cell biology and genetics. Though the human immune system is the primary focus of the course, we study amoeba, social insects, bacteria, plants, and jawless fish to better understand the evolution of protective responses. Students write multiple-draft review papers with graphical abstracts, volunteer with the Immune Deficiency Foundation, present art/performance works and write weekly reflective essays connecting their immunology learning to other parts of their academic or personal lives. My immunological methods course is embedded in my research program investigating the connections between environmental toxins, allergic responses, and chronic pain; students participate in scientific conversations and critique scaffolded by preparatory writing assignments, map meta-arguments from sub-fields of published literature, cooperatively design, and execute experiments, and write a collaborative scientific paper. I use my upper-level seminar courses—Neuroimmunology and Cancer Immunology to teach more advanced students about public communication of science. In our college's First Year Course program I offer semester-long immunology-themed courses: *AIDS/Influenza/Malaria - ancient pathogens in a brave new world* explores the persistence and re-emergence of infections and inflammatory diseases in vulnerable populations around the world and *Bodies on Fire* centers on the global pandemic of inflammatory diseases. These courses do not have pre-requisites and are structured around connecting patient/physician memoirs, popular science books, and science journalism with the scientists and scientific discoveries they describe and typically ask students to explore these connections through writing, movement, and art.

Historian William Cronon describes the essence of liberal education as "gaining the power and the wisdom, the generosity, and the freedom to connect"—through the acts of listening, reading, writing, talking, solving puzzles, seeking complex truths, seeing other perspectives, working in a community and being willing to both lead and follow in honest and imaginative ways (2). Structurally, a liberal arts education connects the natural and physical sciences, humanities, social sciences, quantitative thinking, and artistic inquiry. Even as they engage deeply with methods and analyses in particular areas of study, students learn to appreciate different ways of making meaning of our world with tools from different disciplines. They learn to recognize and interrogate the societal structures and deep assumptions that drive the ways in which such bodies of knowledge are constructed within and across academic disciplines.

Immunology is a perfect fit for a liberal arts education. While traditional practices such as variolation and uses of immunomodulatory foods and botanical medicines have existed for thousands of years in societies around the globe, the constructs of cellular and circulating immune mechanisms have been articulated in the context of academic biomedicine only as recently as the late 1800s. And within these 200 years, paradigms have been swiftly proposed, critiqued, modified and transformed into an ever more complex and nuanced understanding of immunity (3). Concepts of preservation of self over "non-self" have morphed into understandings of danger, disruption, repair, and memory embedded deep within cell lineages, epigenetic imprints and tissue architectures. Mechanisms once described more bluntly as "killing pathogens" are now understood as highly regulated, selective, tunable responses to commensal and non-commensal microbes that constitute the multi-species ecosystems of multicellular hosts. While the immune system gives us critical protection for survival, virtually every global health concern from emerging infections, allergies and asthma, autoimmunity, chronic pain, and other psychiatric, cardiovascular, and metabolic imbalances are all fueled by these same mechanisms of inflammation, shifted by context to become harmful and pathological. Author Chimamanda Ngozi Adichie, in her TED Talk "*The Danger of a Single Story*," warns that assuming a single story about a people leads to dangerous misconceptions, and learning to listen for the many different stories is essential for cross-cultural understanding (4). Immune responses, with their double-edged nature, provide a natural set of case studies in the importance of "many stories." Immune responses demand careful contextual analyses, and to study them closely is to learn to grapple with complexity and uncertainty—an essential skill in today's rapidly changing, connected yet divergent world.

TOOLKITS FOR LIFE, WORK, AND STORYTELLING

Another advantage of studying immunology is its immediate personal and social relevance. Students only have to look at their own bodies, experiences of well-being and illnesses, and their environments for applications of what they learn. For many students, one immunology-related class might be their only sustained experience with the discipline, but the lessons they draw from it have the potential to remain relevant and useful in their lives. As a powerful example of this, I have observed my Neuroimmunology students particularly resonate with learning about the role inflammation plays in mental health. Students on college campuses are experiencing anxiety and depression at unprecedented levels, and managing neurological diagnoses while removed from their families and support systems (5). Understanding the roles of pathological inflammation intertwined with these mental health conditions, exploring the connections of stress, diet, and rest to these neuro-inflammatory pathways are empowering for students; appreciating the "bodily" basis of psychological challenges appears to make them seem more tractable. While these lessons do not take the place of the counseling and/or psychiatric support they or their peers need and receive, I have observed that students do find this scientific parsing of the mind-body connection to be of practical use.

Many immunology students are drawn to careers in biomedical research and its applications in the practices of medicine and/or public health. Immunological research—discovery, translational, academic, clinical, industrial—and its applications in drug development, medical technologies, and public health interventions are at once scientific and social endeavors. Countering anti-vaccine movements, crafting community, and government public health responses to disease outbreaks, regulating environmental toxicants in food, water, and air all contain important immunological arguments at their core. Being able to understand and speak the language of immunology and tell its stories to specialist as well as general audiences so they can be truly heard is an important skill for students to practice. Iteratively learning to read the often dense and technical immunological literature and synthesizing and communicating these findings in their own written and spoken words is both preparation for future work in biomedical fields and a core tenet of a liberal arts education—the importance of listening, reading, speaking, arguing, and writing. These skills are not unique to the study of immunology, but immunology offers undergraduates and their professors in a liberal arts context a rich and pragmatic field within the biomedical sciences in which to practice them. Students in my courses and research laboratory write literature reviews, give talks and present posters on their research at conferences, and collaborate with me on writing papers and grant proposals for scientific audiences. However, they also write white papers and reflective essays connecting their learning in immunology to other disciplines, prepare educational materials for community organizations, teach secondary school students and mentor younger peers and, in doing so, practice translating the technical jargon of scientific communication into information that their audiences need and can use.

A spacious liberal arts education makes room for multi-disciplinary training, provides opportunities for immersive learning and community engagement and asks students to connect their learning to the world in *different* ways, giving them opportunities to make this complicated and compelling field their own. The perceived "difficulty" of immunology can be deconstructed in this more permissive, integrative environment to allow creative strategies for making meaning and finding purposeful engagement with the subject.

MAPS AND METAPHORS FOR A WORLD IN CRISIS

Immune systems are synergistic wholes of interconnected parts continuously stirred up by new discoveries that complicate existing knowledge and demand new ideas and interpretations; this has been so since Paul Ehrlich sketched his intricate visions of cells shedding neutralizing anti-toxins and butted heads with Ilya Metchnikoff's cheeky but utterly prescient observation that immunity might just look like hungry amoeba out to forage (6). In the last two decades, our view of the immune system has been transformed by newly discovered innate cell subsets, the regulation of immunity by microbial and viral symbionts, the control of immune responses by metabolic switches, and the realization that all cells, not just the ones that we recognize as immune cells, participate in and regulate immune responses of multicellular organisms. This framework of synergistic interactions and multi-factorial outcomes can provide our students with maps and metaphors useful beyond immunology, for broader understandings of complex social and planetary processes.

The precarious balance of protective vs. harmful immune responses is a mirror of the collateral costs of inequities, state-sanctioned violence, and xenophobia in our societies. Chronic inflammation and accompanying adverse health outcomes are materially correlated with lower socio-economic status, lack of access to nutritious foods, stressful living conditions and unstable access to healthcare (7). That any immune response takes a toll on the living tissue it is trying to protect from real or imagined threats parallels the effect that xenophobic, reactive intolerance, and unregulated violence can have on a community or society at large. Just as our own cells and those of our commensal symbionts maintain a collaborative understanding that we disrupt at our peril, our local and global communities are sensitive to the behavior of individuals and cooperation between the diverse populations who live in them. Tolerance, balance, homeostasis, repair are technical terms with specific immunological meanings that are just as relevant to our social fabric as they are to our understanding of healthy and disease states of our bodies. And likewise, jingoistic militarized language about the immune system vanquishing pathogens can echo intolerant social rhetoric. The nuance and care required to understand and modulate immune responses and their outcomes serve as object lessons in how we speak and act as individual and collectives in social and political arenas.

An immunological framework can also be applied to the relationship of humans with our planet as a whole. Human-induced climate change has driven our planet and its inhabitants to a perilous state of imbalance, with rapid rise in temperature and sea levels, catastrophic weather events, heat stress, food shortages, displacement of peoples, biodiversity loss, emerging pathogens (such as SARS-Cov2), and exacerbation of poverty and conflict, all of which create negative health outcomes for those who are most vulnerable and have the least access to resources. The United Nations Intergovernmental Panel on Climate Change (8) advocates for immediate, massive, and collective action to mitigate this crisis if we are to survive. Our students are joining their climate activist peers—Greta Thunberg, Isra Hirsi, Xiye Bastida, and others in climate strikes and actions to emphasize the urgency of the situation. The literal health effects of climate change are, and will be marked by inflammatory processes in our individual bodies, and sharp increases in global disease burdens; it is as if the entire planet is in a state of chronic inflammatory distress. Everything is connected and what we do individually, and collectively, to our bodies and to our world comes back to us. Teaching about our immune systems in integrative, socially relevant ways can help our students make meaningful connections between the content of their learning and the larger global context in which they live.

BEYOND INFORMATION

In her book *Teaching to Transgress* (9), feminist author and educator bell hooks says:

> *To educate as the practice of freedom is a way of teaching that anyone can learn. That learning process comes easiest to those of us who teach who also believe that there is an aspect of our vocation … is not merely to share information but to share in the intellectual and spiritual growth of our students.*

In information-dense, rapidly evolving fields of study, it is natural to feel overwhelmed by the responsibility to share information as accurately and comprehensively as possible before our limited time with any one group of students comes to a close. I am grateful that immunology—the beautiful, maddening, messy field that it is—keeps me humble and honest about the work I really want to do with my students and the way in which I want to do it. It resolutely refuses to be told as a "single story" and any arcane details memorized for exams are known to have modest shelf lives in any case. So with each passing year, I am challenged to re-imagine how I can best help my students be as prepared as possible to hear and understand all of the immunological stories that have not been written yet—to be able to know the workings of their future bodies and minds a little better, to understand and appreciate why a pandemic coronavirus can ravage one body it infects and leave another unscathed, to be able to use these stories to build healthy lives and communities, and make new discoveries.

In her more recent book, *Teaching Community: A Pedagogy of Hope* (10), bell hooks says: "It is imperative that we (teachers) maintain hope even when the harshness of reality suggests otherwise." I take these words to heart. Much of western biomedical science has been built around concepts of illness rather than wellness and I wonder whether it is simply too overwhelming to keep coming back to narratives and mechanisms of morbidity, dysfunction, and imbalance. Here again, the spaciousness of a liberal arts framework allows both instructors and students to be more open to leavening the difficult topics with moments of beauty and fun. Psychologist Alison Gopnik has demonstrated that children who "pretend play," in elaborate, unreal scenarios with the aid of language, props and gestures, are able to respond correctly to counterfactual questions about a novel real-world causal relationship (11). While the evolutionary imperative for play may well be to develop robust cognitive functions, children play because it is a lot of fun. The paradox of play is that in order to be able to reach a variety of practical benefits in the long run, one must be somewhat less concerned with immediate accomplishments of goals in the short run. Eating a cardamom and orange cream-filled choux bun pulled out of a patisserie "lymph node" might not immediately seem central to learning about immune systems but it is delicious and it distills the joy of learning and sharing in a way that sticks in our brains and hearts—both my students' and mine. A liberal arts education with its emphasis on connective and integrative inquiry aims to be transformative, to crack the world open a little bit wider for every student with every course of study, every class, every discipline. But it is not only the student who is transformed, it is also the teacher. Teaching immunology as a liberal art has made me a more curious, capable and happier immunologist than I had known I could be.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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Using Clinical Cases to Restore Basic Science Immunology Knowledge in Physicians and Senior Medical Students

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The majority of medical students and many physicians find basic science immunology confusing and the teaching of immunology to be uninteresting. Physicians undergoing training in a range of disciplines treat patients with immunological disease, including allergy/immunology and rheumatology. It is essential for senior medical students and physicians to understand the pathology of immune diseases and the pharmacology of immune interventions. In order to optimize this learning, underlying concepts of basic immunology need to be revised, or sometimes learned for the first time. Teachers may need to overcome baseline attitudinal negativity. Medical students and postgraduates are more able to relate to basic immunology if approached through a clinical route. Case presentations and case-based discussions are a familiar format for medical students and physicians, though typically utilized to enhance understanding of clinical presentation, investigation, and treatment. Hence, they may be more receptive to "difficult" immunology concepts when presented in a familiar teaching framework. Although there is data supporting case-based learning for basic immunology in medical students, there is little data in physicians. Extrapolating from the medical student literature, I devised a program of clinical cases for physicians whereby understanding the immunopathological basis of the condition and/or its immunological treatment was employed as a platform to appreciate the basic science immunology in more depth. A variety of cases were selected to illustrate different immunological topics. The sessions were small group and highly interactive in nature. As this programme has only recently been introduced, formal evaluation has yet to be concluded.

Keywords: postgraduate, education, rheumatology, immunodeficiency, interactive, case-based learning

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INTRODUCTION

Immunology is considered difficult to understand, inducing trepidation in many medical students and physicians. It is essential to translate the subject in a comprehensible manner and disseminate knowledge in a practical fashion. The majority of medical students find basic immunology confusing (1, 2). Medical postgraduates in training are variously known in different countries as residents, fellows, junior doctors, and specialty registrars. In this article, I will use the terms *medical postgraduates* and *physicians* interchangeably. They are even more removed than medical

students from their basic science immunology learning, and many also find immunology perplexing. The relevance of immunology to clinical practice cannot be underestimated. Physicians undergoing training in a wide range of disciplines treat patients with immunological disease, including allergy/immunology and rheumatology. Furthermore, there are curriculum requirements for basic science immunology for certain specialties (3, 4).

In clinical medicine, there is improvement in understanding, though by no means complete, regarding immunopathogenesis of many diseases. Consequently, an increasing number of immune therapies have been licensed, are used off-label, or are in clinical trials. Therefore, it is essential for senior medical students and physicians to understand the pathology of immune diseases and the pharmacology of immune interventions. In order to optimize this learning, underlying concepts of basic immunology need to be revised, or in some cases learned for the first time.

TABLE 1 | Barriers to learning Immunology in senior medical students and postgraduates.

Pre-existing conceptions or misconceptions of Immunology as a "difficult" discipline
Variability of knowledge retained since undergraduate/early medical school teaching
Advances in knowledge since undergraduate/early medical school teaching
Tendency to "switch off" to basic science topics, as compared to "clinical" topics
Becoming overwhelmed by the complexity of pathways, and the number of new pathways
Ever increasing lists and lists of CD numbers, cell subsets, cytokines; curriculum-megaly
Inappropriate selection of Teachers and Lecturers
More removed than medical students from their basic science Immunology learning*

Row marked applies only to medical postgraduates.*

CHALLENGES

There is little data available in the literature regarding teaching of basic science immunology to medical postgraduates, in contrast to several research studies regarding medical students (1, 2, 5–10). In some cases, therefore, we may need to extrapolate to some degree from such studies of senior medical students, while recognizing the limitations of this approach, and considering important differences. We may also extrapolate from studies of other basic science topics, rather than specifically of immunology.

There are a number of challenges faced by both teachers and medical students and postgraduates in (re)learning basic science immunology. These are summarized in **Table 1**. There may be an underlying attitude toward immunology during medical school days; indeed, Dr. Amolak Bansal reported that 75% of medical students found immunology hard to understand, and only 1/3 found undergraduate immunology teaching to be interesting (1). Anecdotally, physician attitudes toward basic science immunology remain largely unchanged compared with their undergraduate days. The teacher may therefore have to already surmount potential baseline attitudinal negativity. Amongst clinical medical students, 29% identified pathology as the subject with the least practical application, compared with physiology (66%) (11). Students became more negative in their views regarding basic science courses with their seniority (12).

It is well-recognized that senior medical students forget a considerable amount of the basic science learned during the first two years of medical school (13–16). For example, in an older study of a traditional curriculum, retention of anatomy knowledge was comparable to that of nonsense syllables (14). However, perhaps surprisingly, physicians do not forget as much basic science as might be expected. In a long-term study, performance decreased from approximately 40%−45% correct answers for medical students to 30% correct answers for doctors after 24 years of practice (17). Although more removed than medical students from basic science immunology learning, medical postgraduates training in relevant specialities will be still be closer to medical school learning than consultant or attending physicians. Concepts of signal transduction, genetics, and molecular biology, which all overlap with immunology teaching, will not be so distant. For medical students, immunology is just one of many basic science subjects, and many senior students may consider it to be of limited relevance to their chosen future specialty. In contrast, medical postgraduates should prove more motivated and receptive, given the direct relevance of immunology to their chosen specialty.

Selection of appropriate teachers and lecturers is a critical challenge. Clinician lecturers may have insufficient up-to-date basic science knowledge, while basic science lecturers may find the clinical correlation difficult (2). Researchers may focus in too much depth on a specific pathway, or on their own research. In my own experience between teaching biomedical technologists, senior medical students, and physicians, the latter group struggles with the basic science aspects, while the technologists often find that the clinical jargon and abbreviations/acronyms are taken for granted. Overall, a balance of teachers is important, sometimes combining teachers of different academic/clinical backgrounds, which we have done for small group teaching.

IMPLEMENTATION

Rationale

Medical students and postgraduates are more able to relate to basic immunology if approached through a clinical route (1, 5, 6). Case presentations and case-based discussions are a familiar format for senior medical students and physicians, though typically they are utilized to enhance understanding of clinical presentation, investigation, and treatment. Hence, they may be more receptive to "difficult" immunology concepts when presented in a familiar teaching framework (6). Recall of basic science knowledge in clinical practice is enhanced by integration of basic science concepts with clinical content during medical school teaching (18–21). This approach has been used to good effect with senior medical students to better integrate basic science and clinical medicine (13, 18, 22, 23). In particular,

Spencer et al. (13) recommended re-exposure to basic sciences in the final year of medical school to augment understanding of clinical medicine. Kulasegaram goes beyond the concept of curricular integration, with the notion of cognitive integration—the "integrated understanding of basic and clinical sciences within the mind of the individual learner" (24, 25).

Over 20 years ago in Australia, Dr. Amolak Bansal recommended the use of problem-specific learning and the emphasis on clinical relevance in immunology teaching for medical students (1). A Chinese study has shown the benefit of a small group patient-oriented problem-solving (POPS) system in comparison to traditional lectures in immunology (26). Eighty-eight of students preferred the POPS, which was reflected in significantly higher test scores in the POPS group compared with the lecture group. However, the authors concluded the limitation on a practical basis would be having sufficient teaching staff to implement the POPS system widely. While this could be a limiting factor for senior medical students, it would not be a constraint for postgraduates given the much smaller numbers of physicians training in immunological specialties. There is only limited data for case-based instruction in immunology for physicians. For example, there is evidence for physicians reverting to use of knowledge in basic biomedical science, i.e., working back from basics when encountering complex/difficult clinical cases (10). Simulation with a case of inborn error of immunity (IEI) has been used for 2nd year medical students, with a summative immunodeficiency objective structured clinical examination question to assess the students' recognition of an IEI and their clinical reasoning (27). Clinical correlation exercises have been used for medical students in an immunology/microbiology study to prioritize from a list of diagnostic tests, justify selection of these and any additional tests, and consider the differential diagnosis. Cases included HTLV-1-leukemia, myeloma, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE) (9). Stuart reported favorable impact in both student satisfaction and examination scores of oral case presentations compared with didactic lectures alone for undergraduate medical students (8). Sannathimmappa (7) reported positive influence in final year medical students for a case-based approach in immunology and microbiology.

Implementation in Practice

Immunology teaching is relevant to a wide range of physicians, including those training in:

- Allergy/Immunology
- Clinical Microbiology
- Hematology-Oncology
- Immunopathology (Clinical Laboratory Immunology)
- Infectious Diseases
- Intensive Care Medicine (Critical Care Medicine)
- Nephrology (Renal Medicine)
- Neurology
- Pulmonology (Respiratory Medicine)
- Rheumatology
- Transplantation (organ-based, stem-cell)

Novack has recently described in detail the development of the case-based teaching of medical students (23). Extrapolating from the literature in medical students, I have introduced the case-based format into our immunology teaching programme for medical postgraduates. In order to overcome the physicians' pre-existing apprehension, I devised a programme of clinical cases where understanding the immunopathological basis of the condition and/or its immunological treatment could be used as a platform for understanding the basic science immunology in more depth. A variety of cases were selected to illustrate a range of different immunological topics. The balance of the cases can be altered depending on the medical specialty of the postgraduates. For example, a case repertoire with a focus more on autoimmunity would be more useful for rheumatology and nephrology, compared with a focus more on host defense for infectious diseases, clinical microbiology, and clinical immunology trainees. Cases can therefore include allergy, autoimmunity, immunodeficiency, and transplantation. By focusing on clinical cases matching the interest of the physician, we gain their attention; and then try to maintain it during the explanation and discussion of the underpinning basic science. The setting is small group teaching, and the cases are presented initially by the lecturer using PowerPoint® slides. The cases are interspersed with multiple choice and open questions for the physicians, deliberately rotating between the audience. The questions mainly focus on the scientific rather than clinical aspects of the cases. The questions provide the focus of the discussion and identify areas of pre-existing knowledge and learning needs. The setting is very interactive, and the session is planned and timed so that it relies on the contributions of the physicians. It is important to be as positive and encouraging as possible, and to avoid overwhelming the audience with a soup of CD numbers, and cytokines. During the course, the physicians are encouraged to bring their own cases—this very much augments their interest and enhances the learning opportunity. I have detailed some of the cases below.

Case 1: Allergy/Immunology/Rheumatology—Chronic mucocutaneous candidiasis

Although only a minority of immune disease has been demonstrated to have a monogenic basis, these genetic defects, in particular, can enable detailed explanation of the normal immune processes. A patient with chronic mucocutaneous candidiasis due to homozygous AIRE mutation, with multi-organ involvement, and multiple autoantibodies initially presented to the Pediatric Rheumatology service. This case was used to explore and contrast normal T-cell development and the acquisition of thymic (central) tolerance. The number of recognized IEIs is increasing at a dramatic rate. In 2017, the International Union of Immunological Societies noted 320 IEIs with single gene defects, whereas the 2019 version has 430 IEIs (28, 29). While this presents a challenge to clinicians to keep up with the literature, it also presents an excellent opportunity for case-based teaching of immunological mechanisms. Discussion of immunodysregulatory disorders such as IPEX (immune dysregulation, polyendocrinopathy, enteropathy, and X-linked) enhanced the explanation of peripheral tolerance and FoxP3+ T-regulatory cells. Up until a few years ago,

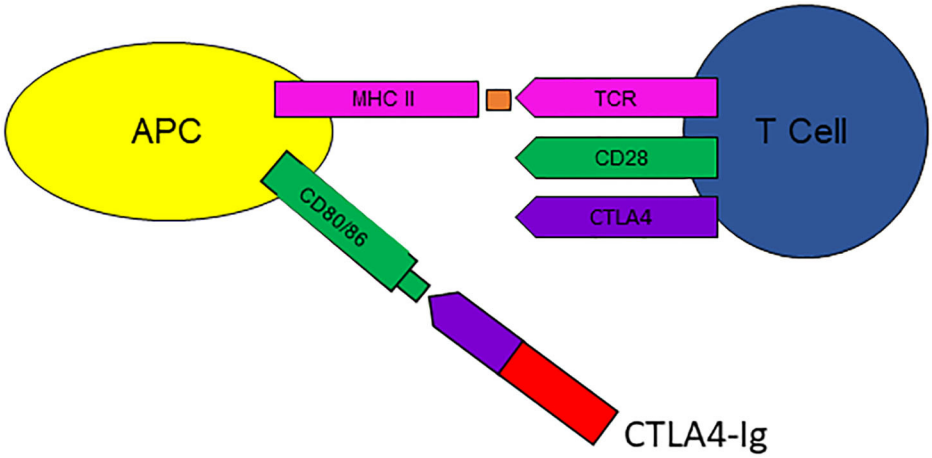

FIGURE 1 | CTLA4-Ig (abatacept) binds to CD80/86 on antigen presenting cells (APC), interfering with activation of T-cells via CD28, thus preventing signal 2. Courtesy Zunairah Karim. TCR, T-cell receptor; MHC ii, major histocompatibility complex class II.

the finding of autoimmunity and immunodeficiency in the same patient was considered paradoxical (30), and such cases represent an opportunity to illustrate the concept of immunodysregulation (31).

Case 2: Allergy/Immunology—Common variable immunodeficiency

Common variable immunodeficiency (CVID) is considered primarily an antibody deficiency disorder. However, there is a subgroup who also develop autoimmune manifestations such as cytopenia, inflammatory bowel disease, and interstitial lung disease. A number of underlying mutations have been demonstrated including in LRBA (lipopolysaccharide-responsive and beige-like anchor protein) and CTLA4 (cytotoxic T-lymphocyte antigen-4), a potent T-cell inhibitory receptor. LRBA colocalizes with CTLA4 in endosomal vesicles and LRBA deficiency increases CTLA4 turnover, resulting in reduced CTLA4 protein in FoxP3+ T-regulatory and activated conventional T-cells (32). The elucidation of the interaction of LRBA and CTLA4, and the mechanism for CTLA4 trafficking and control of immune responses, not only provided an explanation of the underlying pathogenesis, but lead to the off-label clinical use of CTLA4-immunoglobulin (CTLA4-Ig, abatacept) in CVID lung disease. This is an excellent example of where the basic immunology explains the clinical efficacy of the therapy.

Case 3: Rheumatology—CTLA4-Ig and rheumatoid arthritis

CTLA4-Ig is a fusion protein composed of the extracellular domain of CTLA4 with the Fc region of IgG1. It is primarily licensed for the treatment of RA, a common illness with a prevalence of 1%, and is currently in clinical trials in a number of other autoimmune diseases (AID). Presenting a case of its use in RA was an enabler for discussing the concepts of co-stimulation and signal 2, B-cell-T-cell, and antigen-presenting cell-T-cell interactions (**Figure 1**). The range of different co-stimulatory molecules was considered, and the importance of the CTLA-4:CD80/86 interaction to immune homeostasis—applying control of the T-cell immune response, and counterbalance to the activating interaction of CD28:CD80/86. Thus, exploring the mechanisms and use of immunological interventions can ameliorate basic science understanding.

Case 4: Nephrology/Neurology/Rheumatology—Systemic vasculitis treated with B-cell depletion therapy

B-cell depletion therapies (BCDT) are utilized in a range of AID, including multiple sclerosis, lupus nephritis, RA, and systemic vasculitis. The physicians were presented with a case of systemic vasculitis treated with multiple medications, including BCDT, over the course of the disease. The patient developed antibody deficiency, and the physicians were asked to work through the case. Thus, secondary hypogammaglobulinemia developing in patients treated with BCDT provided an opportunity to illustrate the normal process of B-cell development, and of antibody production. The questions posed to the audience included the molecular targets of BCDT, and establishing the mechanism of the antibody deficiency. The most commonly utilized BCDT, rituximab, targets CD20, which is restricted to B-cells, rather than plasma cells. Early reports in rituximab-treated patients showed that immunoglobulin levels were maintained, and hypogammaglobulinemia was considered unlikely because the long-lived plasma cells do not express CD20. However, more recent studies demonstrate that repeated BCDT cycles may lead to sustained B-memory cell depletion, with subsequent failure to replenish plasma cells.

In some cases, the knowledge gained in understanding immunopathogenesis was discovered more serendipitously than might be realized. This is important to emphasize, as there is a common misconception of the relative contribution that personalized medicine has made to date. In the 1990s, RA was largely considered a T-cell-mediated disease. Rituximab was introduced for B-cell lymphoma in 1997, and Prof Jo Edwards considered that this could also have efficacy

in RA. His seminal article on BCDT in RA lead to the introduction of this treatment for a remarkable range of AID (33). However, the exact mechanism of BCDT in AID remains elusive: for example, in immune thrombocytopenia, the clinical improvement is much faster than any purported effects on autoantibodies.

Case 5: Infectious diseases, Clinical Microbiology—HIV infection

The central role of CD4 T-cells in protective immunity can be illustrated by HIV infection, which progresses to acquired immunodeficiency syndrome in some cases. The predisposition to opportunistic infections and malignancy occurs in relation to the CD4+ T-cell count, with the risk escalating as the CD4+ T-cell count reduces. This enabled a detailed discussion of the central role of CD4+ T-helper cells in adaptive immunity. The physicians could appreciate their critical role in the activation of CD8+ cytotoxic T-cells to counter viral infections, in the activation of macrophages to kill intracellular bacteria, and in providing help to B-cells to produce high affinity antibody.

Case 6: Nephrology/Rheumatology—SLE treated with anifrolumab

Physicians are welcome to bring their own cases, which they have worked up, or which they would like to understand more clearly with respect to the underlying basic immunology. This can be done in a flipped classroom model. A parallel can be drawn with medical physiology teaching for intensive care medicine residents, which they also considered a difficult subject to understand (34). Our sessions are in small groups and very interactive. Physicians are free to ask questions throughout, and a recent discussion point related to the use of "omics" data in the clinical management of the patient. This is likely to be an increasingly encountered scenario. The case was of severe SLE, which was introduced by one of the physicians in training. The limitations of measuring the interferon signature in patients with SLE were discussed following the recent anifrolumab (interferon-receptor antagonist) trial (35, 36). This allowed a detailed discussion of the multiple immune pathways which may be dysregulated in SLE, beyond the interferon axis, including both innate and adaptive immune responses.

DISCUSSION

Although the initial response of the medical postgraduates has been favorable, as this format has been recently introduced, it requires formal evaluation and detailed comparison, which remains to be undertaken. Currently, the physicians complete a simple 5-question evaluation of the programme, based on a Likert scale, with additional room for free comments. Although all the physicians sit the Fellowship examinations in their medical specialty, there is no formal examination specific to the programme. Preliminary evaluation in year 1 since the programme commenced has been undertaken. Eighty percent of physicians considered basic science immunology to be a difficult subject. Eighty percent felt that the case-based format was useful for understanding basic science immunology, with 60% considering this approach better than didactic lectures. We plan to formally evaluate and assess more detailed feedback from the programme over a longer period, and report this in a subsequent publication.

There are limitations to what this approach can achieve. There is a risk of oversimplification, in that the teaching focuses on the pathways and medications relevant to the clinical cases which are presented. There is a time limitation in terms of the number of cases presented, and the mechanisms which can be illustrated during the course. As a potential consequence, the physician may consider the immune system in terms of a set of disparate pathways, rather than appreciating the immune system as a whole, with its intricate coordination. To counter this, during the teaching programme, the links between parts of the immune response, particularly between innate and adaptive immunity, e.g., case 6, and between cell types, e.g., cases 3, 5 are emphasized. The importance of control of the immune response is illustrated, e.g., cases 1, 2.

Another risk is that medical students and postgraduates may concentrate on the clinical, rather than the immunological, aspects of the cases (22, 37, 38). However, the questions which act as the focal point of the discussion mainly focus on the scientific rather than clinical aspects of the cases. Senior medical students and physicians may focus their attention on pathways which appear more frequently in examination questions. Focusing on esoteric cases can give the erroneous impression that immunological conditions are rare and unimportant, with similar implication for the underlying basic science (39, 40). This is particularly important to avoid for senior medical students, who might otherwise be left with an enduring misconception regarding immune diseases. Hence, it is important to present a wide mixture of patients, in particular to include cases which the medical student or physician is likely to encounter during his/her routine clinical practice. The case mix can be varied according to the specialty of the physician in training. While learning basic science from IEIs has tremendous potential, it carries the caveat that many such IEIs are very rare, particularly in adult medicine. It is essential to emphasize the benefit to the physician/medical student in this context is not in learning the clinical details of the specific IEI, but in appreciating the underlying immunological mechanisms. Encouraging the clinicians to also bring cases to present themselves will challenge them to consider the underlying immunology, and personalize the learning experience for the clinician and their colleagues. There are online resources available which provide further examples of relevant cases, e.g., http://www.immunologyclinic.com/cases.asp (41). Development of further online resources is needed, and their utilization is encouraged.

While recognizing the above limitations, my impression is that the senior medical student and postgraduate will still

gain valuable basic science knowledge which is relevant to his/her future medical, or surgical, practice. In conclusion, the understanding of basic science immunology is extremely important to senior medical students and a whole range of physicians in training. We consider that both senior medical students and postgraduates are more able to relate to basic immunology if approached through a clinical route. Although the initial response of the students has been positive, the efficacy of this case-based format requires formal evaluation and detailed comparison over a longer time period.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

The author confirms being the sole contributor of this work and has approved it for publication.

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