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*ImmunoHorizons* 2022, 6 (5) 312-323
doi: https://doi.org/10.4049/immunohorizons.2200004
http://www.immunohorizons.org/content/6/5/312







*ImmunoHorizons* is an open access journal published by
The American Association of Immunologists, Inc.,
1451 Rockville Pike, Suite 650, Rockville, MD 20852

ISSN 2573-7732.

ImmunoHorizons

RESEARCH ARTICLE

Immunology Education

# Antigen and Immunogen: An Investigation into the Heterogeneity of Immunology Terminology in Learning Resources

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## ABSTRACT

The need to focus on immunology education has never been greater. The coronavirus disease 2019 pandemic has revealed that a significant proportion of our society is vaccine hesitant. Some of this hesitancy may stem from a general lack of understanding of how the immune system and immunological interventions work. In addition, social media platforms undercut public health efforts by quickly propagating a multitude of misconceptions and erroneous information surrounding the science behind these interventions. The responsibility to be advocates for science is well recognized by immunology researchers, educators, and public health professionals, as evidenced by the rich body of resources developed to communicate science to the lay audience. Scientific jargon, however, can be a barrier to effective communication and can negatively impact learning and comprehension. The field of immunology is especially laden with discipline-specific terminology, which can hamper educators' efforts to convey key concepts to learners. Furthermore, a lack of consistency in accepted definitions can complicate students' conceptual understanding. Learning resources, including textbooks, published in print or available online, and exclusively digital resources, continue to serve as the primary sources of information for both educators and students. In this article, we describe a vast heterogeneity in learning resource glossary descriptions of two key conceptual terms: *antigen* and *immunogen*. We provide a perspective on pedagogical strategies to address these critical terms. Using current knowledge, we recommend an approach to standardize the definitions of the terms *antigen* and *immunogen* within the immunology educator community. *ImmunoHorizons*, 2022, 6: 312–323.



Received for publication January 12, 2022. Accepted for publication April 28, 2022.

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This work was supported by a National Science Foundation Award (2120806 to S.P., R.T.T., and L.B.J.), the Biosciences Department at Minnesota State University Moorhead, the Department of Microbiology at the University of Alabama at Birmingham, the Microbiological Sciences Department at North Dakota State University, the Biology Department of Biology at Frostburg State University, and the Biology Department at Labette Community College.

**Abbreviations used in this article:** COVID-19, coronavirus disease 2019; DAMP, damage-associated molecular pattern; OER, open educational resource; PAMP, pathogen-associated molecular pattern; PRR, pattern recognition receptor.

The online version of this article contains supplemental material.





https://doi.org/10.4049/immunohorizons.2200004

*ImmunoHorizons* is published by The American Association of Immunologists, Inc.

## INTRODUCTION

Immunology is a rapidly evolving discipline (1). In addition to fast-paced discoveries in the field, immunological content is chockfull of discipline-specific jargon, which comes with pedagogical challenges. To understand key concepts, instructors and students must master the ever-growing web of technical language, complex acronyms, and abbreviations in immunology texts and articles. Educators strive to teach key concepts so that students maintain motivation to pursue biology and are well-prepared to tackle advanced content in later courses. Regardless of the level or extent of knowledge intended, educational resources (e.g., textbooks and digital learning resources) are critical in delivering course content, influencing what is taught, and serving as vital resources in the classroom (2, 3). Unlike research articles, textbooks present key concepts in a carefully organized format for students (also known as scientists-in-training) and the general public to understand. Key terms are often bolded and included in glossaries so that the niche language of immunology does not impede students from understanding major concepts. In digital resources, the key terms are often hyperlinked directly to a glossary definition. Consistency in the description of the key terms is essential for novice learners so that misconceptions are avoided. Surprisingly, evidence suggests that inconsistencies in definitions and concepts are still encountered in well-vetted learning resources (2, 4–8). In this article, we analyzed the inconsistencies in the definition of two key immunological terms: *antigen* and *immunogen*.

Understanding immunology is critical for training the next generation of scientists and medical practitioners (9), but the point at which students first encounter key terms is likely to be outside of a formal immunology course. For example, vaccine science, which has permeated digital resources (e.g., https://www.cdc.gov), news articles, and social media, as it makes its way into public dialogue and policies, is rooted in immunology. Immunology content may also be introduced in middle and high schools (10) or courses for nonmajors in colleges, such as human biology, microbiology for prenursing students, anatomy and physiology, public health, among others (11, 12). Immunology is not offered as a stand-alone course at most 2-y colleges, with the rare exceptions of medical laboratory technologist programs. Formal education in immunology typically happens in a graduate-level course, a one-semester upper-level undergraduate course, or a module within a microbiology or physiology course. For each of these routes, learners can encounter immunological concepts and terminology that differ, depending on the learning resources (e.g., textbooks, digital resources) used and the disciplinary expertise of educators that serve as a foundation for learning.

Traditionally, immunology textbooks have been an important source of in-depth knowledge. In addition, open educational resources (OERs; e.g., OpenStax textbooks and resources available through Howard Hughes Medical Institute's Biointeractive) available digitally, under an open license or in the public domain that permits no-cost access, use, adaptation, and redistribution with no or limited restrictions (13), are being increasingly adopted by instructors due to equitable access for students and flexibility for the instructor (14). In addition to standard published textbooks and OERs, a new wave of digital educational resources, such as Khan Academy, has left its mark on the educational landscape. When considering concept definitions, the reach of these digital tools cannot be overlooked. For example, Khan Academy serves more than 100 million users per year (15).

With the use of rapid tests for coronavirus disease 2019 (COVID-19) diagnosis, the word *antigen* has achieved common usage (16), whereas awareness of the term *immunogen* lags. For instance, a Google trends database search for "antigen" show a stark increase since May 2020, whereas the term "immunogen" remained constant over the past 5 years (Fig. 1). At the time of performing this analysis, Google's English Dictionary provided by Oxford Languages defined *antigen* as "a toxin or other foreign substance which induces an immune response in the body, especially the production of antibodies." Definition of the term *immunogen* is not provided through Google's English Dictionary but is included in other digital sources. For example, the Merriam-Webster dictionary defines *immunogen* as "a substance that produces an immune response" and reports that its first use was in 1959 without providing a citation. The use of the word *immunogenic* can be dated as far back as 1917 (17).

Unlike the term *immunogen*, the origin of the term *antigen* has been well documented. *Antigen* was coined by Ladislav Deutsch, also known as Lásló Detre, a Hungarian researcher, who used the phrase "substances immunogènes ou antigenes" in a French article in 1899 (18). Although Deutsch described an "antigen" as bacterial products that may turn into Abs (18), an Austrian scientist, E.P. Pick, described "antigens" as proteins in 1912 (19), and Mazumdar described "antigen" as any substance to which an animal can make Abs (20). The work of Bordet (21), Ehrlich (22), and many others showed that antigens could be composed of a variety of biomolecules. The historical context and the discoveries that led to its current definition were reviewed by authors such as Jean Lindenmann (23), Pauline Mazumdar (20), and Klaus Eichmann (24). Like several other immunological concepts, the term *antigen* has evolved as scientists uncovered the chemical nature of the substances that interact with Abs, TCRs, MHC molecules, and pattern recognition receptors (PRRs), leading to a variety of contexts and subdisciplines in which the term applies. The evolution of the definition of antigen reflects the exploratory nature of experimental science based on emerging knowledge from the bench. Nonetheless, we anticipate that contemporary immunologists and educators would agree that a standard definition of antigen is fundamental, not only to understanding immunobiology but also biotechnology, medicine, medical laboratory science, and many other related applications (Fig. 2).

To formalize an approach to undergraduate immunology education, a group of university educators recently undertook the task of initiating a community discussion on key concepts

https://doi.org/10.4049/immunohorizons.2200004

in immunology (25–27). One thing that became evident through these discussions was that disciplinary experts were interpreting the term *antigen* differently. We hypothesized that this discrepancy may have originated from variability in the authoritative textbooks and learning resource definitions. This prompted us to explore and analyze the definition of the term *antigen* in varied educational resources. Several of the resources that were a part of our analysis listed *antigen* as synonymous with *immunogen*. Therefore, in this analysis, we compare the definitions of the terms *antigen* and *immunogen* provided in the glossaries of widely adopted immunology textbooks and other educational resources that contain immunology-related content. Based on our analysis, we recommend a conceptual framework for these terms in the context of undergraduate education, to foster consistency and to reflect the current state of immunological knowledge.

## MATERIALS AND METHODS

### *Data collection*

The coauthors of this article were surveyed to determine the most commonly used educational resources (i.e., textbooks and digital resources), and based on their recommendations, 49 educational resources in four categories were reviewed and analyzed for the definitions of *antigen* and *immunogen*: (1) immunology textbooks ($n$ = 13; Supplemental Table I); (2) commonly used digital resources and OERs ($n$ = 12; Supplemental Table II); (3) microbiology textbooks ($n$ = 10; Supplemental Table III); and (4) other nonimmunology/microbiology textbooks that include immunology-related topics, such as biochemistry, biotechnology, cell and molecular biology, genetics, general biology, human anatomy and physiology, medical laboratory practice, medical terminology, and zoology ($n$ = 14; Supplemental Table IV).

Within each textbook's narrative, the terms *antigen* and *immunogen* can be used in varying contexts. For example, if the discussion pertains to Ab titers, then an "antigen" may be referred to as a substance that triggers Ab production, and its T cell interactions may not be mentioned at all. In contrast, glossary definitions are intended to be all-encompassing of the varying contexts in which a term could be used. Thus, to ensure consistency, we compared only the glossary definition of the terms *antigen* and *immunogen* or *immunogenicity* (if *immunogen* was not included) in the 49 chosen educational resources.

### *Data analysis*

Once the definitions were collected, two of the authors (S.L.E. and S.P.) analyzed the definitions to identify broad themes emerging from these definitions, and they developed a codebook (Figs. 3–7). Next, three authors (S.P., R.L.S.-T., and A.L.) independently coded the data, exchanged notes on themes after the first round of coding, and revisited and finalized the codebook. After this consensus discussion, the three coders independently coded the data once again. The relative frequency of each code category was computed using Microsoft Excel (Microsoft Corporation, Redmond, WA), and graphs were plotted using GraphPad Prism 9.0 (GraphPad Software, San Diego, CA). The $p$ values were computed using a nonparametric statistical test for categorical data with small sample sizes (Fisher's exact test) using R (version 3.6.1). Cohen's κ interrater reliability score was computed using an R (version 3.6.1) using the psych package and was found to be in an acceptable range (>0.8–1) for all categories of data (28).

## RESULTS

### Immunogen *is not a common term in educational resources, and there is variation in whether* immunogen *is defined as synonymous with* antigen

On analysis of the glossary definition of *immunogen/immunogenicity*, three categories emerged: (1) glossaries that do not mention (code category DNM) the term *immunogen*; (2) glossaries that mention *immunogen* as nonsynonymous with *antigen* (code category NS); and (3) glossaries that mention *immunogen* as synonymous with *antigen* (code category S). Code descriptions and specific examples of glossary definitions representing each of the three code categories are depicted in Fig. 3A. The Cohen's κ interrater score for coding this dataset was 1.

The analysis showed that 55% of textbooks surveyed did not mention the term *immunogen* in the glossary (Fig. 3B).

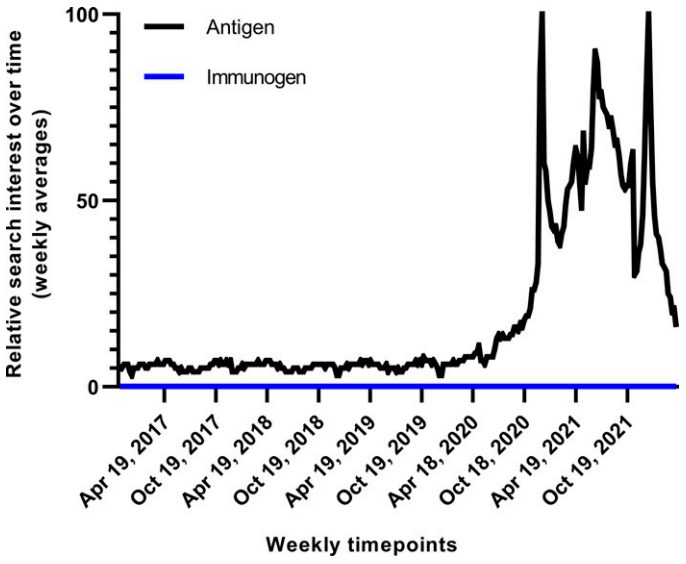


**FIGURE 1. Relative search interest in the terms antigen (black line) and immunogen (blue line) based on worldwide Google searches for these terms over the past 5 y.**

Numbers represent weekly averages for search interest relative to the highest point on the chart for the given region and time. A value of 100 is the peak popularity for the term. A value of 50 means that the term is half as popular. A score of zero means there were not enough data for this term. The data were retrieved from https://trends.google.com on April 13, 2022, 11.30 AM CST.

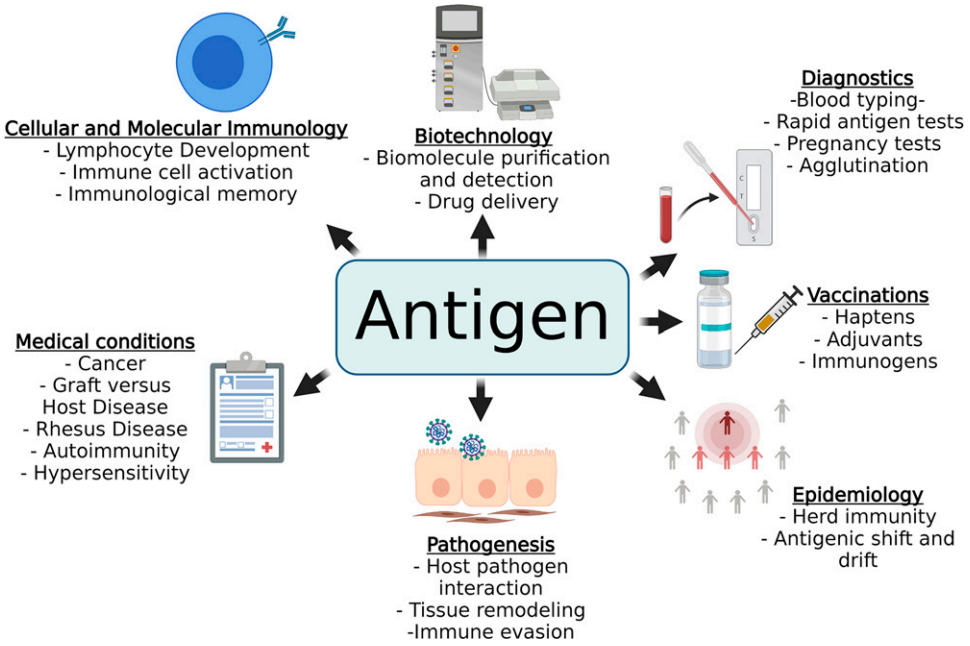


**FIGURE 2. Varied contexts in which the term *antigen* is used.**
Schematic created by the authors using https://biorender.com.

Whereas 33% of the textbooks indicated that *antigen* is not synonymous with *immunogen*, 12% of textbooks mentioned that *antigen* is synonymous with *immunogen* (Fig. 3B). In immunology-specific textbooks, *immunogen* is predominantly defined as nonsynonymous with *antigen* (Fig. 3C). In contrast, microbiology textbooks had an approximately equal split between the three code categories (Fig. 3C). Most digital resources did not mention the term *immunogen*, and none of the "other biology" textbooks mentioned the term *immunogen* (Fig. 3C).

A

| Coding criteria: based on whether or not immunogen is listed as synonymous with antigen. | | |
|---|---|---|
| **Code** | **Explanation** | **Example glossary definitions** |
| **DNM** | The educational resource Does Not Mention the term immunogen in the glossary | • Not applicable |
| **NS** | Glossary definition of immunogen is Not Synonymous with that of antigen | • A substance capable of eliciting an immune response. All immunogens are antigens, but some antigens (e.g. haptens) are not immunogens<br>• Any substance that can provoke an immune response |
| **S** | Glossary definition of immunogen is Synonymous with that of antigen | • Same as antigen<br>• Substance capable of inducing an immune response (as well as reacting with the products of an immune response); often used as a synonym for antigen |

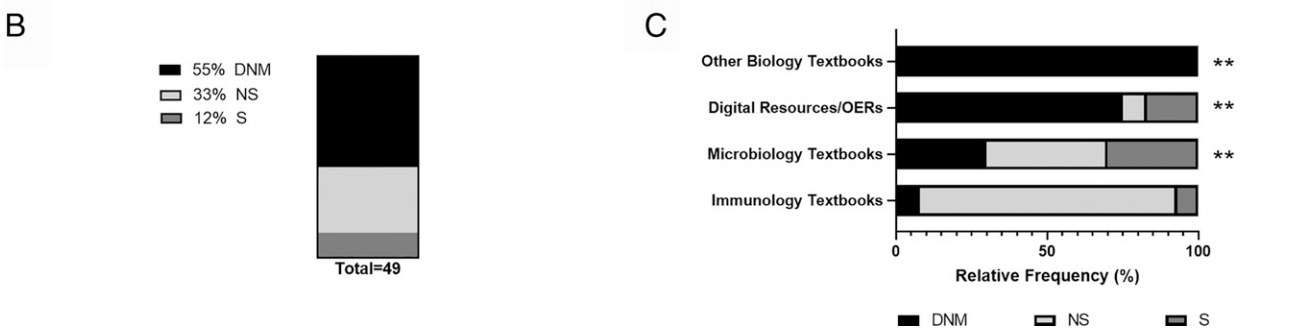


**FIGURE 3. Immunogen's glossary definition analysis based on whether it was defined as synonymous with antigen.**
(**A**) The codes assigned, their description, and representative examples. (**B**) A total of 49 educational resources were scanned for the definition of *immunogen*, and the overall relative frequency of code distribution is depicted. (**C**) The relative frequency of various codes per resource type: immunology textbooks ($n$ = 13), microbiology textbooks ($n$ = 10), digital resources/OERs ($n$ = 12), and other biology ($n$ = 14) resources. $^{**}p < 0.0001$ represents significant differences with respect to immunology textbooks, as per Fisher's exact test.

https://doi.org/10.4049/immunohorizons.2200004

### *The definition of* antigen *is inconsistent across educational resources*

The glossary definition of *antigen* in different learning resources was examined next. Because of the large diversity in how *antigen* was defined in these texts, four different thematic categories were identified: (1) whether the substance binds to immune cell receptors and/or activates the immune system (Fig. 4); (2) whether the substance interacts with BCRs and Abs, both TCRs and BCRs, or a receptor in the immune system with no specific details noted (Fig. 5); (3) the biochemical nature of the substance itself (protein, polysaccharide, lipid, or nucleic acid) (Fig. 6); and (4) whether *antigen* is defined exclusively as a substance that is foreign or nonself (Fig. 7).

*Textbooks vary in describing* antigen *as a molecule that* only *reacts with or binds to immune cell receptors* or *reacts with* and *activates the immune system.* On analysis of the glossary definition of *antigen* to determine whether antigen was described based on the molecule's capability to bind to immune cell receptors and/or activate the immune response, six code categories emerged: (1) a molecule that activates (code category A), stimulates, or triggers an immune response; (2) a molecule that is recognized by, reacts with, or binds to an immune cell receptor (code category ReB); (3) a substance that is recognized by, reacts with, or binds to an immune cell receptor *and* activates/stimulates/triggers an immune response (code category ReB+A); (4) a substance that is recognized by, reacts with, or binds to an immune cell receptor *and* may activate/stimulate/trigger an immune response (code category ReB+MA); (5) not applicable (code category NA) for when antigen is not described based on the criteria used for this analysis or is not mentioned in the glossary; and (6) does not mention (code category DNM) the term *antigen* (Fig. 4A). Code descriptions and specific examples of glossary definitions representing each code category are depicted in Fig. 4A. The Cohen's κ interrater score for this dataset was 0.84.

Thirty-nine percent of textbooks (Fig. 4B), primarily immunology specific (Fig. 4C), mention antigen as a substance that is recognized by or reacts with or binds to an immune cell receptor (code category ReB) without mentioning anything about its capability to activate an immune response. Thirty-three percent of textbooks (Fig. 4B), mostly microbiology based (Fig. 4C), describe antigen as a substance that activates immune response (code category A). Whereas 18% of textbooks describe antigen as a substance that is recognized by or reacts with or binds to an immune cell receptor and activates the immune response (code category ReB+A), only 6% describe it as a substance that is recognized by or reacts with or binds to an immune cell receptor and *may* activate the immune response (code category ReBD+MA). Two percent of resources ($n$ = 1 digital resource/OER) define

A

| Coding criteria: based upon the molecule's capability to bind to immune cell receptors and/or activate the immune response. | | |
|---|---|---|
| **Code** | **Explanation** | **Example glossary definitions** |
| **A** | Glossary definition describes antigen as a substance that that **A**ctivates/stimulates/triggers an immune response | • Any substance (usually a protein or carbohydrate) that induces the production of antibodies by immune cells. Usually is a substance that is "foreign" to the host. |
| **ReB** | Glossary definition describes antigen as a substance that is **Re**cognized by/**Re**acts with/**B**inds to an immune cell receptor | • Any substance (usually foreign) that binds specifically to an antibody or a T-cell receptor |
| **ReB+A** | Glossary definition describes antigen as a substance that is **Re**cognized by/**Re**acts with/**B**inds to an immune cell receptor + (and) **A**ctivates/stimulates/triggers an immune response | • Any foreign substance that can bind to specific lymphocyte receptors and induce an immune response |
| **ReB+MA** | Glossary definition describes antigen as a substance that is **Re**cognized by/**Re**acts with/**B**inds to an immune cell receptor + (and) **M**ay **A**ctivates/stimulates/triggers an immune response | • A macromolecule that reacts with cells of the immune system and which may or may not have a stimulatory effect |
| **NA** | **N**ot **A**pplicable – either antigen's definition was not included in the glossary or not defined per the criteria for this classification | • An antigen is anything that is foreign to the human body. It can be a virus, it can be a bacteria, and in some cases your own body will appear as foreign. |
| **DNM** | The educational resource **D**oes **N**ot **M**ention the term antigen in the glossary | • Not applicable |

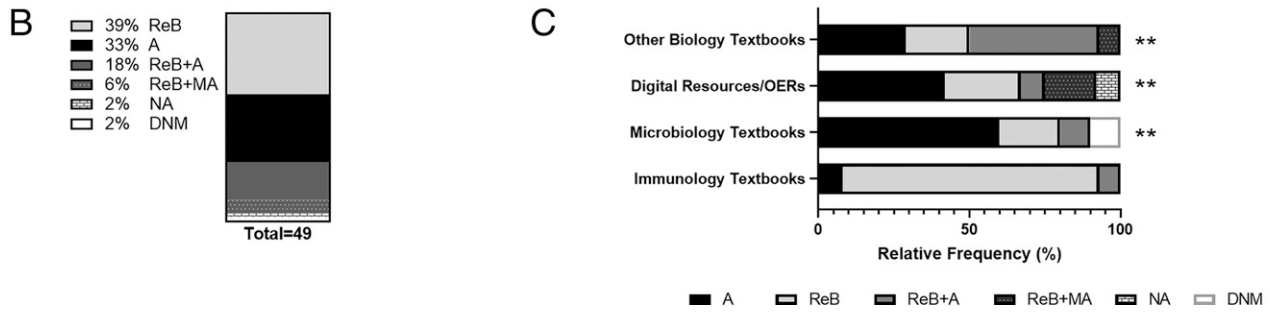


**FIGURE 4. Antigen's glossary definition analysis based on the molecule's ability to bind to immune cell receptors and/or activate the immune response.**

(**A**) The codes assigned, their description, and representative examples. (**B**) A total of 49 educational resources were analyzed for the definition of *antigen*, and the overall relative frequency of code distribution is depicted. (**C**) The relative frequency of various codes per resource type: immunology textbooks ($n$ = 13), microbiology textbooks ($n$ = 10), digital resources/OERs ($n$ = 12), and other biology ($n$ = 14) resources. **$p < 0.0001$ represents significant differences with respect to immunology textbooks, as per Fisher's exact test.

A

| Coding criteria: based upon the molecule's ability to interact with B lymphocytes and antibodies only or both B and T lymphocytes or immune components generally. | | |
|---|---|---|
| **Code** | **Explanation** | **Example glossary definitions** |
| **HIS** | Glossary definition describes antigen as a substance that activates/binds to components of Humoral Immune System (B-cell receptors or Antibodies) | • Any substance (usually a protein or carbohydrate) that induces the production of antibodies by immune cells. Usually is a substance that is "foreign" to the host. |
| **AIS** | Glossary definition describes antigen as a substance that activates/binds to Adaptive Immune System's components (T- and B- cell receptors) | • Molecules specifically recognized by receptors of the adaptive immune system |
| **IS** | Glossary definition describes antigen as a substance that activates/binds to Immune System's components. The definition does not mention specific arm of immune system that is targeted | • A small piece of biological material (protein, carbohydrate, lipid, or nucleic acid) that can be recognized by the immune system. Antigens from pathogens or abnormal cells trigger an immune response |
| **DNM** | The educational resource Does Not Mention the term antigen in the glossary | • Not applicable |

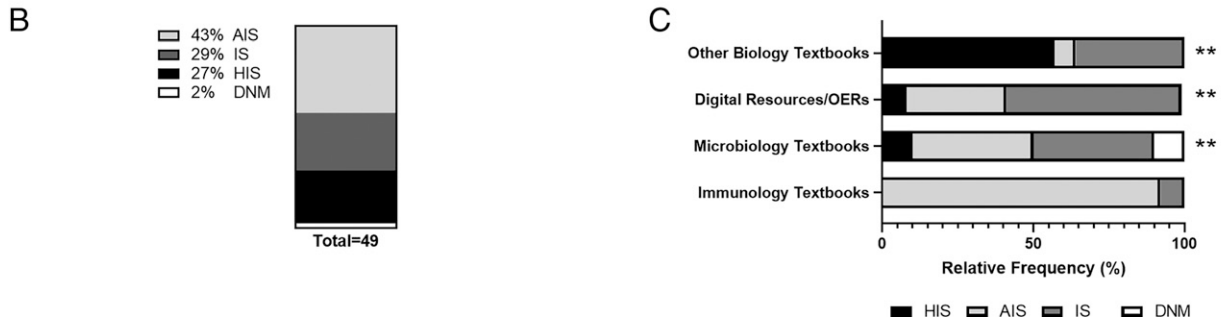


**FIGURE 5. Antigen's glossary definition analysis based on the molecule's capability to interact with humoral immunity, adaptive immunity, or immune system generally.**

(**A**) The codes assigned, their description, and representative examples. (**B**) A total of 49 educational resources were scanned for the definition of *antigen*, and the overall relative frequency of code distribution is depicted. (**C**) The relative frequency of various codes per resource type: immunology textbooks ($n = 13$), microbiology textbooks ($n = 10$), digital resources/OERs ($n = 12$), and other biology ($n = 14$) resources. **$p < 0.0001$ represents significant differences with respect to immunology textbooks, as per Fisher's exact test.

*antigen* in a way that does not lend itself to the analysis in this category (code category NA) (Fig. 4A–C), and 2% percent of resources ($n = 1$ microbiology textbook) do not mention (code category DNM) the term *antigen* in the glossary (Fig. 4A–C).

*Textbooks vary in how they define an antigen's capability to interact with various arms of the immune system—humoral, adaptive, or none specified.* On analysis of the glossary definition of *antigen*, based on a molecule's capability to interact with BCRs, TCRs and BCRs, or immune cell receptors generally, four categories emerged: (1) glossaries that describe *antigen* as a molecule that interacts with components of the humoral immune system (code category HIS) that includes BCRs and Abs; (2) glossaries that describe *antigen* as a molecule that activates or binds to adaptive immune system (code category AIS) components (TCRs and BCRs); (3) glossaries that describe *antigen* as a substance that interacts with immune system (code category IS) components, and no specific arm of the immune system is mentioned; and (4) glossaries that do not mention the term *antigen* (code category DNM) (Fig. 5A). Code descriptions and specific examples of glossary definitions representing each code category are depicted in Fig. 5A. The Cohen's κ interrater score for this dataset was 0.94.

We determined that 43% of textbooks (Fig. 5B), mostly immunology based (Fig. 5C), mention *antigen* as a substance that interacts with TCRs and BCRs and stimulates an adaptive immune response. Twenty-nine percent of the textbooks do not distinguish between TCRs and BCRs and instead note a target of the immune system in a general sense (Fig. 5B). Twenty-seven percent of resources (Fig. 5B), mostly digital (Fig. 5C), retain the older definition of *antigen*: a molecule that interacts only with B lymphocytes or only leads to Ab production (20). One microbiology textbook did not mention the definition of *antigen* in the glossary (Fig. 5B, 5C).

*Textbooks vary in how the biochemical identity of an antigen is defined.* Further analysis of the definition of *antigen*, based on its biochemical identity, led to classification into four categories: (1) glossaries that describe *antigen* as any molecule (code category AM), without specific mention of its biochemical composition; (2) glossaries that describe *antigen* as a protein-only or protein and polysaccharide molecule (code category PM); (3) glossaries that describe *antigen* as a protein, polysaccharide, nucleic acid, or lipid molecule (code category PNLM); and (4) glossaries that do not mention the term *antigen* (code category DNM) (Fig. 6A). Code descriptions and specific examples of glossary definitions representing each code category are depicted in Fig. 6A. The Cohen's κ interrater score for this dataset was 0.96.

Most textbooks (76%), in all categories, do not mention the biochemical composition and describe *antigen* as any molecule (code category AM) (Fig. 6B). *Antigen* was described as a protein or a polysaccharide molecule (code category PM) in 14% of textbooks. Eight percent of textbooks in all but the "other biology" category mention *antigen* as a molecule that could be a protein, polysaccharide, nucleic acid, or lipid (code category PNLM) (Fig. 6B, 6C). One microbiology textbook did not mention the definition of *antigen* in the glossary (code category DNM) (Fig. 6B, 6C).



https://doi.org/10.4049/immunohorizons.2200004

A

| Coding criteria: based upon the biochemical nature of the molecule. | | |
|---|---|---|
| **Code** | **Explanation** | **Example glossary definitions** |
| **AM** | Glossary definition describes antigen as **A**ny **M**olecule and does not mention any specific details about its biochemical nature | • Any molecule or molecular fragment that either is recognized by an antibody or B-cell receptor or can be bound by an MHC molecule and presented to a T-cell receptor |
| **PM** | Glossary definition describes antigen as a **P**rotein or a **P**olysaccharide **M**acromolecule | • A molecule that can bind specifically to an antibody or generate peptide fragments that are recognized by a T-cell receptor |
| **PNLM** | Glossary definition describes antigen as a **P**rotein or a **P**olysaccharide or a **N**ucleic Acid or a **L**ipid **M**acromolecule | • A molecule that binds to an antibody or a TCR. Antigens that bind to antibodies include all classes of molecules. Most TCRs bind only peptide fragments of proteins complexed with MHC molecules.<br>• A small piece of biological material (protein, carbohydrate, lipid, or nucleic acid) that can be recognized by the immune system. Antigens from pathogens or abnormal cells trigger an immune response |
| **DNM** | The educational resource **D**oes **N**ot **M**ention the term antigen in the glossary | • Not applicable |

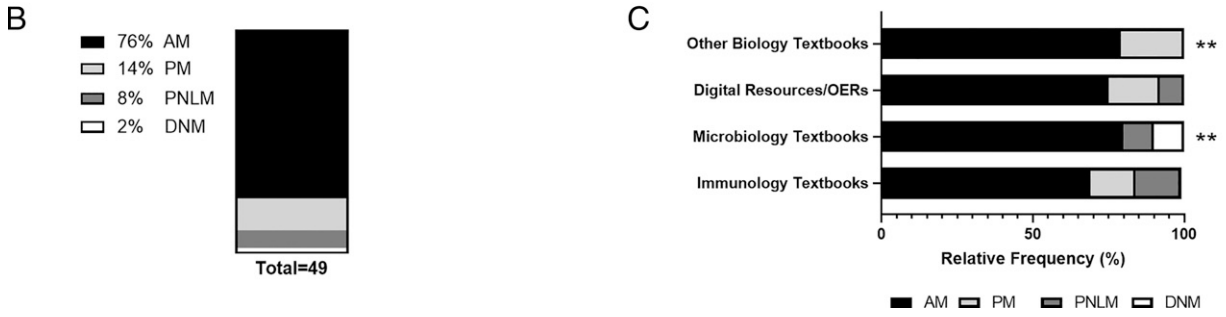


**FIGURE 6. Antigen's glossary definition analysis based on the biochemical nature of the molecule.**
(**A**) The codes assigned, their description, and representative examples. (**B**) A total of 49 educational resources were scanned for the definition of antigen, and the overall relative frequency of code distribution is depicted. (**C**) The relative frequency of various codes per resource type: immunology textbooks ($n$ = 13), microbiology textbooks ($n$ = 10), digital resources/OERs ($n$ = 12), and other biology ($n$ = 14) resources. **$p < 0.0001$ represents significant differences with respect to immunology textbooks, as per Fisher's exact test.

*Textbooks vary in describing the origin of* antigen *as foreign versus a more inclusive definition that encompasses altered (e.g., tumor) or self (e.g., auto) antigens*. Lastly, the definition of *antigen*, based on origin, led to three code categories: (1) glossaries that describe *antigen* as any molecule (code category ANY), (2) glossaries that describe *antigen* as nonself or foreign (code category NSel), and (3) glossaries that do not mention the term *antigen* (DNM) (Fig. 7A). Code descriptions and specific examples of glossary definitions representing each code category are depicted in Fig. 7A. The Cohen's κ interrater score for this dataset was 1.

Most textbooks (78%) describe *antigen* as any molecule (code category ANY), leaving it to the instructors' interpretation of whether it is a self, nonself, or altered self-antigen (Fig. 7B). Twenty percent of textbooks describe *antigen* as nonself or foreign (Fig. 7B), and 2%; ($n$ = 1 microbiology textbook) do not include the definition of *antigen* in the glossary (Fig. 7B). The three code categories were represented in all categories of resources (Fig. 7C).

## DISCUSSION

In this study, we explored the degree of discrepancy in definitions across educational resources for the key immunological terms "antigen" and "immunogen," to find a common language that could be used to converse with both experts and novices. *Antigen* is a widely used term in textbooks, scientific literature, and other learning resources, although in different contexts. In cellular and molecular biology, the term *antigen* is used in the context of lymphocyte development, immune cell activation, and immunological memory. In biotechnology, *antigen* is used in terms of biomolecule purification and detection and for drug delivery. In diagnostics, *antigen* is used in terms of blood typing, pregnancy tests, rapid antigen tests, and agglutination. Similarly, *antigen* is used in different contexts in vaccinology, epidemiology, pathogenesis, and immune system–related medical conditions, such as cancer, autoimmune disorders, and hypersensitivity disorders. Therefore, in our previous study (25), it was not surprising that understanding antigen–Ab interactions was rated as a very important skill for students to learn. Although critically important for understanding immunology, the definition of *antigen* may also vary, depending on the instructor's background and the textbook being used.

### *Comprehension of disciplinary terms is important*

In contemporary times, definitions can easily be obtained with a few keystrokes and a web browser. However, to master the scientific language, students need to define a term and confidently use the term within the correct context (29). Mastering disciplinary vocabulary is a critical component of comprehension (30, 31) and allows one to fluently communicate the context and ideas related to these terms with peers, colleagues, mentors, and the general public. Scientific communication is a core competency for undergraduate life science education (32). Effective science communication skills predict trainees'

A

| Coding criteria: based upon whether or not the molecule is described as foreign/non-self only. | | |
|---|---|---|
| **Code** | **Explanation** | **Example glossary definitions** |
| **ANY** | Glossary definition describes antigen as **A**NY molecule – does not describe it based on its origin | • A molecule that reacts with antibody and the specific receptors on T and B cells.<br>• Any molecule or molecular fragment that either is recognized by an antibody or B-cell receptor or can be bound by an MHC molecule and presented to a T-cell receptor |
| **NSel** | Glossary definition describes antigen as a **N**on-**Self** or a foreign molecule | • Any foreign substance that can bind to specific lymphocyte receptors and so induce an immune response<br>• Foreign or "non-self" protein that triggers the immune response |
| **DNM** | The educational resource **D**oes **N**ot **M**ention the term antigen in the glossary | • Not applicable |

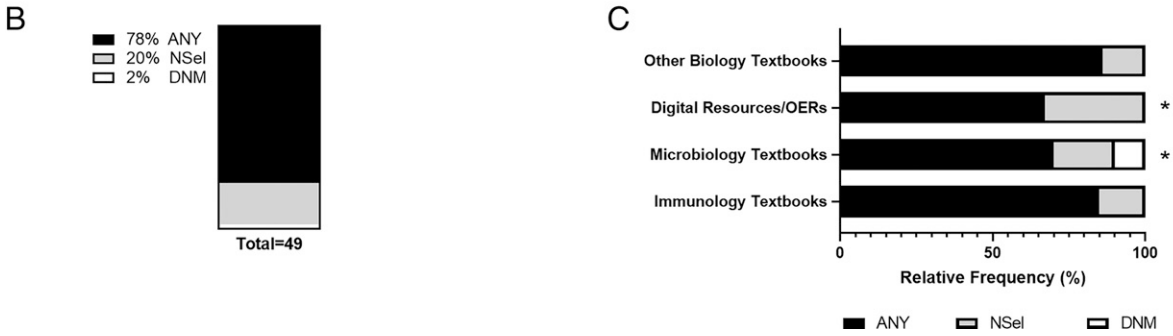


**FIGURE 7. Antigen's glossary definition analysis based on whether the molecule is described as foreign or nonself.**
(**A**) The codes assigned, their description, and representative examples. (**B**) A total of 49 educational resources were scanned for the definition of *antigen*, and the overall relative frequency of code distribution is depicted. (**C**) The relative frequency of various codes per resource type: immunology textbooks ($n$ = 13), microbiology textbooks ($n$ = 10), digital resources/OERs ($n$ = 12), and other biology ($n$ = 14) resources. *$p < 0.001$ represents significant differences with respect to immunology textbooks, as per Fisher's exact test.

intentions to persist in science and are critical for career success in science, technology, engineering, and mathematics (33). Consequently, difficulty in comprehending the discipline-specific language is likely to impede a learner's ability to establish a sufficient conceptual understanding (34, 35). Due to their abstract nature, the understanding of molecular terms in biology is perceived by students as particularly difficult (36). Multiple, ambiguous definitions for a particular concept can impede understanding by both educators and students alike. If disciplinary experts encounter difficulties in understanding these key terms, then the difficulties for novices are likely to be amplified.

### *The distinction between antigen and immunogen is critical for comprehension of immunological mechanisms*

The majority of resources analyzed in this study (55%) did not include the term *immunogen* in their glossaries. *Immunogen* was predominantly found in immunology textbooks, to a certain extent in microbiology textbooks and digital resources, but was absent from other biology textbooks. On the contrary, all educational resources, except for a single microbiology textbook (2% of the total), included the term *antigen* in the glossary, suggesting that, as compared with *antigen*, *immunogen* is not a common term in disciplines other than immunology. This mirrors the trends that we observed on Google search trends, demonstrating that "antigen" is a more widely used term than "immunogen."

The reason for delving into the definition of *immunogen* in the first place was prompted by definitions that described *antigen* and *immunogen* as synonymous (12% of the total), or those that mentioned *antigen* as a molecule that activates the immune response (51% of the total). Although the term may be used elsewhere in the texts, the absence of *immunogen* in glossaries is a missed opportunity to add clarity to the definition of *antigen*. Specifically, *immunogenic* is an adjective that describes an antigen's ability to activate immune responses. Most immunology textbooks described *antigen* as a molecule that is recognized by, reacts with, or binds to an immune cell receptor. However, a surprisingly large number of resources described *antigen* as a substance that activates the immune system (~33% of the total) or a substance that binds and activates (~18% of the total) the immune system. Using these terms synonymously can be a source of grave misconception.

How scientists describe these terms can critically influence the types of hypotheses generated and experimental questions addressed. For example, knowledge of the viral antigenic sites recognized by Abs does not necessarily indicate which immunogenic structure initiates the production of Abs in the immunized host. Failure to differentiate between antigenicity and immunogenicity may lead to failures in developing synthetic peptide vaccines against viral diseases (37–39). How an immune response is measured has been a matter of great debate (40), and a lack of clarity regarding the difference between the two terms can further impede the understanding of advanced concepts associated with immunological cascades, such as haptens, adjuvants, allergens, tolerogens, etc.



https://doi.org/10.4049/immunohorizons.2200004

### *The distinction between ligands for lymphocyte antigen receptors and PRRs is critical*

Further analysis showed that immunology textbooks define *antigen* as a molecule that interacts with adaptive immune components, i.e., lymphocyte antigen receptors. When compared with other resources, inconsistencies were evident. A significant proportion of educational resources (~27%) retain an older definition of *antigen* as "Ab generating," which implies that antigens interact only with B lymphocyte antigen receptors. Another significant proportion of resources (~29%) identify *antigen* as a molecule that interacts with the immune system generally—and leaves it to the reader's interpretation of whether this relates to only the lymphocyte antigen receptors or both the lymphocyte antigen receptors and PRRs.

The nuanced distinction between lymphocyte antigen receptor ligands and pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) is critical to driving home other advanced concepts in immunology, such as the extent of specificity associated with innate and adaptive immune responses. These molecular terms are abstract and not intuitive for novices to grasp (36). This distinction is also foundational for understanding how and why the lymphocyte antigen receptors are more diverse in recognizing a myriad of antigens, whereas the diversity among germline-encoded PRRs is limited, yet highly effective.

The distinction between PRR ligands (specifically called PAMPs and DAMPs) and lymphocyte antigen receptor ligands is critical for researchers interested in comparative immunology and evolutionary biology–related questions. The adaptive immune system is a relatively new branch of the immune system and arose ~500 million years ago in jawed fish (41). Invertebrates lack the typical adaptive immune components. Nonetheless, invertebrates are being increasingly recognized as important model organisms for ecoimmunology-based studies, which have implications for evolutionary medicine, emerging infectious disease, public health, One Health, conservation, and wildlife management (42–46). The varied use of the term *antigen* is an example of a barrier to interdisciplinary knowledge, communication, and scientific progress.

### *Pedagogical recommendations to approach antigen and immunogen*

As discussed earlier, the definitions of *antigen* and *immunogen* are nuanced, yet critical for novice learners to understand. In Fig. 8, we show a step-by-step approach and contextual map that instructors can use to introduce these terms in a classroom (47, 48). This framework, along with our set of recommendations (Table I), should help educators consistently delineate these terms. To initiate this topic in the classroom, instructors may consider describing the origin of the word *antigen* as "Ab-generating,"

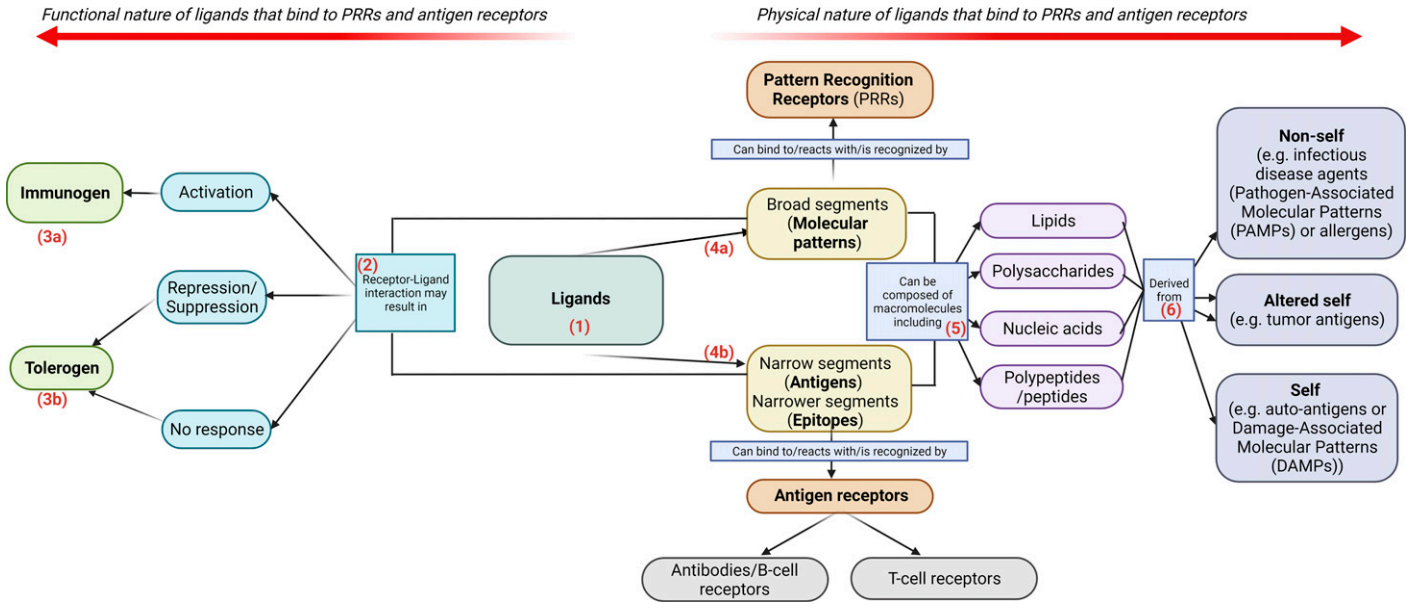


**FIGURE 8. Contextual visual schematic to introduce various nuances associated with the terms *antigen* and *immunogen*.**

Each branch point describes the context as follows: (*1*) The ligands that serve as cues for the immune system bind to their specific receptors. (*2*) This receptor–ligand interaction can elicit activation, repression, or no response from the immune system. (*3a*) The ligands that are capable of activating the immune response are called immunogens, while the functional opposite of immunogens are tolerogens. (*4*) These ligands can be broad or narrow molecular patterns. Typically, broad molecular patterns (e.g., LPSs) bind to the PRRs (e.g., TLR4), and the narrow molecular segments bind to the antigen receptors present on the lymphocytes. The specific portion of an antigen that interacts with the antigen receptor on a lymphocyte (e.g., TCR or BCR or an Ab) is called an epitope. (*5*) These molecular patterns can be made up of lipids, polysaccharides, nucleic acids, or proteins. (*6*) These molecular patterns can originate from non–self-molecules (e.g., infectious disease agents [PAMPs or allergens]), altered self-molecules (e.g., tumor antigens), or the self-molecules (e.g., autoantigens that induce autoimmune response or DAMPs, such as extracellular ATP). Schematic was created by the authors using https://biorender.com.

which can help to couch the terms in a story format and expose students to how the terms continue to evolve with newer immunological discoveries (20, 23, 24). As a general paradigm, ligands would be considered a physical entity that specifically binds to a cognate receptor. A subset of ligands (called antigens) bind specifically to lymphocyte antigen receptors, and another subset (called PAMPs and DAMPs) bind to the PRRs. This approach accommodates the principle that both innate immune cells and cells of the adaptive immune response use different types of receptor that bind to ligands to discriminate self from nonself, while at the same time specifying that antigens bind specifically to lymphocyte antigen receptors. Further classification, as described in Fig. 8, would allow sharing the context associated with these terms.

With the knowledge of γδ-T cells, NK cells, intraepithelial lymphocytes, B1 lymphocytes, etc., we have learned that innate and adaptive immune components are on a spectrum and cannot be separated with a rigid line. There is constant communication between innate and adaptive immune components, and as discussed earlier, invertebrates do not exhibit typical adaptive immune components, and yet can serve as excellent models for comparative and ecoimmunological studies. In addition, most immunology textbooks largely focus on the human/mammalian immune system with innate and adaptive immune mechanisms. This is a missed opportunity to consider terminology and concepts from the perspective of an organism that lacks typical elements of adaptive immunity. Educators may consider pointing out these exceptions and gray areas between innate and adaptive immunity with regard to specific cell types and receptors, in the context of comparative immunology. Lastly, pedagogical studies have shown that before introducing new terms, relating the concept to everyday life scenarios improves student articulation of understanding (49). For this, case studies (e.g., a case centered around the rapid antigen test for COVID-19) or problem-based

**TABLE I. Summary of proposed recommendations for immunology educators to prevent/dislodge student misconceptions related to *antigen* and *immunogen***

| Recommendation | Description |
|---|---|
| 1. Distinguish between *antigen* and *immunogen*. | Clearly distinguish between *antigen* and *immunogen*. Whereas *antigen* is a physical entity that binds to, is recognized by, or reacts with a lymphocyte antigen receptor, an *immunogen* is a functional entity that activates, stimulates, or triggers the immune system components. At this point, instructors may consider introducing the term *tolerogen* to clarify that not all anitigens are capable of activating the immune response. |
| 2. Compare and contrast the ligands that bind to PRRs versus those that bind to lymphocyte's antigen receptors. | We anticipate that because of the wide variation in definitions of *antigen*, the beginner learners and instructors might differ in their understanding of how they describe antigens, depending on the following: (1) the textbooks they were exposed to previously, (2) their understanding of differences between PRRs versus T and B cell antigen receptors, (3) their understanding of immunity in nonvertebrate organisms that lack typical T and B lymphocytes, and (4) their understanding of the blurred line between receptors and ligands used by innate and adaptive immune cells to discriminate self from nonself, referring to cells such as NK cells. Therefore, it is important to assess students' understanding of the terms noted in Fig. 8 at the beginning of a lesson. During the lesson, students can learn to compare and contrast the ligands of PRRs and those of lymphocyte antigen receptors and discuss the exceptions to the generalizations noted in Fig. 8. The lesson can end with a postassessment to gauge students' comprehension. |
| 3. Note the various contexts in which the term *antigen* can be used. | Relating new knowledge with preexisting knowledge and to everyday life scenarios can enhance student articulation of understanding. Because the term *antigen* is a relatively more common term than *immunogen* or *ligand*, it makes sense to explicitly address the definition of *antigen*. Instructors may choose to discuss further nuances associated with the term *antigen*, depending on the audience and relevance, as described in Figs. 2 and 8. |
| 4. Revisit these definitions periodically, in the context of emerging knowledge. | Because immunology is a rapidly evolving discipline, these terms must be periodically revisited, to establish consensus among scientists and educators, such that clear terminology can be shared with novices, early career instructors, and later career instructors. We also hope that immunology-focused societies and disciplinary experts will review emerging disciplinary knowledge to update key terms and disseminate this knowledge to the broader community through periodicals and scholarly literature. |

learning can be highly effective (50) and something to which immunology easily lends itself.

### *Follow-up questions and conclusion*

Although we chose 49 educational resources from varied disciplines of biology, the list is far from comprehensive. Nonetheless, the list was sufficient to highlight the issue at hand and initiate a community discussion. Also, this study focuses on *antigen* and *immunogen*, which are foundational to understanding advanced immunological concepts. We did not investigate the glossary definitions of related advanced terms such as *haptens*, *adjuvants*, and *allergens*. Lastly, the data analyzed in this study were obtained from educational resources. Moreover, this analysis does not address student misconceptions, which will be elucidated in forthcoming studies.

Writing educational materials is an iterative process, and the authors of this article recognize this fully. This article does not intend to criticize particular authors, publishers, or disciplinary experts who might prefer to use the word *antigen* in various contexts. *Antigen* is indeed a very common term, as compared with the other terms noted in Fig. 8. Instead, the analysis brings forth an observation that differences in the way that specific terms are defined can potentially perpetuate misconceptions or reinforce differences across disciplines on the part of instructors and students alike. The educational resources included in this investigation are listed only as examples, to illustrate the point and not as a comprehensive list of resources.

With this study, we hope that educators and educational resource authors will be mindful of the usage of the terms *antigen* and *immunogen* and the varied contexts in which each term applies. Lastly, our analysis and recommendations are based on our current understanding of the immunology literature. Because immunology is a rapidly evolving discipline, these terms must be periodically revisited, to establish consensus among scientists and educators, such that clear terminology can be shared with novice learners, newer instructors, and seasoned instructors. We also hope that immunology-focused societies and disciplinary experts will review emerging disciplinary knowledge to update the key terms and disseminate this knowledge to the broader community through periodicals and scholarly literature (Table I).

## DISCLOSURES

The authors have no financial conflicts of interest.

## ACKNOWLEDGMENTS

Dr. Brian D. Wisenden and Dr. Chris Merkord are duly acknowledged for help with statistical analysis–related questions.

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