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Piecing Complement Together with LEGO Bricks: Impacts on Interest, Confidence, and Learning in the Immunology Classroom

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ABSTRACT
Teaching and learning complex molecular cascades can often be challenging. In immunology, students struggle to visualize immunological processes, such as activation of the complement system, which involves three separate cascades leading to multiple effector functions. Offering learning activities that use tangible modeling can help students learn conceptually difficult content by fostering a visual understanding of concepts, as well as instill confidence and interest in the material. In this article, we describe a learning activity using LEGO bricks that demonstrates the activation of the classical, lectin, and alternative complement pathways and formation of the membrane attack complex. In both an introductory and advanced immunology course, we investigated the effect of the activity on student learning and subject confidence. Performance on examination questions about complement demonstrated that the LEGO activity improved learning in a naive student population (students in introductory immunology), but not in a previously informed student population (students in advanced immunology). In addition, self-reported confidence in the content was significantly higher in students who completed the LEGO activity in the advanced course, but not the introductory course, compared with those who did not do the activity. Students in both courses who did the activity had a positive perception of the activity, with a majority of students reporting that they enjoyed the activity and had more interest in the complement system.

INTRODUCTION
Teaching immunology at any level can be difficult for several reasons. First, as a specific discipline, immunology requires a basic understanding of cell biology, genetics, and microbiology. Second, immunology also requires students to understand distinct terminology before grasping immunological concepts. Finally, many concepts in immunology are not easy to visualize, so the transfer of knowledge can be difficult. Thus, teaching immunology in the undergraduate classroom can be especially challenging because of the varied academic backgrounds of the students, where the unique combination and timing of prior science courses influence the foundational knowledge on which students build.

A step toward increasing student learning and engagement in the immunology classroom is recognizing that not all students learn the same way and providing different instructional methods that appeal to a range of student interests, a characteristic of the differentiated classroom (1). Differentiated instruction is the use of varied learning methodologies to meet the needs of heterogeneous learners in the classroom (2). Although the concept of differentiated instruction is well-known and even “common sense” in some regards, its application is quite varied in primary, secondary, and postsecondary classrooms, and evidence of its positive influence on student outcomes is scarce (3). However, there is evidence that differentiated instruction in high school and college classrooms increases student engagement (4, 5). Importantly, student engagement in activities offered in both the...
classroom and on campus correlates with increased (and higher-level) learning and personal development (6). Thus, acknowledging that students enter the immunology classroom with unique learning preferences, as well as with unique content knowledge, is important for creating a variety of learning activities that can effectively engage students and foster their learning of the material.

The understanding of many complex biological concepts is often difficult, likely because they cannot be directly observed. Creating a mental visualization and grasping the three-dimensional nature of the molecules and structures involved in immunological processes is key to understanding. The use of hands-on, or physical, models is one type of instructional modality that has been shown to improve student understanding (7–11). LEGO bricks are one of the most popular toys worldwide, and their popularity as a teaching tool, particularly for providing a hands-on model, is expanding. LEGO bricks have been used as models for teaching DNA replication (12), protein synthesis (13), concepts in evolutionary developmental biology (14), glucose metabolism (15), and the octet rule (16). Furthermore, the use of LEGO bricks to model respiration and photosynthesis increased student learning and promoted a favorable view of metabolism (17).

An excellent example of a complex molecular pathway is the complement system, a system of >40 soluble proteins, receptors, and regulators, which is best known for its ability to augment and regulate activities in both the innate and adaptive immune systems. The important and complex role of the complement system in protective immune responses is evidenced by the >40 proteins that work cooperatively to activate multiple pathways and execute several functional outcomes, including (but not limited to) phagocytosis, enhancement of vascular permeability, leukocyte recruitment, and pathogen lysis (18). Furthermore, the complement system generates a serine protease cascade that produces complement cleavage products with diverse functions, as well as enzyme complexes that regulate further steps in the complement cascade (19, 20). In addition, while the complement nomenclature continues to evolve, some components have been named based on historical identification rather than function, adding to difficulty in teaching and learning (21). Due to this complexity, the complement system is often considered a daunting subject for students in undergraduate immunology courses, increasing the difficulty associated with teaching about the topic (H.A. Bruns, J.J. Baty, and M.C. Greenlee-Wacker, unpublished observations).

The University of Alabama at Birmingham (UAB) offers a unique 4-year undergraduate immunology major. Students in this program take an introductory immunology course in their sophomore year, concomitantly with courses in the introductory biology and chemistry series (22). Thus, students in the introductory immunology course have varied scientific knowledge, based on the sequence of courses they have completed. Although there are limited educational resources for teaching immunology at the undergraduate level (23), to support individual student success, course instructors address differences in knowledge bases and learning preferences by employing a variety of instructional methods in this course and subsequent courses in the major. In this study, instructors of two of the core courses in the immunology major, MIC 275 (Introduction to the Immune System) taken by sophomores, and MIC 401 (Innate Immunity), an advanced course taken by juniors, provided students the opportunity to do a “hands-on” activity that uses LEGO bricks to demonstrate the multiple activation pathways of the complement system following a short lecture introducing the complement system and its activation pathways. The goal of this study was to (1) determine the efficacy of the activity on student learning and subject confidence and (2) to provide immunology educators with a demonstrated efficacious activity that can be implemented to diversify pedagogical repertoires and aid student learning and confidence in the immunology classroom. In addition, differences in the effectiveness of the learning activity among student populations in an introductory immunology course versus advanced immunology were examined.

**MATERIALS AND METHODS**

**Participants**

Students enrolled in MIC 275 (Introduction to the Immune System) in the spring of 2022 and MIC 401 (Innate Immunity) in the fall of 2021 participated in the class activity. Both of these courses are required for the undergraduate immunology major at UAB, and students enroll in these courses in adjacent semesters (spring semester sophomore year and fall semester junior year). Complement is introduced in MIC 275 and then covered the following semester in more detail in MIC 401. This activity was optional, and students were given the choice to remain in class or leave early after a brief introduction to the complement system. Of the 32 students in MIC 275, 23 participated in the activity. In MIC 401, 19 of 32 students participated in the activity. This study was approved by UAB’s Institutional Review Board (protocol #300008092).

**LEGO model activity**

The purpose of this activity was to provide a supplemental application of the material covered via lecture. Before the class session, students were given a five-question pretest (Table I). At the start of the 75-min class session with the activity, students were given a 35-min lecture introducing the complement system, describing the components, multiple activation pathways, and formation of the membrane attack complex. After the lecture, students were offered a LEGO activity that provided a hands-on model activity for all three activation pathways and formation of the membrane attack complex. Students were given the remainder of the class session (40 min) to complete the activity. This was an optional activity, and students were assured there was no penalty if they chose to leave. Students who chose to participate could work in a group or as individuals, and they were allowed to select any one of three packets that contained a baseplate that represented a pathogen with LEGO bricks (LEGO Group, Billund, Denmark) that

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represented an activating complement protein/complex bound to it. In addition, LEGO bricks that represented the remainder of the entire pathway leading to the membrane attack complex (Fig. 1), along with an instruction sheet (Supplemental Information), were provided to demonstrate the activation pathway and membrane attack complex. Packets for each of the three activating pathways were available. A facilitator guide was provided to instructors. However, modifications to the facilitator guide were made for this publication (Supplemental Information) to provide additional information and alternative modeling options.

**TABLE I. Questions to assess content knowledge**

<table>
<thead>
<tr>
<th>No.</th>
<th>Question</th>
<th>Distractors</th>
<th>Bloom's Level</th>
</tr>
</thead>
</table>
| 1   | Which of the following complement proteins is not a direct component of the membrane attack complex? | *a. C4  
b. C5  
c. C6  
d. C7  
e. C9 | Remember      |
| 2   | Which of the following is characteristic of the alternative complement pathway? | a. It is initiated by the binding of MBL to mannose.  
b. It requires the spontaneous hydrolysis of C3.  
c. It involves C2 and C4.  
d. It does not lead to the activation of the membrane attack complex. | Understand    |
| 3   | When an individual has never previously been exposed to a bacterium, the classical complement pathway is MOST likely activated by which of the following? | *a. C-reactive protein (CRP) binding to the surface of the bacterium  
b. Molecules released from neutrophil granules bound to the surface of the bacterium  
c. The binding of mannose binding lectin to carbohydrates on the bacterium  
d. IgG bound to the surface of the bacterium | Apply         |
| 4   | Which of the following complement proteins binds C3b to form the alternative C3 convertase? | a. Db  
b. Bb  
c. C2b  
d. C5b | Remember      |
| 5   | Which of the following is NOT a molecule that must bind to the surface of a pathogen to activate a complement pathway? | *a. MBL  
b. IgM  
c. Factor D  
d. C3 | Understand    |

Five questions were used for the pretest, unit examinations, and cumulative final examination (MIC 401 only). Asterisks indicate the correct answer.

**Data collection**

Students in both courses were given a quiz with five multiple-choice questions (Table I) before doing the LEGO activity. These questions assessed the ability of students to identify and recognize the proteins of the different complement activation pathways, understand different pathway characteristics, and identify the proteins of the membrane attack complex. These questions were representative of several of Bloom’s taxonomy categories with two questions asking students to “remember,” two questions asking students to “understand,” and one question asking students to “apply.” The same five questions were also included in the unit examinations of both courses and in MIC 401 on the cumulative final examination. Because the same questions were used on the pretest and the posttests (examinations), answers were not given to students after the pretest so as to not encourage rote memorization. Six questions assessing student confidence in the content were included at the end of the MIC 275 U examination and MIC 401 cumulative final (Table II). The week following the unit examination, students were given an anonymous survey (Qualtrics, Provo, UT) and asked to rate their perception of the activity and their learning. The timing of the assessments with regard to the activity and survey varied between courses (Fig. 2). The amount of time from the pretest to the unit examination was identical (27 d). However, in MIC 275, the activity was done 13 d after the pretest, whereas in MIC 401, the activity was done 1 d after the pretest. In MIC 401 only, a cumulative final was given that also included the five content questions.

**Statistical analyses**

All statistics were performed using GraphPad Prism (GraphPad Prism version 9.2.0 for Windows; GraphPad Software, San Diego, CA). Normality was assessed using the Shapiro–Wilk test. Further statistical tests were performed where indicated.

**RESULTS**

In both MIC 275 and MIC 401, content questions were administered before and after the activity (pretest and unit examination), and student performance was assessed. In the introductory course MIC 275, students who completed the LEGO activity had a 58% increase in scores for the content questions on the unit examination compared with the pretest (Fig. 3A). Although average scores on content questions in the unit examination were higher among students who did not participate in the LEGO
activity (31%), these learning gains were not significantly different from the scores on the pretest (Fig. 3A). In contrast, in MIC 401, students performed significantly better on content questions on the unit examination compared with the pretest regardless of completing the LEGO activity (Fig. 3B). There were no differences in either pretest or posttest results between students who did or did not participate in the activity.

To investigate the possibility that the optional nature of this learning activity may have introduced a selection bias that influenced the learning gains observed in MIC 275 (Fig. 3A), student performance on the unit examinations (Fig. 4A, 4C), not just the content questions contained in the examinations, and overall course grades (Fig. 4B, 4D) were compared between students who did the activity and those who did not. There was no statistically significant difference in unit examination performance between the two student populations in either course (Fig. 4A, 4C). There was also no difference in overall course grades between students who did or did not do the LEGO activity in MIC 275 (Fig. 4B). However, students who did the activity in MIC 401 had higher course grades compared with those who did not do the activity (Fig. 4D).

As described earlier, MIC 275 and MIC 401 are sequential courses in the major, but they have different emphasis on content and types of assessment. Unlike MIC 275, in MIC 401, students take a comprehensive final examination. Although the LEGO activity did not improve learning as demonstrated by performance on content questions in MIC 401, it is possible that the use of a hands-on model would aid in student retention of content knowledge. Including the same five pretest questions on the cumulative final examination in MIC 401 provided an opportunity to investigate the effect of the LEGO activity on longer-term retention of content (42 d from the activity to the final). However, as previously observed from the MIC 401 unit examination, no significant difference in learning between student groups was observed, although overall performance on the questions improved. In this instance, all five questions had >75% correct, potentially because of the repeated exposure to the questions (Fig. 5A). For four of the five questions, there was a positive learning gain for students who completed the LEGO activity compared with those who did not (Fig. 5B), with the biggest improvement being question 4 (Table I).

To assess student confidence on content, we asked students six questions about their complement knowledge (Table II) at the end of either the cumulative final in MIC 401 or unit examination in MIC 275. In contrast with the findings about learning, confidence among students who did the LEGO activity in MIC 275 was not significantly higher compared with those who did not do the activity, although self-reported confidence was increased overall (Table II, Fig. 6A). Although learning was not significantly improved by the LEGO activity in MIC 401, confidence in the content was significantly higher among students who completed the LEGO activity (Fig. 6B). In addition, for students in MIC 401 who did the LEGO activity, confidence correlated with increased performance on the unit examination questions about complement content (Fig. 7D). In contrast, this was not observed for students in MIC 275 who did the LEGO activity (Fig. 7B), nor was there any correlation between confidence and question performance among students in either class who did not do the activity (Fig. 7A, 7C).

Overall, students in both courses who did the activity had a positive perception of the activity as assessed by survey questions. More than 80% of students who did the LEGO activity in both courses responded in the affirmative when asked if they enjoyed the activity and >70% when asked whether the activity increased their interest in the content (Table III).

**DISCUSSION**

The purpose of this learning activity is to lessen the difficulty associated with teaching concepts in immunology that are not easily visualized by aiding students in learning about the complement system through the use of LEGO bricks as a hands-on model. The data from this study demonstrated that the LEGO activity improved learning in a naive student population (MIC 275, introductory immunology) compared with students who did not participate in the activity. Interestingly,
The findings from this study support prior findings that active learning has been shown to increase student learning in the STEM (science, technology, engineering, and mathematics) classroom (24–26). However, they also highlight variations in learning outcomes in different student populations, given that the significant learning gains of students who completed the LEGO activity compared with those who did not was observed only in the introductory course and not the advanced immunology course (Fig. 3). Although interesting, this finding is not surprising. It may be simply explained by the fact that all of the students in the advanced course had prior exposure to content when they took the introductory course, MIC 275, the previous semester. The explanation may also not be a simple one, given the vast variation of preferred learning styles and perceptions that occurs between students within a course but also collectively across different courses. Students’ attitudes toward active learning methods compared with traditional lectures are variable. Studies have demonstrated that students prefer traditional lectures over active learning activities (27), while other studies have shown that students have a positive attitude toward active learning methodologies when they can directly connect their usefulness in learning (28, 29). Furthermore, although active learning methods in the science classroom increase student learning, students feel like they learn less (30). It is possible that in the introductory immunology course, the active learning

### Table II. Effect of the LEGO activity on student confidence in the subject

<table>
<thead>
<tr>
<th>Questions</th>
<th>Course</th>
<th>Activity</th>
<th>n</th>
<th>Very Confident (%)</th>
<th>Confident (%)</th>
<th>Not Confident (%)</th>
<th>Unsure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I can describe why the complement system is important.</td>
<td>MIC 275</td>
<td>–</td>
<td>9</td>
<td>44.44</td>
<td>44.44</td>
<td>11.11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>23</td>
<td>52.17</td>
<td>47.83</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I can identify the recognition molecules that activate a specific complement pathway.</td>
<td>MIC 275</td>
<td>–</td>
<td>9</td>
<td>33.33</td>
<td>44.44</td>
<td>22.22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>23</td>
<td>52.17</td>
<td>43.48</td>
<td>4.35</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I can describe the differences between the three activation pathways of complement.</td>
<td>MIC 275</td>
<td>–</td>
<td>9</td>
<td>33.33</td>
<td>47.83</td>
<td>47.83</td>
<td>4.35</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>23</td>
<td>57.89</td>
<td>36.84</td>
<td>5.26</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I can describe the steps of each pathway that leads to the formation of the C3 convertase.</td>
<td>MIC 275</td>
<td>–</td>
<td>9</td>
<td>22.22</td>
<td>55.56</td>
<td>22.22</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>23</td>
<td>69.57</td>
<td>26.09</td>
<td>4.35</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I can describe the steps that are required to form the membrane attack complex.</td>
<td>MIC 275</td>
<td>–</td>
<td>9</td>
<td>22.22</td>
<td>66.67</td>
<td>11.11</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>23</td>
<td>86.96</td>
<td>13.04</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I can identify the recognition molecules that activate a specific complement pathway.</td>
<td>MIC 275</td>
<td>–</td>
<td>13</td>
<td>61.54</td>
<td>30.77</td>
<td>7.69</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>19</td>
<td>68.42</td>
<td>26.32</td>
<td>5.26</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I can describe the differences between the three activation pathways of complement.</td>
<td>MIC 275</td>
<td>+</td>
<td>23</td>
<td>33.33</td>
<td>33.33</td>
<td>33.33</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>19</td>
<td>46.15</td>
<td>46.15</td>
<td>7.69</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>I can describe the steps of each pathway that leads to the formation of the C3 convertase.</td>
<td>MIC 275</td>
<td>–</td>
<td>13</td>
<td>43.48</td>
<td>47.83</td>
<td>15.38</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>19</td>
<td>73.68</td>
<td>21.05</td>
<td>5.26</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Data are depicted as percentage of respondents reporting confidence that they did not (–) or did (+) complete the LEGO activity in both MIC 275 and MIC 401 courses.
style of the LEGO activity was a preferred learning style of more students as compared with the advanced immunology course and thus improved learning gains.

Another factor to consider is the possibility that the nature of the activity was more attractive to higher-performing students and thus resulted in selection bias. Indeed, studies have shown that students perform better academically when learning via their preferred method (4, 5). Furthermore, a recent study demonstrated that honor students and women are more likely to choose collaborative learning environments (31), which may be because of a preference for active learning methods. Although selection bias could have been a factor influencing learning outcomes, the findings from the introductory course demonstrate that the student populations (those who did and did not do the activity) in the introductory immunology course were comparable (Fig. 4A, 4B). However, selection bias may have obscured differences in learning gains in the advanced immunology course such that students completing the activity in MIC 401 did not demonstrate increased learning gains (Fig. 3B) but had increased unit examination scores (Fig. 4C) and significantly increased course grades compared with those who did not do the activity (Fig. 4D). In addition, the optional nature of

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**FIGURE 2. Timeline of the assessments and class activity.**
Differences in the structures of the courses resulted in differences in timing between the pretest, activity, and unit examination.

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**FIGURE 3. Effect of the LEGO activity on student learning.**
Students in MIC 275 (A) and MIC 401 (B) who did not (black circles) or did (gray squares) complete the LEGO activity were given five content questions as a pretest (pre) before the LEGO activity. The same five content questions were given on the unit examination (post). Student performance was assessed by comparing pretest results with posttest results by question. Each data point represents one question. n = 5; error bars represent SD; **p < 0.001, ***p < 0.0001 (two-way ANOVA with repeated measures with Sidak’s post hoc analysis).

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**FIGURE 4. Influence of student population on learning effectiveness of the LEGO activity.**
Unit examination scores and course grades of students in MIC 275 (A and B) and MIC 401 (C and D) who did not (−LEGO) or did (+LEGO) complete the LEGO activity were compared with assessment differences in examination performance. Each data point represents a single student (MIC 275: −LEGO n = 9, +LEGO n = 23; MIC 401: −LEGO n = 13, +LEGO n = 19). Error bars represent SD; *p > 0.05 (Mann–Whitney U test).
this activity led to a smaller proportion of students not participating in the activity, especially in MIC 275 (9 nonparticipants versus 23 participants in MIC 275 and 13 nonparticipants versus 19 participants in MIC 401). Interestingly, the data demonstrate that the activity significantly increased confidence in the material among students who did the activity in the advanced course (Fig. 6B), but not the introductory course, when compared with peers who did not do the activity (Fig. 6A).

FIGURE 6. The LEGO activity increased student confidence on complement.
Percentage of students who did not (−) or did (+) complete the LEGO activity in MIC 275 (A) and MIC 401 (B) reporting confidence. Each data point represents a survey question (n = 6). Individual students responding with “strongly confident” or “confident” were grouped together and represented as “confident.” Differences in level of confidence (confident, not confident, and unsure [when applicable]) were determined by performing a Mann–Whitney U test (*p < 0.05, **p < 0.01). Error bars represent SD.

FIGURE 7. Correlation between content performance and confidence.
Performance on complement questions on the unit examination was compared by self-reported confidence by students who did not complete the LEGO activity in MIC 275 (n = 9) (A) and MIC 401 (n = 13) (B) and students who did complete the LEGO activity in MIC 275 (n = 23) (C) and MIC 401 (n = 19) (D) (Pearson correlation).

However, students in the introductory course who did not participate in the activity reported being not confident more than the students in the advanced course, further highlighting the differences between naive and seasoned students (Table II,
The LEGO activity indicated that students enjoyed doing the activity and had increased interest in learning about the complement system. In contrast, a majority did not agree that the activity helped them understand how the complement system is activated. The findings from this study examining the effectiveness of the learning activity on learning outcomes and confidence highlight the academic diversity encountered in the undergraduate immunology classroom. Although significant learning outcomes and increased confidence were not observed in both the introductory and advanced courses, the overall positive perception of the activity by students suggests that the inclusion of more visual and hands-on activities in the undergraduate immunology classroom may bolster student engagement in the learning process. The findings from this study examining the effectiveness of the learning activity on learning outcomes and confidence highlight the academic diversity encountered in the undergraduate immunology classroom. Although significant learning outcomes and increased confidence were not observed in both the introductory and advanced courses, the overall positive perception of the activity by students suggests that the inclusion of more visual and hands-on activities in the undergraduate immunology classroom may bolster student engagement in the learning process.

### DISCLOSURES

The authors have no financial conflicts of interest.

### ACKNOWLEDGMENTS

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### REFERENCES


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**TABLE III. Student perception of the LEGO activity**

<table>
<thead>
<tr>
<th>Questions</th>
<th>Course</th>
<th>n</th>
<th>Agree (%)</th>
<th>Neutral (%)</th>
<th>Disagree (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doing the LEGO activity made it easier for me to understand how complement is activated.</td>
<td>MIC 275</td>
<td>19</td>
<td>52.63</td>
<td>42.11</td>
<td>5.26</td>
</tr>
<tr>
<td></td>
<td>MIC 401</td>
<td>14</td>
<td>57.14</td>
<td>28.57</td>
<td>14.29</td>
</tr>
<tr>
<td>Doing the LEGO activity made it easier for me to memorize the components of the complement pathways.</td>
<td>MIC 275</td>
<td>19</td>
<td>42.11</td>
<td>36.84</td>
<td>21.05</td>
</tr>
<tr>
<td></td>
<td>MIC 401</td>
<td>14</td>
<td>50</td>
<td>35.71</td>
<td>14.29</td>
</tr>
<tr>
<td>Doing the LEGO activity helped me do better on the examination.</td>
<td>MIC 275</td>
<td>19</td>
<td>47.37</td>
<td>36.84</td>
<td>15.79</td>
</tr>
<tr>
<td></td>
<td>MIC 401</td>
<td>14</td>
<td>28.57</td>
<td>42.86</td>
<td>28.57</td>
</tr>
<tr>
<td>I enjoyed doing the LEGO activity.</td>
<td>MIC 275</td>
<td>19</td>
<td>84.22</td>
<td>10.53</td>
<td>5.26</td>
</tr>
<tr>
<td></td>
<td>MIC 401</td>
<td>14</td>
<td>85.71</td>
<td>14.29</td>
<td>0</td>
</tr>
<tr>
<td>I had more interest in learning about complement by doing the LEGO activity.</td>
<td>MIC 275</td>
<td>19</td>
<td>73.69</td>
<td>10.53</td>
<td>15.79</td>
</tr>
<tr>
<td></td>
<td>MIC 401</td>
<td>14</td>
<td>92.85</td>
<td>7.14</td>
<td>0</td>
</tr>
</tbody>
</table>

Data are depicted as percentage of respondents (who did the LEGO activity) reporting agreement with statements about the activity in both MIC 275 (n = 19) and MIC 401 (n = 14).

Fig. 6). It is also worth noting that although student confidence was not statistically significantly different in MIC 275 students who did the activity compared with those who did not, the data indicate that confidence was higher in students who participated (Table II, Fig. 6). This is especially relevant for traditionally marginalized/excluded students in STEM, where enhancing confidence is particularly important (32, 33). Student perception of a subject influences academic achievement, and enhancing confidence is particularly important (32, 33). Students with more confidence in and enthusiasm for a subject are more likely to do well (34). Also, student confidence in a subject is strongly correlated with performance (35). Thus, it is possible that although those who did the activity did not have improved learning outcomes over those who did not do the activity, the confidence gained in the subject by doing the activity provided learning benefits beyond the subject content of the activity.

Interestingly, the majority of students who did the LEGO activity indicated that they enjoyed doing the activity and had increased interest in learning about the complement system. In contrast, a majority did not agree that the activity helped them understand how the complement system is activated. Prior investigations have demonstrated that a variety of active learning methodologies can improve student attitudes toward learning (36–38), and a recent report demonstrated that graduate and undergraduate students in STEM courses would prefer more active learning and less lecturing than is practiced in their courses currently. Although a preferred universal type of active learning modality was not identified, student responses demonstrated a mostly positive attitude regarding prior active learning experiences (39). Beyond learning outcomes, there were several positive outcomes using this learning activity. The LEGO activity provided an opportunity for instructors to identify student misconceptions and foster robust discussion between peers and instructors. As an example, some students used the LEGO bricks to build a tower of complement protein interactions versus attaching the LEGO bricks directly to the “pathogen” plate, which stimulated a conversation among the instructors and several groups about how and why complement proteins need to assemble on the pathogen surface. Furthermore, students within groups were asking questions that were not asked during lecture, and peers within the groups were providing correct answers (personal observations by instructors).

Although historically reserved for the graduate level, training in immunology is expanding at the undergraduate level. This poses challenges because immunology is multidisciplinary and requires an integrated understanding of science that undergraduates are building on concurrently. This hands-on LEGO bricks learning activity was created to aid in the teaching of challenging material and bolster student engagement in the learning process. The findings from this study examining the effectiveness of the learning activity on learning outcomes and confidence highlight the academic diversity encountered in the undergraduate immunology classroom. Although significant learning outcomes and increased confidence were not observed in both the introductory and advanced courses, the overall positive perception of the activity by students suggests that the inclusion of more visual and hands-on activities in the undergraduate immunology classroom may bolster student engagement that could lead to positive outcomes beyond learning gains.


Learning Complement Activation Using LEGO® bricks

For instructors:
Print the sheets below (pages 2-7) for as many LEGO® sets as you have for the class.

Display the question below on classroom overhead at the start of the activity:

The LEGO® baseplate is the surface of a pathogen. Use the LEGO® bricks to diagram how complement proteins interact with one another to activate the complement pathway and form the Membrane Attack Complex (MAC) on the surface of the pathogen.

1. What is (are) the recognition molecule(s)? So what complement pathway is being activated?
CLASSICAL PATHWAY

1. Here is the list of complement proteins and LEGO® bricks for the CLASSICAL PATHWAY
   a. C2 2x2 Blue, 2x1 Light blue
   b. C4 2x2 Black, 2x1 Gray
   c. C3 2x2 Pink, 2x1 Light pink
   d. C5 2x2 Yellow, 2x1 Light yellow
   e. C6 2x2 Orange
   f. C7 2x2 Purple
   g. C8 2x2 White
   h. C9 1x1 Dark gray

2. Questions to answer
   a. The baseplate has only IgG antibodies attached to it. What other molecules can activate the classical pathway?
   b. What are the components of the C3 convertase?
   c. What are the components of the C5 convertase?
   d. What do the smaller light gray, light pink, and light yellow LEGO® bricks represent?

3. Check your answers and your LEGO® creation with the picture provided in the bag.
(Printed and handed to students along with the baggie of LEGO®s for the lectin pathway)

LECTIN PATHWAY

1. Here is the list of complement proteins and LEGO® bricks for the LECTIN PATHWAY
   a. C2 2x2 Blue, 2x1 Light blue
   b. C4 2x2 Black, 2x1 Gray
   c. C3 2x2 Pink, 2x1 Light pink
   d. C5 2x2 Yellow, 2x1 Light yellow
   e. C6 2x2 Orange
   f. C7 2x2 Purple
   g. C8 2x2 White
   h. C9 1x1 Dark gray

1. Questions to answer
   a. The baseplate has only lectins (mannose carbohydrates) attached to it. Can other molecules activate the lectin pathway?
   b. What are the components of the C3 convertase?
   c. What are the components of the C5 convertase?
   d. What do the smaller light gray, light pink, and light yellow LEGO® bricks represent?

2. Check your answers and your LEGO® creation with the picture provided in the bag.
ALTERNATIVE PATHWAY
1. Here is the list of complement proteins and LEGO® bricks for the ALTERNATIVE PATHWAY
   a. C3 2x2 Brown, 2x1 angle Brown, 2x1 Light brown
   b. Factor B 2x2 Yellow, 2x1 Light yellow (may also be 2x2 Blue, 2x1 Light blue)
   c. C5 2x2 Pink, 2x1 Light pink
   d. C6 2x2 Orange
   e. C7 2x2 Purple
   f. C8 2x2 White
   g. C9 1x1 Dark gray

2. Questions to answer
   a. The baseplate has a brown square but also a different shape that is also brown, what do these represent? There is a light brown smaller LEGO® brick in the bag, what does it represent and why is it not initially attached to the baseplate?
   b. If those “brown” molecules had been created (cleaved) and not stuck to the surface of the pathogen (baseplate), would this complement pathway be activated?
   c. What are the components of the C3 convertase?
   d. What are the components of the C5 convertase?
   e. What do the smaller light brown and light pink LEGO® bricks represent?

3. Check your answers and your LEGO® creation with the picture provided in the bag.
CLASSICAL PATHWAY (folded insert placed in the bag)

1. Questions to answer
   a. The baseplate has only IgG antibodies attached to it. What other molecules can activate the classical pathway?
      i. IgM, CRP can attach to a pathogen and bind C1q
   b. What are the components of the C3 convertase?
      i. C4bC2b
   c. What are the components of the C5 convertase?
      i. C4b2b3b
   d. What do the smaller light gray, light pink, and light yellow LEGO® bricks represent?
      i. They are the smaller cleavage parts C4a, C3a, C5a. C3a and C5a are anaphylatoxins (enhance/activate inflammation).

2. Check your answers and your LEGO® creation with the picture provided in the bag.
LECTIN PATHWAY (folded insert placed in the bag)

1. Questions to answer
   a. The baseplate has only mannose carbohydrates attached to it. Can other molecules activate the lectin pathway?
      i. Any carbohydrate on a pathogen that Mannose-binding ligand (MBL) can bind can activate this pathway
   b. What are the components of the C3 convertase?
      i. C4bC2b
   c. What are the components of the C5 convertase?
      i. C4b2b3b
   d. What do the smaller light gray, light pink, and light yellow LEGO® bricks represent?
      i. They are the smaller cleavage parts C4a, C3a, C5a. C3a and C5a are anaphylatoxins (enhance/activate inflammation).

2. Check your answers and your LEGO® creation with the picture provided in the bag.
1. Questions to answer
   a. The baseplate has a brown square but also a different shape that is also brown, what do these represent?
      i. It represents the C3(H2O) form of C3 – the “tickover”, 1% of C3 undergo spontaneous hydrolysis to expose a bond so that Factor B can bind. Once factor B binds C3(H2O), the complex can be cleaved by factor D. The cleaved complex can attach to the pathogen surface and begin cleaving more C3
   b. If those “brown” molecules had been created (cleaved) and not stuck to the surface of the pathogen (baseplate), would this complement pathway be activated?
      i. No. C3(H2O) are continually made (tickover) but they are quickly inactivated if there is no surface to which they can attach – this is a protective mechanism, so complement is not randomly activated.
   c. There is a light brown smaller LEGO® brick in the bag, what does it represent and why is it not initially attached to the baseplate?
      i. C3a, it is not attached to the baseplate because it is not a part of the activation steps of the alternative pathway
   d. What are the components of the C3 convertase?
      i. C3bBb
   e. What are the components of the C5 convertase?
      i. C3bBbC3b
   f. What do the smaller light brown and light pink LEGO® bricks represent?
      i. Smaller cleavage products, C3a and C5a, which can enhance inflammation as anaphylatoxins

2. Check your answers and your LEGO® creation with the picture provided in the bag.
Learning Complement Activation Using LEGO® bricks

For the instructor, when ready to do the activity:
1. Add the starting molecules, representing each of the pathways, to the baseplates (pictures below). This can also be done ahead of the activity, such as at the start of class.
   a. Depending on how many LEGO® sets are available, this can be done individually or in groups.
2. Display question #1 along with the instructions for students below on the classroom overhead.

Instructions: The LEGO® baseplate is the surface of a pathogen. Your instructor will be adding recognition molecules and complement proteins to the baseplates.

Question 1: What is (are) the recognition molecule(s) and complement proteins attached to the baseplate? So what complement pathway is being activated?

Instructions: Once you pick a plate and correctly identify the pathway from the starting molecule(s), use the LEGO® bricks to diagram how complement proteins interact with one another to activate the complement pathway and form the Membrane Attack Complex (MAC) on the surface of the pathogen.

CLASSICAL

LECTIN

ALTERNATIVE
Once the instructor is ready, students will select a plate, identify the recognition molecule and correct pathway to the instructor. The instructor can then give the corresponding bag of LEGO®s to the group (or individual) to build out the rest of the pathway.

Along with the LEGO® bricks, two printed sheets will also be in the bag:
1. The list of LEGO® brick colors and corresponding questions
2. A photo of a completed activation pathway with MAC for comparison with what they create and answer to the question.

The goal is to diagram how complement proteins interact with one another to activate the pathway and form the Membrane Attack Complex (MAC) on the surface of the pathogen and answer the following questions.

Encourage students to work through the alternative pathway and either the classical or lectin pathways so they can compare the differences and similarities of the pathways.

Also ask, if we had more LEGO®s, what would the baseplate look like if this were a pathogen surface?

Walk around to look at the creations. Ideally, the students would create something like the pictures below. If students stack the LEGO®s, discuss how that would require the proteins to bind to one another instead of binding to the pathogen.
CLASSICAL PATHWAY

1. Here is the list of complement proteins and LEGO® bricks for the CLASSICAL PATHWAY
   a. C2 2x2 Blue, 2x1 Light blue
   b. C4 2x2 Black, 2x1 Gray
   c. C3 2x2 Pink, 2x1 Light pink
   d. C5 2x2 Yellow, 2x1 Light yellow
   e. C6 2x2 Orange
   f. C7 2x2 Purple
   g. C8 2x2 White
   h. C9 1x1 Dark gray

2. Questions to answer
   a. The baseplate has only IgG antibodies attached to it. What other molecules can activate the classical pathway?
      i. IgM, CRP can attach to a pathogen and bind C1q
      ii. Note: many other molecules besides CRP and IgM activate the classical pathway, such as apoptotic cells, beta-amyloid, etc.
   b. What are the components of the C3 convertase?
      i. C4b2b
   c. What are the components of the C5 convertase?
      i. C4b2bC3b
   d. What do the smaller light gray, light pink, and light yellow LEGO® bricks represent?
      i. They are the smaller cleavage parts C4a, C3a, C5a, but also are anaphylatoxins (enhance/activate inflammation)

3. Check your answers and your LEGO® creation with the picture provided in the bag.
Alternative Classical Pathway Modeling

Cascade schematic modified from C.L. Harris et al, Molecular Immunology, 2018
LECTIN PATHWAY
1. Here is the list of complement proteins and LEGO® bricks for the LECTIN PATHWAY
   a. C2 2x2 Blue, 2x1 Light blue
   b. C4 2x2 Black, 2x1 Gray
   c. C3 2x2 Pink, 2x1 Light pink
   d. C5 2x2 Yellow, 2x1 Light yellow
   e. C6 2x2 Orange
   f. C7 2x2 Purple
   g. C8 2x2 White
   h. C9 1x1 Dark gray

2. Questions to answer
   a. The baseplate has only mannose carbohydrates attached to it. Can other molecules activate the lectin pathway?
      i. Any carbohydrate on a pathogen that Mannose-binding ligand (MBL) (or other lectin pathway activator) can lead to activation of this pathway
      ii. Ficolins
   b. What are the components of the C3 convertase?
      i. C4b2b
   c. What are the components of the C5 convertase?
      i. C4b2b3b
   d. What do the smaller light gray, light pink, and light yellow LEGO® bricks represent?
      i. They are the smaller cleavage parts C4a, C3a, C5a, but C3a and C5a also are anaphylatoxins (enhance/activate inflammation)

3. Check your answers and your LEGO® creation with the picture provided in the bag.
Alternative Lectin Pathway Modeling

*The lectin pathway may also be initiated by ficolins and other collectins
Cascade schematic modified from C.L. Harris et al, Molecular Immunology, 2018
ALTERNATIVE PATHWAY

1. Here is the list of complement proteins and LEGO® bricks for the ALTERNATIVE PATHWAY
   a. Brown/lt brown – C3
   b. Yellow/lt yellow – Factor B (may also be Blue/lt blue)
   c. Pink/lt pink – C5
   d. Orange – C6
   e. Purple – C7
   f. White – C8
   g. Dark gray studs – C9

1. Questions to answer
   a. The baseplate has a brown square but also a different shape that is also brown, what do these represent?
      i. It represents the C3(H2O) form of C3 – the “tickover”, 1% of C3 undergo spontaneous hydrolysis to expose a bond so that Factor B can bind. Once factor B binds C3(H2O), the complex can be cleaved by factor D. the cleaved complex can attach to the pathogen surface and begin cleaving more C3
   b. If those “brown” molecules had been created (cleaved) and not stuck to the surface of the pathogen (baseplate), would this complement pathway be activated?
      i. No. C3(H2O) are continually made (tickover) but they are quickly inactivated if there is no surface to which they can attach – this is a protective mechanism, so complement is not randomly activated.
   c. There is a light brown smaller LEGO® LEGO® brick in the bag, what does it represent and why is it not initially attached to the baseplate?
      i. C3a, it is not attached to the baseplate b/c it is not a part of the activation steps of the alternative pathway
   d. What are the components of the C3 convertase?
      i. C3bBb
   e. What are the components of the C5 convertase?
      i. C3bBbC3b
   f. What do the smaller light brown and light pink LEGO® LEGO® bricks represent?
      i. Smaller cleavage products, C3a and C5a, which can enhance inflammation as anaphylatoxins

3. Check your answers and your LEGO® creation with the picture provided in the bag.
Alternative ‘Alternative Pathway’ Modeling

Cascade schematic modified from C.L. Harris et al, Molecular Immunology, 2018

*Tickover and contact with foreign surfaces may generate hydrolyzed C3 (C3H2O) which shares properties with C3b