Mind the Gap: Utilizing *Borrelia burgdorferi*, causative agent of Lyme Disease, as a model to study cells bridging innate and adaptive immunity

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north central United States such as Minnesota and Wisconsin. However, as the climate changes the range of the vector has spread, bringing Lyme disease with it.

Originally, the assumption was that the disease was an acute bacterial infection that could be cleared with one round of antibiotics; however, as the number of cases has increased, a clear subset of patients has emerged that have reoccurring symptoms long after the antibiotics have been stopped. There is current debate on whether this is a result of the bacteria living in a dormant phase and reappearing periodically, or whether it is a case of an autoimmune response that develops as a result of the infection.

STUDENT OUTCOMES:

Students will gain a basic understanding of the immune system and how it functions. More specifically, students will learn about the two different branches of the immune system through a test cell, the MAIT cell, and, at the end of the unit, will decide whether they believe the MAIT cell is more innate-like or adaptive by looking at the way that it functions in the body. Students will utilize data from flow cytometry as well as a case study on Lyme disease to further study the cells of the immune system and comprehend how they function together to keep a person healthy.

LEARNING OBJECTIVES:

At the completion of this unit students will be able to:

- Explain the adaptive and innate immune system
- Explain the cellular features of each type of cell
- Describe the MAIT cell and its role in immunity
- Defend a position on whether the MAIT cell should be categorized in the adaptive or innate immune system
- Analyze data from FACS flow cytometry
- Utilize data to form a position
- Write an argument discussing the position named above

STANDARDS:

The following Common Core and Next Generation Science Standards can be assessed from this unit:

- NGSS HS-LS1-2: Develop and use a model to illustrate the hierarchical organization of interacting systems that provide specific functions within multicellular organisms.
- CCSS.ELA-LITERACY.W.11-12.1: Write arguments to support claims in an analysis of substantive topics or texts, using valid reasoning and relevant and sufficient evidence.
- CCSS.ELA-LITERACY.SL.11-12.1: Initiate and participate effectively in a range of collaborative discussions (one-on-one, in groups, and teacher-led) with diverse partners

on grades 11-12 topics, texts, and issues, building on others' ideas and expressing their own clearly and persuasively.

- CCSS.ELA-LITERACY.SL.11-12.2: Integrate multiple sources of information presented in diverse formats and media (e.g., visually, quantitatively, orally) in order to make informed decisions and solve problems, evaluating the credibility and accuracy of each source and noting any discrepancies among the data.
- CCSS.ELA-LITERACY.RST.I.11-12.1: Cite specific textual evidence to support analysis of science and technical texts, attending to important distinctions the author makes and to any gaps or inconsistencies in the account.
- CCSS.ELA-LITERACY.RST.11-12.8: Evaluate the hypotheses, data, analysis, and conclusions in a science or technical text, verifying the data when possible and corroborating or challenging conclusions with other sources of information.

TIME REQUIREMENTS:

The following amount of time is recommended for the sequence in order to teach the unit in a depth that allows for student retention:

- 1 week pre-teaching innate and adaptive immune system
- 1 week learning the basics of the MAIT cell, and discussing the Lyme Disease application. As we learn, do we think that research should look at MAIT Cells as a potential indicator for Lyme Disease immune response? Why or why not?
- 1 week lab experience with local scientist and data analysis
- 1 week to prepare for Socratic seminar using a graphic organizer explaining the claim, counter claim, and supporting evidence, and then submit a final written opinion citing scientific evidence from readings, the lab experience, and the Socratic seminar.

ADVANCE PREPARATION:

Pre-teaching Immunology:

STUDENT PRIOR KNOWLEDGE:

Prior to beginning this unit, students should have a basic understanding of cells and the way that they function in the body. The immune system is typically taught at the end of an advanced biology or anatomy and physiology class. Therefore, students should have a basic understanding of best practices in the lab, and should have been exposed to multiple types of data for evaluation.

TEACHER FACING MATERIALS:

Document 1: Overview of the reading and writing process:

Immune System, NAIAD	Goal is to introduce students to the basics of immunology.	**Text Dependent Questions:** Student answers the attached questions while exploring the NIAID website to increase understanding around the immune system.
Clarifying notes	Used after website exploration before reading.	This ensures that all students have basic information written in notes prior to the start of the readings.
Socratic seminar	Get students to think and question what they are going to be reading about and what their wonderings are in this manner. Sample MAIT Cell Flow Cytometry Diagram of a MAIT Cell interaction	Give students the picture of a MAIT cell and a FACs plot. Have students write down at least 3 questions on each picture as homework. They can be basic "What is CD4?" or about the picture "Why is that box surrounding one area of the graph?" Have a doc open where students who are not speaking can catch all of the questions. It is important to verbalize to see if the questions build on each other and to see if additional wonderings come.
Post reading after the Socratic seminar	Mucosal-associated invariant T-cells: new players in anti-	

	bacterial immunity MAIT Cells Detect and Efficiently Lyse Bacterially-Infected Epithelial Cells	

Reading process:

Immune Cell 'Defenders' Could Beat Invading Bacteria	Overview of the Nature article that notes the discovery and overview of MAIT cells.	**Double-entry journal.** Have students read the article, summarizing the research on the left side and making personal connections or connections to notes from previous days on the right side. Should establish why students should care about this research and how it impacts them.
MAIT cells are licensed through granzyme exchange to kill bacterially sensitized targets	Original publication on the discovery of MAIT cells	

questions 1. What is the research? 2. Who does it help? 3. Why is this important to me? These questions should be answered in summary form.

Text-dependent questions: Use as a connection to discuss how the immune system plays a role in so many diseases. What are all of the different areas that we think of inflammation?

Fill in the outline	Use notes from the two notecatchers (preparing for the task and reading process).	There is a sample outline provided in the teacher guide. At this point, students should

flow machine. The benefit of this is that it allows an opportunity to create a partnership between the high school and local university.

Recommendation for reaching out:
Roughly a month before the unit begins, research (or assign a student to research) work being done at local universities that relates to immunology. Most PIs are more than happy to discuss their work with teachers and students, and many enjoy sharing in their excitement for immunology. One option is to ask the scientist to come out to the classroom and spend a day explaining their research to students, and to allow students to go through the experimental process of exposing Peripheral Mononuclear Blood Cells (PMBCs) to antibodies which will then be evaluated in flow cytometry. This would help students comprehend what exactly flow
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from the thymus, making them closer to the T cell than MAIT cells are. (Ussher et al., 2014)

C. Counter argument: One argument against this is that MAIT cells originate in the thymus, but the maturation occurs outside of it. While this is true, the maturation and recombination that occurs in the thymus is critical to the designation of adaptive cells.

IV. Body Paragraph 3:
   A. Main point: Ex. MAIT cells produce a cytokine response that recruits other cells to the site of the infection.
   B. Evidence: According to Cosgrove et al. (2013), MAIT cells produce IL17, which is a cytokine used in the inflammatory response and characteristic of innate immune cells.
   C. Counter argument: While the MAIT cell also contains receptors that are traditionally associated with the adaptive immune system, their cytokine response indicates an innate characteristic.

V. Optional Extension: Body Paragraph 4:
   A. From what you know, should MAIT cells be investigated further in relation to Lyme Disease? Why or why not?

VI. Conclusion
   A. MAIT cells are a unique subset of cells that contain features of both the adaptive and innate immune system. While they theoretically could be members of either part of the system, the innate system is the more logical choice because of the characteristics of these cells, such as their limited adaptations, their location of origin, and their production of cytokines.

References

Cosgrove et al. (2013) Early and nonreversible decrease of CD161++ /MAIT cells in HIV infection. Blood. 121:951-61.

Ussher et al. (2014) Mucosal-associated invariant T-cells: new players in anti-bacterial immunity. Front Immunol. 5:450.

Videos to Assist:

It can be helpful to utilize videos, particularly in support of visual learners. The following videos can be used in conjunction with the readings above to help students visualize the processes being discussed.

TLRs: https://www.youtube.com/watch?v=94emS00OIHc

Antigen presentation: https://www.youtube.com/watch?v=LwLYGTS_3EI

B cells and antibodies: https://www.youtube.com/watch?v=548wQ5C6ufQ

T cells: https://www.youtube.com/watch?v=V5wXrxupQmA

STUDENT GUIDE:

RATIONALE:

Write an analogy of the innate immune system.

Compare and contrast the different cells of the innate immune system. How do they all work together to create an effective response?

Inflammation:
Describe the mechanisms of inflammation. What is the purpose?

Describe the cells and chemicals involved in inflammation.

Describe the mechanism of fever and the roles of pyrogens.

Adaptive Immune System:
Cells:
Define immunocompetence and self-tolerance, and distinguish between naive and activated immune cells.

Compare and contrast B cells and T cells in the location where they originate and the location where they end up in the body.

Compare and contrast the defense mechanisms of each cell. When are they most effective, and why?

What is the structure of the antibody, and how does its structure relate to its function?

What differs between the adaptive and innate immune systems?

Vaccinations:
How do vaccines utilize the immune system to create immunity?

Is this immunity adaptive or innate? Explain your answer.

Communication:
A person has a disorder in which the complement system never activates. What would that person expect to see in terms of both intercellular and whole body symptoms?

What are cytokines and how do they function in the immune system?

What are MHCs and how do they assist in intercellular communication?

What are examples of Antigen Presenting Cells and where are they found?

Research frontiers:
Jigsaw the research frontiers and have students teach each other (in table groups of 4, each person picks one of the research frontiers).

Student Handout 2: Evidence Note Catcher to be used throughout the unit

As you complete your reading, utilize this chart to gather evidence of how MAIT cells have characteristics of the innate immune system, and how MAIT cells have characteristics of the adaptive immune system.

	Evidence that MAIT cells belong in innate	**Evidence that MAIT cells belong in adaptive**
Source Title: Source Author: Source Publication: Source Date:		
Source Title: Source Author: Source Publication: Source Date:		
Source Title:		