Teacher Resource for:

Population Dynamics of Immune Responses to Persistent Viruses

Using This Teacher Resource

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GENERAL USE OF Science in the Classroom

Student Learning Goals:

Current views of science education emphasize that “one fundamental goal for K-12 science education is a scientifically literate person who can understand the nature of scientific knowledge.” (From *A Framework for K-12 Science Education*, National Research Council, 2012).

The U.S. National Academy of Sciences defines science as: “Any new finding requires independent testing before it is accepted as scientific knowledge; a scientist is therefore required to honestly and openly report results so that they can readily be repeated, challenged, and built upon by other scientists. Proceeding in this way over centuries, the community effort that we call science has developed an increasingly accurate understanding of how the world works. To do so, it has had to reject all dogmatic claims based on authority, insisting instead that there be reproducible evidence for any scientific claim.”

A very important student learning goal, central to any understanding of “the nature of scientific knowledge,” is to give each student an appreciation of how science is done.

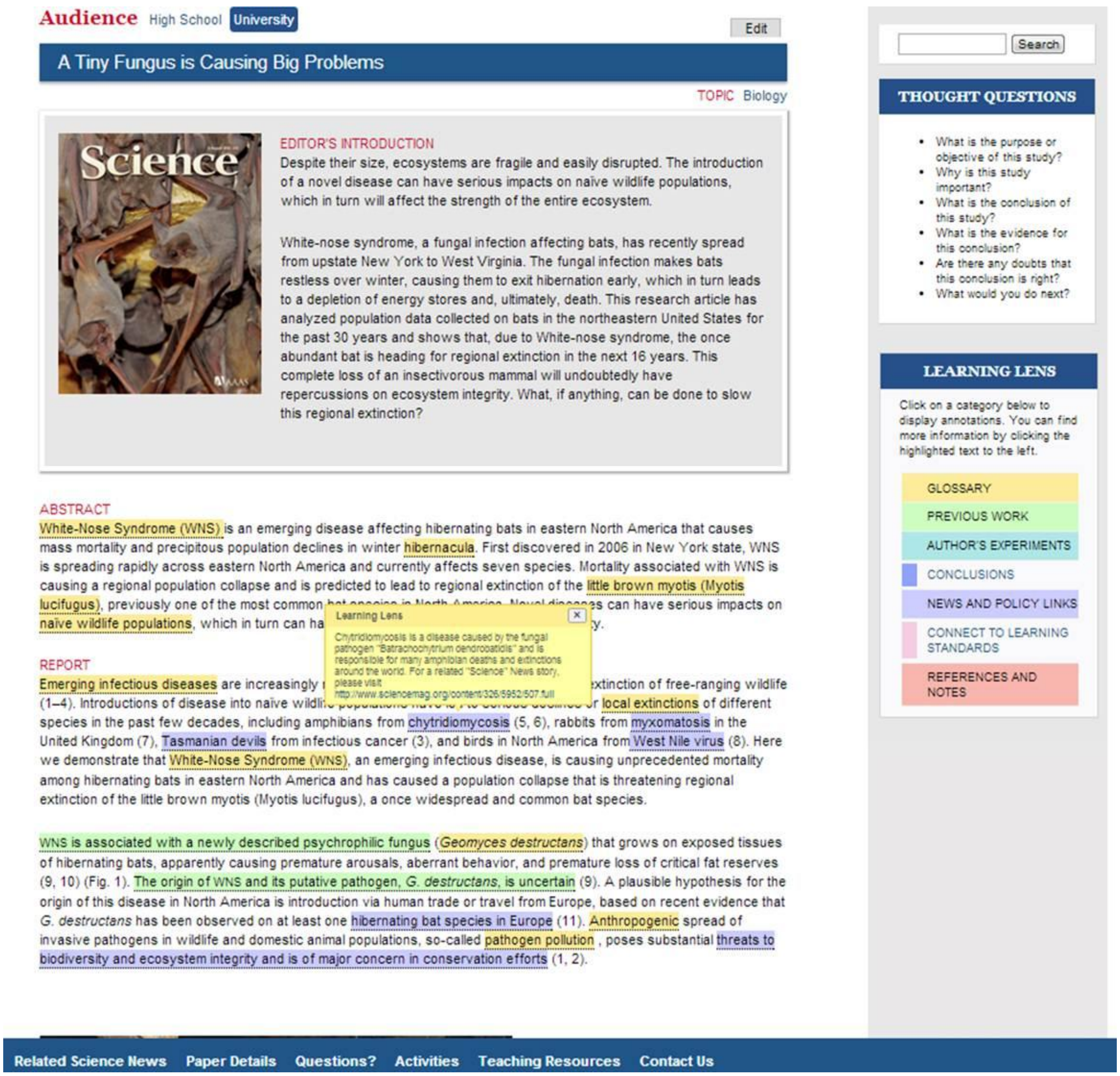
This includes knowing why:

- Scientists must be independent thinkers, who are free to dissent from what the majority believes.
- Science can deal only with issues for which testable evidence can be obtained.
- All scientific understandings are built on previous work
- It is to be expected that one scientist’s conclusions will sometimes contradict the conclusions of other scientists.
- Science is a never-ending venture, as the results from one study always lead to more questions to investigate.

Using This Resource

Learning Lens:

The Learning Lens tool can be found on the right sidebar of each resource and is the source of annotations. Clicking on any of the headings will result in corresponding text of the research article being highlighted. A second click on the highlighted text will produce a text box containing more information about that particular piece of text. Below is an example of the Glossary function of the Learning Lens in use.



An example of the resource with the Glossary, Previous Work, Author's Experiments, News and Policy Links, and References and Notes tools turned on. The Glossary tool is in use.

Learning Notes:

Learning Notes accompany each figure and are designed to help students deconstruct the methods and data analysis contained within each figure.

References:

The Reference section of each resource is annotated with a short statement about how or why each reference relates to the current research study.

Suggestions for Classroom Use:

Four alternative ways to use the SitC reading, questions, and activities:

1. Assign to small groups to complete during class

2. Assign different sections of the article to small groups to complete during class. Use class presentations or jigsaw to teach the entire class what is in the article.

3. Assign to individual students to complete during class or as homework.

4. Assign as an extra credit project.

Interactive student engagement ideas for use after reading the article:

1. Have students write answers to discussion questions (for example, those linked to the standards or those linked to the diagrams).

2. Go over the abstract, as well as information about the purpose and structure of an abstract, and have students write their own abstracts for the articles in language that could be best understood by their peers.

3. Have students edit the current version of the article, or parts of the article, to a simpler reading level.

4. Have students, working alone or in small groups, use the annotated list of references to explain how the scientists who wrote this article built on the published work of at least one independent group of scientists in making their discoveries. In the process, did they produce data that supports the findings of the earlier publication that they have cited in the text? In what way does this article support the statement that scientific knowledge is built up as a “community effort”?

5. Use the article and discussion questions linked to the standards and the diagrams for a teacher-led classroom discussion. The discussion can focus on the nature of science and scientific research, as well as on the science in the article itself.

6. Have students give a classroom presentation about the article, parts of the article, or their answers to discussion questions.

ARTICLE-SPECIFIC MATERIALS

Student Learning Goals:

- Connections to the nature of science from the article
  - What can we learn from applying mathematical modeling to a biological process?

- The importance of this scientific research
  - Further understanding of how a virus can infect different populations in different ways.

- The actual science involved
  - virology
  - epidemiology
  - mathematical modeling
  - differential equations

Connect to Learning Standards:

This resource connects to four sets of learning standards:

Discussion Questions related to these standards are found in Resources for Interactive Engagement

1. The AP Biology Standards

http://media.collegeboard.com/digitalServices/pdf/ap/2012advances/AP-Biology_CED_Fall2012.pdf

- Essential knowledge 3.C.3:
  Viral replication results in genetic variation and viral infection can introduce genetic variation into the hosts (page 66).

2. The Science and Engineering Practices contained in the Next Generation Science Standards

http://www.nap.edu/openbook.php?record_id=13165&page=41

- Practice 1: *Asking Questions*
- Practice 2: *Developing and using models.*

3. Common Core English Language Arts Standards:

http://www.corestandards.org/ELA-Literacy/RST/11-12

- RST.11-12.7: Integrate and evaluate multiple sources of information presented in diverse formats and media in order to address a question or solve a problem.

Summary of the Article for the Teacher:

It is recommended that this not be used by students in place of reading the article.

General Overview:

The problem

It is a matter of common experience that a virus infection can be asymptomatic in one person but cause severe or even fatal infection in another. The human leukaemia retrovirus HTLV-1, for example, causes an aggressive, usually fatal malignancy in ~5% of infected people, and an inflammatory disease of the central nervous system, known as HAM/TSP, in another 2 to 4%; but 90% of infected hosts remain well. The virus that causes these diseases is indistinguishable in sequence from that found in asymptomatic carriers, strongly implying that the outcome of infection is determined by differences in the host response. A much smaller proportion (~0.3%) of individuals remain well, without treatment, during infection with HIV-1.

This work was instigated by an experimental paradox. Cytotoxic T lymphocytes (CTLs) are known to play a central part in antiviral defense, and were thought to be critical in determining the proviral load (the percentage of infected lymphocytes) and therefore the risk of disease, in infection with HTLV-1. But the frequency of HTLV-1-specific CTLs was found to be very similar in asymptomatic HTLV-1 carriers and patients with the inflammatory disease HAM/TSP; while the proviral load differed between these two groups by up to 1000-fold, the difference in CTL frequency was between two-fold and 10-fold.

The hypothesis

We therefore hypothesized that the critical difference between asymptomatic carriers and patients with HAM/TSP or, more accurately, between individuals with a high HTLV-1 proviral load and those with a low proviral load, might lie in the efficiency with which HTLV-1 specific CTLs responded to antigen at the single-cell level. This response would be shown in two main ways: proliferation of the CTL, and killing of the virus-infected “target” cell. We called this property of CTLs the “CTL responsiveness,” and we distinguished this single-cell property from the whole “CTL response,” which is simply the total number of CTLs specific to the virus in a given host. In retrospect, we should have made a better choice of terms, because the terms “responsiveness” and “response” were confusingly close. The term that is now most widely used for single-cell CTL responsiveness or efficiency is “CTL quality.”

The approach

We formulated the mathematical models using parameters that were, at least in principle, experimentally measurable: the population sizes of lymphocytes and viruses. We tried to use the smallest possible number of parameters, following Einstein's dictum that everything should be made as simple as possible, but no simpler.[1] The models were applied to experimental results from the two different pathogenic retroviral infections of humans, HIV-1 and HTLV-1.

The models are ordinary differential equations. Importantly, the equations are interlinked, because they share parameters. Consequently, although it is possible to intuit a simple result from a single differential equation, the interdependency of the different equations precludes intuitive inferences on the behavior of the whole system. It is therefore essential to use computers to calculate the behavior of the cell and virus populations. The book by Nowak and May[2] explains the underlying principles of this type of mathematical modeling and shows how it can be applied to understand the dynamics of viral infections.

Topics covered:

- virology
- epidemiology
- mathematical modeling
- differential equations

Why this Research is Important:

The most important consequence of this work was to focus attention on the efficiency or quality of CTLs at the single-cell level. Since 1996, a great deal of experimental work has demonstrated beyond doubt that CTL quality is indeed one of the chief determinants of the outcome of a viral infection. See Bangham (2009) for a review.[3]

The second main implication of our work was the important conclusion that you cannot infer the efficiency or quality of the host immune response to a persistent infectious organism from the magnitude of that response during the steady-state infection. For example, the frequency of virus-specific CTLs in the circulation gives no guide to their efficacy in controlling the replication of the virus. From this conclusion, it also follows that the response to an immunodominant viral antigen, for example, the antigen recognized by the largest number of CTLs, may not be the protective immune response, and indeed there is experimental evidence for this conclusion. These conclusions influence not only our understanding of the immune response to persistent infection but also the choice of viral antigens that should be used in antiviral vaccines.

Methods used in the Research:

- Mathematical modeling based on data collected from virus interactions with hosts

Conclusions: The behavior of the models strongly supported our hypothesis that small changes in CTL responsiveness or "quality" could be sufficient to cause very different outcomes of the infection; that is a very different viral load during chronic infection, and a different risk of virus-induced disease. The models also provided a straightforward explanation for certain counter-intuitive observations. For example, a positive correlation between HTLV-1 specific CTL frequency and proviral load is observed in vivo. At first sight, this suggests that CTLs fail to control the virus infection. However, there is strong evidence that the CTL response limits HTLV-1 proviral load in vivo. The models demonstrated clearly how this positive correlation arises, and so resolved the paradox.

References

1. This saying is commonly attributed to Einstein. It is believed to originate in his article "On the Method of Theoretical Physics" in Philosophy of Science (1934) **1**, 163-169. "It can scarcely be denied that the supreme goal of all theory is to make the irreducible basic elements as simple and as few as possible without having to surrender the adequate representation of a single datum of experience" (p. 165).

2. M. A. Nowak and R. M. May, 2000. *Virus Dynamics: Mathematical Principles of Immunology and Virology.* Oxford University Press, Oxford.

3. C. R. M. Bangham, 2009. "CTL quality and the control of human retroviral infections." *Eur. J. Immunol*. 39, 1700 - 1712.

Resources for Interactive Engagement:

1. Discussion Questions Associated with the Standards

The AP Biology Standards

Essential knowledge 3.C.3:
Viral replication results in genetic variation and viral infection can introduce genetic variation into the hosts (page 66).

- **What viruses were being studied?**
- **Did these viruses have any unique characteristics?**
- **What happened when the virus replicated in the host?**
- **How did the scientists model this?**

The Science and Engineering Practices that appear in the Next Generation Science Standards

Practice 1: Asking Questions

- **What did the scientists need to know before they could start their study?**
- **How did the scientists select parameters to fit their models around?**
- **Did the scientists ultimately answer their own questions?**

Practice 2: Developing and using models.

- **Does the model the authors built work like they had envisioned?**
- **What can we learn from this model?**

- **Why were the scientists able to make assumptions about their model?**
- **If this models works, what is the next step?**
- **Why did the scientists pick these viruses to model?**

Common Core English Language Arts Standards:

RST.11-12.7: *Integrate and evaluate multiple sources of information presented in diverse formats and media in order to address a question or solve a problem.*

- **What information do the scientists base their first model (equation) on?**
- **How did the scientists connect immunological parameters (host) to the spread of the virus (virus)?**

2. Activities connecting to the data shown in the Article

The Activities are linked to in red tool bar running along the bottom of the page.