AIDS: (Samples)

A Case Study Approach to Covering the Immune System, Viruses and Community Health

20 experiential, higher-order thinking activities for Advanced Placement* (AP), International Baccalaureate** (IB) high school or college students covered in 25-30 class periods

This case study was specifically designed to provide complete, stand-alone coverage of the following required topics:

Virus Structure and Function
Lysogenic and Lytic Life Cycles
Nonspecific Immune System (1st and 2nd Lines of Defense)
Specific Immune System (3rd Line of Defense)
Cell Signaling and Cell Surface Receptors
Monohybrid and Dihybrid Crosses
Evolution of a Pathogen
Community Health Education
Bioethics

This case study also offers partial coverage of the following required topics:

Transcription and Translation
Reproduction
Tissues

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AIDS: A Case Study for Advanced Biology
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This sample includes Activity Seven and Activity Sixteen

Sample Lesson Plan from AIDS Case Study

Activity Seven: Simulating the Specific Immune Response

Teaching Time: 1 class period of 50 minutes

Important: The abbreviations that follow the objectives throughout this case study correspond to the College Board standards required for the AP Biology course; see the catalsytlearningcurricula.com website for a full listing of all corresponding standards.

Objectives:

a) For students to understand, simulate and describe how the immune system responds to natural and artificial agents that disrupt dynamic homeostasis (EK 2.C.2.a, EK 2.D.1.a, EK 2.D.1.b, EK 2.C.2.a, EK 2.D.1.b, EK 2.D.4.b.1, EK 2.D.4.b.2, EK 2.D.4.b.3, EK 2.D.4.b.4, EK 2.D.4.b.5, EK 2.D.4.b.6, LO 2.29, LO 2.30, SP 1.2, SP 1.3, SP 1.4)
b) For students to understand cell signaling that directs the movement of immune system components and gene expression (EK 3.B.2.a, EK 3.B.2.b, LO 3.22, LO 3.23)
c) For students to describe how programmed cell death plays a role in normal tissue development and differentiation (EK 2.E.1.c, LO 2.34)
d) For students to articulate the function of each type of white blood cell during an infection (EK 2.B.1.c.1, EK 2.E.1.b, EK 4.C.1.a, EK 3.D.2.a, EK 3.D.2.b, LO 3.34, LO 3.35, SP 1.5)
e) For students to realize that the diversity of an individual's specific immune response genes can be a factor in evolutionary fitness (EK 1.A.1.c, EK 1.A.2.c, SP 7.1, SP 7.2)
f) For students to simulate how specific surface molecules and chemical signals allow cells to interact, identify self from non-self and perform specific functions (EK 2.B.1.b.1, LO 4.22)

Materials:

For the class: 1-2 decks of playing cards; a sheet of white dot stickers; and a thin-tipped marker. For each student: 2 chenille sticks (aka pipe cleaners); a pair of scissors; 8-10 yellow dot stickers; four nametag/shirt stickers; one marker; one card cut from the "Specific Immune Response Role-playing Cards" handout, which follows this lesson plan; and one copy of the "Specific Immune Response Reflection Questions" handout, which follows this lesson plan.

Procedure:

1. Prior to this activity, make copies of the "Specific Immune Response Role-playing Cards," creating enough to allow one role card per student. Place the other playing cards (from the ordinary deck of playing cards) face down around the room, laying about 1/3 of the cards on desks/chairs and the remaining

cards on the floor. When the students enter the classroom, explain that for this activity the room will represent the body of a human being, the desks/chairs are living body cells that are doing their job (as skin, part of the liver, fibrous connective tissue, calcified bone tissue, etc.), and the playing cards you have placed around the room are the various proteins (clotting factors, insulin, collagen, myosin, etc.) found in body cells and the interstitial fluid outside the cells. For this activity, a messy classroom is actually desirable, as having scraps of paper and debris around the room will add to the students' understanding of certain cells' roles.

2. Tell the students that they are going to learn about the different roles of four types of white blood cells, or leukocytes, by pretending to be each type of cell and then by participating in a simulation in which the four types of cells interact.
3. To teach the students about the generalized role of a macrophage cell, first ask them to write the word "macrophage" on a sticker and place it on their shirt. Ask the students to stand up and quietly tell themselves that they are "a macrophage, a type of white blood cell that can engulf cells, cell fragments, pathogens and other debris found in the body." Tell them that they are going to pretend to be a macrophage by going around the body (the classroom) and engulfing any debris (clutter on desks and on the floor). Macrophage cells do not collect particles found in healthy, living cells, only particles outside of cells or in cells that are broken open or dead. Students can act out the role of the macrophage cells by moving around the room and picking up things that are out of place such as scraps of litter, but they should not pick up any proteins (playing cards) in living cells (desks/chairs). Because macrophages will destroy debris using phagocytosis and break the material down internally using lysosomes, ask the students to engulf debris by wrapping their arms around anything they intend to pick up and then keeping the material with them, as if it has been internalized, until the end of the simulation.
4. When most of the scraps of trash around the room have been cleaned up, you can then turn over a desk/chair and proclaim that the overturned desk represents a cell that has died or has been marked for apoptosis, or cell death. Ask the macrophage cells—it will likely take a few of them—to come engulf this dead cell and remove any spilled contents in the immediate vicinity using phagocytosis.
5. Ask the students if they have any questions about the role of a macrophage, then ask the following questions to uncover any misconceptions:
    a. Based on what you know about the function of a macrophage, how do you think the size of a macrophage cell compares to that of a red blood cell, which carries hemoglobin and carbon dioxide? *(At 21 micrometers in diameter, macrophage cells are rather large—about three times larger than red blood cells, which are approximately 8 micrometers in diameter. If these numbers do not paint a clear enough picture for your students, show them the size comparison visual at the University of Utah Genetics website, http://learn.genetics.utah.edu/content/begin/cells/scale/.*
    b. What do you think determines the lifespan of a macrophage? *(Eventually these leukocytes become full of material they've collected and the*

digestive compounds used to break them down, and some of the material collected may be harmful enough to be a detriment to the cell. So, their lifespan is not long—only a few days, when they are actively ingesting—whereas red blood cells may live up to 90 days.)

c. The roots for the word macrophage mean "big eater." How is this an appropriate name for these cells and how do you think scientists came up with this name? *(White blood cells are substantially larger than red blood cells, and slides of living cells revealed the process of phagocytosis commonly practiced by these cells.)*

6. To teach the students about another type of white blood cell called a B-cell, which has a more specific role, first ask them to each write "B-cell" on the left side of a shirt sticker and then create an original symbol or repeatable doodle on the right side of the sticker. (In the final simulation they perform today, the students will use all of the stickers they make today, so they should set aside—or lightly attach an edge of it to their desk—the "macrophage" sticker they just created as well as the stickers they create in the next few steps, after they finish using them.)
7. Tell the students that all B-cells are unique and original in that each cell can identify a specific protein or polysaccharide (carbohydrate) shape. However, B-cells are only able to look for foreign proteins or polysaccharides that exist in the interstitial fluid (note: historically, the fluid was called "the humors," giving the B-cell response its name, "the humoral response"); they cannot find foreign particles that are inside living cells. Ask the students to look around the room at the unique symbols that have been drawn on their neighbors' shirt stickers. In the simulation they're about to perform, they will use these symbols to identify proteins that are foreign to the body.
8. Ask the students to make two or three Y-shaped forms about 5cm in length (i.e., no longer than their pinkie) using the chenille sticks and the scissors. Explain that these forms represent the Y-shaped antibodies made by B-cells. Explain to the students that the purpose of an antibody is to stick to a foreign particle like a flag so that macrophage cells can recognize the particle, called an antigen, as debris that needs to be consumed. Inform the students that B-cells are able to secrete up to 2,000 antibodies per second if they encounter a foreign particle that matches the specific shape they are able to identify. Thus, B-cells can find and quickly tag thousands of pathogens of a specific type that are infecting the body and causing illness.
9. Remind the students that B-cells are specific for a single type of protein or polysaccharide and that, so far, the Y-shaped antibodies they've created with the chenille sticks are not specific. In order to make their antibodies as specific as those of a real B-cell, the students need to complete them by adding the protein shape that their B-cell is able to identify to each of the upper tips of the Y-shaped antibodies. The tips consist of a variable region called the antigen-binding site. The antigen-binding site can only bind to a specific type of protein or polysaccharide called an epitope. Antigens are foreign particles (viruses, bacteria, pollen, splinters, parasites, etc.) that have entered the body and that may or may not be pathogens. Each type of antigen that enters the body has

many different proteins or carbohydrates on its surface that can be used as epitopes, or areas that are recognized by the antibodies of a B-cell. Ask the students to recreate the symbol they drew on the right side of their shirt sticker on two of the yellow dot stickers. Tell them to fold the yellow dot stickers around the tips of the Y-shaped antibody they created—one on each tip—such that the yellow stickers extend upwards off the antibody. Ask the students to repeat this process for all the antibodies they created (i.e., have them draw the symbol from their B-cell sticker onto more yellow dot stickers that they then fold around the tips of each Y-shaped antibody).

10. While the students are working on the antigen-binding sites for their antibodies, recreate some of the hand-drawn symbols you see on their shirt stickers (choose 6-7 of them), drawing them on the white dot stickers. Discreetly place the white dot stickers (with drawings) on various playing cards that you placed on the floor and desks at the start of this activity. These stickers will act as recognizable antigens in the simulation that will be played after all four types of white blood cells have been introduced.
11. Choose four more hand-drawn symbols from various students' shirt stickers and recreate them on four more white dot stickers. Take a single playing card from the floor and place the four dots on this one card. Have this card ready to use as a prop in the next step.
12. When the students have finished making their antibodies specific for their particular symbol/protein, show them the playing card that has four white stickers with drawings that match some of the students' antibody symbols. Explain that this particular card represents a bacterium that has entered the body and four of the bacterium's surface proteins, or epitopes, match the specific shape of antibodies that are made by four of the B-cells present. Explain that there are hundreds or even thousands of different surface proteins and polysaccharides on the exterior of this one bacterium cell, but of those potential epitopes, only four of them are recognized by the B-cells that are made in this particular human. Explain that the piece of the bacterium that is recognized as a foreign particle is called an antigen and the antigen-antibody interaction allows four different B-cells (in this case) to identify and mark the bacterium for disposal. Ask those B-cells who have made antibodies that match the epitopes on this bacterium to come forward and allow their antibodies to bind with the antigen (each student can hold the tips of their Y-shaped chenille stick up to the surface of the bacterium to simulate the attraction of their antibody to a protein or polysaccharide on the exterior of the bacterium). When there are four different chenille stick antibodies binding with the bacterium (represented by the playing card), ask for a volunteer to act as a macrophage and come engulf (wrap their arms around it to represent phagocytosis) and dispose of this pathogen by tearing it up as if it were being broken down in a lysosome.
13. Explain that when a B-cell finds an antigen to match its antibody, the B-cell will reproduce, making other B-cells of the exact same type called clones or plasma cells. These clone cells will be able to make the same type of antibodies as the original B-cell, so there will be an overwhelming number of white blood cells to

make plenty of antibodies to catch whatever foreign particle is invading the body. To represent the cloning of plasma cells, ask the four B-cells who had matching antibodies for the bacterium to go to the board and draw white blood cells with their particular symbol inside. Write the heading "clones/plasma cells" above the cells they have drawn to remind them of the term.

14. A B-cell that has identified a foreign particle will also make a copy of itself that will be kept as a long-term reminder of the specific epitope it matched. This "memory" B-cell will help the immune system respond quickly if the same type of epitope is ever found in the body in the future. Write the heading "memory B-cells" on a different part of the board. To represent the creation of memory cells, ask the four B-cells who had matching antibodies for the bacterium to go to the board and each draw another white blood cell with their particular symbol inside.
15. Explain that when a foreign particle has been identified by a circulating B-cell, and the activated cell replicates in large numbers, the organism's white blood cell count increases exponentially. To exemplify this, draw many quick circles next to the clone B-cells that were drawn on the board. Tell the students that the cloned B-cells will live in the body for 4-5 days, secreting enormous numbers of Y-shaped antibodies until all foreign particles have been identified and then eliminated by macrophage cells. When the infection has been eliminated, the B-cells will stop replicating and the total number of white blood cells in the body will drop back down to normal levels. To exemplify this, erase all the cloned cells from the board, leaving only the memory B-cells on the board. Ask the students the following questions to determine how much they understand about the function of B-cells:
    a. How are B-cells similar to, and different from, macrophage cells? *(Macrophage cells consume any particle in the body that is not self, while B-cells only tag with antibodies the non-self particles. Also, macrophage cells are generalists—they will consume any type of antibody—while B-cells are specific and will only seek out antibodies of a particular type.)*
    b. If you go to the doctor and she notices that the lymph nodes under your chin and arms are swollen, she may recommend that you have a blood analysis, because the lymph nodes are an area where white blood cells are stationed to detect pathogens. How might the blood sample indicate to the doctor that you are indeed fighting an infection? *(In a normal blood sample there are about 5,000 red blood cells to every 8 white blood cells. So, if your white blood cell count is higher than normal, it indicates that you have probably made clone or plasma cells recently to fight off an infection.)*
    c. Imagine you got the flu three years ago and there was a specific epitope on that particular flu virus that we will call protein A. Your B-cells recognized protein A and used it to make antibodies that eventually destroyed the infection and you gradually went from feeling sick to feeling better. If a new type of flu virus emerges and it has epitopes that include protein A as well as proteins B, C, D and E, how do you think your body will react to this new antigen? *(If your memory B-cells match any of the*

protein or carbohydrate epitopes on the exterior of the new flu virus (in this case, protein A), then they will produce clone/plasma cells and you may never realize your body has been exposed to or fought off this particular antigen. You may feel a little run down for a day or two, or you may not feel any different at all, because of your memory B-cells' efficiency at fighting the new virus using the old epitope.)

16. Now tell the students they are going to learn about the role of another type of white blood cell that also has specificity, in that it can also identify only one type of epitope on any given antigen. This third type of white blood cell is called a cytotoxic T-cell. Tell the students that in order to play the role of a cytotoxic T-cell, they will write "cytotoxic T-cell" on the left side of a new shirt sticker and draw a simple but unique symbol on the right side of the sticker. Ask them to remove the "B-cell" sticker they're wearing and temporarily attach an edge of it, lightly, to their desk, next to their "macrophage" sticker. While the students are drawing cytotoxic T-cell symbols on their stickers, copy two of the symbols you see onto two white dot stickers—one symbol on each sticker—and place both stickers on a playing card that is lying on top of a desk near the front of the room. Place two additional playing cards on the same desk (with no white dot stickers). You will use this desk/chair with these three cards in step 18b, below.
17. Tell your students that instead of making antibodies, which are useful for flagging foreign particles found in the fluid **outside** body cells, cytotoxic T-cells have a method to identify foreign proteins or polysaccharides found **inside** living body cells. Ask the students to recall how, when the human immunodeficiency virus infected the body cell in Activity Three, the cell did not die immediately. In fact, the virus could have spent years inside the cell undetected in the dormant lysogenic phase. Cytotoxic T-cells have the job of looking inside presumably healthy living cells to see if there are any strange proteins or polysaccharides residing in the interior. The presence of foreign proteins or polysaccharides or an unusually high or low percentage of genomic proteins or polysaccharides inside a living cell would indicate that the cell is sick with a pathogen or has become cancerous. Explain to the students how cytotoxic T-cells are able to ask other body cells to present their contents for inspection using a cell-to-cell bridge that contains different interior proteins. Cells that present their contents for inspection are called antigen-presenting cells (APCs), and all nucleated cells can be APCs in the presence of a cytotoxic T-cell. The bridge has some identifying factors on it, so the T-cell inspecting an APC can be sure that it is, in fact, a normal part of the body. Most importantly, the bridge contains a groove where interior proteins can be brought up from the cytoplasm for inspection, so the T-cell can determine if there are any non-self particles inside the APC.
18. Explain to the students that when a cytotoxic T-cell finds a foreign particle inside a body cell, it does several things:
    a. First, it secretes several different cell-signaling proteins called cytokines which summon other white blood cells (macrophages, B-cells and other T-cells) to move towards the site of the infected cell. These cytokines also cause a signal cascade of other effects that together are called the

secondary immune response or inflammatory response. The changes brought on by the cytokines help other white blood cells congregate at the site of the infection while simultaneously alerting the cells of the local tissue to ward off potential pathogens. Cytokines called pyrogens raise the temperature of the surrounding tissue to kill off any pathogens. Cells in the immediate area will release protective proteins such as interleukins, histamines and clotting factors to ward off and stop the spread of infection. Small blood vessels near the damaged tissue will dilate to allow leukocytes to leave the bloodstream and enter the interstitial fluid. All of these secondary immune responses result in swelling, due to the excess fluid and cells that have accumulated in the interstitial area, as well as heat and redness, which in sum is called an inflammatory response.

b. Ask the two students whose cytotoxic T-cell symbols you copied in step 16 above, plus one other student, to come to the front of the room to inspect the contents of a living body cell (i.e., ask the three students to look at the playing cards on the desktop that includes the card on which the white dot stickers with T-cell symbols were placed). Ask the students to each act like a cytotoxic T-cell by picking up and inspecting each playing card. Instruct the students/T-cells to call out, "Cytokines!" if their own symbol (the one on their shirt sticker) matches any of the proteins or polysaccharides found in this cell. Ask the rest of the class how they could simulate the reaction that occurs in the body after the cytotoxic T-cells have started releasing cell signals. For example, the students may simulate the reaction of the neighboring cells by putting up some type of barrier on those cells while also making some action that simulates secretion to depict interleukin, histamines and clotting factors. To encourage scientific thinking, give participation points to students who contribute ideas that have scientific merit or are alert to what would be occurring and have ideas for how to depict it using what is available in the classroom.
c. The second thing that the cytotoxic T-cell will do is destroy the infected cell by punching holes in the cell membrane. Ask the students how they could indicate the death of the cell (flipping a desk on its side has been used previously, so the students might suggest this). Macrophage cells summoned by the cytokines will engulf the dead cell and the spilled contents so that no further infection takes place. Ask the students how this can be simulated (since they already acted out the role of macrophage cells earlier in this activity, this is a review).
d. The cytotoxic T-cell will then produce clone or plasma cells that can identify the same foreign antigen and will seek out antigens of this type. Ask the students to recall what action they performed to represent the cloning of B-cells previously in this simulation (the students should suggest that they now draw a cytotoxic T-cell and its matching antigen symbol on the board under the "clones/plasma cells" heading).
e. Just as B-cells do, each cytotoxic T-cell will make a copy of itself that will be kept as a long-term reminder of the specific foreign particle it matched,

so the immune system can respond quickly if this type of antigen is ever found in the body in the future. This replicated cell is called a memory T-cell. Ask the students to remind you how the making of memory cells was represented previously in this simulation (the students should suggest that they now draw a cytotoxic T-cell with its matching antigen symbol on the board under the "memory B-cells" heading).

19. Tell the students that there is one more type of white blood cell that is important in the specific immune response—the helper T-cell. Tell your students that this leukocyte is similar to a cytotoxic T-cell however, rather than being able to inspect the contents of any nucleated cell, it can only inspect the contents of B-cells and macrophage cells. The job of the helper T-cell is to identify any antigens that have been found by macrophage cells and B- and T-cells with the purpose of coordinating the white blood cells and combating infection more quickly. If a non-self protein or polysaccharide is found by a helper T-cell, the helper T-cell will use a signal cascade of cytokines to draw additional white blood cells to the area of infection and help other white blood cells replicate (make plasma or clone cells) as needed. Have the students make "helper T-cell" shirt stickers, then call forward a few helper T-cells/students and a few students who are willing to play the role of B-cells and macrophages to act out the interactions they would have together. Helper T-cells will ask to see the proteins collected by other T-cells (both helper T-cells and cytotoxic T-cells) and the macrophage cells, so the macrophage cells will need a few playing cards with white stickers on them. Around the room, there may not be playing cards that have stickers matching the students' shirt sticker symbols since not all T-cells will have found non-self particles. If a helper T-cell finds an antigen that is non-self, it should call out "Cytokines!" and the rest of the class should perform whatever actions were specified in step 18b, above, to simulate the results of this type of cell communication.
20. With the four major roles of the specific immune system defined, your students are now ready to perform a dynamic simulation of all the four types of white blood cells working in concert. Remind the students that white blood cells are constantly circulating in the body looking for pathogens, but in a healthy individual with a good nonspecific immune response their job is relatively easy because pathogens are not common in high numbers except when there is an illness. Ask the students what they think white blood cells spend most of their time doing. *(White blood cells spend most of their time circulating without finding antigens.)*
21. Distribute the role-playing cards, giving one to each student and making sure that there is an approximately equal number of students playing each type of role. Be sure to give B-cell roles to the students whose symbols you copied onto white dots in step 8 above. These students will be important in making the simulation work, since they have a symbol/antibody on their shirt sticker that matches the antigen you have drawn on the white dots placed on the playing cards.

22. Ask the students to each read the description of their role and put on the appropriate shirt sticker that they made during the previous steps, which should still be lightly attached to the edge of their desk.
23. Begin the simulation by inviting the white blood cells (all of the students except for any you may have designated to be part of the signal cascade) to circulate within the body (the room). Each type of leukocyte should be playing its role of engulfing broken cells or foreign particles (macrophages), looking for matching antigens in the interstitial fluid (B-cells), looking for matching antigens within living cells (cytotoxic T-cells), or looking for non-self antigens inside B-cells and macrophage cells (helper T-cells).
24. Eventually a B-cell will find one of the antigens (matching white dot stickers) you placed on a playing card in step 10, above. The B-cell student with the antibody that matches the antigen should begin the process of making clones and secreting antibodies (i.e., they should place on the playing card a yellow dot sticker on which they've drawn their matching symbol--this is an abbreviated way to create models of antibodies). Macrophage cells may find the antigens that are marked by the antibodies (yellow dot stickers). Eventually a helper T-cell will ask a macrophage cell to present its collection of antigens. If a helper T-cell notices any non-self proteins or polysaccharides (i.e., playing cards with stickers that have symbols drawn on them), they should yell "Cytokines!", thus bringing other white blood cells to the area to offer help and starting a cascade of secondary immune responses. If the non-self particle is found in a macrophage cell, realize that there will not be any clone cells made to help with the immune response until a B-cell or T-cell identifies an epitope in the antigen that has a matching symbol.
25. After all of the antigens that have matching antibodies have been found, the simulation is over and you are ready to go on to the next step.
26. Ask individual students to describe the actions they performed in their role and share their understanding of what happened during the simulation. Be sure to ask at least one student from each of the four leukocyte roles to relate their experience.
27. Now ask the students to each swap roles with another person. Before performing the simulation again, with everyone in new roles, you will first need to disperse all of the collected playing cards, again putting them around the room, on desks and the floor. As the students each put on the appropriate shirt sticker, recreate 3-5 of the B-cell or T-cell symbols from their stickers on white dots stickers and place the dots on random playing cards around the room (on desks or the floor, and maybe put more than one sticker on some of the cards rather than just one on each), so that there will be some antigens (again, about 3-5) to match the antibodies of some of the students playing B-cells and/or receptors to match those of some of the students playing T-cells. Now, perform the simulation again, and as many times as necessary, until the students understand the roles of each of the four types of white blood cells in a specific immune response.
28. Discuss the role-playing simulation as much as needed for all students to understand what was occurring during it. Ask the students to read the part of

their textbook that covers the cell-mediated and antigen-mediated immune response. Assign the "Specific Immune Response Reflection Questions" handout for homework in order to assess each student's depth of understanding.

Specific Immune Response Role-playing Cards

Cytotoxic T-cells (and clones of cytotoxic T-cells)

Background information:

- You are part of the specific immune system (aka cell-mediated response).
- You travel around the body, killing body cells that contain antigens that match your specific Class I MHC proteins.

In this simulation you will do the following:

1. You will travel around the room looking into living cells (desks/chairs) to see if they have any antigens that match your type of receptor (the symbol on your shirt sticker).
2. When the helper T-cell calls for help by yelling "Cytokines!", you must go see if that helper T-cell has an antigen that matches your specific Class I MCH protein receptor (the symbol on your sticker).
3. If you find a cell that contains your specific protein receptors, you must:
    a. Destroy the cell (turn the desk/chair over and spill any contents).
    b. Make clones of yourself so that there are more cytotoxic T-cells to help you find the exact same antigen in other cells (draw clones on the board).
    c. Make a memory T-cell of yourself (draw memory cells on the board), so that this type of antigen can be recognized rapidly in the future if there is a second exposure.
    d. Continue performing steps 1-3 above throughout the simulation.

Helper T-cells

Background information:

- You are part of the specific immune system (aka the cell-mediated response).
- You travel around the body, asking antigen-presenting cells (APCs) to show you what antigens they have found in the body.
- You orchestrate a specific response by calling T-cells and B-cells to action if you find a foreign particle has been presented to you by an APC.

In this simulation you will do the following:

1. Travel around the body, asking APCs (macrophage cells, B-cells and T-cells) to show you an antigen, if they have any.
2. If you find an antigen in one of the APCs, you need to yell, "Cytokines, cytokines, calling all leukocytes!"
3. Make a memory helper T-cell of yourself (draw yourself and the type of antigen you found on the board), so that this type of antigen can be recognized rapidly if there is a second exposure in the future.
4. Continue to repeat the above three steps throughout the simulation.

Macrophage Cells

Background information:

- You are part of both the non-specific and specific immune system.
- You travel around the body engulfing foreign (non-self) particles called antigens that are outside of cells; and any particle that is flagged with antibodies; and dead or dying cells.
- You are an antigen-presenting cell (APC), which means you are expected to show helper T-cells the antigens (or non-self particles) you have found while performing your job.

In this simulation you will do the following:

1. Travel around the body, engulfing anything that is not a living body cell—cell fragments, dead cells (overturned chairs), foreign particles (playing cards with stickers on them) or anything marked with antibodies (yellow dot stickers).
2. If a helper T-cell asks you to present your cell content, show it all of the antigens (playing cards) you have collected while performing your job.
3. Continue the above two steps throughout the simulation regardless of what is going on around you.
4. If you hear a helper T-cell yell, "Cytokines!", go to its location and engulf any dead cells or cell fragments in the area.

B-cells (and clones of B-cells)

Background information:

- You are part of the specific immune system (aka the cell-mediated response).
- You travel around the body, seeking antigens outside of cells that match your specific type of antibodies.
- You are an antigen-presenting cell (APC), which means you must show helper T-cells the antigens (or non-self particles) you have found while performing your job.

In this simulation you will do the following:

1. Travel around the body, seeking antigens (playing cards) that are in the extra-cellular fluid but only if they, or a part of them, match your antigen receptors exactly.
2. If you have found a matching antigen, you must do the following:
    a. Secrete antibodies and stick them on the antigen (create yellow stickers with your antigen receptor symbol drawn on them and put them on the antigen/playing card).
    b. Make clones of yourself (draw on the board).
    c. Make memory cells (draw on the board), so that this type of antigen can be recognized rapidly if there is a second exposure in the future.
3. If a helper T-cell asks you to present your cell content, you must show the antigens (playing cards) you've collected while performing your job—that is, if you have found any matching antigens at this point.

Specific Immune Response Reflection Questions

Answer these questions on a separate sheet of paper using examples when necessary.

1. Explain the task of each type of cell:
   a. Macrophage cells
   b. B-cells
   c. Cytotoxic T-cells
   d. Helper T-cells

2. The first line of defense is considered a general or nonspecific form of immune system response. Would you call the role played by macrophage cells nonspecific or specific? Defend your response.

3. How are B-cells and T-cells similar? How are they different?

4. How are cytotoxic T-cells and helper T-cells similar? How are they different?

5. Explain why B-cell response is called "antibody-mediated" while T-cell response is called "cell-mediated"?

6. What does it mean to be an APC? Which cells can be APCs? What is the purpose of an APC?

7. Only vertebrates have a specific immune response (the response seen with T-cells and B-cells). Explain how specific immunity is an advantage over non-specific immune response.

8. Give one example of cell signaling from each of the following: the second line of defense, an antibody-mediated response, and a cell-mediated response.

9. Explain how the human body would respond to each of the following:
   a. A vaccination for a bacterial illness
   b. A second exposure to the chicken pox
   c. A transplanted organ
   d. Exposure to a lysogenic virus
   e. The presence of a cancerous tumor

10. The diversity in the family of genes called the human leukocyte antigen (HLA) system determines what range of epitopes can be detected by white blood cells. Some of the HLA genes have as many as 100 different possible alleles for a particular gene locus, each of which can produce a different type of antibody. How do you think the diversity of this group of genes plays a role in natural selection?

11. How do you think immune response affects the evolution of living pathogens such as bacteria or viruses?

Specific Immune Response Reflection Questions

Teacher's Version

1. Explain the task of each type of cell:
   a. Macrophages – *These cells consume anything that is not self.*
   b. B-cells – *These cells find foreign particles in the extracellular spaces.*
   c. Cytotoxic T-cells – *These cells find foreign particles inside other cells.*
   d. Helper T-cells – *These cells find foreign particles inside B-cells and macrophage cells.*

2. The first line of defense is considered a general or nonspecific form of immune system response. Would you call the role played by macrophage cells nonspecific or specific? Defend your response. *Macrophage cells are considered nonspecific because they do not look for one particular type of antigen; they respond to any protein or polysaccharide that is tagged for destruction by chemical signals or antibodies. However, students may point out that macrophage cells play a very significant role in the specific immune response.*

3. How are B-cells and T-cells similar? How are they different? *B-cells and T-cells are both white blood cells, they both are looking for specific proteins or polysaccharides that are non-self, and all B- and T-cells contain a single specific antibody that matches a particular type of antigen. They differ in that B-cells look for antigens in the places outside of cells, while T-cells look for antigens inside of cells.*

4. How are cytotoxic T-cells and helper T-cells similar? How are they different? *Both types of T-cells are able to connect physically with other cells to examine the molecules that may be antigens (foreign, non-self particles), however cytotoxic T-cells use a molecular bridge called a Class I MHC while helper T-cells use a molecular bridge called a Class II MHC. Both of these types of cells are looking for non-self particles, however when each type of cell finds an antigen they respond quite differently. Cytotoxic T-cells will puncture the infected cell while helper T-cells gather all types of leukocytes to the site of the infection to allow other types of white blood cells to help clean up and contain the infection. Both types of T-cells release cytokines and other chemical signals to illicit a greater immune response from other leukocytes and neighboring body cells, and both helper and cytotoxic T-cells will create memory cells to respond faster to a future attack from the same type of antigen.*

5. Explain why B-cell response is called "antibody-mediated" while T-cell response is called "cell-mediated"? *B-cells produce proteins called antibodies when they find an antigen. Once the antigen is tagged by antibodies for destruction it will be engulfed by a macrophage cell and destroyed, therefore the response is termed antibody-mediated. On the other hand, T-cells interact with proteins that are on the surface of other cells, creating a bridge that allows them to examine the proteins and*

polysaccharides found within a particular cell. Cell-to-cell interaction is required for T-cells to recognize the presence of a non-self particle before attacking an infected cell, therefore it is termed a cell-mediated response.

6. What does it mean to be an APC? Which cells can be APCs? *An APC is an antigen-presenting cell, or any cell that can show a T-cell the foreign particles it has found in the body. Macrophages, B-cells and any other nucleated body cells are able to present antigens, so they are all considered to be APCs. Some body cells, such as mature red blood cells, are not nucleated and so they are not able to form MHC bridges and present antigens to T-cells.*

7. Only vertebrates have a specific immune response (the response seen with T-cells and B-cells). Explain how specific immunity is an advantage over non-specific immune response. *B-cells and T-cells allow a body to remember any foreign particles that have attacked it in the past, because B- and T-cells make memory cells when they find a matching antigen on their receptor or antibody sites. These memory cells enable the body to respond very quickly if the antigen is ever present in the body again.*

8. Give one example of cell signaling from each of the following: the second line of defense, an antibody-mediated response, and a cell-mediated response. *From the second line of defense, the students may use any example of chemicals that call white blood cells to the location of an injury or notify tissue cells in the immediate area of an infection. Some of these chemical signals include histamines, prostaglandins, chemokines, pyrogens, interferons, interleukin cytokines or other chemical signals of infection, distress or repair. Antibody-mediated response examples could include the way an antibody is used to signal cell destruction to a macrophage cell or the chemical signals given by a B-cell to alert helper T-cells. Cell-mediated response examples might include signals that a T-cell gives to an APC to make it show the T-cell intercellular proteins from that cell such as chemokines or cytokines.*

9. Explain how the human body would respond to each of the following:
    a. A vaccination for a bacterial illness: *The broken skin at the needle wound would trigger the second line of defense, calling proteins to the area to warm it and make it swell with fluids, use macrophages to remove broken cells, form a scab with platelets and protein fibers and heal the broken tissue with new cell growth. The foreign bacterial cells or particles from the vaccination would trigger the macrophage cells, B-cells and T-cells to the area to consume the invading cells. Macrophage cells and B-cells would consume the bacterial cells in the extracellular space. If any antigens match the antibodies of the B-cells, the B-cells would begin to make clones so there would be more B-cells with the matching antibody to tag the intruders. T-cells would go around to the antigen-presenting cells and ask to see what protein particles have been collected so far by the macrophages and B-cells and to see if any antigen particles have entered healthy body cells. If any antigens match the antibodies of the T-cells,*

the T-cells would begin to make clones so there would be more T-cells with the matching receptor to tag the intruders. Macrophage cells would go around eating any bacterial cells or particles tagged with antibodies made by the B-cells or destroyed by T-cells.

b. A second exposure to the chicken pox: *Chicken pox is a virus, so some of the virus particles in the bloodstream, mucus membranes or other extracellular spaces would be eaten by macrophage cells or tagged with antibodies by B-cells. If any antigens match the antibodies of the B-cells or the memory B-cells, these cells would begin to make clones so there would be more B-cells with the matching antibody to tag the intruders. T-cells would go around to the antigen-presenting cells to see what protein particles have been collected so far by the macrophages and B-cells. If any antigens match the receptors of the T-cells or memory T-cells, these cells would begin to make clones so there would be more T-cells with the matching receptors of the intruders. Macrophage cells would go around eating any bacterial cells or particles tagged with antibodies made from B-cells or destroyed by T-cells.*

c. A transplanted organ: *If a foreign object such as a transplanted organ is introduced to the body, the B-cells would tag the non-self tissue with antibodies. T-cells would ask the transplanted organ cells to present the proteins that are in their interior; some of these proteins would be considered non-self. Both the B- and T-cells would make clones of any cells that contain matching antibodies or receptors respectively, and these clones would come out in force from the bone and thymus tissue to attack the introduced organ. Because the immune system is so good at finding foreign tissue or foreign materials in the body, and the response can be so intense, the immune system of a transplant patient must be suppressed with medicines to keep the patient's body from rejecting the new organ. These drugs keep the B- and T-cells from noticing the foreign tissue so the new organ is safe from attack, but they also keep the patient's immune system from noticing other types of infection, so the patient is always at a high risk of getting sick from illnesses their body would normally have noticed.*

d. Exposure to a lysogenic virus: *A lysogenic virus "hides" its DNA in the DNA of the host cell, thus it can go undetected for extended periods of time. If the viral DNA is not actively producing proteins, the T-cells will not realize the virus is present. However, if the virus begins to force the host cell to make new viral particles, the foreign proteins that are made will be noticed by T-cells during APC presentation. Secreted viral particles in the extracellular space will be noticed by B-cells and macrophage cells. Eventually the immune system is alerted as T-cells and B-cells find the viral particles inside and outside the host cells. The B-cells and T-cells will make clones of the cells that have antibodies or receptors matching the antigen particles. The virus particles will be tagged by B-cells, the host cells will be perforated by T-cells and then macrophage cells will clean up all tagged and damaged material. If the virus remains*

dormant in some cells of the body while the immune system is active, the virus can rise up again for another sneak attack on the body at a later date.

e. The presence of a cancerous tumor: *Cancer cells go unnoticed by B-cells because they are not in the extracellular space. A macrophage cell will eat a cancer cell if the cell gives a signal to begin apoptosis (cell death), but cancer cells tend to live longer than normal without sending out the proper cell death signals. T-cells are the immune system's method of detecting cancer cells because T-cells can ask any nucleated cell to present the proteins or polysaccharides that are present in the interior of the cell. When a cancer cell presents particles to a T-cell, the T-cell may detect the presence of an unusual protein that is making the cancer cell grow in an uncontrolled manner to create a tumor. Sometimes the T-cell will detect a normal protein or polysaccharide, but if the percentage of these particles is different than what would be expected, the T-cell will initiate an immune response. If the T-cell detects an unusual particle or protein ratio, the T-cell will make clones and attack the cancerous cells that contain the protein. If no unusual proteins are detected, then the cancerous cells will continue to grow in an uncontrolled manner, creating a larger tumor or tumors that branch off into several different areas of the body, blocking the function of organs or vessels.*

10. The diversity in the family of genes called the human leukocyte antigen (HLA) system determines what range of epitopes can be detected by white blood cells. Some of the HLA genes have as many as 100 different possible alleles for a particular gene locus, each of which can produce a different type of antibody. How do you think the diversity of this group of genes plays a role in natural selection? *A wide variety of alleles on the HLA genes means that white blood cells are able to produce a wide variety of different types of antibodies. The greater the variety of antibodies, the greater the number of different epitopes that can be detected. An individual will have better immunity to infection if their antibodies are able to recognize one or more epitopes on a pathogen. Greater diversity in a person's HLA alleles equates to a stronger immune system. An organism with a stronger immune system may live longer and be healthier, two factors which may impact the organism's ability to produce a greater number of viable offspring.*

11. How do you think immune response affects the evolution of living pathogens such as bacteria or viruses? *If a pathogen is attacked by the immune system and wiped out by white blood cells before it is able to reproduce, then the pathogen will not pass on its genetic information. If a pathogen can go undetected in the body long enough to reproduce, then the bacteria or virus will have successfully produced bacterial and virus particles that are identical to themselves. Whatever methods a pathogen uses to slip past the immune system will be passed on to the new generation of pathogens. Like any other environmental pressure, the immune system acts on a population to remove the organisms that are less fit and to allow the survival of organisms that are more fit to deal with whatever type of selection pressure is in effect. Over time, only pathogens that are resistant to or able to elude or defeat the*

immune system long enough to reproduce will continue to exist in the environment. Certain pathogens have survived the human immune system and evolved in certain ways because of their interaction with it: the common cold, the flu, HIV or enveloped viruses and retroviruses in general.

Sample Lesson Plan from AIDS Case Study

Activity Sixteen: The Evolution of a Virus

Teaching Time: 1 class period of 50 minutes

Objectives:

a) For students to identify the factors influencing the evolution of a virus (EK 1.C.3.a, EK 1.C.3.b, EK 2.C.2.a, EK 3.C.3.a.4, SP 1.2, SP 1.4)
b) For students to describe how drug resistance develops based on survival of the fittest within a population under intense selection pressure (SP 1.5, SP 6.4, SP 7.1, SP 7.2)
c) For students to recognize how variation, mutation, adaptations, environmental pressures and chance impact the evolutionary process (EK 1.A.1.a, EK 1.A.1.c, EK 1.A.1.d, EK 1.A.1.e, EK 1.A.1.f, EK 1.A.2.a, EK 1.A.2.b, EK 3.C.1.d.1, EK 3.C.3.a.6, LO 3.28)
d) For students to be able to discuss an example situation in which random changes in genes result in phenotypic variations that significantly increase or decrease the fitness of an organism and in which humans impact the variation in another species (EK 1.A.2.b, EK 1.A.2.c, EK 1.A.2.d, EK 3.C.1.b.1, LO 3.24)
e) For students to create diagrammatic and mathematical models of drug resistance to predict what will happen to a population in the future (LO 1.3, LO 1.13, LO 1.25, SP 1.1, SP 1.3, SP 2.1, SP 2.2, SP 2.3)
f) For students to evaluate data-based evidence that describes changes in the genetic makeup of a population and connect those data to changes in a population over time (EK 1.A.4.a, LO 1.4, LO1.5, LO 1.9, LO 1.10, LO 1.12, LO 1.26, LO 4.26)

Materials:

For each student: one bag of ~50 red beads; one bag containing ~50 beads of a color other than red—use several different colors of beads to make bags for the class, with each bag containing only one color. For the class: one bag of ~100 red beads; one bag of paper clips.

Procedure:

1. Ask the students to recall the rate of compliance data they collected. Let the students know that an individual compliance rate of greater than 95% is needed to control the replication and proliferation of HIV. Tell them that they are going to play a game that demonstrates why such a high compliance rate is necessary.
2. The game the students are going to play is a permutation of the game called “tag.” You may choose to play this game outdoors or in an open space such as the school cafeteria, but there should be designated

boundaries for the play area such that it is small enough that the students can eventually be caught when being chased. You may also deem it necessary to establish safety rules--for example, you may decide to make it a walking game, in which anyone running is automatically "killed," or you may insist that students only tag each other on the arm (so that other body parts are not touched). Choose one (in a small class of 3-10), two (in a small class of 12-20) or three students (in a class larger than 20) to act as the drug or medication while all the other students act as the virus particles in this simulation. Give each HIV particle one bag of colored beads to represent its genome (each student should only have one color of beads in their bag representing the only type of genetic information they contain). Give one student the bag of ~100 red beads and discreetly tell the recipient that they cannot be killed by the medication in this game, so they will remain alive and will continue moving even after they have been tagged (only if students ask them why they continue moving after being tagged should they answer, "I'm resistant to this medication."). Tell the class that the medication students will chase the virus particle students and kill them with a touch on the arm. Announce the boundaries, explaining that the space inside the boundaries represents the body. Explain to the students that HIV cannot live in the open air, so anyone straying outside the boundaries of the body will die instantly. Tell the students that when they die they must "freeze" on the spot where they were caught and not interfere with the other students in the game. However, any virus particle that is still alive can approach a dead virus and give them ~10 beads from their own bag, allowing them back into the game as a product of replication with a new genome represented by a different color of beads. Replicated virus particles that are back in the game can now continue playing. If a student was given red beads when they were brought back into the game, they have the ability to evade the medications and so cannot be killed. Thus, the student who carries the bag of red beads will need to tell each virus they bring back into the game (through replication) that they will now be resistant to the medication and cannot be killed. Students brought back into the game can also bring other players back into the game, by giving each person 2-3 beads to represent their new genome. Until the medication kills all the virus particles, the ones that remain alive will continue to replicate when they have the opportunity to do so. If a person is tagged while replicating (getting new beads) then both virus particles will be killed.

3. Allow the students to play the game until only the medication students and the students with the red beads are left moving. Ask a student who has a red bead to explain to the entire class why they were not killed by the medication (because they are resistant to the drug being used). Tell the students that this mutant virus is called HIV strain R ("R" for the red bead). Ask the student who was originally given the bag of red beads to describe what happened during the game (they should be able to explain from their

point of view how they were able to evade the medication and continue to replicate, making other drug resistant viruses).

4. Explain to the students that HIV has a very high mutation rate because it lacks the proof-reading enzymes that correct mutated or incorrectly replicated DNA. Explain that without the proof-reading mechanisms in place, thousands of new HIV particles are produced during each replication with small changes in the HIV genome occurring often. Tell the students that each of the different colors of beads represented different mutated versions of HIV. Tell the class that the mutation rate for HIV is actually higher than that of any known organism, so this particular virus often has many different variants or mutant types in the body at any given moment, if it is replicating freely. However, most mutations are either deleterious or of no consequence, so most mutations that occur don't alter a virus's resistance to a particular medication. But because HIV creates mutations during replication so often, a small percentage of the mutants will be resistant and will evade the drug being used to control the spread of the infection to other T-cells if the virus is allowed to replicate freely. Ask the students to hypothesize or explain how a particular mutated virus particle (the red virus) was resistant to the medication while other mutants are killed (the red virus was mutated in such a way that it was not recognized by the drug, while the other mutants were still recognized by the drug).
5. Explain that if a person does not take their medication exactly as prescribed, the virus will begin to replicate and invade other cells. The higher the number of new cells infected, the higher the number of mutants made by reverse transcriptase. So, uncontrolled replication due to a person not taking their medication exactly on time leads to a higher probability of one the mutant viruses being a drug-resistant variation.
6. Tell the class that the HIV-positive patient they have been inhabiting has been given a new medication to control the HIV strain R they now represent, but sometimes the patient forgets to take their medication. Tell the students that you will yell out "No drugs in the system" once or twice during the next round of the game to represent the times when the patient forgets to take their medication. When this happens, the students acting as the medication must stand in place without moving for one full minute (you can time them and tell them when they can move again). During the entire game, with or without medication, the virus particles that are alive can continue to replicate just as they did in the last game.
7. Tell the students that in this second round, they are going to pretend that they are now replicated offspring of the mutant virus, and so they contain RNA that is like the mutant strain R. Choose new people to represent the new type of medication. Ask the remaining students to take a bag of red beads so they can play another round. While the students are procuring their bags, secretly give a bag of paper clips to one student. Discreetly tell the person receiving this bag that they will be resistant to the new drug and when they replicate (i.e., when they make new viral particles using a

person who is frozen) they will give the new virus particle paper clips instead of beads to represent the mutant genome they now have.

8. Tell the class that the new medication can kill all the new viral mutants of HIV strain R (those students who are holding red beads). Remember to call out "No drugs in the system" once or twice during this round of the game so the students can see how this impacts the balance between viral replication and viral death. Allow the students to play the tag game until only students with paper clips remain alive.
9. Ask one of the students who was killed to explain what they observed in this round (everyone of HIV strain R was killed by the new medication except the virus particles that have a new mutation and resistance to the new medication). Ask a student with a paper clip to confirm their peer's description or add to the explanation as needed. Tell the students that this new paper clip strain is HIV strain P. Ask the class to explain how this new mutant strain P can be controlled. They should be able to tell you that a new medication must be used since the current medication will not kill the new strain P. They should also mention that the patient has to be more compliant with their medication regimen in order to make sure the new strain does not have the opportunity to replicate and thus create new mutants. If the students are not able to draw these conclusions, play another round of the game (you can use the colored beads again, but choose a different color to represent a mutant form that is drug resistant).
10. As either an individual assessment or as a group discussion, ask the students how the game could be played to demonstrate what would happen in a person who has an even lower rate of compliance, and what would happen if multiple medications were used. When students extend a simulation or predict an outcome, you have a unique opportunity to see how much they understand. Allow the students to share their predictions and debate any inconsistencies or have them answer these two questions on paper in class, or for homework, so that you can make accurate individual assessments.
11. Tell the students that some scientists argue that AIDS medications are creating more and more mutants that are potentially more deadly. However, we know that a person infected with HIV is likely to die younger without medications than they would if they took medications. Ask the students to think of their response to the following question, without sharing their response aloud: "Do you think administering medications for AIDS to extend the life of an individual is worth the risk of creating HIV strains that might be resistant to all known HIV drugs in the population?" Ask the students to work in groups, with a neighbor, or individually on paper (for an individual assessment) to argue their perspective using scientific support, and then have them share their ideas with the rest of the class.
12. Tell the students that models are commonly used to explain a process or make predictions of what could occur next in a process. Ask the students to each draw a diagram that depicts the evolution of a pathogen so they

can visualize how the population of HIV and mutant forms of HIV are affected differently by a medication (*the students may draw a Venn diagram with overlapping circles containing viruses that are susceptible to the medications and those that evade the medications; they may draw the process in a form that resembles a bell-shaped, directional selection graph or they may choose some other way to represent the process, depending on what seems fitting to them).* Ask several students to share their representations with the rest of the class.

13. It is helpful for a dynamic model or diagrammatic model to be converted to a mathematical equation that can be used to make quantitative predictions. Ask the students to each create a mathematical equation that reflects the game they just played. The equation must show the mechanism for evolution using numeric information or variables that are represented by numbers. If you or your students have never created a mathematical equation before, you may use the example of how a generalized equation can be used to describe the area of a rectangle (A = length x width) regardless of the actual measure of each side of the rectangle. The tag game the students played simulates the viral death rate as caused by anti-HIV drugs, with a baseline replication rate occurring anytime there are viruses remaining. So, your students may suggest using a growth equation to represent the replication of the virus (exponential growth would be the most appropriate for the replication rate of a virus) and they may use a decay equation to represent the viral death rate as caused by the medicine. If you have helped your students develop their mathematical model thus far, ask them to propose a mathematical way to show what happens when a mutant evades the medication. Give them time and encouragement to attempt this, let them talk through their ideas and give them support, but try not to solve the problem for them. There are many different possible solutions, all of which are attempts to represent something that cannot be predicted in absolute terms, so allow room for many proposals, each of which might have merits and flaws.
14. For individual assessment, ask the students to look up the Red Queen Hypothesis and explain how drug resistance is an example of this phenomenon. Ask the students to explain the origin of the name of this hypothesis and describe how HIV resistance to ART medications is an example of evolution. Ask the students to read the chapters in their textbook that cover evolution as a follow-up to this activity.

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