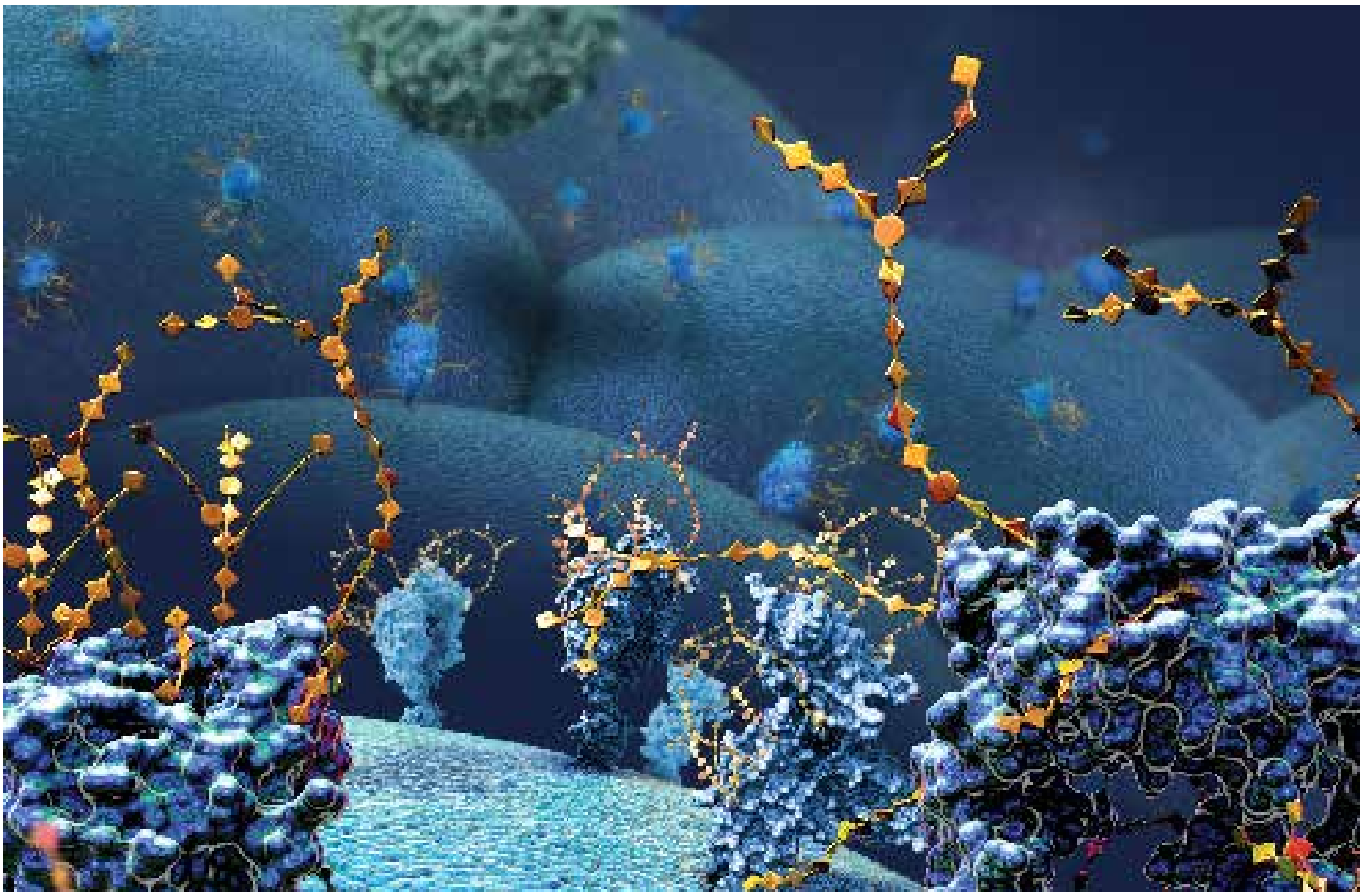
ScienceNews
IN HIGH SCHOOLS | EDUCATOR GUIDE



April 1, 2017

Cancer's Sweet Cloak

SOCIETY FOR
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SN EDUCATOR GUIDE

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Cancer's Sweet Cloak

About this Issue

The article "Cancer's sweet cloak" (9.7 readability score) describes how cancer cells coat themselves with extra sugars to avoid detection from the immune system, and how therapeutics in development might destroy that protective sugar coating. Students can focus on details in the article, follow connections to earlier articles about cancer, explore cross-curricular connections to other major science topics and analyze a graph of data from one of the cancer experiments featured in the article.

Science News for Students provides related articles written at lower Lexile levels. "Implant traps cancer cells on the move" (6.8 readability score) and "Scientists say: Carcinogen" (7.0 readability score) include Power Words that define key cancer-related terms for students.

Connections to Curricula:

- Molecular structures
- Sugars
- Proteins
- Lipids
- Cell signaling
- Cell cycle
- Cancer
- Immune system
- Biochemistry
- Nutrition
- Genetics
- Logarithmic scale
- Antibodies

What's in this Guide?

- Article-Based Observation: These questions focus on reading and content comprehension by drawing on information found in the article "Cancer's sweet cloak." Observations about cell-surface sugars and their ability to hide cancer cells from the immune system are highlighted.
- Quest Through the Archives: Since uncontrolled cell growth was first recognized as a problem, scientists have been searching for effective therapies. With Internet access and your school's digital access to *Science News*, your students can use this short section to explore the history of cancer therapy research as reported by *Science News* since 1922.
- Cross-Curricular Discussion: These questions and extension prompts connect to the article "Cancer's sweet cloak" and encourage students to think in more detail about scientific areas related to the article. The section is subdivided roughly by science subdiscipline for educators who would like to focus on one particular topic area. The extension prompts are either more topic specific or more conceptually advanced. **Chemical and Physical Sciences** questions focus on molecular structures and properties of sugars, proteins, lipids and combinations of those molecules. **Biological Sciences** questions cover the immune system and cancer. **Engineering and Experimental Design** questions involve various potential applications of information from the article.
- Activity: Using a set of guided questions, students can work in pairs to analyze a graph of data from one of the cancer experiments described in "Cancer's sweet cloak." Analysis will require students to understand logarithmic scales and to explore cancer treatment possibilities.

Standards Alignment

Next Generation Science	Common Core
From Molecules to Organisms: Structures and Processes: HS-LS1-1, HS-LS1-2, HS-LS1-4, HS-LS1-6	ELA Standards: Reading Informational Text (RI): 1, 2, 4, 5, 7
Biological Evolution: Unity and Diversity: HS-LS4-3, HS-LS4-4, HS-LS4-6	ELA Standards: Writing (W): 1, 2, 3, 4, 6, 7, 9
Matter and Its Interactions: HS-PS1-3	ELA Standards: Speaking and Listening (SL): 1, 2, 4, 6
Engineering Design: HS-ETS1-1, HS-ETS1-2	ELA Standards: Reading for Literacy in Science and Technical Subjects (RST): 1, 2, 3, 4, 5, 7, 8, 9
	ELA Standards: Writing Literacy in History/Social Studies and Science and Technical Subjects (WHST): 1, 2, 4, 6, 7, 9

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Article-Based Observations

Directions: Read the article "Cancer's sweet cloak" and pay close attention to the diagram titled "Surface tension." Then answer these questions:

1. **How does the author describe a cell's surface in the opening paragraphs? What is a role of cell-surface sugars and proteins as discussed in the article?**

2. **In terms of immune response, why are cell-surface molecules important? Why are some tumor cells not detected by the immune system?**

3. **How do protein-based immune therapies work? Why are other types of therapies being explored?**

4. **Chemist Carolyn Bertozzi of Stanford University studies cell-surface sugars. Why is it difficult to study sugars?**

5. **How does Carolyn Bertozzi hope to apply her surface-sugar research?**

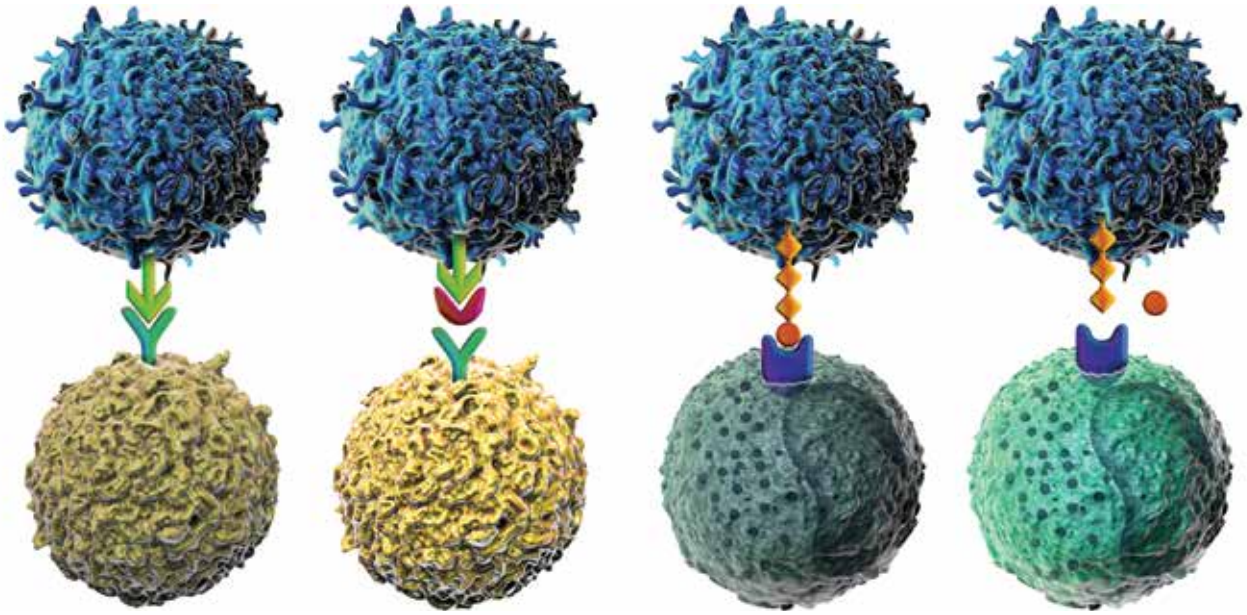
6. **What is a macrophage? What have biologist Paul Crocker and his team discovered about macrophages?**

7. **Explain how sialic acids might serve as a cloak. How did scientists determine that tumors have this cloak?**

8. **What is Herceptin? How did Carolyn Bertozzi and her coworkers use it as part of an immune therapy plan?**

9. **Imagine that you are writing a newspaper headline for a story about the research described in this article. Your space is limited and you need to catch readers' attention. Write a short headline that summarizes the article.**

10. **Using the article as a reference, fully label the diagram below and summarize the immune therapies described by the diagram. Which therapies are already used and which are potential treatments?**



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Responses to Article-Based Observation:

1. **How does the author describe a cell's surface in the opening paragraphs? What is a role of cell-surface sugars and proteins as discussed in the article?** Possible student response: The author likens the cellular surface to Earth's terrain. Sugar molecules extend from cell-surface proteins like the "large fronds" of "palm trees." The cell-surface sugar molecules help cells communicate.

2. **In terms of immune response, why are cell-surface molecules important? Why are some tumor cells not detected by the immune system?** Possible student response: Cell-surface molecules interact with immune system cells to either trigger or silence an immune response. To avoid detection by immune cells, tumor cells have adopted molecular modifications to their cell-surface molecules.

3. **How do protein-based immune therapies work? Why are other types of therapies being explored?** Possible student response: Current protein therapies block interactions that suppress the immune system. For example, the PD-L1 protein on a tumor cell is blocked and thus cannot interact with the PD-1 protein to silence T cell response. Current protein-based immune therapies do not work for all types of cancer or for all patients.

4. **Chemist Carolyn Bertozzi of Stanford University studies cell-surface sugars. Why is it difficult to study sugars?** Possible student response: Even though sugars are prolific on the surface of cells, they are hard drug targets. The author describes sugars as having "unpredictable diversity." The type and location of nucleotides in a protein's DNA sequence helps determine its three-dimensional structure. But sugars are the product of many possible enzymatic reactions, which result in many possible conformations.

5. **How does Carolyn Bertozzi hope to apply her surface-sugar research?** Possible student response: Bertozzi and her team have found that manipulating sugars on the surface of tumor cells has the potential to expand an exciting new class of cancer drugs. Similar to surface proteins, Bertozzi describes cell-surface sugars as molecular fingerprints, telling a roving immune cell, "This one's OK. Move along." Since these sugars can conceal a tumor cell from the body's immune system, interrupting the intercellular communication by trimming off the sugar may lead to potential new cancer therapies.

6. **What is a macrophage? What have biologist Paul Crocker and his team discovered about macrophages?** Possible student response: The word macrophage is Greek for "big eater." A macrophage is part of the innate immune response — it finds and devours pathogens and dying cells. In 1986, Crocker's team discovered a protein that makes macrophages sticky and later named it sialoadhesin. Checking for signature sequences in the gene that codes for sialoadhesin, researchers were excited to discover that the protein was part of a group of proteins, later named "Siglecs," that bind to cell-surface sialic acids.

7. **Explain how sialic acids might serve as a cloak. How did scientists determine that tumors have this cloak?** Possible student response: Cell-surface sugars act like a cloak to disguise tumor cells from immune cells. When sialic acid on a tumor cell binds with Siglec proteins on a natural killer cell, the immune system ignores the tumor. If the Siglec protein is not blocked, the natural killer cell attacks the tumor. Certain pathogens, such as the bacteria that cause gonorrhea or streptococcal infections, coat themselves with sialic acids to hide from the immune system. Several years ago, scientists wondered if cancer cells use a similar trick. That suspicion had roots in a strange but widespread observation — huge amounts of sialic acids clustered on the surfaces of tumor cells. In the late 1990s while starting up her lab at the University of California, Carolyn Bertozzi saw sialic acids as a potential marker for cancer. Bertozzi's group determined a method of adjusting sialic acid levels on cells to show that sialic acid amount does in fact affect immune response.

8. **What is Herceptin? How did Carolyn Bertozzi and her coworkers use it as part of an immune therapy plan?** Possible student response: Herceptin is a cancer drug that recognizes a protein called HER2 on the surface of many breast tumors. As an antibody, Herceptin binds to HER2 and marks the tumor cell for destruction by innate immune cells. Bertozzi and her team fused a sialidase enzyme with Herceptin to deliver sialidase to tumor cells.

9. **Imagine that you are writing a newspaper headline for a story about the research described in this article. Your space is limited and you need to catch readers' attention. Write a short headline that summarizes the article.** Possible student response: Trimming sugar could lead to new cancer therapy.

10. **Using the article as a reference, fully label the diagram below (Page 2 of Blackline Master 1) and summarize the immune therapies described by the diagram. Which therapies are already used and which are potential treatments?** Possible student response: Current immune therapies interfere with protein interactions between cancer and T cells. Potential treatments could target interactions between sialic acids on tumors and sugar-binding Siglec proteins on natural killer cells.

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Quest Through the Archives:

Directions: After reading the article "Cancer's sweet cloak," use the archives at www.sciencenews.org to answer these questions:

1. **Search for the earliest published article about cancer research in the *Science News* archives. What does it discuss?**

2. **Search for an article that summarizes other innovations in cancer treatment. Describe the treatment.**

3. **Search for an article that describes how the immune system may be affected by a person's diet. Summarize the article and pull a quote from the article that supports your summary.**

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Responses to Quest Through the Archives:

1. **Search for the earliest published article about cancer research in the *Science News* archives. What does it discuss?** Possible student response: "Doctors doubtful of cancer serum," published 6/28/1924, discusses the work of Dr. T.J. Glover of Toronto, who claimed to have made a cancer-curing serum. The American Medical Association expressed doubts, with the assistant to the editor of its journal stating that "Evidence indicates that controlled tests of the Glover cancer serum made by Francis Carter Wood, director of cancer research, Columbia University, show that the treatment has not the slightest effect on the growth of tumors of animals."

2. **Search for an article that describes other innovations in cancer treatment. Describe the treatment.** Possible student response: "Immunotherapy attacks aberrant cervical growth," published online 1/29/2014, describes a possible immunotherapy to fight precancerous lesions in women. The treatment injection contains a mix of proteins, genes and a virus and is designed to alert the immune system to cells commandeered by human papillomavirus.

3. **Search for an article that describes how the immune system may be affected by a person's diet. Summarize the article and pull a quote from the article that supports your summary.** Possible student response: "Typical American diet can damage immune system," published 5/18/2015, discusses the effect of poor nutrition on cellular function. Evidence suggests that unhealthy foods may disrupt immune defenses to promote inflammation, infection, autoimmune disease and cancer. The article states, "There is also evidence that certain kinds of fats and refined sugar, consumed in excess, may compromise the inner lining of the intestine, allowing microscopic leaks that trigger unrelenting immune activation."

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Cross-Curricular Discussion

After students have had a chance to review the article "Cancer's sweet cloak," lead a classroom discussion based on the questions that follow. You can copy and paste only the questions that apply to your classroom into a different document for your students. Before starting the discussion, have your students watch Carolyn Bertozzi in "The sugar coating on your cells is trying to tell you something," a TedxStanford video. You may also encourage your students to explore some additional resources listed below.

Recommended textbook references on the biochemistry of sugars and other molecules, cancer and the immune system:

- Theodore E. Brown *et al. Chemistry: The Central Science*. 14th ed. Pearson, 2017. (See Chapter 24 on biological molecules.)
- Lisa Urry *et al. Campbell Biology*. 11th ed. Pearson, 2016. (See Chapter 5 on biological molecules; Chapters 11, 12 and 18 on various aspects of cancer; and Chapter 43 on the immune system.)
- Denise R. Ferrier. *Lippincott Illustrated Reviews: Biochemistry*. 7th ed. LWW, 2017.
- Lauren Sompayrac. *How Cancer Works*. Bartlett, 2004.
- Lauren Sompayrac. *How the Immune System Works*. 5th ed. Wiley, 2016.
- Lauren Pecorino. *Molecular Biology of Cancer: Mechanisms, Targets and Therapeutics*. 4th ed. Oxford, 2016.
- Abul K. Abbas, Andrew H. Lichtman, and Shiv Pillai. *Cellular and Molecular Immunology*. 9th ed. Elsevier, May 26, 2017.

CHEMICAL AND PHYSICAL SCIENCES

Discussion Questions:

1. Summarize the molecular composition of proteins. [*Proteins are long chains of amino acids joined together by peptide bonds. Amino acids have an amine or ammonia (-NH_2 or -NH_{3+}) group at one end that assumes a positively charged state at normal physiological conditions (pH approximately 7), a carboxylic acid (-COOH or -COO^- with double bonds between one of the oxygens and the carbon) on the other end that assumes a negatively charged state at normal physiological conditions, and a CH bonded to a hydrocarbon side chain referred to as R. There are 20 common amino acids, which differ from each other in their side chains. Those side chains can be anything from a simple hydrogen to complex rings of atoms. Shorter proteins are sometimes called peptides.*]
2. What are lipids? Describe their typical chemical composition and physical properties. [*Lipids are fatty*

acids, triglycerides, cholesterol and other similar molecules. They are composed of mostly carbon (C) and hydrogen (H) atoms, so they don't have much electrical charge or electrical polarity. Because water molecules (H_2O) are very polar (fairly negative oxygen and fairly positive hydrogens), lipids are hydrophobic — they are insoluble in water. Thus lipids will float on the top of water or form clumps. That's why you have to use soap (another lipid) to get greasy residue off dinner plates, instead of simply rinsing them with water. Among other things, lipids form the outer membranes of cells. Lipids in soap and in cell membranes have charged phosphates connected to one end; the charged end can interact with water.]

3. What are carbohydrates or, more simply, sugars? [*Sugars, or carbohydrates, are composed of carbon (C), hydrogen (H) and oxygen (O). The most well-known example is glucose (simple or blood sugar, $C_6H_{12}O_6$). Other examples are fruit sugar (fructose), table sugar (sucrose) and milk sugar (lactose). Individual sugars can be strung together in various ways to make everything from starch to cell walls. Sugars may be called glycans or saccharides when they are part of other molecules.*]

Extension Prompts:

4. Define a peptide bond and the reaction that occurs when it is formed. [*Peptide bonds form as a result of a dehydration synthesis reaction between two amino acids. Specifically, the carboxyl group of one amino acid bonds with the amino group of a second amino acid and a water molecule is produced.*]
5. What is meant by secondary, tertiary and quaternary structures of a protein? [*Interactions of the amino acids within a sequence as well as interactions with the surrounding environment contribute to a protein's secondary, tertiary and quaternary structures. Alpha-helixes and beta-sheets (parallel- and antiparallel-pleated sheets) are secondary structures. Tertiary structures are formed when all of the alpha-helixes and beta-sheets fold into a three-dimensional structure. When proteins are made up of more than one polypeptide chain, the three-dimensional organization of the protein subunits is called the quaternary structure.*]
6. What are lipoproteins? What are glycoproteins? What are glycolipids? [*Lipoproteins: soluble proteins that combine with lipids to transport them in blood plasma. Glycoproteins: sugar and protein molecules bonded together. Glycolipids: sugar and lipid molecules bonded together*.]

Chemical and Physical Sciences Question Bank

Summarize the molecular composition of proteins.

What are lipids? Describe their typical chemical composition and physical properties.

What are carbohydrates or, more simply, sugars?

Define a peptide bond and the reaction that occurs when it is formed.

What is meant by secondary, tertiary and quaternary structures of a protein?

What are lipoproteins? What are glycoproteins? What are glycolipids?

BIOLOGICAL SCIENCES

Discussion Questions:

1. What biological job can be served by sugars attached to proteins? [*Sugars can help the protein fold in a particular way for a specific function, give the protein a unique shape and/or sticky surface that can be recognized by some receptor, or protect the protein from degradation, among other examples.*]
2. Though they are complementary systems, what are the major distinctions of the innate/nonspecific and adaptive/acquired immune systems? How does the adaptive immune system specifically attack things that should not be in your body? How does the innate immune system nonspecifically attack things that should not be in your body? [*The innate immune system provides nonspecific defense against pathogens. Macrophages and natural killer cells respond quickly, and have membrane receptors with broad specificity. These immune cells can respond to both unique and common signals from pathogenic microorganisms. The membrane receptors that mediate adaptive immunity selectively respond to specific pathogens. Adaptive immunity is typically classified as either cell-mediated or antibody-mediated. In cell-mediated immunity, a cell binds through receptors to its target cell — known as contact-dependent signaling. An antibody-mediated response occurs when secreted antibodies combine with pathogens to make them more visible to immune cells.*]
3. How is cell growth and division controlled in normal cells? [*Cells need growth factor molecules made by the body to sustain continued growth. Cells have receptors that operate as sensors to detect the right growth factors, internal signaling pathways to communicate the signal and suppressor pathways to block cell division or even kill a cell if the correct signals are not received.*]

Extension Prompts:

4. In terms of cell growth and division, what is one of the major differences between cancer cells and normal cells? [*Cancer cells grow and divide when they are not supposed to, whereas normal cell growth is controlled. Cancer cells may have some combination of hyperactive growth factor receptors and growth factor internal signaling pathways, as well as mutated and inactive suppressor pathways that promote this growth.*]
5. How do cancer cells avoid getting attacked by the immune system? How do bacteria avoid getting attacked by the immune system? [*Among other ways, cancer cells can cover themselves with specific proteins or extra sugar molecules that silence the immune system. Bacteria can also have cell-surface "sugar cloaks." They have sugar-rich walls of peptidoglycan or lipopolysaccharide, and some surround themselves in a polysaccharide capsule for an extra protective coat of sugar. After bacteria encounter host defense cells, they may rapidly adapt in other ways to avoid immune detection.*]

Biological Sciences Question Bank

What biological job can be served by sugars attached to proteins?

Though they are complementary systems, what are the major distinctions of the innate/nonspecific and adaptive/acquired immune systems? How does the adaptive immune system specifically attack things that should not be in your body? How does the innate immune system nonspecifically attack things that

should not be in your body?

How is cell growth and division controlled in normal cells?

In terms of cell growth and division, what is one of the major differences between cancer cells and normal cells?

How do cancer cells avoid getting attacked by the immune system? How do bacteria avoid getting attacked by the immune system?

ENGINEERING AND EXPERIMENTAL DESIGN

Discussion Questions:

1. How can monoclonal antibodies be used to treat cancer? [*Monoclonal antibodies — identical antibodies that all specifically bind to the same molecular target — can be designed to bind to a surface feature that is found on certain cancer cells but not normal cells, or at least is found in much greater quantities on cancer cells. Then the monoclonal antibodies can be mass-produced and injected into patients. When they bind to the cancer cells, they can attract the attention of the immune system. In some cases, monoclonal antibodies are designed to carry a toxin that can be delivered to cancer cells.*]
2. If you had a two-part molecule as a drug and you wanted to test its effect compared with the individual drugs, how would you generally design the experiment? [*Test one molecule by itself, the other molecule by itself and then the two molecules linked together. If it is a successful possible treatment, the effect of either molecule by itself should be much smaller than the effect of the two linked molecules.*]

Extension Prompts:

3. What is the EC_{50} or IC_{50} of a therapeutic, and why should it be as low as possible? [*The concentration of the therapeutic required to achieve half the maximum effect is called the effective concentration or inhibitory concentration for 50 percent of the effect, EC_{50} or IC_{50}. These concentrations are commonly used as a measurement of a drug's potency. The lower it is, the less of a therapeutic you have to produce, store and administer. Minimizing the concentration of a therapeutic required to achieve a beneficial effect also minimizes the chance that there will be unwanted side effects or toxicity.*]
4. Based on the immunotherapies mentioned in the article, your knowledge of cell growth and division, and the different types of immune responses, suggest another possible cancer treatment strategy. [*Answers will vary but may focus on preventing cancer cell division or manipulating cell-surface sugars in another way.*]

Engineering and Experimental Design Question Bank

How can monoclonal antibodies be used to treat cancer?

If you had a two-part molecule as a drug and you wanted to test its effect compared with the individual drugs, how would you generally design the experiment?

What is the EC_{50} or IC_{50} of a therapeutic, and why should it be as low as possible?

Based on the immunotherapies mentioned in the article, your knowledge of cell growth and division, and the different types of immune responses, suggest another possible cancer treatment strategy.

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Teacher's Guide: Mowing Down Cancer Cells

Class time: 30-50 minutes.

Purpose: To analyze a graph of data from an experiment testing two different cancer treatments against laboratory-cultured cancer cells.

Notes to the teacher: After students have had a chanced to review the article "Cancer's sweet cloak," pass out the accompanying Student Guide (Blackline Master 3) and rulers.

If your students are unfamiliar with the concept of a log scale, explain what it is and how to make approximate measurements on it before students start working. Students may also view this Khan Academy video on logarithmic scales. The main idea to emphasize is that the major tick marks on a log axis represent factors of 10 (1, 10, 100, 1,000 and so on). In this way, it's possible to show a wider range of values on one graph. That means the halfway point between the values of 1 and 10 is not 5.5 as students might expect, but roughly 3. In order to find the halfway point, one must take the square root of the product of the left tick mark's value (1) and the right tick mark's value (10). For example, the square root of 10 (because 1 x 10 = 10) is about equal to 3.16. See visualization here. The value 2 is somewhat to the left of that midpoint, and all the other values (4 through 9) are scrunched up closer and closer between the midpoint and the next tick mark. For another example, if two adjacent tick marks indicate 100 and 1,000, the midpoint between them is roughly 316. Take the square root of the product of the left tick mark's value (100) and the right tick mark's value (1,000). The square root of 100,000 (100 x 1,000 = 100,000) is about equal to 316. Two hundred is somewhat left of the midpoint and 400 through 900 get closer and closer together between the midpoint and 1,000.

Introduction:
The graph titled "Effect of HER2 antibody plus sialidase on immune activity" is from an experiment with laboratory-cultured populations of ZR-75-1 human breast cancer cells, which compared with normal breast cells have elevated (but not astronomical) levels of the HER2 protein on their surfaces. HER2 protein is a growth factor receptor, which helps to sense signals from the environment telling cells to grow. If cells have too much HER2, they can grow and divide too much, a hallmark of cancer cells.

The graph shows the effect of two different treatments on these cells:

- Herceptin, or trastuzumab, an antibody that specifically binds to the HER2 protein.
- Herceptin-sialidase, the same antibody connected to a bacteria-produced sialidase enzyme that trims sialic acid sugars.

For each of these two treatments, the graph plots the "Percent cytotoxicity" (the percent of cancer cells killed by natural killer cells) versus the treatment concentration in picomolar (pM = 10^{-12} M). Circles show measured data points, and curves extrapolate the apparent trend for the data points.

Questions:

1. Using your ruler and a calculator, add and label the pM concentration for at least five additional tick marks on the x-axis.

2. If you were repeating this experiment, what additional concentration might you want to test? What result would you expect to see? [*Based on the trend lines drawn, students should pick at least one or two concentrations around 100–200 pM. They should expect to see an intermediate cytotoxicity.*]

3. Using a ruler, approximately what is the lowest percent cytotoxicity? [*Approximately 2 to 3 percent cytotoxicity.*]

4. Why might there be a nonzero amount of cytotoxicity even with no treatment? [*Cell death occurs. Even individual cancer cells that are kept well-fed in a laboratory experiment can die.*]

5. Using a ruler and estimating from the log scale on the x-axis, approximately what is the highest treatment concentration tested? [*Approximately 20,000 pM.*]

6. At the highest concentration of the Herceptin only treatment, approximately what is the percent cytotoxicity? How much larger is that value (in percentage points) than the lowest measured cytoxicity? [*Approximately 12–13 percent cytotoxicity total, or approximately 10 percent more cytoxicity than with no treatment.*]

7. At the highest concentration of Herceptin-sialidase treatment, approximately what is the percent cytotoxicity? How much larger is that value than the lowest measured cytoxicity (in percentage points)? [*Approximately 32–33 percent cytotoxicity total, or approximately 30 percent more toxicity than with no treatment.*]

8. At the highest concentration, approximately how much more cytotoxicity does Herceptin-sialidase cause than Herceptin (approximately what multiplicative factor)? [*Roughly 2.5–3 times more cytotoxicity, depending on whether you are talking total cytotoxicity or cytotoxicity above the lowest level recorded.*]

9. Using a ruler and estimating from the log scale on the horizontal axis, at approximately what concentration does Herceptin have half of its maximum possible effect? [*Approximately 1,000 pM.*]

10. Using a ruler and estimating from the log scale on the horizontal axis, at approximately what concentration does Herceptin-sialidase have half of its maximum possible effect? [*Approximately 100 pM or a smidgen over that.*]

11. Herceptin and Herceptin-sialidase treatments require different concentrations to achieve half of their maximum effects. What's the fraction of Herceptin-sialidase required relative to Herceptin alone? [*To achieve a half-maximal effect, roughly 1/10 as much Herceptin-sialidase is required as Herceptin. The concentration required to achieve half the maximum effect is called the effective concentration or inhibitory concentration, for 50 percent of the effect, EC_{50} or IC_{50}. The lower it is, the less of a treatment you have to take.*]

12. Based on what you know, by what mechanism(s) does Herceptin kill ZR-75-1 breast cancer cells in this experiment? [*Herceptin blocks HER2 growth factor receptors, so cells get fewer signals telling them to grow. Some cells will likely die.*]

13. Based on what you know, by what mechanism(s) does the Herceptin-sialidase treatment kill ZR-75-1 breast cancer cells in this experiment? [*Herceptin-sialidase contains Herceptin that blocks HER2 growth factor receptors, but it also contains sialidase that clips sialic acid sugars on the cell surface. With their sialic acid sugar disguise shaved off, the cancer cells are recognized and killed by natural killer cells.*]

14. Which treatment does a better job of killing ZR-75-1 breast cancer cells? How is that shown in this experiment, and what difference in mechanism explains that difference in results? [*Based on this study, the Herceptin-sialidase combination is much more effective at killing ZR-75-1 cells than Herceptin alone is killing approximately 2.5–3 times more cells at roughly 1/10 the required concentration. Because it has the sialidase enzyme, it clips sialic acid sugars on the surface of targeted cells and triggers an immune response.*]

15. Why is it important to test both Herceptin and Herceptin-sialidase in the same experiment? What else might you want to see tested at the same time and why? [*Herceptin is a control to see if the effects of the Herceptin-sialidase treatment are due only to the benefits of Herceptin binding to HER2, or whether the sialidase enzyme is also playing a role. It might also make sense to test sialidase by itself, just to make sure it does not cause the same levels of cytotoxicity at the concentrations observed for the coupled Herceptin-sialidase.*]

16. What experiments could you do with cultured cells to test how safe Herceptin and Herceptin-sialidase treatments might be? [*It is great to show that these treatments kill breast cancer cells, but it is also very important to show that they do not kill normal breast cells, or other types of normal cells. Tests could look at normal cells and even a breast cancer cell line that does not have elevated levels of HER2.*]

17. Would you expect Herceptin and Herceptin-sialidase to be effective against all types of breast cancer cells? Why or why not? [*Herceptin and Herceptin-sialidase both target cells with elevated levels of HER2, but some breast cancer cell types have normal amounts of HER2. The sialidase portion works by stripping off sugars, but it is possible that cancer cells exist that don't rely on sugars as a cloak but have found some other way to keep the immune system from attacking.*]

18. Name an additional factor that might affect the success of Herceptin-sialidase treatment in a whole animal or human? [*A human or animal immune system might recognize the bacteria-produced sialidase as foreign and attack the molecule or its carriers.*]

19. How could you change the design of Herceptin-sialidase to help minimize problems in a whole animal or human? [*Ideally the sialidase (and the rest of the treatment) should come from the species or individual in which it is being used, so that it will not be recognized as foreign by the immune system. Even that is no guarantee because the immune system might react to how the molecules are connected.*]

20. How could you change the design of Herceptin-sialidase to target other types of cancer cells? [*One end of Herceptin-sialidase is the Herceptin antibody that binds to HER2 that is found in excess on the surface of some breast cancer cell types. That end could be replaced with an antibody that binds to some other protein that is found in excess on the surface of some other cancer cell types. But tests need to show the success of these approaches because some cancer cell types do not have excess surface proteins, and some proteins abundant on cancer cells are also abundant on normal cells.*]

21. If you changed the design of Herceptin-sialidase to target some other type of cancer cells, what sort of simple experiments could you do with cultured laboratory cells? [*Link sialidase to another antibody that binds to some other protein found in excess on the surface of some other cancer cell type. Test that antibody, antibody-sialidase and sialidase alone against cultured cancer cells to measure the percent cytotoxicty at a wide range of concentrations. Also, do the same experiment with cells that have a normal amount of that target protein on their surfaces, in order to test for undesirable toxicity in normal cells.*]

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Cancer's Sweet Cloak

Student Guide: Mowing Down Cancer Cells

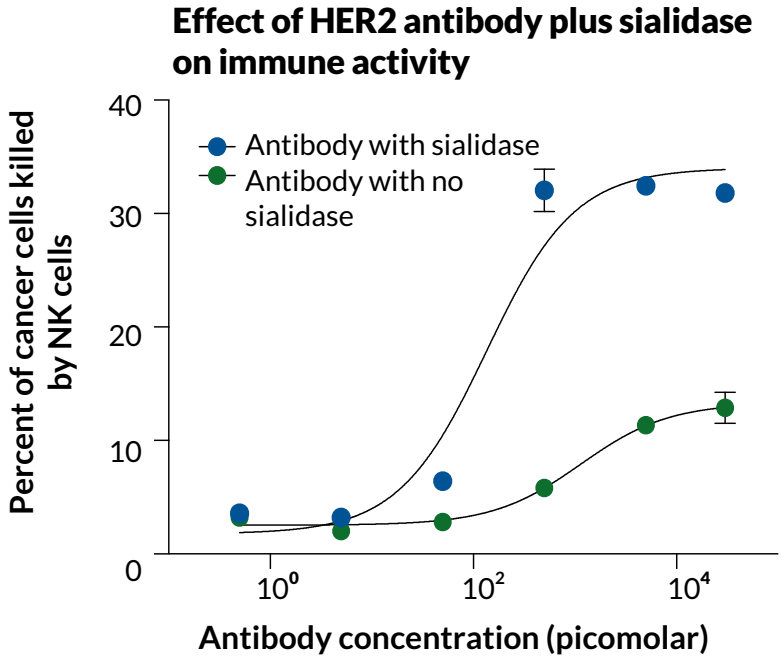
Purpose: To analyze a data graph from an experiment testing two different cancer treatments against laboratory-cultured breast cancer cells.

Introduction: The graph titled "Effect of HER2 antibody plus sialidase on immune activity" is from an experiment with laboratory-cultured populations of ZR-75-1 human breast cancer cells, which compared with normal breast cells have elevated (but not astronomical) levels of the HER2 protein on their surfaces. HER2 protein is a growth factor receptor, which helps to sense signals from the environment telling cells to grow. If cells have too much HER2, they can grow and divide too much, a hallmark of cancer cells.

The graph shows the effect of two different treatments on these cells:

- Herceptin, or trastuzumab, an antibody that specifically binds to the HER2 protein.
- Herceptin-sialidase, the same antibody connected to a bacteria-produced sialidase enzyme that trims sialic acid sugars.

For each of these two treatments, the graph plots the "Percent cytotoxicity" (the percent of cancer cells killed by natural killer cells) versus the treatment concentration in picomolar (pM = 10^{-12} M). Circles show measured data points, and curves extrapolate the apparent trend for the data points.



Directions: Analyze the graph and explore cancer immune therapy treatments by answering these related questions:

1. Using your ruler and a calculator, add and label the pM concentration for at least five additional tick marks on the x-axis.

2. If you were repeating this experiment, what additional concentration might you want to test? What result would you expect to see?

3. Using a ruler, approximately what is the lowest percent cytotoxicity?

4. Why might there be a nonzero amount of cytotoxicity even with no treatment?

5. Using a ruler and estimating from the log scale on the x-axis, approximately what is the highest treatment concentration tested?

6. At the highest concentration of the Herceptin only treatment, approximately what is the percent cytotoxicity? How much larger is that value (in percentage points) than the lowest measured cytoxicity?

7. At the highest concentration of Herceptin-sialidase treatment, approximately what is the percent cytotoxicity? How much larger is that value than the lowest measured cytoxicity (in percentage points)?

8. At the highest concentration, approximately how much more cytotoxicity does Herceptin-sialidase cause than Herceptin (approximately what multiplicative factor)?

9. Using a ruler and estimating from the log scale on the horizontal axis, at approximately what concentration does Herceptin have half of its maximum possible effect?

10. Using a ruler and estimating from the log scale on the horizontal axis, at approximately what concentration does Herceptin-sialidase have half of its maximum possible effect?

11. Herceptin and Herceptin-sialidase treatments require different concentrations to achieve half of their maximum effects. What's the fraction of Herceptin-sialidase required relative to Herceptin alone?

12. Based on what you know, by what mechanism(s) does Herceptin kill ZR-75-1 breast cancer cells in this experiment?

13. Based on what you know, by what mechanism(s) does the Herceptin-sialidase treatment kill ZR-75-1 breast cancer cells in this experiment?

14. Which treatment does a better job of killing ZR-75-1 breast cancer cells? How is that shown in this experiment, and what difference in mechanism explains that difference in results?

15. Why is it important to test both Herceptin and Herceptin-sialidase in the same experiment? What else might you want to see tested at the same time and why?

16. What experiments could you do with cultured cells to test how safe Herceptin and Herceptin-sialidase treatments might be?

17. Would you expect Herceptin and Herceptin-sialidase to be effective against all types of breast cancer cells? Why or why not?

18. Name an additional factor that might affect the success of Herceptin-sialidase treatment in a whole animal or human?

19. How could you change the design of Herceptin-sialidase to help minimize problems in a whole animal or human?

20. How could you change the design of Herceptin-sialidase to target other types of cancer cells?

21. If you changed the design of Herceptin-sialidase to target some other type of cancer cells, what sort of simple experiments could you do with cultured laboratory cells?