The War of the 21st Century:

The Cell Cycle, Cancer and Clinical Trials

UF Center For Precollegiate Education & Training

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The War of the 21st Century: The Cell Cycle, Cancer and Clinical Trials was developed as a part of Biomedical Explorations: Bench to Bedside which was supported by the National Center for Research Resources and the Division of Program Coordination, Planning, and Strategic Initiatives of the National Institutes of Health through Grant Number R25RR023294. Additional support provided by the University of Florida (UF) and the UF Center for Precollegiate Education and Training.

The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health.

Additional information regarding the Bench to Bedside project is available at http://www.cpet.ufl.edu/bench.

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Last updated: July 2013

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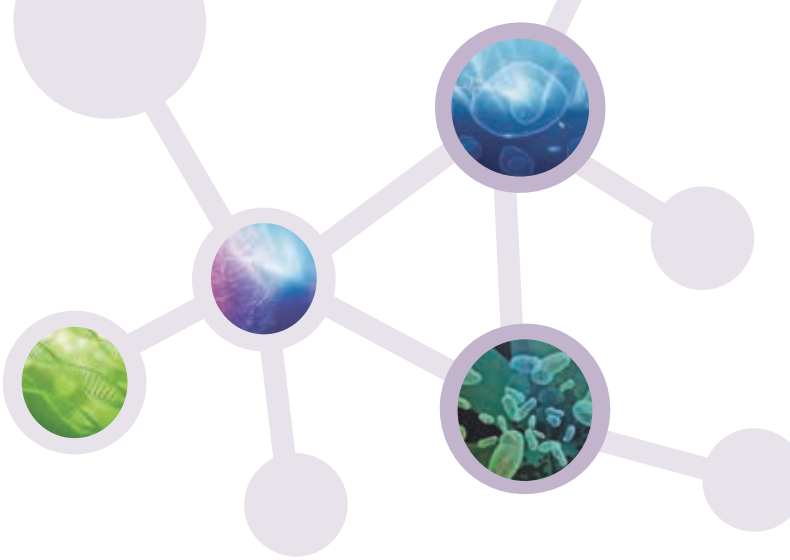
Supported by the National Institutes of Health



Contents

Introduction

Cancer is a word that seems to exist in everyone's vocabulary in the 21st century. We all have at least one person in our lives that has been touched by cancer: a mother, father, brother, sister, cousin, uncle, aunt, friend, neighbor, co-worker and the list goes on. In this unit we strive to provide students with an opportunity to learn more about the mechanisms of cancer and help students realize that even though all cancers are unique, all cancers are the result of mutations in the cell cycle. We also show students how translational medicine is leading the way to new, less invasive, treatments for cancer patients through clinical trials.

Author's Note

We chose to develop a unit centered around clinical trials for new anti-cancer drugs for several reasons. The first was addressed in the introduction: statistically everyone has been touched by cancer in some way. Secondly, we had the wonderful learning opportunity to spend two weeks in the summer of 2012 interning in Dr. Christopher Cogle's University of Florida clinical and research laboratory where we actually performed IC_{50} drug studies on cancerous human cell lines. We hope with the combination of personal experiences we provide to our students and the heart touching stories woven into our material that students will be intrigued and engaged in learning the material and perhaps even inspired to join the fight against cancer in the future. Lastly, we both felt very strongly that the role of checkpoints in the cell cycle is often overlooked in the typical high school biology classroom and that we not only wanted to expand on that particular content area but to utilize student driven, inquiry style learning methods.

Big Ideas

1. The development of cancer is a multi-step process that requires mutations in both tumor suppressor genes and proto-oncogenes.
2. Translational medicine is the application of traditional "bench research" to better the human condition and create novel treatments for many diseases, especially cancer.
3. New drugs developed in research labs must be tested via clinical trials before they are available on the market.

Tips about this Curriculum

Lesson Plan Format: All lessons in this curriculum unit are formatted in the same manner. In each lesson you will find the following components:

KEY QUESTION(S): Identifies key questions the lesson will explore.

OVERALL TIME ESTIMATE: Indicates total amount of time needed for the lesson, including advanced preparation.

LEARNING STYLES: Visual, auditory, and/or kinesthetic.

VOCABULARY: Lists key vocabulary terms used and defined in the lesson. Also collected in master vocabulary list.

LESSON SUMMARY: Provides a 1-2 sentence summary of what the lesson will cover and how this content will be covered. Also collected in one list.

STUDENT LEARNING OBJECTIVES: Focuses on what students will know, feel, or be able to do at the conclusion of the lesson.

STANDARDS: Specific state benchmarks addressed in the lesson. Also collected in one list. This curriculum is also aligned with common core and Next Generation Science Standards (NGSS)

MATERIALS: Items needed to complete the lesson. Number required for different types of grouping formats (Per class, Per group of 3-4 students, Per pair, Per student) is also indicated.

BACKGROUND INFORMATION: Provides accurate, up-to-date information from reliable sources about the lesson topic.

ADVANCE PREPARATION: This section explains what needs to be done to get ready for the lesson.

PROCEDURE WITH TIME ESTIMATES: The procedure details the steps of implementation with suggested time estimates. The times will likely vary depending on the class.

ASSESSMENT SUGGESTIONS: Formative assessment suggestions have been given. Teachers should feel free to create additional formative and summative assessment pieces.

EXTENSIONS (ACTIVITIES/LITERATURE): There are many activities and reading sources available to augment and enhance the curriculum. They have been included. If you find additional ones that should be added, please let us know.

RESOURCES/REFERENCES: This curriculum is based heavily on primary sources. As resources and references have been used in a lesson, their complete citation is included as well as a web link if available.

STUDENT PAGES: Worksheets and handouts to be copied and distributed to the students.

TEACHER MASTERS: Versions of the student pages with answers or the activity materials for preparation.

Collaborative Learning: The lessons in this curriculum have been developed to include many collaborative learning opportunities. Rather than presenting information in lecture format and teacher driven, the activities involve the students in a more engaged manner. For classrooms not accustomed to using collaborative learning strategies, have patience. It can be difficult to communicate instructions, particularly for students who are visual learners. For these students, use of visual clues such as flowcharts and graphics can help them understand how they are to move to different groups.

Groups: Most of the lessons are carried out in groups. While it isn't necessary for students to remain in the same groups the entire unit, if they work well together, it may foster students to think deeper as they are comfortable with their teammates and willing to ask questions of each other.

Inquiry-based: The lessons in the curriculum invite students to be engaged and ask questions. They work through background information in a guided fashion, but are challenged to think beyond what they have read or done. The teacher serves as the facilitator in these activities, not the deliverer of information.

Technology: Lessons have been written to be mindful of varying availability of technology in schools and homes. Some of the lessons would be very well suited to online environments and if your students are able, you might wish to engage in some of the technology modifications.

Content: Often we teach in a manner that is very content heavy. With high-stakes testing the norm, students are pushed to memorize and regurgitate numerous isolated facts. There is so much content that must be covered in a biology class, for example, that often it is difficult to synthesize those discrete facts into a compelling context or a story.

Implementation Notes: This module should ideally follow a basic unit on cellular division. Students should already understand the basic mechanics of mitosis and meiosis. Students may also be familiar with the concept of the cell cycle and it's two major phases: interphase and cellular division, but will not be required to have a deep understanding of the subphases of interphase
(Gap 1, Synthesis, Gap 2 and/or checkpoints) before beginning this curriculum module.

Science Subject: Biology

Grade and Ability Level: 9-12 students in regular or advanced biology

Science Concepts: cell cycle, DNA, mutations, protein structure, protein function, genetics, cancer, experimental design

Icon Key

Teacher Pages

Student Handout/ Worksheets

Extension

Teacher Answer Key

Student Reading

Lesson Summaries

LESSON ONE:
Cancer Warriors: A Personal Story of Translational Medicine

Cancer Myth Survey
Cancer Warrior w/Discussion Question Guide-Introducing Translational Medicine
Patient Story-Clinical Trials
Journal Entry

LESSON TWO:
Preparing for War: A History of Cancer

Timeline Activity

LESSON THREE:
Keeping it all in Check: The Life of a Cell in the Cell Cycle

Cell Cycle Interactive Wheel-A Tri Layer Activity
Proto-oncogenes and Tumor Suppressor genes Activity

LESSON FOUR:
Losing Control: The Cell Cycle and Cancer

What Happens When Genes Lose Control? Activity
Cancer Concept Map
Extension: What's the Risk? Game

LESSON FIVE:
Going to War: Clinical Trials

Clinical Trials Webquest
Clinical Trials Role Play
Close Read of *"Do Clinical Trials Work?"*
Experimental Design Practice
Extension: Exploration of Local Clinical Trials

LESSON SIX:
Fighting the Battle: Conducting a Clinical Assay

Students will complete a simulation assay in which they will dilute a "drug stock" (4.2 buffer) into cell culture media (water) and apply a reagent (0.5% methyl red: 0.5% bromothymol blue) to determine "AML cell death"

LESSON SEVEN:
In the Situation Room: Fighting Cancer in the Future

Journal Review of Current/Ongoing Cancer Research: Team Literature Review-Present to Class
Revising Student Survey and Journal Responses

Lesson Sequencing Guide

Since each classroom teacher knows his or her students best, the teacher should decide the sequencing of lessons. Below is a suggested pacing guide that can be used when planning to use this curriculum.

	Day 1	Day 2	Day 3	Day 4	Day 5
Week 1	Lesson 1 Cancer Warriors: A Personal Story of Translational Medicine (Hooks and Journal Reflections: Begin Screening Cancer Warrior)	Lesson 1 Cancer Warriors: A Personal Story of Translational Medicine (Complete Screening of Cancer Warrior, Discussion Question Review)	Lesson 1 Cancer Warriors: A Personal Story of Translational Medicine (Translational Medicine and Research)	Lesson 2 Preparing for War: A History of Cancer	Lesson 3 Keeping it all in Check: The Life of a Cell in the Cell Cycle
Week 2	Lesson 4 Losing Control: The Cell Cycle and Cancer *Extension Activity: What's the Risk Game*	Lesson 5 Going to War: Clinical Trials *Extension Activity: Exploring Local Clinical Trials*	Optional, but strongly suggested: *Pipette Practice*	Lesson 6 Fighting the Battle: Conducting a Clinical Assay (Running the Lab)	Lesson 6 Fighting the Battle: Conducting a Clinical Assay (Analyzing the Results)
Week 3	Lesson 7 In the Situation Room: Fighting Cancer in the Future (Analyzing Articles)	Lesson 7 In the Situation Room: Fighting Cancer in the Future (Reporting)			

Instructor Note: The above sequencing is based on 45 minute class periods

Vocabulary

Acute Myeloid Leukemia (AML): Acute myeloid leukemia (AML) is cancer that starts inside bone marrow, the soft tissue inside bones that helps form blood cells. The cancer grows from cells that would normally turn into white blood cells. Acute means the disease develops quickly.

Angiogenesis: the physiological process involving the growth of new blood vessels from pre-existing vessels

Metastasis: the spread of a cancer from one organ or part to another non-adjacent organ or part The plural is metastases

Chemotherapy: Chemotherapy (also called chemo) is a type of cancer treatment that uses drugs to destroy cancer cells. Chemotherapy works by stopping or slowing the growth of cancer cells, which grow and divide quickly. But it can also harm healthy cells that divide quickly, such as those that line their mouth and intestines or cause hair to grow.

Angiostatin: is a naturally occurring protein found in several animal species, including humans. It is an endogenous angiogenesis inhibitor (i.e., it blocks the growth of new blood vessels)

Endostatin: a broad spectrum angiogenesis inhibitor and may interfere with the pro-angiogenic action of growth factors

Cancer: disease caused by an uncontrolled division of abnormal cells in a part of the body.

Human Genome Project: an international project to map the entire genetic material of a human being that was completed in 2003.

Mastectomy: surgical removal of all or part of a breast, sometimes including excision of the underlying pectoral muscles and regional lymph nodes, usually performed as a treatment for cancer.

Cell Cycle: the regular pattern of growth, DNA replication and cell division that occurs in eukaryotic cells.

Interphase: the time during the cell cycle, in which the cell is not actively dividing.

Cellular Division: process by which one parent cell produces daughter cells after copying genetic material

Prophase: first phase of mitosis; chromatin condenses, nuclear envelope breaks down, centrosomes migrate to opposite poles

Metaphase: second phase of mitosis, chromosomes align along the cell's equator

Anaphase: third phase of mitosis; chromatids separate and are pulled to opposite sides of the cell by spindle fibers

Telophase: last phase of mitosis; a complete set of chromosomes is positioned at the poles of the cell, nuclear envelop reforms, chromosomes uncoil and spindle fibers disassemble.

Cytokinesis: process by which the cytoplasm divides

Gap 1: or post-mitotic phase; is a period in the cell cycle during interphase, before the S phase; this phase is the major period of cell growth during its lifespan.

Gap 2: orpre-mitotic phase, is the third and final subphase during interphase of the cell cycle which directly proceeds cellular division

Gap 0: a period in the cell cycle in which cells exist in a quiescent state

Synthesis (S-Phase): the part of the cell cycle, during interphase, in which DNA is duplicated, between G1 and G2

Checkpoint: control mechanisms that ensure the fidelity of cell division

p53: tumor suppressor gene that expresses the protein p53.

Proto-Oncogene: normal gene that can become an oncogene due to mutations or over expression

Oncogene: a gene that contributes to the production of a cancer. *Oncogenes* are generally mutated forms of normal cellular genes (proto-*oncogenes*) In tumor cells, they are often mutated or expressed at high levels.

Mutation: a permanent change in the DNA sequence of a gene. Mutations in a gene's DNA sequence can alter the amino acid sequence of the protein encoded by the gene.

Tumor Suppressor Gene: a gene that reduces the probability that a cell in a multicellular organism will turn into a tumor cell. A mutation or deletion of such a gene will increase the probability of the formation of a tumor.

Clinical Trials: research studies that involve people and test new ways to prevent, detect, diagnose, or treat cancer and other diseases

Informed Consent: process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, or whether to continue participating in it

Placebo: is a simulated or otherwise medically ineffectual treatment for a disease or other medical condition intended to deceive the recipient. Sometimes patients given a placebo treatment will have a perceived or actual improvement in a medical condition, a phenomenon commonly called the **placebo effect**.

Protocol: describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary

In Vitro: studies in biology that are conducted using components of an organism that have been isolated from their usual biological surroundings in order to permit a more detailed or more convenient analysis than can be done with whole organisms. Simply "outside the body."

IC_{50}: a measure of how effective a drug is. It indicates how much of a particular drug or other substance is needed to inhibit a given biological process by half.

Serial Dilution: is the stepwise dilution of a substance in solution. Usually the dilution factor at each step is constant, resulting in a geometric progression of the concentration in a logarithmic fashion

Cytotoxicity: the quality of being toxic to cells Examples of toxic agents are chemicals used in chemotherapy, an immune cell or some types of venom.

Cell Culture Assay: is any method which is used to assess the cytotoxicity (toxicity to cells) of a material. This refers to the *in vitro* assessment of material to determine whether it releases toxic chemicals in sufficient quantities to kill cells either directly or indirectly through the inhibition of cell metabolic pathways. Cell culture evaluations are the precursor to whole animal studies and are a way to determine if significant cytotoxicity exists for the given material.

Next Generation Sunshine State Standards – Science

Benchmark	Lesson						
	1	2	3	4	5	6	7
SC.912.L.14.6 Explain the significance of genetic factors, environmental factors, and pathogenic agents to health from the perspectives of both individual and public health.		X			X		X
SC.912.L.16.3 Describe the basic process of DNA replication and how it relates to the transmission and conservation of the genetic information.			X				
SC.912.L.16.4 Explain how mutations in the DNA sequence may or may not result in phenotypic change. Explain how mutations in gametes may result in phenotypic changes in offspring.				X			
SC.912.L.16.8 Explain the relationship between mutation, cell cycle, and uncontrolled cell growth potentially resulting in cancer.	X	X	X	X	X	X	X
SC.912.L.16.10 Evaluate the impact of biotechnology on the individual, society and the environment, including medical and ethical issues.	X	X		X	X	X	X
SC.912.L.16.14 Describe the cell cycle, including the process of mitosis. Explain the role of mitosis in the formation of new cells and its importance in maintaining chromosome number during asexual reproduction.			X	X			
SC.912.L.18.11 Explain the role of enzymes as catalysts that lower the activation energy of biochemical reactions. Identify factors, such as pH and temperature, and their effect on enzyme activity.			X				
SC.912.N.1.1 Define a problem based on a specific body of knowledge, for example: biology, chemistry, physics, and earth/space science, and do the following: 1. pose questions about the natural world, 2. conduct systematic observations, 3. examine books and other sources of information to see what is already known, 4. review what is known in light of empirical evidence, 5. plan investigations, 6. use tools to gather, analyze, and interpret data, 7. pose answers, explanations, or descriptions of events, 8. generate explanations that explicate or describe natural phenomena (inferences), 9. use appropriate evidence and reasoning to justify these explanations to others, 10. communicate results of scientific investigations, and 11. evaluate the merits of the explanations produced by others.	X	X			X	X	X

Next Generation Sunshine State Standards – Science (cont.)

Benchmark	Lesson						
	1	2	3	4	5	6	7
SC.912.N.1.2 Describe and explain what characterizes science and its methods.	X				X		X
SC.912.N.1.3 Recognize that the strength or usefulness of a scientific claim is evaluated through scientific argumentation, which depends on critical and logical thinking, and the active consideration of alternative scientific explanations to explain the data presented.	X	X			X		X
SC.912.N.1.4 Identify sources of information and assess their reliability according to the strict standards of scientific investigation.	X				X		X
SC.912.N.1.5 Describe and provide examples of how similar investigations conducted in many parts of the world result in the same outcome.		X			X	X	X
SC.912.N.1.6 Describe how scientific inferences are drawn from scientific observations and provide examples from the content being studied.	X	X			X		X
SC.912.N.1.7 Recognize the role of creativity in constructing scientific questions, methods and explanations.	X	X			X	X	X
SC.912.N.2.4 Explain that scientific knowledge is both durable and robust and open to change. Scientific knowledge can change because it is often examined and re-examined by new investigations and scientific argumentation. Because of these frequent examinations, scientific knowledge becomes stronger, leading to its durability.	X	X			X		X
SC.912.N.3.5 Describe the function of models in science, and identify the wide range of models used in science.	X	X			X	X	
SC.912.N.2.5 Describe instances in which scientists' varied backgrounds, talents, interests, and goals influence the inferences and thus the explanations that they make about observations of natural phenomena and describe that competing interpretations (explanations) of scientists are a strength of science as they are a source of new, testable ideas that have the potential to add new evidence to support one or another of the explanations.		X	X			X	
SC.912.N.4.1 Explain how scientific knowledge and reasoning provide an empirically-based perspective to inform society's decision making.	X	X		X	X		X
SC.912.N.4.2 Weigh the merits of alternative strategies for solving a specific societal problem by comparing a number of different costs and benefits, such as human, economic, and environmental.				X	X		X

Next Generation Science Standards

Performance Expectations: High School Life Science	Lesson						
	1	2	3	4	5	6	7
HS-LS1-1. Construct an explanation based on evidence for how the structure of DNA determines the structure of proteins which carry out the essential functions of life through systems of specialized cells.			X	X			
HS-LS1-2. Develop and use a model to illustrate the hierarchical organization of interacting systems that provide specific functions within multicellular organisms.			X	X			
HS-LS1-4. Use a model to illustrate the role of cellular division (mitosis) and differentiation in producing and maintaining complex organisms.			X	X			
HS-LS3-1. Ask questions to clarify relationships about the role of DNA and chromosomes in coding the instructions for characteristic traits passed from parents to offspring.	X		X	X	X	X	X
HS LS3-1. Ask questions to clarify relationships about the role of DNA and chromosomes in coding the instructions for characteristic traits passed from parents to offspring.			X	X			

Science and Engineering Practices	Lesson						
	1	2	3	4	5	6	7
Constructing Explanations and Designing Solutions Construct an explanation based on valid and reliable evidence obtained from a variety of sources (including students' own investigations, models, theories, simulations, peer review) and the assumption that theories and laws that describe the natural world operate today as they did in the past and will continue to do so in the future.			X	X		X	
Developing and Using Models Develop and use a model based on evidence to illustrate the relationships between systems or between components of a system.			X	X			
Using Mathematics and Computational Thinking Use mathematical and/or computational representations of phenomena or design solutions to support explanations.						X	
Engaging in Argument from Evidence Evaluate the claims, evidence, and reasoning behind currently accepted explanations or solutions to determine the merits of argument.	X				X		X
Obtaining, Evaluating, and Communicating Information Communicate scientific information (e.g., about phenomena and/or the process of development and the design and performance of a proposed process or system) in multiple formats (including orally, graphically, textually, and mathematically.	X		X	X	X	X	X
Connection to the Nature of Science Scientific Investigations Use a Variety of Methods Scientific inquiry is characterized by a common set of values that include: logical thinking, precision, open-mindedness, objectivity, skepticism, replicability of results, and honest and ethical reporting of findings.	X		X	X	X	X	X

Next Generation Science Standards (cont.)

Cross Cutting Concepts	Lesson						
	1	2	3	4	5	6	7
Systems and System Models Models (e.g., physical, mathematical, computer models) can be used to simulate systems and interactions—including energy, matter, and information flows—within and between systems at different scales.			X	X		X	
Structure and Function Investigating or designing new systems or structures requires a detailed examination of the properties of different materials, the structures of different components, and connections of components to reveal its function and/or solve a problem.			X	X		X	
Scale, Proportion, and Quantity The significance of a phenomenon is dependent on the scale, proportion, and quantity at which it occurs.						X	
Cause and Effect Empirical evidence is required to differentiate between cause and correlation and make claims about specific causes and effects.			X	X	X	X	X
Connections to Nature of Science — Science is a Human Endeavor Technological advances have influenced the progress of science and science has influenced advances in technology. (HS-LS3-3) Science and engineering are influenced by society and society is influenced by science and engineering.	X	X			X	X	X

Common Core State Standards – Florida

Reading Standards for Literacy in Science and Technical Subjects	Lesson						
	1	2	3	4	5	6	7
CCSS.ELA-Literacy.RST.9-10.1 Cite specific textual evidence to support analysis of science and technical texts, attending to the precise details of explanations or descriptions.					X		X
CCSS.ELA-Literacy.RST.9-10.2 Determine the central ideas or conclusions of a text; trace the text's explanation or depiction of a complex process, phenomenon, or concept; provide an accurate summary of the text.	X				X		X
CCSS.ELA-Literacy.RST.9-10.3 Follow precisely a complex multistep procedure when carrying out experiments, taking measurements, or performing technical tasks, attending to special cases or exceptions defined in the text.				X	X	X	
CCSS.ELA-Literacy.RST.9-10.4 Determine the meaning of symbols, key terms, and other domain-specific words and phrases as they are used in a specific scientific or technical context relevant to GRADES 9–10 TEXTS AND TOPICS.				X			
CCSS.ELA-Literacy.RST.9-10.5 Analyze the structure of the relationships among concepts in a text, including relationships among key terms (e.g., FORCE, FRICTION, REACTION FORCE, ENERGY).					X		X
CCSS.ELA-Literacy.RST.9-10.6 Analyze the author's purpose in providing an explanation, describing a procedure, or discussing an experiment in a text, defining the question the author seeks to address.					X		
CCSS.ELA-Literacy.RST.9-10.7 Translate quantitative or technical information expressed in words in a text into visual form (e.g., a table or chart) and translate information expressed visually or mathematically (e.g., in an equation) into words.			X			X	
CCSS.ELA-Literacy.RST.9-10.8 Assess the extent to which the reasoning and evidence in a text support the author's claim or a recommendation for solving a scientific or technical problem.					X		
CCSS.ELA-Literacy.RST.9-10.9 Compare and contrast findings presented in a text to those from other sources (including their own experiments), noting when the findings support or contradict previous explanations or accounts.	X				X		X

Common Core State Standards – Florida (cont.)

Writing Standards for Literacy in Science and Technical Subjects	Lesson						
	1	2	3	4	5	6	7
CCSS.ELA-Literacy.WHST.9-10.1 Write arguments focused on DISCIPLINE-SPECIFIC CONTENT					X		X
CCSS.ELA-Literacy.WHST.9-10.4 Produce clear and coherent writing in which the development, organization, and style are appropriate to task, purpose, and audience.					X		X
CCSS.ELA-Literacy.WHST.9-10.7 Conduct short as well as more sustained research projects to answer a question (including a self-generated question) or solve a problem; narrow or broaden the inquiry when appropriate; synthesize multiple sources on the subject, demonstrating understanding of the subject under investigation.					X		
CCSS.ELA-Literacy.WHST.9-10.9 Draw evidence from informational texts to support analysis, reflection, and research.					X		X

Common Core Math Practices: Grades K-12	Lesson						
	1	2	3	4	5	6	7
MP4: Create models			X	X			
MP5: Use appropriate tools strategically						X	
MP6: Attend to precision						X	
MP8: Look for and express regularity in repeated reasoning				X			

Cancer Warriors: A Personal Story of Translational Medicine

1

Vocabulary:

Acute Myeloid Leukemia (AML): Acute myeloid leukemia (AML) is cancer that starts inside bone marrow, the soft tissue inside bones that helps form blood cells. The cancer grows from cells that would normally turn into white blood cells. Acute means the disease develops quickly.

Angiogenesis: the physiological process involving the growth of new blood vessels from pre-existing vessels

Metastasis: the spread of a cancer from one organ or part to another non-adjacent organ or part The plural is metastases

Chemotherapy: Chemotherapy (also called chemo) is a type of cancer treatment that uses drugs to destroy cancer cells. Chemotherapy works by stopping or slowing the growth of cancer cells, which grow and divide quickly. But it can also harm healthy cells that divide quickly, such as those that line ther mouth and intestines or cause hair to grow.

Angiostatin: is a naturally occurring protein found in several animal species, including humans. It is an endogenous angiogenesis inhibitor (i.e., it blocks the growth of new blood vessels)

Endostatin: a broad spectrum angiogenesis inhibitor and may interfere with the pro-angiogenic action of growth factors

KEY QUESTION(S):
- Why is studying the mechanisms of cancer important?
- Why would testing possible drugs for cancer treatment be important?
- What is translational medicine?

TIME ESTIMATE:
- Advanced Preparation: ~1.5 hours (55 minutes will be devoted to screening and familiarizing yourself with the PBS video Cancer Warrior in preparation for the class discussion questions)
- Student Procedure: Three 50 minute periods

LEARNING STYLES:
- Visual and auditory

Lesson Summary:

Students will reflect upon their own knowledge and experiences with cancer by completing the Cancer: Truth or Myth survey and responding to three short journal prompts. Students will then screen the PBS video: Cancer Warrior, answering discussion questions at particular moments in the film to introduce clinical trials. Finally, students will read the story of Barbara Bradfield from *The Emperor of All Maladies: A Biography of Cancer* to hook student interest in cancer biology and translational medicine.

Student Learning Objectives:

The student will be able to...
1. Propose the causes and treatments of cancer
2. Predict the phases of clinical trials
3. Describe translational medicine

Standards:

SC.912.L.16.8
SC.912.L.16.10
SC.912.N.1.1
SC.912.N.1.2
SC.912.N.1.3
SC.912.N.1.4
SC.912.N.1.6
SC.912.N.1.7
SC.912.N.2.4
SC.912.N.2.5
SC.912.N.4.1

Materials:

Student Page: Cancer Survey: Myth or Truth? data collection worksheet
PBS NOVA Film: Cancer Warrior
Student Page: **Cancer Warrior** Discussion Guide
Teacher Page: **Cancer Warrior** Discussion Guide
Computers with internet access or phones with texting capabilities

Background Information:

For a brief overview of cancer see PubMed cancer page at http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0002267/

For more detailed information about what cancer is and information on specific cancer types see the National Cancer Institute website at http://www.cancer.gov/cancertopics

For more information on telomeres and their relationship to cancer visit the University of Utah Learn Genetics page at http://learn.genetics.utah.edu/content/begin/traits/telomeres/ If you want even more information about telomeres you can listen to this University of Utah Learn Genetics podcast http://learn.genetics.utah.edu/content/begin/traits/telomeres/bbcawthon050929.mp3

Advance Preparation:

1. Watch Cancer Warrior and familiarize yourself with the Discussion Questions
2. Read through the Barbara Bradfield story
3. Print the student handout: Cancer Warrior-Discussion Questions (one per student)
4. Print the Clinical Trial-A Personal Story of Translational Medicine to read aloud during class time.
5. Print Student Page: Cancer Survey: Myth or Truth? Data worksheet (one per student)
6. Create an account at polleverywhere.com (accounts are free)
7. Type questions for the cancer survey in as 15 different polls. (Note polls are automatically deleted after 30 days)

Procedure and Discussion Questions with Time Estimates:

Day ONE:

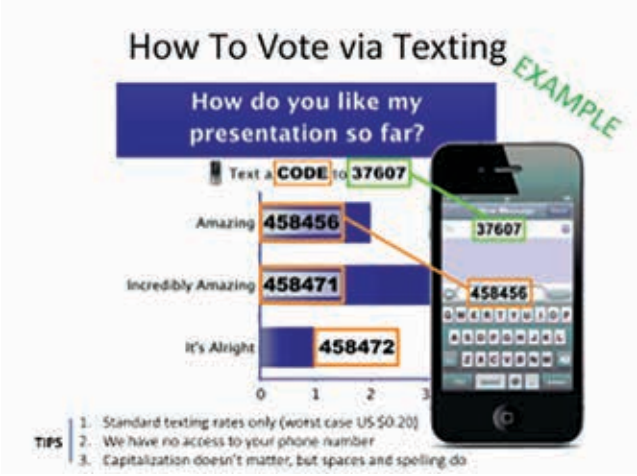
1. **(1-2 min)** Ask students the following questions (give students a moment to look around/count classmates with hands raised after each question):
   a. Raise your hand if you know/have an idea of what cancer is. (Ask students to share what they know)
   b. Raise your hand if you know some who has cancer/has lost their life to cancer.
   c. Raise your hand if that someone is a family member
2. **(1-2 min)** Read and/or display the following quote from The Emperor of all Maladies on the board:
   "In 2010, about six hundred thousand Americans, and more than 7 million humans around the world, will die of cancer. In the United States, one in three women and one in two men will develop cancer during their lifetime. A quarter of all American deaths, and about 15 percent of all deaths worldwide, will be attributed to cancer. In some nations, cancer will surpass heart disease to become the most common cause of death."
3. **(1-3 min)** Ask students the following questions, in response to the quote:
   a. If any of the statistics in the quote are shocking or surprising to you, raise your hand. (give students a moment to look around/count classmates with hands raised)
   b. If you just raised your hand, what part of the quote surprised you and why? (call on a few students to share their responses)

4. **(25 min)** Have the students vote on the 15 questions by texting or sending their answers in over the internet. **Note before the lesson you must create a free account at polleverywhere.com and type in each question as a separate poll.** You will need to clear the data after every class if you are doing this lesson with multiple sections. See the figures below for instructions on how to have students vote. Student should record their own personal answer and class data on their student answer sheet which will be used again in lesson seven.

** You may also choose to complete this activity using the Four Corners Polling Method if your students do not have the appropriate electronic devices or if your room does not have a good wireless signal **

Four Corners Polling Directions

1. Assign one number to each corner of the room to represent the numbers on the scale in the survey. Students stand in the middle of the room.
2. As you read a statement students move to the corner of the room they believe represents the correct answer.
3. Ask one student from each corner to share ideas with the whole class.
4. After the discussion is complete students then return to the center of the room and the next statement is read. This continues for all 15 statements.



Day TWO:

1. **(5-7 min)** Pass out Student Page: Cancer Warrior Discussion Question Guide.
   a. Give students 3-4 minutes to answer the pre-questions about translational medicine and angiogenesis.
   b. Ask for student volunteers to share their responses to the pre-questions.
2. **(54 min)** NOTE: may carry over to Day THREE depending on class lengths
   Watch the PBS NOVA film Cancer Warrior. Encourage students to ask questions, pausing the film for clarification, understanding checks and informal discussion as necessary.
3. Ask students to retain the Student Page: Cancer Warrior Discussion Question Guide to use during Day THREE.

Day THREE:

1. Finish any of the film that was not screened during Day TWO and give students time to finish any questions they did not complete during the film.
2. **(12-15 min)** Lead the students in a group review of the Cancer Warrior Discussion Questions. This could be done in several ways: allow individual students to respond to each question, assign questions to groups of students to compare answers and then share out their collective response, etc.
3. **(3-5 min)** Pass out Student Page: A Personal Story of Translational Medicine and read together as a class. Ask students for their reactions, etc.
4. **(10-15 min)** Project the following journal questions on the board and ask students to write a response for each one (3-4 sentences minimum). Collect the journals and keep them to be reviewed by the students again during Lesson 7.

Day THREE
Journal Questions:

1. How has cancer impacted your life personally?
2. Starting in 1971 Richard Nixon declared a war on cancer, allocating five million dollars to research. Do you think the government should continue to fund this type of research? Why or why not?
3. Based on your current knowledge, the screening of Cancer Warrior and Barbara Bradfield's story what questions would be essential for a scientist researching cancer to focus on? Why?

Assessment Suggestions:

- Collect Student Page: Cancer Warrior Discussion Question Guide
- Collect Journal Questions
- In lesson seven students will examine how their answers and the class answers have changed as a result of this unit.

Resources/References:

- Cancer Survey: Myth or Truth? activity adopted from the University of Rochester http://lifesciences.envmed.rochester.edu/lessonsCancer.html
- PBS NOVA: Cancer Warrior
- Mukherjee, Siddhartha. The Emperor of All Maladies: A Biography of Cancer. New York: Scribner, 2010. Print.

Cancer Truth or Myth Survey Data

Below is a survey of 15 statements about cancer. For the purposes of this survey, a cancer "Truth" is defined as a statement that you believe is supported by scientific evidence. A cancer "Myth" is defined as a statement that you believe is an opinion or an idea that is not supported by scientific evidence.

Vote using the following scale for each "Statement about Cancer"
1 = I'm sure this is true.
2 = I think this might be true.
3 = I think this might be a myth.
4 = I'm sure this is a myth.

STATEMENTS ABOUT CANCER	YOUR RESPONSE (1, 2, 3, or 4)	CLASS RESPONSE (record the number of students who responded with each number above the number)
1. If your parents had cancer, you may be at a higher risk of developing cancer.		____ ____ ____ ____ 1 2 3 4
2. All cancers are caused by same genetic mutations.		____ ____ ____ ____ 1 2 3 4
3. Everyone who participates in a clinical trial for a new drug or treatment benefits.		____ ____ ____ ____ 1 2 3 4
4. Young peoples' lifestyles affect their chances of getting cancer later in life.		____ ____ ____ ____ 1 2 3 4
5. Cancer is caused by changes in genetic material.		____ ____ ____ ____ 1 2 3 4
6. Everyone with the same type of cancer gets the same kind of treatment.		____ ____ ____ ____ 1 2 3 4
7. The only treatments for cancer are surgery, radiation, and chemotherapy.		____ ____ ____ ____ 1 2 3 4
8. Some types of cancer are contagious.		____ ____ ____ ____ 1 2 3 4
9. Cancer patients involved in clinical trials always receive the investigational drug or treatment.		____ ____ ____ ____ 1 2 3 4
10. Cancer is caused by changes in genetic material.		____ ____ ____ ____ 1 2 3 4

CANCER TRUTH OR MYTH SURVEY DATA (PAGE 2)

STATEMENTS ABOUT CANCER	YOUR RESPONSE (1, 2, 3, or 4)	CLASS RESPONSE (record the number of students who responded with each number above the number)
11. Tumors must have a blood supply to survive.		_____ _____ _____ _____ 1 2 3 4
12. Age is a risk factor for cancer.		_____ _____ _____ _____ 1 2 3 4
13. New cancer fighting drugs move through clinical trials quickly.		_____ _____ _____ _____ 1 2 3 4
14. Many mutations are required for someone to develop cancer.		_____ _____ _____ _____ 1 2 3 4
15. Cancer is the leading cause of death in the United States.		_____ _____ _____ _____ 1 2 3 4

Cancer Warrior Discussion Question Guide

Pre Questions: Answer the following based on your current knowledge.

1. What is translational medicine?

2. Using prefixes/suffixes, what does angiogenesis mean?

Answer the following questions based on information provided in the film: *Cancer Warrior*

3. What does Dr. Folkman mean by "we all have a clock, theirs is just running faster?" Do you think this is a philosophical statement, or biological one? Why?

4. Do you think patients who are entering a Phase I clinical trial (which looks at the side effects of the drug, not its effectiveness) are setting themselves up for failure? Why or why not?

5. Why do some chemotherapies stop working in patients?

6. Use your knowledge of cellular requirements to explain why Dr. Folkman's hypothesis of angiogenesis could be valid, in spite of the resistance and criticism he received from his fellow researchers.

7. If science is based on observation, why did researchers still criticize Dr. Folkman's hypothesis of angiogenesis after the rabbit eye experiments?

CANCER WARRIOR DISCUSSION QUESTION GUIDE (PAGE 2)

8. The discovery of what molecule proved angiogenesis? How was it discovered?

9. Why did Robert Demato think thalidomide could be used to treat cancer? Give specific reasons.

10. Tim is in remission but still on thalidomide; why does he have the side effect of numbness/tingling in his fingers and toes?

11. Why was the inhibitor protein searched for in mouse urine?

12. Explain the naming of angiostatin; do you think it's a good name? Why?

13. What is the relationship between angiostatin and endostatin?

14. Why was Duane Gay removed from the clinical trial? What is the benefit of having strict protocols during clinical trials if it means patients must be taken off them, thus losing access to the medication?

Cancer Warrior Discussion Question Guide

Pre Questions: Answer the following based on your current knowledge.

1. What is translational medicine?

The process of turning biological discoveries "at the bench" into drugs and medical devices that can be used in the treatment of patients "at the bedside"

2. Using prefixes/suffixes, what does angiogenesis mean?

Angio= blood, genesis=new

Answer the following questions based on information provided in the film: *Cancer Warrior*

3. What does Dr. Folkman mean by "we all have a clock, theirs is just running faster?" Do you think this is a philosophical statement, or biological one? Why?

All living organisms have a predetermined lifespan, those people with terminal illnesses will have a shorter lifespan, thus a "faster running clock."

NOTE: Some students will say this is philosophical, but studies of telomeres have indicated this is also biological. Students may not know this, so be sure to bring it up during group discussion.

4. Do you think patients who are entering a Phase I clinical trial (which looks at the side effects of the drug, not its effectiveness) are setting themselves up for failure? Why or why not?

Student answers will vary.

5. Why do some chemotherapies stop working in patients?

Their cancer cells develop mutations that cause resistance to the drugs.

6. Use your knowledge of cellular requirements to explain why Dr. Folkman's hypothesis of angiogenesis could be valid, in spite of the resistance and criticism he received from his fellow researchers.

His hypothesis could be valid because all cell types need a source of blood for nutrient and gas exchange. If a tumor is a collection of "new cells" they would need a "new blood source."

7. If science is based on observation, why did researchers still criticize Dr. Folkman's hypothesis of angiogenesis after the rabbit eye experiments?

Fellow researchers needed to see the biological mechanism behind the observations he made with the rabbit's eye, because they still felt his idea was too "out there."

CANCER WARRIOR DISCUSSION QUESTION GUIDE (PAGE 2)

8. The discovery of what molecule proved angiogenesis? How was it discovered?

A heprin binding protein proved angiogenesis, which was discovered using liquid column chromatography of tissue from a lab rat tumor.

9. Why did Robert Demato think thalidomide could be used to treat cancer? Give specific reasons.

Demato thought that thalidomide could treat cancer because it stops blood vessel growth. (causing birth defects in children whose mothers took the drug while pregnant.)

10. Tim is in remission but still on thalidomide; why does he have the side effect of numbness/tingling in his fingers and toes?

Tim likely experiences the numbness because no new blood vessels are being formed in his extremities.

11. Why was the inhibitor protein searched for in mouse urine?

The inhibitor protein was searched for in mouse urine because it was hypothesized to be a biological molecule the body naturally produces. Substances that are not used by the body get excreted.

12. Explain the naming of angiostatin; do you think it's a good name? Why?

Statin means "to stop", so yes, "stop blood" is a good name.

13. What is the relationship between angiostatin and endostatin?

Angiostatin and Endostatin are both angiogensis inhibiting molecules.

14. Why was Duane Gay removed from the clinical trial? What is the benefit of having strict protocols during clinical trials if it means patients must be taken off them, thus losing access to the medication?

Duane Gay's tumors had grown beyond the strict limits allowed by the University of Wisconsin's Endostatin protocol.

A clinical trial is a highly controlled experiment; you can only test one variable at a time.

Preparing for War: A History of Cancer

2

Vocabulary:

Angiogenesis: the development of new blood vessels.

Cancer: disease caused by an uncontrolled division of abnormal cells in a part of the body.

Human Genome Project: an international project to map the entire genetic material of a human being that was completed in 2003.

Mastectomy: surgical removal of all or part of a breast, sometimes including excision of the underlying pectoral muscles and regional lymph nodes, usually performed as a treatment for cancer.

Oncogene: a gene that contributes to the production of a cancer. *Oncogenes* are generally mutated forms of normal cellular genes (proto-*oncogenes*)

Tumor Suppressor Gene: A protective gene that normally limits the growth of tumors. When a tumor suppressor gene is mutated (altered), it may fail to keep a cancer from growing.

KEY QUESTION(S):
- How old is cancer?
- Where are we in the "war" against cancer?

TIME ESTIMATE:
- Advanced Preparation: 45 minutes (25 minutes to assemble timeline pieces; 20 minutes background reading)
- Student Procedure: 45 minutes

LEARNING STYLES:
- Visual and auditory

Lesson Summary:

Working in groups, students will read cancer fact cards and use text clues to sequence the events in the discovery and treatment of cancer. This lesson illustrates scientific discovery as a collaborative effort of many individuals building on prior knowledge and developing unique ideas to explore.

Note: *Students are not expected to understand everything that is written on the cards, but should be able to use contextual clues to put the cards in the correct order. You may want to refer back to the cards as students expand their knowledge of the cell cycle and cancer in lessons 3 and 4.*

Student Learning Objectives:

The student will be able to...
1. Sequence scientific discoveries
2. Discover that science is a collaborative effort
3. Consider the role technology has played in the rapid advances in biomedical science during the last twenty years

Materials:

Student Page: The Road to Treatment Timeline Cards (1 per student group)

Teacher Page: The Road to Treatment Timeline Cards for Wall (1 set for teacher use)
Student worksheet: The Road to Treatment Timeline Cards (1 per student or student group)

EXTENSION ACTIVITIES:
Explore either of the History of Cancer Timelines on *CancerQuest* by the Emory Winship Cancer Institute

Background Information:

Background information needed for this assignment is at the beginning of the guide and included in the information on the timeline cards. Teachers should read the information cards prior to the start of the lesson.

Advance Preparation:

- Prepare the student timeline cards for each student group. For extended use, consider cardstock and/or laminating.
- Prepare the wall timeline cards. You may want to print these in color. For extended use, consider cardstock and/or laminating.
- Make copies of the student worksheet, one per student or student group.
- Draw a timeline on the board or on the wall to affix the enlarged cards. Include 2500BC – 2011.

Procedure and Discussion Questions with Time Estimates:

1. **(5 min)** Discuss student responses to journal questions from Lesson One and answer any student questions about Cancer Warrior.
2. **(2 min)** Tell the students they will now look at historical and current (2011) events and place them in chronological order. Have the students work in groups of 3-4. (3 min) Once students are assembled in groups of 2-4 and settled, distribute one envelope of time line cards to each group.
3. **(15-20 min)** Allow the students to order the cards and complete the worksheet. Move around the groups and alert them to clues in the cards if needed.
4. Using the teacher timeline, place the first card on the timeline.
   a. Call on a group to place the next as they give their one sentence summary. Ask the class if they agree with this choice.
   b. Continue around the groups until all cards have been placed, addressing disagreements by asking questions to lead the students to the correct answer.
5. Once the timeline is complete, help lead students to the following conclusions:
   - Cancer is not a new disease; it has been around for at least 4,000 years. Men and women have been waging a "war" on cancer for thousands of years and cancer research has had many "victories" and many "losses" through this time.
   - Cancer is not one disease, but rather a collection of many diseases that all involve abnormal cell growth. This uncontrolled cell growth is caused by mutations, specifically changes in genes that regulate cell division and death. This makes finding one "cure all" treatment unlikely.
   - What we know about the physiology of and how we treat cancer has changed dramatically over time because of the work of many scientists. Scientists today are able to develop new therapies today by building on information provided by past scientists and collaborating with other scientists.

6. For advanced students, you may want to have them discuss the following quote from *The Emperor of all Maladies* by Siddhartha Mukherjee*:*

   "*How, precisely, a future generation might learn to separate the entwined strands of normal growth remains a mystery. But this much is certain: the story, however it plays out, will contain indelible kernels of the past. It will be a story of inventiveness, resilience, and perseverance against…a relentless and insidious enemy among human diseases. But it will also be a story of hubris, arrogance, paternalism, misperception, false hope, and hype, all leveraged against an illness that was just three decades ago widely touted as being "curable" within a few years." (page 7)*

You might ask students to provided examples from the timeline (or their own prior knowledge) of the hubris, paternalism, misperception, false hope and hype that Mukherjee is referencing.

Assessment Suggestions:

- Student worksheet can be collected to access objective 1.
- Students can be asked to journal about any new information they were surprised to learn about during the activity to access objectives 2 and 3.

Resources/References:

- Mukherjee, Siddhartha. *The Emperor of All Maladies: A Biography of Cancer*. New York: Scribner, 2010. Print.
- "Introduction to a Timeline of Cancer." *CancerQuest*. Emory Winship Cancer Institute, n.d. Web. 04 July 2012. http://www.cancerquest.org/cancer-timeline-introduction.html

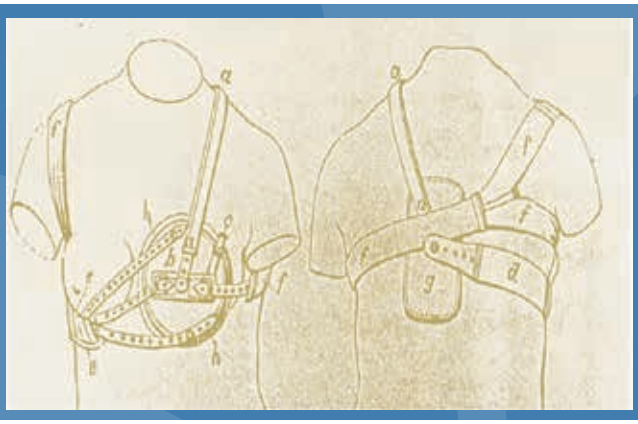
EXTENSION LITERATURE:
Read Germanine's story aloud to the class from the book *The Emperor of All Maladies: A Biography of Cancer.* This story tells the personal history of one patient as she participates in a clinical trial, goes into remission, relapses and eventually dies from are rare kind of cancer called a gastrointestinal stromal tumor (GIST). The story ends with the author's thoughts on our struggle against cancer and could lead to some interesting class discussions. The story is on pages 467-470 of the book.

Notes:

Preparing for War: A History of Cancer (page 1)

The first medical description of cancer was found in an Egyptian papyrus. The papyrus contained the teaching of the Egyptian physician Imhotep and described a case of breast cancer as "a bulging tumor in the breast…like touching a ball of wrappings." Imhotep wrote about many medical techniques; however in the case of cancer therapy he noted "(There) is none." Archeologists have also found a two thousand year old Egyptian mummy in the Alexandrian catacombs with a tumor invading the pelvic bone.

Medieval surgeons attack cancer using primitive surgical methods. Johannes Scultetus describes a mastectomy, the surgical removal of the breast cancer, using fire, acid and leather binding.



Surgeons devise increasingly aggressive operations to attack cancer. William Stewart Halsted at Johns Hopkins University pioneered the radical mastectomy, an operation to remove the breast, the muscles beneath the breast and the associated lymph nodes. Halsted writes about one women's case in his journal saying, "the patient was a young lady who I was loath to disfigure." In the etching above Halsted drew an idealized patient. However, in reality most patients were older women with large tumors.

Preparing for War: A History of Cancer (page 2)

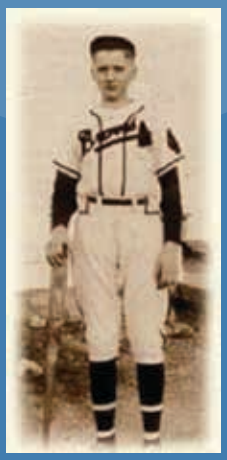
When radium was discovered by Marie and Pierre Curie, doctors began to deliver high doses of radiation to tumors. Conferences and societies on high dose radiation were held and one Chicago physician noted that, "I believe this treatment is an absolute cure for all forms of cancer." However, radiation itself was carcinogenic and Marie Curie died from a leukemia caused by decades of work with X-rays.

Hippocrates gives an account of a woman from Abdera who had a carcinoma of the breast with a bloody discharge from her nipple. Although Hippocrates was able to stop the bleeding the patient still died. He also noted that when menstrual bleeding ceased, breast cancer became more prevalent. He identified stages of cancer, noting that, as the disease progresses, the patient develops a bitter taste, refuses food, develops a shooting pain from breast to neck, complains of thirst and becomes emaciated. From this point, death was certain. Hippocrates was the first to use the words "carcinos" and "carcinoma" to describe tumors, and the term "cancer" was coined. "Cancer" is derived from the Greek word "karkinos," or crab, which is thought to reference the appearance of blood vessels on tumors resembling a crab's claws reaching out.

Senator Matthew Neely, a former lawyer from West Virginia, asked Congress to advertise a reward of $5 million for "information leading to the arrest of human cancer." In response to Neely and magazine articles in *Time* and *Life Magazines*, President Roosevelt signs the National Cancer Institute Act. This act created the National Cancer Institute (NCI) that was tasked with coordinating cancer research and care. However, months after NCI was created the battle against cancer was quickly overshadowed by the events of World War II.

Preparing for War: A History of Cancer (page 3)

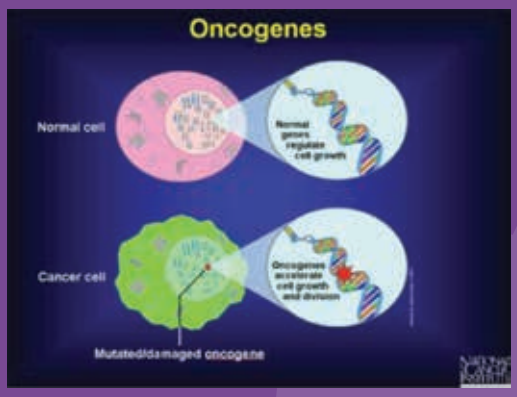
During World War II, tons of mustard gas was accidentally released into the Bari harbor in Italy during an air raid. The gas decimated normal white blood cells in the body of soldiers, leading doctors to consider using similar chemicals to kill cancers of white blood cells. Chemotherapy, chemical warfare on cancer cells, was literally inspired by war.



Dr. Sydney Faber created the Jimmy Fund which had "Jimmy" a twelve year old baseball fan as the unofficial mascot for children's cancer. Jimmy's story began in 1948, when Gustafson was a 12-year-old patient of Dr. Farber, founder of the Children's Cancer Research Foundation (eventually renamed Dana-Farber Cancer Institute) and a pioneer of modern chemotherapy. Dubbed "Jimmy" to protect his privacy, Gustafson was selected to speak on Ralph Edwards' national radio program, "Truth or Consequences," which was broadcast from the boy's hospital room. The Jimmy Fund became one of the most powerful cancer advocacy organizations. The Jimmy fund raised $231,000 for cancer research during the first year.

The first DNA microchip was constructed and used to measure gene expression levels in plants. This technology has advanced and is now used to study cancer in humans. Currently 'gene chips' are being investigated as tools in the development of individualized cancer treatment plans.

Preparing for War: A History of Cancer (page 4)

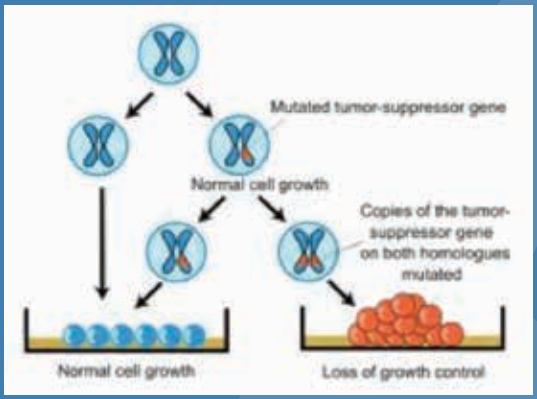


The first oncogene was discovered and was termed src (pronounced sarc as in *sarcoma*). Src was first discovered as an oncogene in a chicken retrovirus. An oncogene is a gene that has the potential to cause cancer. In tumor cells, they are often mutated or expressed at high levels. J. Michael Bishop and Harold E. Varmus of the University of California, San Francisco demonstrated that oncogenes were activated proto-oncogenes, found in many organisms including humans. For this discovery Bishop and Varmus were awarded the Nobel Prize in Physiology or Medicine in 1989. Currently, dozens of oncogenes have been identified in human cancer. Many cancer drugs target the proteins encoded by oncogenes.

In his state of the Union address President Nixon said, "I will also ask for an appropriation of an extra $100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal." The picture above shows Dr. Sidney Farber (far left) was a White House guest of Pat (second from right) and President Richard Nixon after the president declared his "War on Cancer" and passed the National Cancer Act. When the president appointed 18 members to a National Cancer Advisory Board the following March, Dr. Farber was granted a four-year term.

Preparing for War: A History of Cancer (page 5)

The first tumor suppressor gene, Rb (for retinoblastoma) was isolated. This gene was also one of the first associated with an inherited (familial) form of cancer



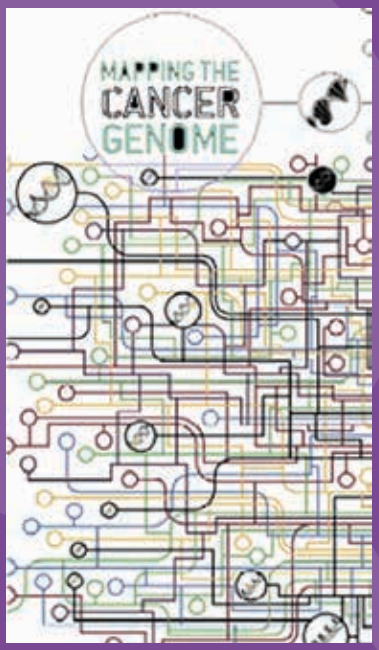
Even though Judah Folkman published a paper in 1971 proposing angiogenesis plays a major role in cancer development, it wasn't until this year that Endostatin, an angiogenesis inhibitor was tested in clinical trials. Folkman though preventing angiogenesis could inhibit tumor growth by starving the tumor of vital nutrients. This theory was originally disregarded by most in the field, but is now fully accepted. In this year the Phase III clinical trial, the addition of Endostatin to the standard chemotherapeutic regimen, began. The trial showed significant and clinically meaningful improvement in response rate, median time to progression, and clinical benefit rate compared with the chemotherapeutic regimen alone.

Preparing for War: A History of Cancer (page 6)

The FDA approves Gardasil, a vaccine that protects against the human papillomavirus (HPV). HPV is known to be the major cause of cervical cancer. Merck & Co. conducted a Phase III study named Females United to Unilaterally Reduce Endo/Ectocervical Disease This clinical trial was a randomized double-blind study with one controlled placebo group and one vaccination group. Over 12,000 women aged 16–26 from thirteen countries participated in the study. Each woman was injected with either Gardasil or a placebo on day 1, month 2, and month 6. In total, 6,082 women were given Gardasil and 6,075 received the placebo. Subjects in the vaccine group had a significantly lower occurrence of high-grade abnormal cervical tissue growth related to HPV-16 or HPV-18 than did those in the placebo group. During February of this year, the independent Data and Safety Monitoring Board recommended the clinical trials be terminated on ethical grounds, so that young women on the placebo could receive Gardasil.

The biotech company Genentech gained FDA approval for Herceptin (trastuzumab). Barbara Bradfield was among the first women to be treated with Herceptin. Herceptin specifically attacks breast cancer cells that are over producing the HER2 protein. Barbara is the longest survivor of the treatment, with no hint of her cancer remaining today. However, Hercpetin costs about $70,000 for a full course of treatment and is not always covered by insurance.

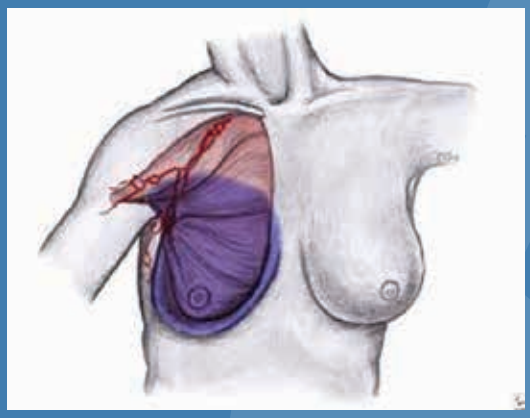
Preparing for War: A History of Cancer (page 7)



The Human Genome Project that was completed in 2003. Scientists are currently working on the Cancer Genome Atlas. The Cancer Genome Atlas (TCGA) began as a three-year pilot in 2006 with an investment of $50 million each from the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI). The TCGA pilot project confirmed that an atlas of changes could be created for specific cancer types. It also showed that a national network of research and technology teams working on distinct but related projects could pool the results of their efforts and make the data publicly accessible. The pilot project proved that making the data freely available would enable researchers anywhere around the world to make and validate important discoveries. The success of the pilot led the National Institutes of Health to commit major resources to TCGA to collect and characterize more than 20 additional tumor types. Francis Collins, the leader of the Human Genome Project says, "When applied to the 50 most common types of cancer, this effort could ultimately prove to be the equivalent of more than 10,000 Human Genome Projects in terms of sheer volume of DNA to be sequenced. The dream must therefore be matched with ambitious but realistic assessment of emerging scientific opportunities for waging a smarter war."

Gleevec is the first of a new class of drugs that act by specifically inhibiting a certain enzyme – a receptor tyrosine kinase – that is characteristic of a particular cancer cell, rather than non-specifically inhibiting and killing all rapidly dividing cells. Of the 54 patients who received high doses of the drug in the phase I clinical trial to treat chronic myelogenous leukemia, 53 showed a complete response within days of starting Gleevec. The success of Gleevec showed that highly specific, non-toxic therapy is possible.

Preparing for War: A History of Cancer (page 8)

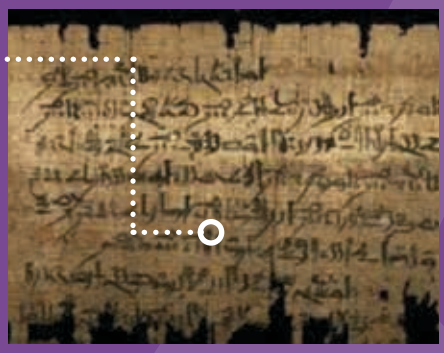


The results of a trial showing that radical mastectomies were not more effective than simple mastectomies were published. The trial had 1,765 patients in 34 centers in the United States and Canada. Patients were randomized into three groups: one treated with the radical mastectomy (a surgical procedure in which the breast, underlying chest muscle, and lymph nodes of are removed), the second with simple mastectomy (the entire breast tissue is removed, but the muscle and lymph nodes are not) and the third with surgery followed by radiation. The results of breast cancer recurrence, relapse, death, and distant cancer metastasis were statistically identical among all three groups. The group treated with the radical mastectomy had a much higher morbidity rate, but gained no benefit in survival, recurrence, or mortality. The radical mastectomy is rarely performed today.

Studies establishing the link between cigarette smoking and lung cancer were published. However, early warning labels on cigarette packages avoided the word "cancer." Explicit warning labels were not required until decades later. Although smoking rates have fallen in most developed nations, active marketing and bold political lobbying allows the tobacco industry to flourish in some countries, creating a new generation of smokers (and future cancer victims).

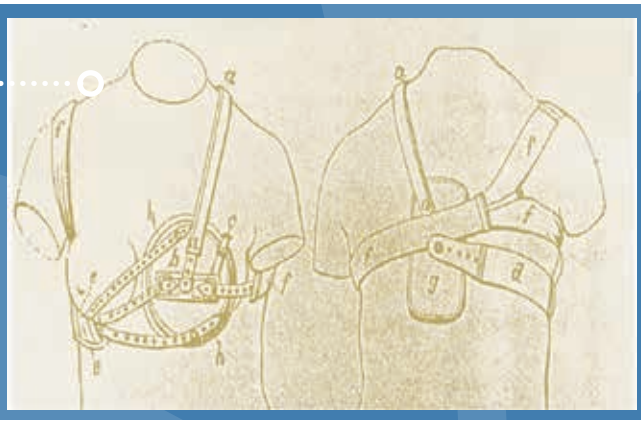
Preparing for War: A History of Cancer (page 1)

2500 BCE



The first medical description of cancer was found in an Egyptian papyrus. The papyrus contained the teaching of the Egyptian physician Imhotep and described a case of breast cancer as "a bulging tumor in the breast…like touching a ball of wrappings." Imhotep wrote about many medical techniques; however in the case of cancer therapy he noted "(There) is none." Archeologists have also found a two thousand year old Egyptian mummy in the Alexandrian catacombs with a tumor invading the pelvic bone.

1595-1645



Medieval surgeons attack cancer using primitive surgical methods. Johannes Scultetus describes a mastectomy, the surgical removal of the breast cancer, using fire, acid and leather binding.

1890s

Surgeons devise increasingly aggressive operations to attack cancer. William Stewart Halsted at Johns Hopkins University pioneered the radical mastectomy, an operation to remove the breast, the muscles beneath the breast and the associated lymph nodes. Halsted writes about one women's case in his journal saying, "the patient was a young lady who I was loath to disfigure." In the etching above Halsted drew an idealized patient. However, in reality most patients were older women with large tumors.

Preparing for War: A History of Cancer (page 2)

1896

When radium was discovered by Marie and Pierre Curie, doctors began to deliver high doses of radiation to tumors. Conferences and societies on high dose radiation were held and one Chicago physician noted that, "I believe this treatment is an absolute cure for all forms of cancer." However, radiation itself was carcinogenic and Marie Curie died from a leukemia caused by decades of work with X-rays.

460-377 BCE

Hippocrates gives an account of a woman from Abdera who had a carcinoma of the breast with a bloody discharge from her nipple. Although Hippocrates was able to stop the bleeding the patient still died. He also noted that when menstrual bleeding ceased, breast cancer became more prevalent. He identified stages of cancer, noting that, as the disease progresses, the patient develops a bitter taste, refuses food, develops a shooting pain from breast to neck, complains of thirst and becomes emaciated. From this point, death was certain. Hippocrates was the first to use the words "carcinos" and "carcinoma" to describe tumors, and the term "cancer" was coined. "Cancer" is derived from the Greek word "karkinos," or crab, which is thought to reference the appearance of blood vessels on tumors resembling a crab's claws reaching out.

1937

Senator Matthew Neely, a former lawyer from West Virginia, asked Congress to advertise a reward of $5 million for "information leading to the arrest of human cancer." In response to Neely and magazine articles in *Time* and *Life Magazines*, President Roosevelt signs the National Cancer Institute Act. This act created the National Cancer Institute (NCI) that was tasked with coordinating cancer research and care. However, months after NCI was created the battle against cancer was quickly overshadowed by the events of World War II.

Preparing for War: A History of Cancer (page 3)

December 2, 1938

During World War II, tons of mustard gas was accidentally released into the Bari harbor in Italy during an air raid. The gas decimated normal white blood cells in the body of soldiers, leading doctors to consider using similar chemicals to kill cancers of white blood cells. Chemotherapy, chemical warfare on cancer cells, was literally inspired by war.

1948

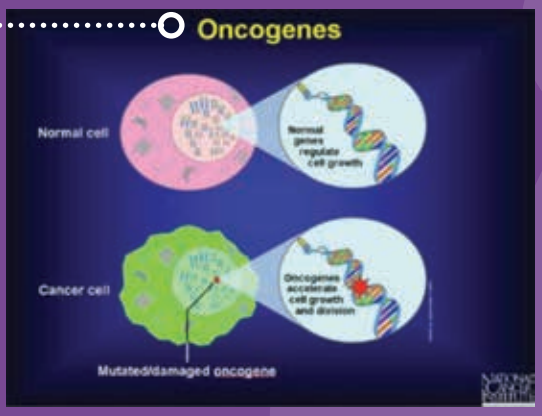
Dr. Sydney Faber created the Jimmy Fund which had "Jimmy" a twelve year old baseball fan as the unofficial mascot for children's cancer. Jimmy's story began in 1948, when Gustafson was a 12-year-old patient of Dr. Farber, founder of the Children's Cancer Research Foundation (eventually renamed Dana-Farber Cancer Institute) and a pioneer of modern chemotherapy. Dubbed "Jimmy" to protect his privacy, Gustafson was selected to speak on Ralph Edwards' national radio program, "Truth or Consequences," which was broadcast from the boy's hospital room. The Jimmy Fund became one of the most powerful cancer advocacy organizations. The Jimmy fund raised $231,000 for cancer research during the first year.

1995

The first DNA microchip was constructed and used to measure gene expression levels in plants. This technology has advanced and is now used to study cancer in humans. Currently 'gene chips' are being investigated as tools in the development of individualized cancer treatment plans.

Preparing for War: A History of Cancer (page 4)

1976



The first oncogene was discovered and was termed src (pronounced sarc as in *sarcoma*). Src was first discovered as an oncogene in a chicken retrovirus. An oncogene is a gene that has the potential to cause cancer. In tumor cells, they are often mutated or expressed at high levels. J. Michael Bishop and Harold E. Varmus of the University of California, San Francisco demonstrated that oncogenes were activated proto-oncogenes, found in many organisms including humans. For this discovery Bishop and Varmus were awarded the Nobel Prize in Physiology or Medicine in 1989. Currently, dozens of oncogenes have been identified in human cancer. Many cancer drugs target the proteins encoded by oncogenes.

1971

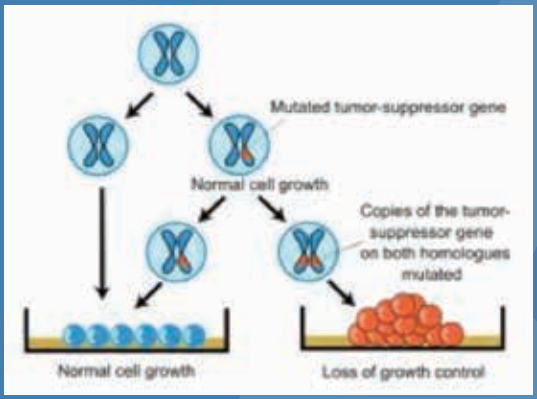
In his state of the Union address President Nixon said, "I will also ask for an appropriation of an extra $100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal."

The picture above shows Dr. Sidney Farber (far left) was a White House guest of Pat (second from right) and President Richard Nixon after the president declared his "War on Cancer" and passed the National Cancer Act. When the president appointed 18 members to a National Cancer Advisory Board the following March, Dr. Farber was granted a four-year term.

Preparing for War: A History of Cancer (page 5)

1986

The first tumor suppressor gene, Rb (for retinoblastoma) was isolated. This gene was also one of the first associated with an inherited (familial) form of cancer



1994

Even though Judah Folkman published a paper in 1971 proposing angiogenesis plays a major role in cancer development, it wasn't until this year that Endostatin, an angiogenesis inhibitor was tested in clinical trials. Folkman though preventing angiogenesis could inhibit tumor growth by starving the tumor of vital nutrients. This theory was originally disregarded by most in the field, but is now fully accepted. In this year the Phase III clinical trial, the addition of Endostatin to the standard chemotherapeutic regimen, began. The trial showed significant and clinically meaningful improvement in response rate, median time to progression, and clinical benefit rate compared with the chemotherapeutic regimen alone.

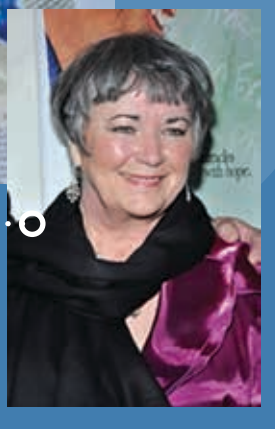
Preparing for War: A History of Cancer (page 6)

2006

The FDA approves Gardasil, a vaccine that protects against the human papillomavirus (HPV). HPV is known to be the major cause of cervical cancer. Merck & Co. conducted a Phase III study named Females United to Unilaterally Reduce Endo/Ectocervical Disease This clinical trial was a randomized double-blind study with one controlled placebo group and one vaccination group. Over 12,000 women aged 16–26 from thirteen countries participated in the study. Each woman was injected with either Gardasil or a placebo on day 1, month 2, and month 6. In total, 6,082 women were given Gardasil and 6,075 received the placebo. Subjects in the vaccine group had a significantly lower occurrence of high-grade abnormal cervical tissue growth related to HPV-16 or HPV-18 than did those in the placebo group. During February of this year, the independent Data and Safety Monitoring Board recommended the clinical trials be terminated on ethical grounds, so that young women on the placebo could receive Gardasil.

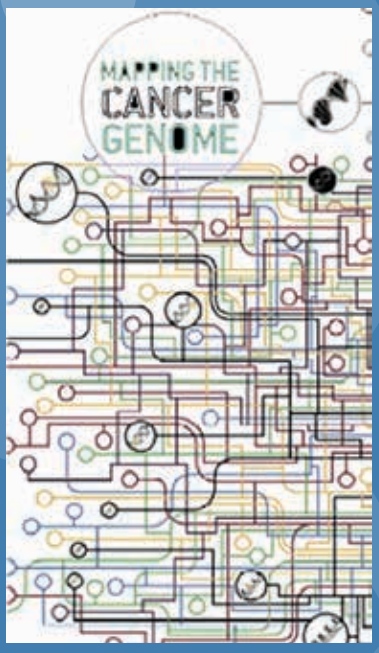
1998

The biotech company Genentech gained FDA approval for Herceptin (trastuzumab). Barbara Bradfield was among the first women to be treated with Herceptin. Herceptin specifically attacks breast cancer cells that are over producing the HER2 protein. Barbara is the longest survivor of the treatment, with no hint of her cancer remaining today. However, Hercpetin costs about $70,000 for a full course of treatment and is not always covered by insurance.



Preparing for War: A History of Cancer (page 7)

Present Day



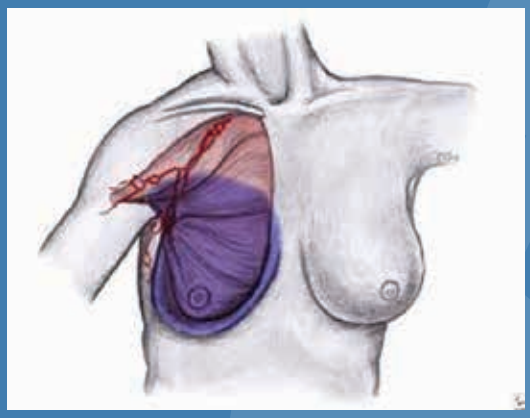
The Human Genome Project that was completed in 2003. Scientists are currently working on the Cancer Genome Atlas. The Cancer Genome Atlas (TCGA) began as a three-year pilot in 2006 with an investment of $50 million each from the National Cancer Institute (NCI) and National Human Genome Research Institute (NHGRI). The TCGA pilot project confirmed that an atlas of changes could be created for specific cancer types. It also showed that a national network of research and technology teams working on distinct but related projects could pool the results of their efforts and make the data publicly accessible. The pilot project proved that making the data freely available would enable researchers anywhere around the world to make and validate important discoveries. The success of the pilot led the National Institutes of Health to commit major resources to TCGA to collect and characterize more than 20 additional tumor types. Francis Collins, the leader of the Human Genome Project says, "When applied to the 50 most common types of cancer, this effort could ultimately prove to be the equivalent of more than 10,000 Human Genome Projects in terms of sheer volume of DNA to be sequenced. The dream must therefore be matched with ambitious but realistic assessment of emerging scientific opportunities for waging a smarter war."

2000

Gleevec is the first of a new class of drugs that act by specifically inhibiting a certain enzyme – a receptor tyrosine kinase – that is characteristic of a particular cancer cell, rather than non-specifically inhibiting and killing all rapidly dividing cells. Of the 54 patients who received high doses of the drug in the phase I clinical trial to treat chronic myelogenous leukemia, 53 showed a complete response within days of starting Gleevec. The success of Gleevec showed that highly specific, non-toxic therapy is possible.

Preparing for War: A History of Cancer (page 8)

1981



The results of a trial showing that radical mastectomies were not more effective than simple mastectomies were published. The trial had 1,765 patients in 34 centers in the United States and Canada. Patients were randomized into three groups: one treated with the radical mastectomy (a surgical procedure in which the breast, underlying chest muscle, and lymph nodes of are removed), the second with simple mastectomy (the entire breast tissue is removed, but the muscle and lymph nodes are not) and the third with surgery followed by radiation. The results of breast cancer recurrence, relapse, death, and distant cancer metastasis were statistically identical among all three groups. The group treated with the radical mastectomy had a much higher morbidity rate, but gained no benefit in survival, recurrence, or mortality. The radical mastectomy is rarely performed today.

1950s

Studies establishing the link between cigarette smoking and lung cancer were published. However, early warning labels on cigarette packages avoided the word "cancer." Explicit warning labels were not required until decades later. Although smoking rates have fallen in most developed nations, active marketing and bold political lobbying allows the tobacco industry to flourish in some countries, creating a new generation of smokers (and future cancer victims).

Preparing for War: A History of Cancer

NAME DATE

Directions: Complete the chart below based on the timeline cards.

Date	One sentence summary of card
2500 BCE	
460-377 BCE	
1595-1645	
1890	
1896	
1937	
1938	
1948	
1950s	

PREPARING FOR WAR: A HISTORY OF CANCER (PAGE 2)

Date	One sentence summary of card
1971	
1976	
1981	
1986	
1994	
1995	
1998	
2000	
2006	
Present Day	

Preparing for War: A History of Cancer

NAME DATE

Directions: Complete the chart below based on the timeline cards.

Date	One sentence summary of card
2500 BCE	*First written description of cancer is found in Egyptian writing.*
460-377 BCE	*Hippocrates is the first to use the term cancer.*
1595-1645	*Surgeons perform crude mastectomies.*
1890	*Surgeons begin performing radical mastectomies.*
1896	*High doses of radiation are used to treat tumors.*
1937	*The National Cancer Institute is created.*
1938	*Scientists begin studying the use of chemicals (chemotherapy) as a treatment for cancer.*
1948	*Dr. Sydney Farber creates the Jimmy Fund, a cancer advocacy organization.*
1950s	*Studies linking smoking and lung cancer are published.*

PREPARING FOR WAR: A HISTORY OF CANCER (PAGE 2)

Date	One sentence summary of card
1971	*Nixon declares a "War on Cancer" and signs the National Cancer Act.*
1976	*The first oncogene (gene that can cause cancer) is discovered.*
1981	*A study showing that simple mastectomies are just as effective (and have a lower rate of mortality) as radical mastectomies is published.*
1986	*The first tumor-suppressor gene is discovered.*
1994	*Endostatin, a drug that inhibits angiogenesis, is tested in clinical trials.*
1995	*DNA microchips are invented and can be used to measure gene expression in cancer cells.*
1998	*The FDA approved the use of the drug Herceptin to treat certain types of breast cancer.*
2000	*Gleevac is successfully used to treat chronic myelogenous leukemia.*
2006	*The FDA approves the first cancer preventing vaccine, Gardacil, which protects against the human papillomavirus.*
Present Day	*The Cancer Genome Atlas project is researching and publishing all the possible changes in genes for specific cancers.*

Keeping it All in Check: The Life of a Cell in the Cell Cycle

3

Vocabulary:

Anaphase: third phase of mitosis; chromatids separate and are pulled to opposite sides of the cell by spindle fibers

Cell Cycle: the regular pattern of growth, DNA replication and cell division that occurs in eukaryotic cells.

Cellular Division: process by which one parent cell produces daughter cells after copying genetic material

Checkpoint: control mechanisms that ensure the fidelity of cell division

Cytokinesis: process by which the cytoplasm divides

Gap 0: a period in the cell cycle in which cells exist in a quiescent state

Gap 1: or post-mitotic phase; is a period in the cell cycle during interphase, before the S phase; this phase is the major period of cell growth during its lifespan.

Gap 2: or pre-mitotic phase, is the third and final subphase during interphase of the cell cycle which directly proceeds cellular division

Interphase: the time during the cell cycle, in which the cell is not actively dividing.

Metaphase: second phase of mitosis, chromosomes align along the cell's equator

p53: tumor suppressor gene that expresses the protein p53.

Prophase: first phase of mitosis; chromatin condenses, nuclear envelope breaks down, centrosomes migrate to opposite poles

Proto-Oncogene: normal gene that can become an oncogene due to mutations or over expression

Synthesis (S-Phase): the part of the cell cycle, during interphase, in which DNA is duplicated, between G1 and G2

Telophase: last phase of mitosis; a complete set of chromosomes is positioned at the poles of the cell, nuclear envelope reforms, chromosomes uncoil and spindle fibers disassemble.

KEY QUESTION(S):
- What are the major stages of the cell cycle, including the sub stages of interphase?
- What are checkpoints and why are they essential for the proper development of a cell before, after and during cellular division?
- What is the role of tumor suppressor genes and oncogenes in cancer development?

TIME ESTIMATE:
- Advanced Preparation: ~45 minutes
- Student Procedure: One 50 minute period

LEARNING STYLES:
- Visual, auditory and kinesthetic

Lesson Summary:

In this teamwork activity small groups of students (3-5) will work together to label a blank cell cycle with three layers of "labeling cards." Each layer of information will increase the complexity level from review, to use of context clues, to deductive reasoning in order to ultimately identify critical stages of the cell cycle and how they are controlled by gene cascades. Students will then explore the role of tumor suppressor genes and oncogenes in regulating the cell cycle.

Standards:

SC.912.L.16.3
SC.912.L.16.8
SC.912.L.16.14
SC.912.L.18.11
SC.912.N.3.5

EXTENSION

- Have students play the NobelPrize.org game: Control the Cycle: http://www.nobelprize.org/educational/medicine/2001/index.html

Implementation Note: The game only takes ~4 minutes to play, if all the correct choices are made on the first round, however realistically allow at least 10-15 minutes for students to play the game.

Student Learning Objectives:

The student will be able to...

1. Use context clues to determine the cell cycle is a representation of the "life events of a cell"
2. Identify the two major stages of the cell cycle (Interphase and Cellular Division) and their subphases.
3. Distinguish between the basic mechanics of each stage and subphase of the cell cycle.
4. Recognize that checkpoints are present at three locations in the cell cycle to ensure proper growth and proliferation of cells
5. Draw the conclusion that a cascade of genes and protein interactions are responsible for the function of the cell cycle checkpoints.

Materials:

- Large, Blank Cell Cycle Diagram (on posterboard or chart paper), 1 per group
- Large, Blank Cell Cycle Diagram to be projected on white/smart board
- 1 set of each "round" of Cell Cycle Diagram labeling cards, 3 sets in all per group (each on different colored paper)
- Tape/ Dry Erase Markers
- Teacher Answer Key (Completed Cell Cycle Diagram)

Background Information:

The following websites were used to prepare this lesson. A surface review of each one should be sufficient for the instruction of the lesson:

The Cell Cycle: http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/C/CellCycle.html

Cell Cycle, on Wikipedia (correct citations present and verified): http://en.wikipedia.org/wiki/Cell_cycle

Advance Preparation:

1. Review background information about the cell cycle and checkpoints
2. Print student handouts
3. Transfer Large, Blank Cell Cycle Diagram for each group onto poster board/chart paper
4. Print (on colored paper) and cut out each of the three layers of labeling for the blank cell cycle-1 complete set for each group.
5. Project Blank Cell Cycle Diagram onto a white board or smart board for class discussion.
6. Download the You Tube video "It's Too Late to Apoptize" if you do not have access to You Tube in the classroom.

Procedure with Time Estimates:

1. **(At the start of class)** Pass out Large, Blank Cell Cycle Diagram and a roll of tape to each group of 3-4 students.
2. **(1-2 min)** Instruct students this is a team activity in which they will activate their background knowledge of the cell cycle/cellular division (mitosis) and use deductive reasoning to label other parts of the cell cycle that they might not be as familiar with.
3. **(4 min)** Pass out the first set of labeling cards to each group and tell them they have 3 minutes to tape the correct labeling card to its corresponding part of the cell cycle (interphase, cellular division, prophase, metaphase, anaphase, telophase, cytokinesis)
   a. Circulate around the room ensuring that each group is correctly labeling the diagram (this should be review, but assist groups where necessary)

4. **(4 min)** Pass out the second set of labeling cards and give students ~3-4 minutes to read each descriptive card, pair it with its correct phase of the cell cycle and tape both cards to the corresponding segment of the blank cell cycle diagram. (Gap 1 (G1), Gap 1 descriptive card, Gap 2 (G2), Gap 2 descriptive card, Synthesis (S Phase), Synthesis descriptive card)
   a. Circulate around the room ensuring that each group is correctly labeling the diagram; nudge groups in the right direction as needed.
5. **(4 min)** Pass out the third set of labeling cards and instruct students to correctly place G_0 ("gee-zero") on the diagram (after Gap 1). Allow ~3-4minutes for students to read the description of each checkpoint, tape the label to the correct "stoplight" on the diagram
   a. Circulate around the room ensuring that each group is correctly labeling the diagram; nudge groups in the right direction as needed.
   b. Pass out the Apoptosis and Apoptosis descriptive cards during this round.
      i. Discuss with students either in small groups, or as a whole class, the process of cell fate during the restriction point checkpoint. *TEACHER NOTE: "Cell fate" is the phrase we use to simply the process of a cell undergoing apoptosis, entering G_0 or continuing through the cell cycle for another round of cellular division.*
6. **(8-10 min)** Review the labeling of each section/checkpoint together as a class, using the blank diagram on the board. Either call on individual students to help, or assign a phase to each group to share out.
7. **(10-15 min)** Have the students explore the animation at www.yourgenome.org/downloads/animations.shtml -click on the Role of Cancer Genes animation- (either individually or together as a class) and determine the role of proto-oncogenes and tumor suppressor genes.
   a. Make sure to highlight how many mutations are required in each type of gene to cause mutation (two mutations to inactivate a tumor suppressor gene and one mutation to turn a proto-oncogene into an oncogene). TEACHER NOTE: *An important difference between oncogenes and tumor suppressor genes is that oncogenes result from the activation (turning on) of proto-oncogenes, but tumor suppressor genes cause cancer when they are inactivated (turned off).*
   b. Next hand students the gene cards. Have students search on the Internet to determine if each gene is a proto-oncogene or a tumor suppressor gene.
   c. Instruct students to tape the genes in the correct boxes at the bottom of their diagram *TEACHER NOTE: Have students save completed cell diagrams for Lesson 4.*
8. **(3 min)** As a wrap up to this lesson show students the "It's Too Late to Apoptize Video" at http://youtu.be/mHOX43-4PvE and ask them why it's relevant to what they learned today.

Assessment Suggestions:

- Student Handout can be collected to assess all student learning objectives.
- Students construct a concept map using the lesson vocabulary to show connections between the stages of the cell cycle, physical cell mechanisms and control of the checkpoints.

Resources/References:

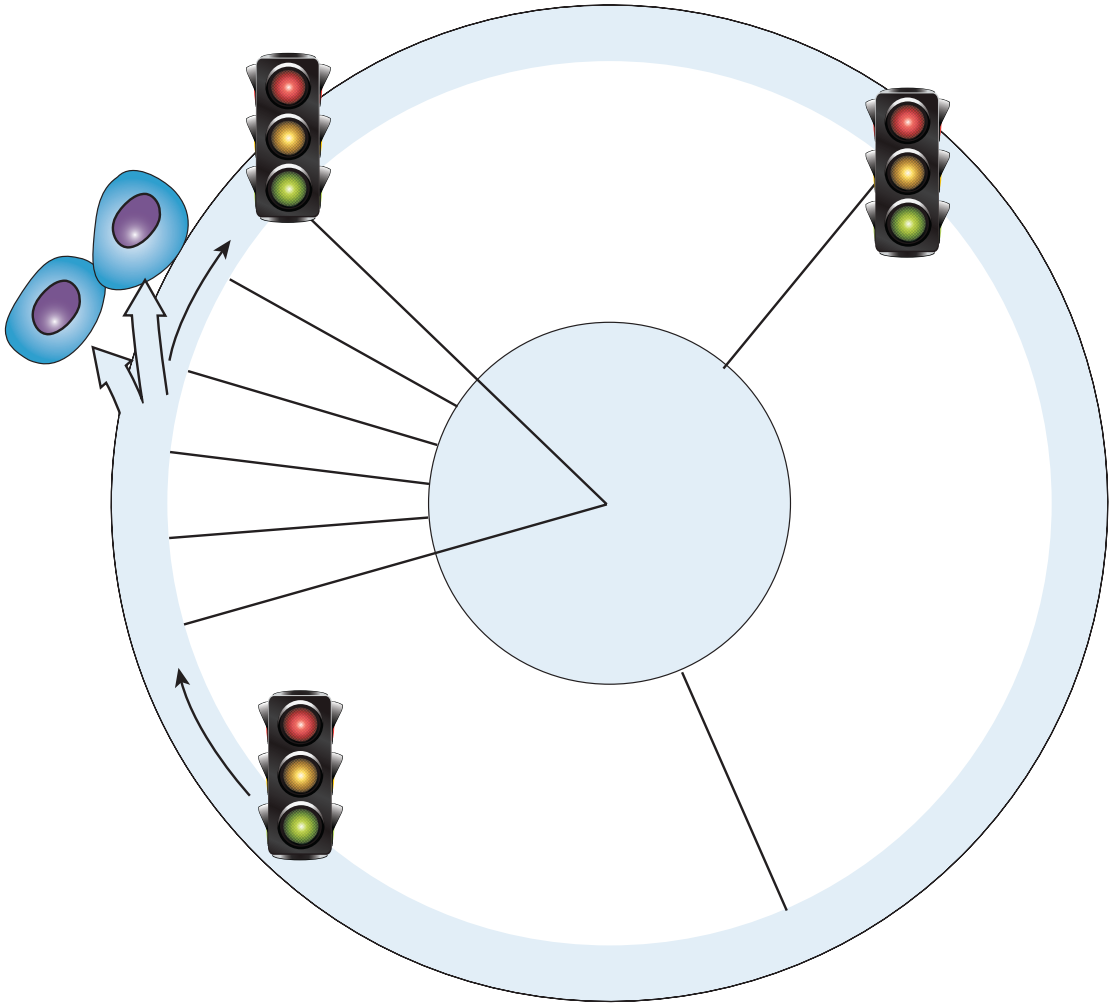
- Pardee, A. (1989). "G1 events and regulation of cell proliferation". *Science* 246 (4930): 603–8. Yarden RI, Pardo-Reoyo S, Sgagias M, Cowan KH, Brody LC. (2002) *BRCA1 regulates the G2/M checkpoint by activating Chk1 kinase upon DNA damage.* Nat Genet; 30:285-9.
- Musacchio, Andrea; Edward D. Salmon (2007). "The spindle-assembly checkpoint in space and time". *Nat Rev Mol Cell Biol* 8 (5): 379–393

EXTENSION

- There is also a great animation with more detail on the function of p53: www.dnalc.org/view/960-Causes-Smoking-p53.html
- Show animation of the cell cycle with both normal and abnormal checkpoint behavior: Checkpoints and Cell Cycle Control by Harvard College and MCB-HHMI Outreach: http://outreach.mcb.harvard.edu/animations/checkpoints.swf

Blank Cell Cycle

Note: This image should be enlarged on a poster board or chart paper so the labels will fit on it. Consider laminating for future use.



Proto-Oncogene	Tumor Suppressor Gene

Student Labeling Cards

Set One: The Basics

Note: Print on colored paper (preferably different from Set Two and Set Three) and cut into "cards." Each group will need one complete set. Consider laminating for future use.

Interphase	Cellular Division
Prophase	Metaphase
Anaphase	Telophase
Cytokinesis	

Student Labeling Cards

Set Two: Stages of Interphase

Note: Print on colored paper (preferably different from Set One and Set Three) and cut into "cards." Each group will need one complete set. Consider laminating for future use.

Gap 1 (G_1)	• Cells grow • Organelles are replicated • Cells carry out their normal function, depending on cell type
Gap 2 (G_2)	• Cells grow • Cells carry out their normal function, depending on cell type • Cells prepare to divide
Synthesis (S-Phase)	DNA is replicated

Student Labeling Cards

Set Three: Checkpoints

Note: Print on colored paper (preferably different from Set One and Set Two) and cut into "cards." Each group will need one complete set. Consider laminating for future use.

Restriction Point

- Determines if a cell should divide, enter G_0, or delay division for a short period of time.
- Considers if the environment is suitable for cellular proliferation

Post Replication

- Screens DNA for mutations

Spindle Assembly (SAC)

- Monitors the interaction between improperly connected kinetochores and spindle microtubules
- Controlled by measurement of tension between sister kinetochores

G_0

- Normal Cell Function until cellular reproduction is required.

Apoptosis

- Programmed cell death
- This may occur when an cell becomes damaged or deregulated, such as during tumor development

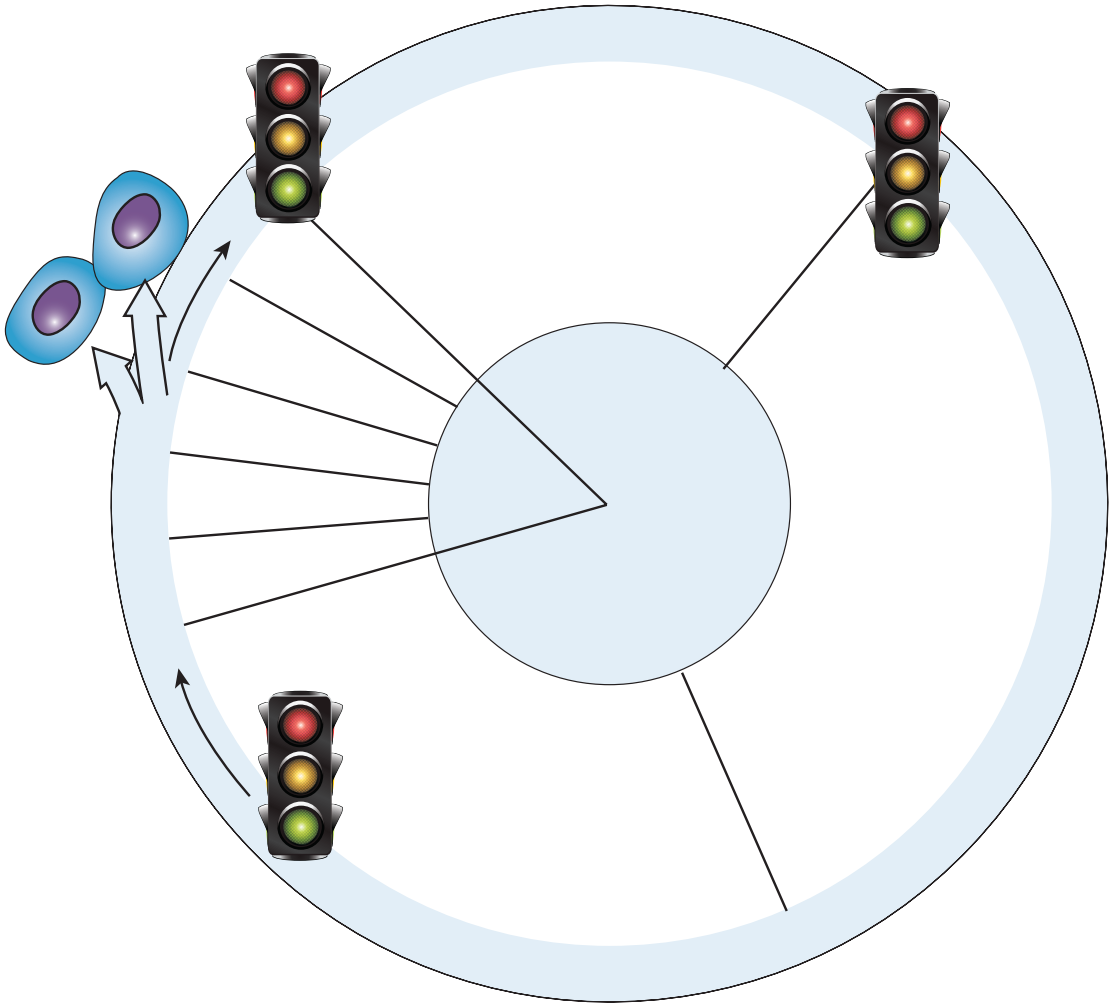
Student Labeling Cards

Genes

Note: Print on colored paper (preferably different from prior sets) and cut into "cards." Each group will need one complete set. Consider laminating for future use.

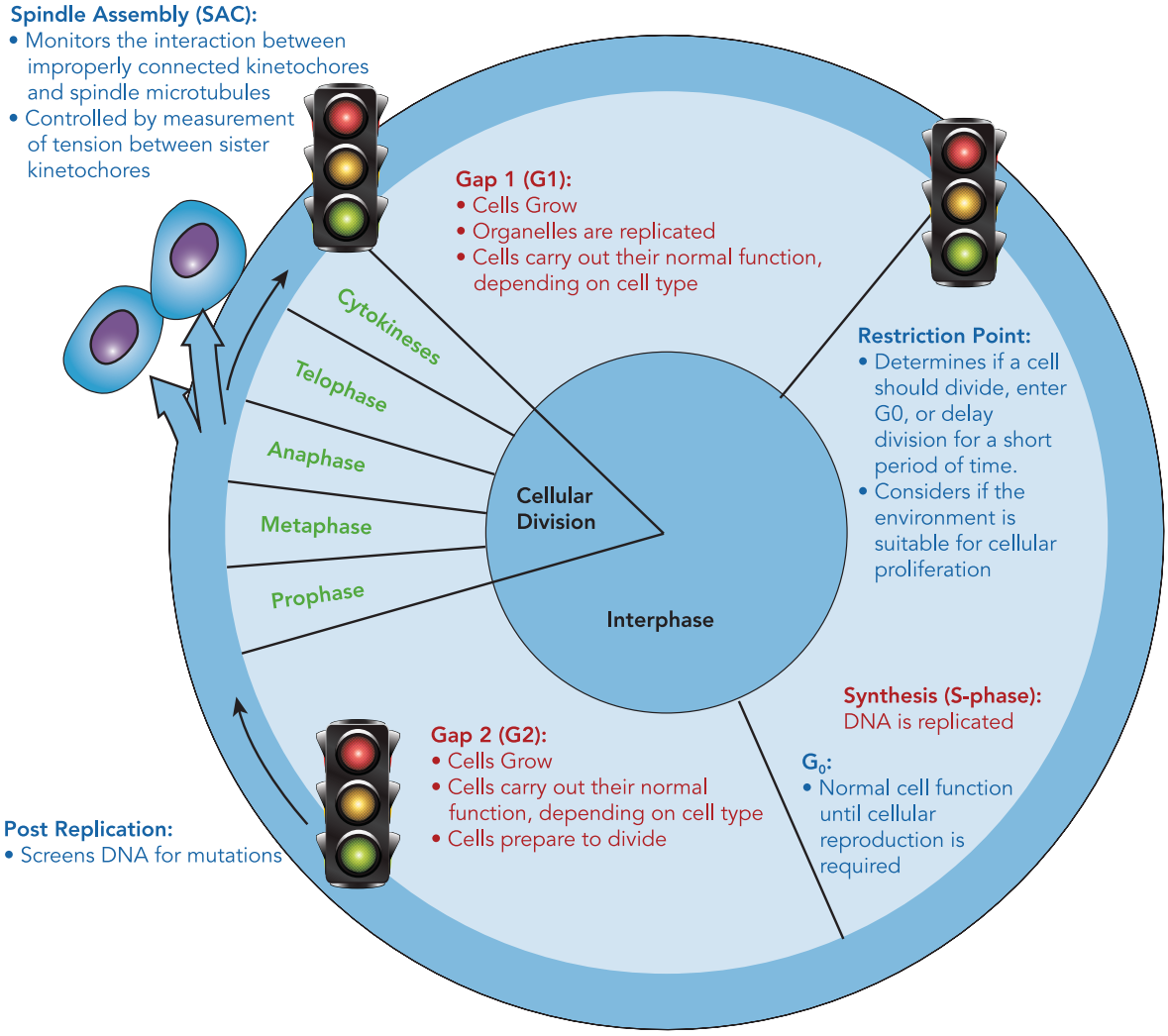
HER-2	p53
Rb	BRCA-1
ras	src
APC	myc

Keeping it All in Check: The Life of a Cell in the Cell Cycle



Proto-Oncogene
Examples: How many mutations are required to cause cancer? _____
Tumor Suppressor Gene
Examples: How many mutations are required to cause cancer? _____

Keeping it All in Check: The Life of a Cell in the Cell Cycle



Proto-Oncogene
• *p53* • *BRACA-1* • *Rb* • *APC*
Tumor Suppressor Gene
• *src* • *ras* • *HER-2* • *myc*

Keeping it All in Check: The Life of a Cell in the Cell Cycle

4

Vocabulary:

Oncogene: is a gene that has the potential to cause cancer. In tumor cells, they are often mutated or expressed at high levels.

Proto-oncogene: a normal gene that can become an oncogene due to mutations or increased expression

Mutation: a permanent change in the DNA sequence of a gene. Mutations in a gene's DNA sequence can alter the amino acid sequence of the protein encoded by the gene.

Tumor Suppressor Gene: a gene that reduces the probability that a cell in a multicellular organism will turn into a tumor cell. A mutation or deletion of such a gene will increase the probability of the formation of a tumor.

KEY QUESTION(S):
- When mutations arise in proto-oncogenes and/or tumor suppressor genes what changes occur in the cell cycle?
- Why is cancer development a multi-step process?

TIME ESTIMATE:
- Advanced Preparation: ~30 minutes
- Student Procedure: 1 class period, ~45 minutes each

LEARNING STYLES:
- Visual, auditory and kinesthetic

Lesson Summary:

Students will use knowledge of the cell cycle, checkpoints and the types of genes controlling the checkpoints from Lesson Three to predict how mutations in both proto-oncogenes and tumor suppressor genes affect the cell cycle and cellular division to determine when cancer could develop. Students will complete a formative activity in which they randomly draw mutation types as a "cause" of cancer and determine the effect on the individual.

Student Learning Objectives:

The student will be able to...
1. Apply the concepts of the control of the cell cycle, gene mutation and cancer development.
2. Recognize that the development of cancer is a varied, multi-step process.

Standards:

SC.912.L.16.3 SC.912.L.16.8 SC.912.L.16.14

Materials:

- Completed Group Cell Cycle Diagram and/or completed student handout from Lesson Three
- Student Page: What Happens When Genes Lose Control?
- Cell Cycle & Cancer Cause and Effect Cards
- Paper bags for the Cause Cards (two for each group)
- Student Page: Development of Cancer Concept Map
- Computers with internet access

Background Information:

Read the article "Cell Cycle Control by Oncogenes and Tumor Suppressors: Driving the Transformation of Normal Cells into Cancerous Cells" from Scitable by Nature. http://www.nature.com/scitable/topicpage/cell-cycle-control-by-oncogenes-and-tumor-14191459

Read the literature on "Oncogenes, Tumor Suppressor Genes, and Cancer" by the American Cancer Society, found here: http://www.cancer.org/acs/groups/cid/documents/webcontent/002550-pdf.pdf

Advance Preparation:

- Print Student Page: What Happens When Genes Lose Control? (one per student)
- Print Student Page: Development of Cancer Concept Map (one per student)
- Prepare Cancer Cause and Effect cards by printing them on colored paper (three different colors for the three different categories are suggested) and possibly laminating for future use. (Each set per group will consist of the following: bag one containing the proto-oncogene cards, bag two containing the tumor suppressor gene cards, the set of three effect cards)

Procedure and Discussion Questions With Time Estimates:

1. **(4 min)** Show the 1:09 minute video clip on the relationship between oncogenes and tumor suppressor genes adapted from the National Institutes of Healthy "Cell Biology and Cancer" curriculum Student Activities 2 – Cancer and the Cell Cycle and available on YouTube: http://www.youtube.com/watch?v=eoWRZbtqB_s
   a. Briefly ask students to summarize the video as a review from Lesson Three and address any questions/misconceptions.
2. **(6-8 min)** Pass back group Cell Cycle Diagrams from Lesson 3 and copies of the student page What Happens When Genes Lose Control?
   a. Pass out the complete set of three effect cards to each group.
   b. Randomly pass out one of the cause gene cards to each group (from either the proto-oncogene set or the tumor suppressor gene set- if possible it would be best if each group had a different card)
   c. Students will record the change from the cause gene card under the **cause** column on their What Happens When Genes Lose Control? student page and then write what the possible outcome of that change is under the **effect** column; choosing from the three effect cards. This is round one.
3. **(5-7 min)** Ask each group to share what was on their gene card (the cause) and what effect they think it had on the cell cycle.
   a. Ideally the process of sharing out with the whole group should cause some debate, as students may not agree with other groups chosen effect, and this will cause friendly debate between the groups.
   b. After all the groups have shared and the informal debate wanes inform the students that NONE of their groups should "have cancer" yet because the development of cancer is a multi-step process involving the mutation of multiple genes.
4. **(10 min)** Pass out the Student Page: Development of Cancer Concept Map as well as project a copy onto the screen.
   a. Using the Teacher Page as a guide, ask the students leading questions to complete the empty portions of their concept map.
      *i. Remember the emphasis of this lesson is that **both** the tumor suppressor gene must be inactivated **and** the oncogene must be activated before cancer development is possible.*

5. **(20-25 min)** Instruct students to return to the Student Page: What Happens When Genes Lose Control.

For the remaining rounds 2-4, students will draw one card from the proto-oncogene bag and one card from the tumor suppressor gene bag and using their knowledge of mutations in these genes choose the correct effect card. They should record their results on their Student Page. *TEACHER NOTE: It is suggested that students leave out the Development of Cancer Concept Map on their desk as a reference as their complete this activity.*

Assessment Suggestions:

- Collect Student Page: What Happens When Genes Lose Control?

Resources/References:

- http://www.nobelprize.org/nobel_prizes/medicine/laureates/2002/
- Croce, C. M. "Oncogenes and Cancer." *New England Journal of Medicine* 358.5 (2008): 502-11. Print.

EXTENSION

• Have students play the "What's Your Risk" game, included in this curriculum unit.

What Happens When Genes Lose Control?

Use your completed Cell Cycle Diagram from Lesson Three to predict the possible outcome of the cell (the effect) based on the event on your gene scenario card (the cause).

Proto-Oncogene "Cause" Cards:
No mutations are present in Scr
Mutation is present in one copy of Scr
Mutation is present in both copies of Scr
No mutations are present in Ras
Mutation is present in one copy of Ras
Mutation is present in both copies of Ras

What Happens When Genes Lose Control?

Tumor Suppressor Gene "Cause" Cards:
No mutations are present in p53
Mutation is present in one copy of p53
Mutation is present in both copies of p53
No mutations are present in BRAC-1
Mutation is present in one copy of BRAC-1
Mutation is present in

What Happens When Genes Lose Control?

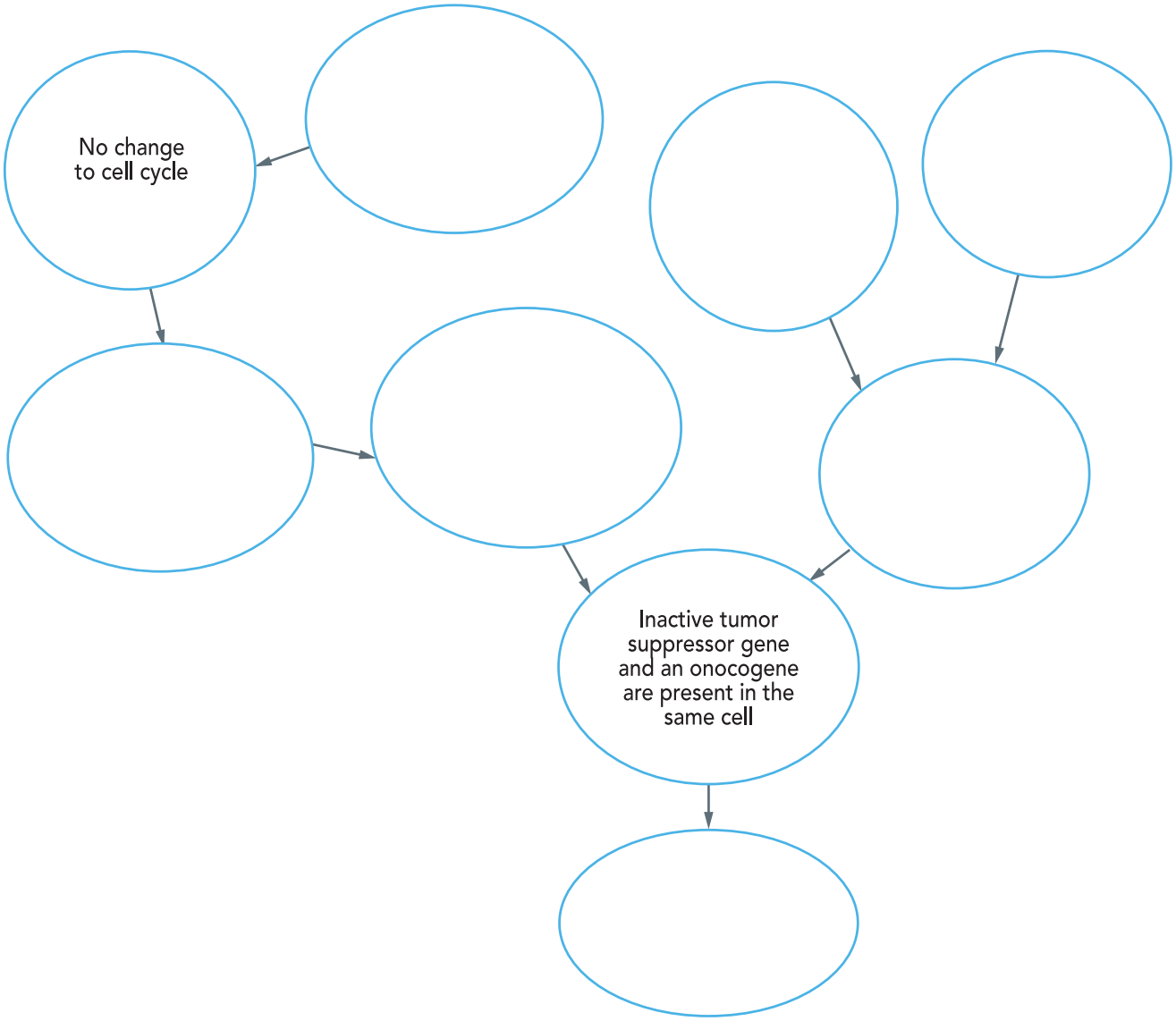
Effect Cards:
Apoptosis occurs at a checkpoint.
The individual does not develop cancer.
Apoptosis does not occur at the checkpoint.
Cancerous cell continues through the cell cycle and divides producing numerous cancer cells; the individual develops cancer.
No mutations are present.
The cell cycle continues as normal; the individual does not develop cancer.

What Happens When Genes Lose Control?

Use your completed Cell Cycle Diagram from Lesson Three to predict the possible outcome of the cell (the effect) based on the event on your gene scenario card (the cause).

	CAUSE	EFFECT
Round 1		
	CAUSE	EFFECT
Round 2		
	CAUSE	EFFECT
Round 3		
	CAUSE	EFFECT
Round 4		

Development of Cancer Concept Map



Concept Map Key Words and Phrases:

a. the tumor suppressor gene is now inactivated

b. individual develops cancer

c. one copy of a tumor suppressor gene is mutated

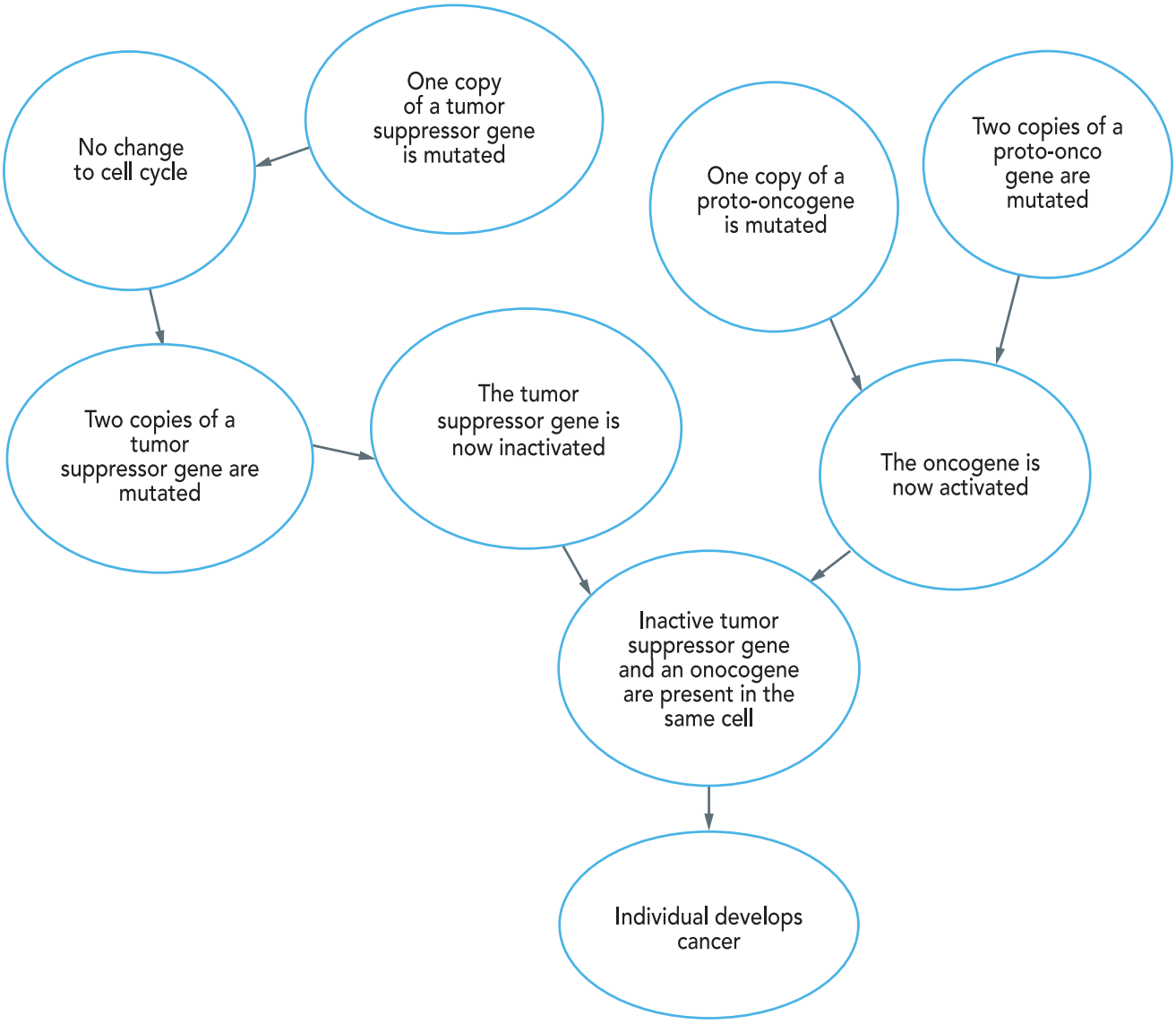
d. one copy of a proto-oncogene is mutated

e. two copies of a tumor suppressor gene are mutated

f. two copies of a proto-oncogene are mutated

g. the oncogene is now activated

Development of Cancer Concept Map



Notes:

EXTENSION ACTIVITY:

What's Your Risk?

4a

Extension Lesson Summary:

In this extension to Lesson Four, students will continue to apply their knowledge of cell cycle controlling genes and the multi-step process of cancer development. An additional layer of complexity is introduced in the "What's Your Risk" game by asking students to now consider how environmental, behavioral and preexisting conditions impact cancer development.

Materials:

- Cell Cycle & Cancer Cause and Effect Cards, in bags from Lesson Four
- Risk Factor Game Pieces, in a paper bag
- Student Page: Development of Cancer Concept Map

Advance Preparation:

- Print Student Page: What's Your Risk (one per student)
- Prepare *What's Your Risk?* Cards by printing them on colored paper and possibly laminating for future use. (one bag per group)

Procedure and Discussion Questions with Time Estimates:

1. **(15-20 min)** This activity is very similar to the "What Happens When Genes Lose Control?" activity from Lesson Four, with the addition of a third bag of "risk factors"
   a. In each of 4 rounds students will draw one card from the proto-oncogene bag, one card from the tumor suppressor gene bag and one card from the risk factor bag. Combining the results of all three cards students then choose the correct effect card. They should record their results on their Student Page. *TEACHER NOTE: For a negative risk factor the mutation is specific to the type of gene (tumor suppressor or proto-oncogene) specified on the card. For positive behaviors the student may use the card to eliminate a mutation on either the tumor suppressor gene or the proto-oncogene).*
   b. Students should continue to work in their group to complete the "What's Your Risk" student page.

Assessment Suggestions:

- Collect Student Page: What Happens When Genes Lose Control?

Game Pieces: What's Your Risk?

You always wear broad spectrum sunscreen that protects against UVA and UVB rays and is SPF 30 or higher. You also reapply at least every two hours.

This behavior prevents one mutation.

Skin cancer is the most common of all cancer types. More than 3.5 million skin cancers are diagnosed each year in the United States. Both UVA and UVB rays cause DNA damage.

You frequently use tanning beds and never wear sunscreen. This leads to a mutation in a proto-oncogene.

According to the American Cancer society being overweight or obese likely raises a person's risk of getting at least 13 types of cancer. Your weight affects your immune system, levels of certain hormones and proteins, and how the body's cells grow and divide.

You are one of the 2/3 of Americans who are overweight. This leads to a mutation in a tumor suppressor gene.

You are healthy eater. You pay attention to portion size and approximately 50% of your diet consists of fruits and non-starchy vegetables. You limit the amount of added sugars, white bread, cakes, cookies and fried foods in your diet.

This behavior prevents one mutation.

Tobacco smoke contains more than 7,000 chemicals and compounds. Hundreds of these are toxic, and at least 69 are cancer causing.

You are a smoker. This behavior causes one mutation in a tumor suppressor gene.

Your mother and sister have breast cancer. You see a genetic counselor and find out that you have a mutation in your BRCA-1 gene.

You have one mutation in a tumor suppressor gene.

Research indicates that the more alcohol a person drinks (particularly the more a person drinks on a regular basis) the higher his/her risk is of developing an alcohol associated cancer. Based on data from 2009, about 19,500 cancer deaths were cancer related. Alcohol related cancers include head and neck cancer, esophageal cancer, liver cancer and breast cancer.

You are a heavy alcohol drinker. This behavior causes one mutation in a tumor suppressor gene.

Game Pieces: What's Your Risk?

Research shows that people who use both alcohol and tobacco have much greater risks of developing cancers of the oral cavity, pharynx (throat), larynx and esophagus than people who use either alcohol or tobacco alone. The risks associated with using both tobacco and alcohol are multiplicative which means that they are greater than would be expected from adding the individual risks associated with alcohol and tobacco together.

You are a heavy drinker and smoker. This behavior causes two mutations; one in a proto-oncogene and one in a tumor suppressor gene

Radioactive materials that decay spontaneously produce ionizing radiation, which has enough energy to strip away electrons from atoms or break some chemical bonds. The damage caused by radiation can affect the genes controlling the cell cycle.

You worked in the reactor at the Fukushima nuclear power plant during the earthquake and were exposed to large doses of radiation. This exposure caused two mutations. One in each copy of your tumor suppressor gene.

You realize that avoiding tobacco (or deciding to stop using it) is one of the most important health decisions you can make.

You are a non-smoker. This behavior prevents one mutation.

İn addition to helping your control your weight, physical activity may lower the risk of breast and colon cancer.

You get at least 150 minutes a week of moderate aerobic activity or 75 minutes a week of vigorous physical activity. This behavior prevents one mutation.

Cancer prevention includes protection from certain viral infections. Human papillomavirus (HPV) is a sexually transmitted virus that can lead to cervical and other genital cancers.

You receive the HPV vaccine (Gardasil). This prevents one mutation.

Age is a risk factor for cancer.

You are 65 years old. You have one mutation in a tumor suppressor gene.

What's Your Risk?

Predict the possible outcome of the cell (the effect) based on the event s on your three scenario cards (the causes).

	CAUSE	EFFECT
Round 1		
	CAUSE	EFFECT
Round 2		
	CAUSE	EFFECT
Round 3		
	CAUSE	EFFECT
Round 4		

What's Your Risk?

Answer the following questions based on your knowledge of cancer and information learned during the game.

1) List several risk factors that contribute to the development of cancer.

2) List several behaviors that can reduce a person's risk for developing cancer.

3) a) Explain the statement "Cancer is a multistep process." Refer to the role of specific genes and the environment in your answer.

b) Knowing that cancer is not caused by one cellular event, would you expect cancer to occur more frequently in younger or older people? Why?

4) a) Explain why a person who smokes has a higher risk of developing cancer.

b) Given your answer above, explain why all people who smoke do not develop cancer.

Notes:

Going to War

5

Vocabulary:

Clinical trials: research studies that involve people and test new ways to prevent, detect, diagnose, or treat cancer and other diseases

Informed consent: process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, or whether to continue participating in it

Placebo: a simulated or otherwise medically ineffectual treatment for a disease or other medical condition intended to deceive the recipient. Sometimes patients given a placebo treatment will have a perceived or actual improvement in a medical condition, a phenomenon commonly called the placebo effect.

Protocol: describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary

KEY QUESTION(S):
- What are clinical trials and why are they important?
- Why do clinical trials need to follow strict guidelines?
- What is the purpose of a placebo?

TIME ESTIMATE:
- One 50 minute period

LEARNING STYLES:
- Visual and auditory

Lesson Summary:

Students complete a webquest to learn about clinical trials as homework the night before the lesson. In class students will explore the relationships between patients, doctors, medical researchers, drug companies, and the IRB in a role-play as an individual with relapsed leukemia entering a clinical trial. Students will then perform a close read of a recent article on the effectiveness of clinical trials. As a final formative assessment students will practice designing their own clinical trials using a guided student worksheet.

Student Learning Objectives:

The student will be able to...
1. Differentiate between the four phases of a clinical trial
2. Design a scientific experiment
3. Recognize the importance of placebos and control groups in a scientific experiment

Standards:

SC.912.L.16.8
SC.912.L.16.10
SC.912.N.1.1
SC.912.N.1.2
SC.912.N.1.3
SC.912.N.1.4
SC.912.N.1.6
SC.912.N.1.7
SC.912.N.2.4
SC.912.N.2.5
SC.912.N.4.1

Materials:

- Computers with internet access
- Copies of student webquest (1 copy per student)
- Copies of New York Times Article: Do Clinical Trials Work? (1 copy per student)
- Copies of Student Page: Close Reading Guide for Do Clinical Trials Work? (1 copy per student)
- Copies of Student Page: Clinical Trial Design (1 copy per student)
- Clinical Trials Web Cards
- Ball of string

EXTENSIONS:

- Have students research local clinical trials in their region, using the extension: Exploring Local Clinical Trials, included in this curriculum unit.

Background Information:

Clinical trials are research studies that involve humans to test new ways to prevent, detect, diagnose, or treat cancer and other diseases. Clinical trials are conducted in phases. The trials at each phase have a different purpose and help scientists answer different questions:

In Phase I trials, researchers test an experimental drug or treatment in a small group of people (20-80) for the first time to evaluate its safety, determine a safe dosage range, and identify side effects.

In Phase II trials, the experimental study drug or treatment is given to a larger group of people (100-300) to see if it is effective and to further evaluate its safety.

In Phase III trials, the experimental study drug or treatment is given to large groups of people (1,000-3,000) to confirm its effectiveness, monitor side effects, compare it to commonly used treatments, and collect information that will allow the experimental drug or treatment to be used safely.

In Phase IV trials, post marketing studies delineate additional information including the drug's risks, benefits, and optimal use.

Every clinical trial has a protocol that describes what will be done in the trial, how the trial will be conducted, and why each part of the trial is necessary. National and international regulations and policies have been developed to protect the rights, safety, and well being of people who take part in clinical trials and to ensure that trials are conducted according to strict scientific and ethical principles. Informed consent is a process through which people learn the important facts about a clinical trial to help them decide whether or not to take part in it, or whether to continue participating in it. Many states require that insurance companies cover the costs of routine care for people taking part in a clinical trial. In other states, voluntary agreements between the states and insurance companies include such a provision. However, coverage varies by state, by health insurance plan, and by type of clinical trial. From http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials

Advance Preparation:

- Teacher should read through the entire lesson, student pages, and familiarize himself with the clinicaltrials.gov site.
- Read the article New York Times article *Do Clinical Trials Work?* and be prepared to address any student questions/misconceptions about the piece.
- Make copies of webquest, close reading guide and clinical trial design student pages for each student.
- Prepare Clinical Trials Web cards by printing them on colored paper, cutting between the "speaker paragraphs" and possibly laminating for future use.

Procedure and Discussion Questions with Time Estimates:

1. Assign the clinical trials webquest as homework the night before the lesson. Alternatively, if using the Webquest during class, allow approximately 30 minutes for completion.
2. **(8-10 min)** Instruct students to stand/sit in a circle. Pass out the Clinical Trials Web cards randomly to students, ensuring the cards are equally distributed amongst the circle of students (not all clumped at one end of the circle, for example). and that the three "John" cards go to the same student. Students must determine the order of events and in the process will see how all the people involved are interconnected. The web should start and end with John.

a. To begin the activity, students who have the cards should simply read the title, so all the students in the class know who the "players" in the Clinical Trial Web are.
b. As indicated the web should begin with John I, who will hold the end of the ball of string while he reads his card.
c. The class can then decide who the next likely person in the story should be.
d. The ball of yarn should be passed from "John", to the next card holder ("John" keeps the end of the string, the next student will hold the piece of the continuous string in front of them and so on, creating the visual web)
e. See the teacher page for the suggested order. The students may come up with a different order, which is fine, just debrief with them at the end.

3. **(5 min)** Review student answers to the homework questions in the webquest. Make sure students understand the difference between a blind and double blind trial, as well as the purpose of a placebo.
4. **(15-20 min)** Students will complete a close read of article Do Clinical Trials Work? following the guided student page. *Instructor Note: There are various "styles" of close reading; we have chosen to include a simple guide for close reading often used in the science classroom as a support activity for English and reading instruction.*
   a. Pass out the Student Page: Do Clinical Trials Work? and a copy of the article to each student. Instruct students to follow the guided process on the handout, answering questions as needed.
   b. After the students complete the second read of the article answer invite them to share the questions they generated about the article, annotated as the ?, also allow students to share their "surprise you" ! annotates as well, if time permits. Allow group discussion, so the students can attempt to answer each other's questions, correcting misconceptions where necessary. Instructor Note: Depending on your students' reading level a group read of the article may be beneficial prior to students completing the reflective writing portion of the assignment.
   c. Instruct students to complete the reflective writing portion of the Student Page, using support from the text, as well as factual information from the webquest, in their answer.
5. **(15 min)** Students will practice designing scientific experiments from given scenarios.
   a. Divide the class into four groups and have each group design one phase of the clinical trial, as indicated on the Student Page: Clinical Trials Design.
   b. Discuss the answers as a whole class. Make sure to highlight the goal of each phase of the trial
   c. Lastly, instruct students to complete the remaining two design questions in class, or as homework, for additional practice and to demonstrate mastery.

Assessment Suggestions:

- Teachers could collect the webquest worksheet to assess student knowledge of clinical trials.
- Instruct students to create a concept map showing the relationship between the individuals portrayed in the Clinical Trials Web activity.
- Teachers should collect the experimental design worksheet to assess student's understanding of placebos, control groups and the importance of well-designed experiments.

Resources

- www.clincialtrials.gov
- http://www.cancer.gov
- Trujillo, Angelica, Christie McGee, and Christopher R. Cogle. "Angiogenesis in Acute Myeloid Leukemia and Opportunities for Novel Therapies." *Journal of Oncology* 2012 (2012): 1-9. Print.

Notes:

Clinical Trials Webquest

Go to http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials and answer the following questions:

1. Fill out the table below describing what happens in each phase of a clinical trial.

PHASE	DESCRIPTION OF WHAT HAPPENS
Pre-Clinical	• Lab and animal studies
Phase I	
Phase II	
Phase III	
Phase IV	

2. List and describe the five most common types of clinical trials.

3. What are eligibility criteria and why are they important?

4. Describe the role of an Institutional Review Board (IRB) in a clinical trial. Who makes up the Institutional Review Board?

5. What is informed consent? What happens if you want to leave a clinical trial before the end of the study?

6. Describe the risks and benefits of participating in a clinical trial.

BENEFITS	RISKS

7. Explain randomization and why it is important in clinical trials?

8. Who is responsible for the costs associated with clinical trials?

9. Go to http://clinicaltrials.gov/ct2/info/glossary and define the following terms

Randomized Trial:

Blind:

Double Blind:

Placebo:

Clinical Trials Webquest

Go to http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials and answer the following questions:

1. Fill out the table below describing what happens in each phase of a clinical trial.

PHASE	DESCRIPTION OF WHAT HAPPENS
Pre-Clinical	• *Lab and animal studies*
Phase I	• *Safety study* • *20-80 people*
Phase II	• *Safety study* • *Identify side effecs* • *Measure effectiveness* • *100-200 people*
Phase III	• *Measure effectiveness* • *Monitor side effects* • *1,000-3,000 people*
Phase IV	• *Monitor long-term side effects*

2. List and describe the five most common types of clinical trials.

Teacher note: There are different types of trials for other diseases.

Treatment: *These trials test the effectiveness of new treatments or new ways of using current treatments in people who have cancer.*

Prevention: *These trials test new interventions that may lower the risk of developing certain types of cancer. Most cancer prevention trials involve healthy people who have not had cancer; however, they often only include people who have a higher than average risk of developing a specific type of cancer.*

Screening:*These trials test new ways of finding cancer early.*

Diagnostic: *These trials study new tests or procedures that may help identify, or diagnose, cancer more accurately.*

Quality of life or supportive care: *These trials focus on the comfort and quality of life of cancer patients and cancer survivors. New ways to decrease the number or severity of side effects of cancer or its treatment are often studied in these trials.*

3. What are eligibility criteria and why are they important?

Eligibility criteria are guidelines for who can and cannot participate in the trial. Enrolling people who have similar characteristics helps ensure that the outcome of a trial is due to the intervention being tested (the independent variable) and not to other factors.

4. Describe the role of an Institutional Review Board (IRB) in a clinical trial. Who makes up the Institutional Review Board?

The IRB reviews all aspects of a clinical trial to make sure that the rights, safety, and well-being of trial participants will be protected. An IRB must have at least five members, including one scientist, one person who is not a scientist, and one person who is not affiliated with the institution where the trial is taking place and who is not an immediate family member of someone who is affiliated with that institution.

5. What is informed consent? What happens if you want to leave a clinical trial before the end of the study?

Informed consent is a process through which people 1) learn the important facts about a clinical trial to help them decide whether or not to take part in it, and 2) continue to learn new information about the trial that helps them decide whether or not to continue participating in it. Anyone can choose to leave a trial at any time.

6. Describe the risks and benefits of participating in a clinical trial.

BENEFITS	RISKS
• *Access to promising new interventions that are generally not available outside of a clinical trial.* • *The intervention being studied may be more effective than standard therapy.* • *Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.* • *The results of the trial may help other people who need cancer treatment in the future.* • *Trial participants are helping scientists learn more about cancer*	• *The new intervention being studied may not be better than standard therapy, or it may have harmful side effects.* • *Trial participants may be required to make more visits to the doctor than they would if they were not in a clinical trial and/or may need to travel farther for those visits.* • *Health insurance may not cover all patient care costs in a trial.*

7. Explain randomization and why it is important in clinical trials?

The trial participants are assigned to their individual groups by random assignment, or randomization. Randomization helps ensure that the groups have similar characteristics. This balance is necessary so the researchers can have confidence that any differences they observe in how the two groups respond to the treatments they receive are due to the treatments and not to other differences between the groups.

8. Who is responsible for the costs associated with clinical trials?

The costs of care for people participating in a clinical trial fall into two general categories: 1) routine care costs and 2) research costs. Routine care costs are costs associated with treating a person's cancer whether or not they are in a trial. These costs are usually covered by health insurance, but requirements vary by state and type of health plan. Research costs are costs associated with conducting a clinical trial; these costs may include the costs of extra doctor visits, extra tests, and procedures that are required for the trial but would not be part of routine care. Research costs are usually covered by the organization that sponsors the trial. The National Institute of Health (NIH) funds many research trials, particularly in the early phases before drug companies invest in the project.

9. Go to http://clinicaltrials.gov/ct2/info/glossary and define the following terms

Randomized Trial: *A study in which participants are randomly (i.e., by chance) assigned to one of two or more treatment arms of a clinical trial. Occasionally placebos are utilized*

Blind: *A randomized trial is "Blind" if the participant is not told which arm of the trial he is on. A clinical trial is "Blind" if participants are unaware of whether they are in the experimental or control arm of the study; also called masked.*

Double Blind: *A clinical trial design in which neither the participating individuals nor the study staff knows which participants are receiving the experimental drug and which are receiving a placebo (or another therapy). Double-blind trials are thought to produce objective results, since the expectations of the doctor and the participant about the experimental drug do not affect the outcome; also called double-masked study.*

Placebo: *A placebo is an inactive pill, liquid, or powder that has no treatment value. In clinical trials, experimental treatments are often compared with placebos to assess the treatment's effectiveness.*

Clinical Trials Web Activity

Teacher Instructions: *See procedure above. Salary amounts have been included for most positions to encourage science career discussion. The intended order for the cards is listed below:*

John Part I • Primary Care Physician • Oncologist • University of Florida Principal Investigator • Drug Company CEO • Clinical Trial Nurse • John Part II • IRB Member • Lab Tech • John Part III

John Part I ($45,00 Manager of a Locally Owned Hardware Store)
I was diagnosed in August 2011 with AML. It didn't fit into a subtype according to my doctors and I was only one of three people known in the world to have these particular chromosomal changes. I underwent intense chemotherapy and a bone marrow transplant. I was in remission successfully by October 2012 and finished chemo in December 2012. Ever since I entered remission, I've been getting stronger and stronger. My health has been better than I ever remember and I even started going to the gym.
The past few weeks though I've noticed changes, I've been bruising easily, I've been out of breath walking the shortest distance and I'm tired way more than usual. Am I just imagining these symptoms or could they point to a relapse? I keep trying to tell myself that they are just phantom symptoms because it's coming up to my one-year remission anniversary next week.

John Part II
I received the results of my bone marrow biopsy and my AML is back. A nurse who works in the oncologist's office told me about a clinical trial that I qualify for. I'm a nervous because this is a Phase I clinical trial and there could be negative side effects, but at this point it's my only option. Even if this new drug doesn't help me, at least I will be helping people in the future and contributing to scientists' knowledge of AML.

John Part III
I have been part of the clinical trial for 3 months now and so far things look good. My blood cell counts are returning to normal. There is no guarantee that the drug will continue to work and I might relapse again, but I remain optimistic.

Primary Care Physician ($180,000)
John came into my office complaining of shortness of breath and bruising. I first saw John in August of 2011 when he came in complaining of the same symptoms. As John has only been in remission from AML since October of 2012, I immediately suspected the worst…John's AML was back. I recommended he see an AML expert again.

Lab Tech($32,000)
My job is to process patient samples and measure patient's complete blood count (CBC). I sometimes have to work late or come in on weekends, because samples arrive at various times and must be processed immediately. I report the results to the principal investigator. Even though I never see the patient, I still hope that what I am doing makes a difference. I am excited because the patients' blood cell counts in this trial seem to be returning to normal.

CLINICAL TRIALS WEB ACTIVITY (PAGE 2)

Oncologist ($295,000)
AML is the most common type of acute leukemia. More than 11,900 new cases occur in the United States each year, mostly in older adults. The average age of a person with AML is 65 years. The symptoms of AML are caused by low numbers of healthy blood cells and high numbers of leukemia cells.
White blood cells fight infection. Low numbers can lead to fever and frequent infections.
Red blood cells carry oxygen throughout the body. Low numbers can lead to anemia — feeling tired or weak, being short of breath and looking pale.
Platelets control bleeding. Low numbers can lead to easy bleeding or bruising and tiny red spots under the skin (petechiae).
High numbers of leukemia cells may cause pain in the bones or joints.
I was very concerned when John came back to my office. Five-year survival varies from 15–70%, and relapse rate varies from 33–78%, depending on the subtype of AML. Patients with relapsed AML post bone marrow transplant, may be offered treatment in a clinical trial, as conventional treatment options are limited. I'm going to see if there are any clinical trials that John will qualify for.

University of Florida Primary Investigator (MD-PhD) ($165,000)
I have been working on AML for the last 10 years. I recently read an article about pazopanib. VEGF is a chemical signal produced by cells that stimulates the growth of new blood vessels. When VEGF is overexpressed, it can contribute to disease. Solid cancers need an adequate blood supply or they will not be able to grow. Hence, cancers that can express VEGF are able to grow and metastasize. Pazopanib has already been approved to treat renal cancer and I wondered if it could be used to treat AML. I began tests on in vitro AML cell lines and then moved into experiments with mice. I have obtained some very promising results and am now looking for funding to start a phase I clinical trial.

Sanofi (drug company) CFO Chris Viehbacher (Salary $4.71 million)
The uncertainties…Can you get a drug approved? What's it going to pay? "Research and development is either a huge waste of money or too, too valuable. It's not really anything in between. The reality is the best people who have great ideas in science don't want to work for a big company…. So, in other words, if you want to work with the best people, you're going to have go outside your own company and work with those people …I've decided that our company should start working with more outside companies, startup biotechs, with universities." I just read a paper about a researcher at the University of Florida who might have a promising new treatment for AML.

Institutional Review Board (IRB) Member (salary is NOT paid from clinical trial money to prevent bias)
I have been asked to serve as an IRB member for a clinical trial testing the effect of a new drug on AML patients. I will make sure that all the informed consent forms are written and filled out properly. Before, during and after the trial I will be reviewing all protocols and make sure they are implemented correctly to ensure patient safety and produce valid results.

Clinical Trial Nurse (CTN) ($57,000)
My job is to help identify qualified patients for clinical trials. I explain the protocols to patients and make sure they understand all potential risks and benefits. During the trial, I work to identify trends in side effects and work with the principal investigator to develop and evaluate patient management strategies. I also work with caregivers, primary care physicians and other hospital staff to ensure the best patient care and produce reliable results.

Close Reading Guide for "Do Clinical Trials Work?"

How to Close Read:

1. **First Reading:** Read the article in completion, to determine the gist of the article.
2. **Second Reading:** Carefully re-read the article writing a 2-3 word summary to the left of each paragraph and annotating other details to the right of each paragraph, using the following guide:

A Note to Students about Annotating:
You might not find it necessary to complete every one of the suggested annotations on the guide for each paragraph.

Remember, you are using the annotations to draw out the key points of the article, as well as focus on your interests and possible areas of confusion, which you will discuss with your teacher and your classmates before your final reflection on the article.

3. **Reflective Writing:** Consider the following quote from the article you just read:

   "Listen, it's not lost on anybody that about 95 percent of drugs that enter clinical testing fail to ever get approved," says Dr. Barron. "It's not hard to imagine that at least some of those might have failed because they work very, very well in a small group. We can't continue to have failures due to a lack of appreciation of this heterogeneity in diseases."

   Using evidence from the article and your knowledge of how clinical trials are run from the webquest you completed, respond to the following prompt, using formal paragraph structure:

   Why is it necessary to have regulations and strict controls in clinical trials? What are some weaknesses in the current clinical trial model that lead to the failure of 95% of the drugs that undergo clinical testing? Do you think the current clinical trial model should be changed? Why or why not?

_____

_____

_____

_____

_____

_____

_____

Clinical Trial Design

Combrestatin was discovered in the 1970s from the South African Bush Wallow. Combrestatin breaks down microtubules and prevents spindle formation.

1. What would be the effect of combrestatin on acute myeloid leukemia (AML) cells?

2. Design Phase I, II, III and IV double blind clinical trials to test the effects of combrestatin on in vitro AML cells. In your experiment be sure to include the following:

Independent Variable: _____

Dependent Variable: _____

Experimental Group (Arm): _____

_____

Control Group (Arm): _____

Clearly state the goal for each phase of the clinical trial:

Phase I:

Phase II:

Phase III:

Phase IV:

CLINICAL TRIAL DESIGN (PAGE 2)

Use the in class model and your knowledge of experimental design to complete the following clinical trial proposals:

Pazopanib is used to treat advanced renal cell carcinoma (RCC, a type of cancer that begins in the cells of the kidneys) in adults. Pazopanib is in a class of medications called tyrosine kinase inhibitors. It works by slowing or stopping the spread of cancer cells. Researchers want to see if pazopanib is also effective on AML cells. Design an experiment to test the effects of pazopanib on in vitro AML cells.

Scientists are studying the effects of bevacizumab (and angiogensis inhibitor) on colon cancer. They want to determine if adding bevacizumab to chemotherapy is more effective than chemotherapy alone. Design a Phase III clinical trial to determine which treatment method is more effective. Would this study be more effective as a double blind study? Why or why not?

Clinical Trial Design

Combrestatin was discovered in the 1970s from the South African Bush Wallow. Combrestatin breaks down microtubules and prevents spindle formation.

1. What would be the effect of combrestatin on acute myeloid leukemia (AML) cells?

Chromosomes would no longer be able to separate into sister chromatids, thus no viable cells would be produced from the cycles of cellular division under Combrestatin conditions.

2. Design Phase I, II, III and IV double blind clinical trials to test the effects of combrestatin on in vitro AML cells. In your experiment be sure to include the following:

Independent Variable: *combrestatin*

Dependent Variable: *CBC count (number of leukemia cells)*

Experimental Group (Arm): *Group that receives combrestatin (or group that receives combrestatin and standard care)*

Control Group (Arm): *Group that receives the standard care*

Clearly state the goal for each phase of the clinical trial.

Phase I: *Twenty patients would be enrolled in the Phase I trial. In the experimental group, ten of the patients would receive combrestatin and standard AML therapy. In the control group the other ten patients would receive only standard AML therapy. In order to make this a blind trial, the nurses would not know which patients were in each group or what medication they were administering (combrestatin or the placebo). The number of leukemia cells in a blood sample would be counted before the trial began and then each week for every patient for six months. In this trial patients would receive low doses of combrestatin because the purpose of a phase I trial is to determine if the drug is safe for human use. In order to control as many variables as possible (and make sure any differences between the two groups were due to the combrestatin and not any other factors) the patients in the two groups would have approximately the same age, gender and race distribution.*

Phase II: *If the drug was found to be safe in the Phase I trial, then a phase II trial would be conducted. Two Hundred patients would be enrolled in the Phase II trial. In the experimental group, 100 of the patients would receive combrestatin and standard AML therapy. In the control group the other 100 patients would receive only standard AML therapy. In order to make this a blind trial, the nurses would not know which patients were in each group or what medication they were administering (combrestatin or the placebo). The number of leukemia cells in a blood sample would be counted before the trial began and then each week for every patient for six months. This trial would increase the dose of combrestatin to determine its efficacy and side effects. In order to control as many variables as possible (and make sure any differences between the two groups were due to the combrestatin and not any other factors) the patients in the two groups would have approximately the same age, gender and race distribution.*

Phase III: *If the drug was found to be safe, effective, and did not produce severe side effects in the Phase II trial, then a phase III trial would be conducted. One thousand patients would be enrolled in the Phase III trial. In the experimental group, 500 of the patients would receive combrestatin and standard AML therapy. In the control group the other 500 patients would receive only standard AML therapy. In order to make this a blind trial, the nurses would not know which patients were in each group or what medication they were administering (combrestatin or the placebo). The number of leukemia cells in a blood sample would be counted before the trial began and then each week for every patient for six months. This trial continues to determine its efficacy and side effects of combrestatin. In order to control as many variables as possible (and make sure any differences between the two groups were due to the combrestatin and not any other factors) the patients in the two groups would have approximately the same age, gender and race distribution.*

CLINICAL TRIAL DESIGN (PAGE 2)

Phase IV: *If the drug was approved by the FDA and on the market, the drug company might conduct a phase IV trial. An even greater number of patients would be enrolled in the Phase IV trial. The purpose of the phase IV trial would be to gain additional information about the drugs side effects, benefits and optimal uses. There would be no control arm.*

Use the in class model and your knowledge of experimental design to complete the following clinical trial proposals:

Pazopanib is used to treat advanced renal cell carcinoma (RCC, a type of cancer that begins in the cells of the kidneys) in adults. Pazopanib is in a class of medications called tyrosine kinase inhibitors. It works by slowing or stopping the spread of cancer cells. Researchers want to see if pazopanib is also effective on AML cells. Design an experiment to test the effects of pazopanib on in vitro AML cells.

Independent Variable: pazopanib

Dependent Variable: number of cells that die (or conversely the number of living cells at the end of the experiment)

Experimental Group (Arm) cells that receives pazopanib

Control Group (Arm) cells that receive more media

Constants: cells grown in same media, cells incubated at the same temperature, cells grown in the same type of containers, receive the same amount of light

In this phase III trial four cell cultures each containing 4 million cells/ml (the same amount of cells) will be prepared. The cultures will contain the same media, incubated at the same temperature, be the same size and receive the same amount of light. Two of the cell cultures will be given 2μL of pazopanib everyday for one week and the two other cultures will be given 2 μL of media. At the end of the week the number of cells alive in each culture will be measured using the appropriate assay.

Scientists are studying the effects of bevacizumab (and angiogenesis inhibitor) on colon cancer. They want to determine if adding bevacizumab to chemotherapy is more effective than chemotherapy alone. Design a Phase III clinical trial to determine which treatment method is more effective. Would this study be more effective as a double blind study? Why or why not?

Independent Variable: bevacizumab

Dependent Variable: amount of cancer cells in biopsy sample

Experimental Group (Arm) Patients that receives bevacizumab and chemotherapy

Control Group (Arm) Patients that receive only chemotherapy

Constants: Patients would all have the same stage of colon cancer, be between the ages of 35-55 and approximately 50% of the subjects in each group would be female and 50% would be male.

One thousand patients would be enrolled in the Phase III trial. In the experimental group, 500 of the patients would receive bevacizumab and chemotherapy. In the control group the other 500 patients would receive only chemotherapy. The number of cancer cells in biopsy would be counted before the trial began and then each week for every patient for six months. In order to control as many variables as possible (and make sure any differences between the two groups were due to the combrestatin and not any other factors) the patients in the two groups would have approximately the same age, gender and race distribution.

I would know if the bevacizumab and chemotherapy were more effective then chemotherapy alone if the patients in the experimental group had a more significant reduction in the % of cancer cells in their biopsy samples than those patients in the control group who just received chemotherapy.

This study would be more effective as a double blind study, because it would eliminates bias and produces more objective results, since the expectations of the doctors, nurses and the patients about the experimental drug do not affect the outcome

Notes:

EXTENSION ACTIVITY:

Exploring Local Clinical Trials

5a

Extension Lesson Summary:

In this extension to Lesson Five, students will continue to investigate the process and purpose of clinical trials by searching for active clinical trials in their region on clincialtrials.gov.

Materials:

- Student Page: Clinical Trials Search
- Computers with Internet Access

Advance Preparation:

- Print Student Page: Clinical Trials Search (1 per student/student group)

Procedure and Discussion Questions with Time Estimates:

1. **(20-25 min)** Distribute Clinical Trial Search Worksheet to each student or student group. Instruct students they will be searching for clinical trials online and answering questions on the clinical trial search worksheet (can be completed as a group or individual activity)
2. **(8-10 min)** Have each student/student group share one clinical trial of interest with the whole class, using the worksheet as a guide, as a wrap up to the extension lesson.

Assessment Suggestions:

- Collect Student Page: Clinical Trials Search

Clinical Trials Search

Go to clinicaltrials.gov and click on the search for clinical trials link. Choose 2 types of cancer from the list below (or a type that is not listed, but that you are interested in) and search for clinical trials that are actively recruiting in the state. Answer the following questions for each clinical trial. You may need to use the glossary on the website to look up any vocabulary words you do not understand.
Suggested Cancer Types:

- Kaposi Sarcoma
- Astrocytomas, Childhood
- Chronic Myelogenous Leukemia (CML)
- Retinoblastoma
- Hepatocellular (Liver) Cancer
- Hodgkin Lymphoma
- Pancreatic Cancer
- Non-Hodgkin Leukemia
- Non-Small Cell Lung Cancer
- Ovarian Cancer
- Parathyroid Cancer
- Melanoma
- Merkel Cell Carcinoma
- Brain Stem Glioma, Childhood

1. What type of cancer did you choose? _____

Describe the basic characteristics of this type of cancer (check out the National Cancer Institute website at http://www.cancer.gov/cancertopics/types/alphalist) _____
_____
_____

What is the name of the clinical trial? _____

What phase is the clinical trial? _____

What is the purpose of the clinical trial? _____

How many patients is the trial enrolling? _____

What outcomes will the scientist measure _____
_____
_____

List at least three criteria patients must meet to be eligible for the trial. _____
_____

List three criteria that would make a patient ineligible for the trial. _____
_____

What locations is this trial being conducted in? _____

If you were diagnosed with this type of cancer would you participate in this clinical trial? Why or why not?
_____
_____
_____
_____

CLINICAL TRIALS SEARCH (PAGE 2)

2. What type of cancer did you choose? _____

Describe the basic characteristics of this type of cancer (check out the National Cancer Institute website at http://www.cancer.gov/cancertopics/types/alphalist) _____

_____

_____

What is the name of the clinical trial? _____

What phase is the clinical trial? _____

What is the purpose of the clinical trial? _____

How many patients is the trial enrolling? _____

What outcomes will the scientist measure _____

_____

_____

List at least three criteria patients must meet to be eligible for the trial. _____

_____

List three criteria that would make a patient ineligible for the trial. _____

_____

What locations is this trial being conducted in? _____

If you were diagnosed with this type of cancer would you participate in this clinical trial? Why or why not?

_____

_____

_____

_____

Notes:

Fighting the Battles: Conducting a Clinical Assay

6

Vocabulary:

In Vitro: studies in biology that are conducted using components of an organism that have been isolated from their usual biological surroundings in order to permit a more detailed or more convenient analysis than can be done with whole organisms. Simply "outside the body."

IC_{50}: a measure of how effective a drug is. It indicates how much of a particular drug or other substance is needed to inhibit a given biological process by half.

Serial dilution is the stepwise dilution of a substance in solution. Usually the dilution factor at each step is constant, resulting in a geometric progression of the concentration in a logarithmic fashion

Cytotoxicity: the quality of being toxic to cells Examples of toxic agents are chemicals used in chemotherapy, an immune cell or some types of venom.

Cell Culture Assay: is any method which is used to assess the cytotoxicity (toxicity to cells) of a material. This refers to the *in vitro* assessment of material to determine whether it releases toxic chemicals in sufficient quantities to kill cells either directly or indirectly through the inhibition of cell metabolic pathways. Cell culture evaluations are the precursor to whole animal studies and are a way to determine if significant cytotoxicity exists for the given material.

KEY QUESTION(S):
- What is the best dose of drug to obtain an IC_{50} death rate of cancer cells?

TIME ESTIMATE:
- Advanced Preparation: ~45 minutes:
- Student Procedure: 2 class period, ~45 minutes each

LEARNING STYLES:
- Visual and kinesthetic

Lesson Summary:

In this simulation assay students will perform a serial, log dilution of an anti-proliferation "drug" to determine the best dose to obtain a 50% death rate of cancer cells. Students will prep their dilutions and plate the "cells" on the first day. After a 24 hour "incubation" a colorimetric reagent will be added to the plate and students will visually determine the best dose of drug. Students will also be given a data set of values from an actual IC_{50} experiment on KG1 cancer cells to analyze and finally design a follow up experiment based on the data.

Student Learning Objectives:

The student will be able to...
1. Determine the best dose to obtain an IC_{50} in a simulated biotechnology assay.
2. Analyze data and graph sample data from an actual IC_{50} assay performed in a cancer research lab.
3. Design the next step in the IC_{50} experimental process, as if in preparation to take the drug to clinical trial.

Standards:

SC.912.L.16.10
SC.912.N.1.1
SC.912.N.1.5
SC.912.N.1.7
SC.912.N.3.5

Materials:

• Student Page: IC_{50} Assay Protocol & Analysis

Lab Materials (see advanced preparation for specifics)

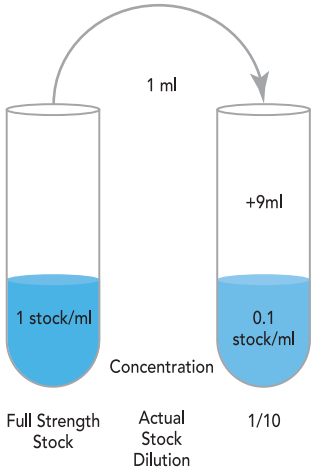
- Water (tap is fine) with yellow food coloring (1-2 drops per 15 ml water), ~5 ml per group in a 15 ml conical tube
  - o This will be referred to as the "cells in media"
- 1:1 ratio of pH 3 & pH 7 buffer (will create a ~4 pH solution), 200 µL per group, in an Eppendorf tube
  - o This will be referred to as the "drug stock"
- 1:1 ratio of 0.5% methyl red: 0.5% bromothymol blue, 100 µL per group, in an Eppendorf tube
  - o This is the colorimetric reagent
- To be used Day TWO Only!
- 1.5 ml Eppendorf tube (6 empty tubes per group)
- 96 well plate (1 per group)
- p200 pipettor and tips
- rack for Eppendorf tube

Background Information:

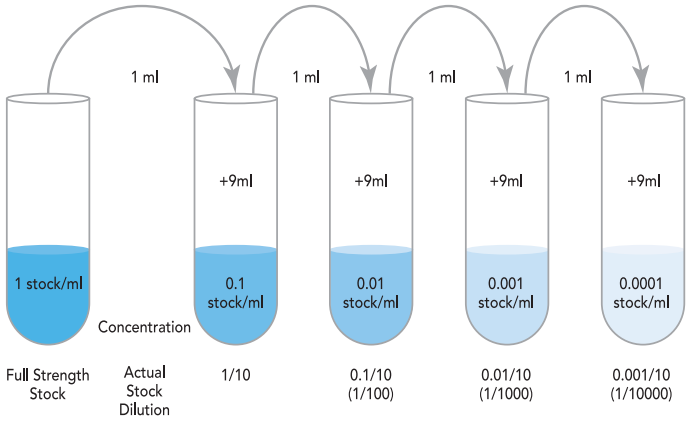
When researchers are developing a new drug to kill cancer cells they want to find the lowest dose of the drug that will successfully kill the cells, but not have as many side effects as higher doses. When researchers are testing a new drug in vitro they perform serial dilutions to determine the IC_{50} (the concentration of drug that kills 50% of the cells). Students will be using simulated solutions to perform serial dilutions of a "drug" and then perform an assay (modeled off of the XTT protocol) to determine the IC_{50} of the drug.

Part I Serial Dilutions

The first step in making a serial dilution is to take a known volume (usually 1 ml) of stock and place it into a known volume of distilled water (usually 9 ml). This produces 10 ml of the dilute solution. This dilute solution has 1 ml of extract /10 ml, producing a 10-fold dilution. (i.e. the amount of stock in each ml of the diluted solution is 0.1 ml.)



The technique used to make a single dilution is repeated sequentially using more and more dilute solutions as the "stock" solution. At each step, 1 ml of the previous dilution is added to 9 ml of distilled water. Each step results in a further 10-fold change in the concentration from the previous concentration.



The values shown in the tubes are the amount (in ml) of the stock solution present in each ml of the dilute solution.

The dilution of the original stock solution is shown below the tubes.
(Source http://biology.kenyon.edu/courses/biol09/tetrahymena/serialdilution2.htm)

Watch this serial dilution animation it is recommended you show this to students.
http://education.wichita.edu/saltymicro/ecology_interactives/serial_dilution.html

Part II Cell Assay

In research XTT can be effectively used in cell proliferation, cytotoxicity, and apoptosis assays. XTT is reduced to a soluble, brightly colored orange derivative by a mix of cellular effectors. Students will use simulated XTT to measure the effects of various doses of a "drug" on cell proliferation.

The XTT cell proliferation assay was first described in 1988 by Scudiero *et al.* (3) as an effective method to measure cell growth and drug sensitivity in tumor cell lines. XTT is a colorless or slightly yellow compound that when reduced becomes brightly orange. The plot of the XTT assay data should provide a curve with a linear portion. This is the area that will show the greatest sensitivity to changes induced by the experimental parameters. Absorbance values that are **higher** than control conditions indicate an **increase in cell proliferation** and viability. Absorbance values that are **lower** than control conditions indicate a **decrease in cell proliferation** and may be the result of cellular necrosis or apoptosis.

This is the specific XTT cell proliferation protocol used in the lab from ATTC manufacturing.
http://www.atcc.org/attachments/16747.pdf

Advance Preparation:

1. Print copies of the Student Page: IC_{50} Assay Protocol & Analysis (One per student)
2. Prepare enough materials per group (see Materials, above)

Procedure and Discussion Questions with Time Estimates:

TEACHER NOTE: *this simulation lab requires precise pipetting using a 96 well plate. If your classes are not familiar with using pipettemen, we strongly encourage you to do a practice with colored water, such as the Designer Plates (Bokor, 2012) activity prior to beginning Day ONE of Lesson Six. Bokor, J. (2012). You Sank My…Bacteriophage? The American Biology Teacher, 74(6), 422-423 and available at www.cpet.ufl.edu*

Day ONE:

1. **(1 min)** Pass out the Student Assay Protocols to each student, who should already be sitting in groups of 3-4.
2. **(1-2 min)** Explain to the students that they will be testing the effectiveness of a new anti-cancer drug that is preparing to go into a clinical trial to treat patients with AML. The industry standard is to calculate the IC_{50}, or the dose of drug that will kill 50% of the cancer cells. We will be testing this drug today, in vitro, in human cell culture, before the drug is administered to patients in the clinical trial.
3. **(3-4 min)** Briefly go over the Student Assay Protocols, ensuring students understand the serial dilution process and answer any questions students may have. *TEAHCER NOTE: See student protocol for specifics.*
4. **(30-40 min)** If materials are not already at the student tables, pass them out and allow students to begin.
   a. Circulate the room, assisting students when necessary.
5. **(1-2 min)** After each group has finished plating their assay, collect the plate to be "incubated" for 24 hours.

Day TWO:

1. **(1-2 min)** Return the assay plates to each group and provide them with a tube of the colorimetric reagent.
2. **(1-2 min)** Ensure students know how to apply the reagent to their plate and that students are aware of the post lab questions and data analysis.
3. **(40 min)** Circulate the room, assisting students as they read the colorimetric scale, determine their IC_{50} dose and then perform basic statistics on the sample data provided. Also, assist students in completing the experimental design element of the post lab.

Students should see the following result (but in triplicate):

Color Scale:
Red: No Cell Proliferation
Orange: Less than 25% Cell Proliferation
Yellow: 40-59% Cell Proliferation
Green: Over 60% Cell Proliferation

The 1000nM dose should produce the yellowish color, indicating 40-59% cell proliferation in that well, or the IC_{50} dose.

Background Information on Serial Dilutions

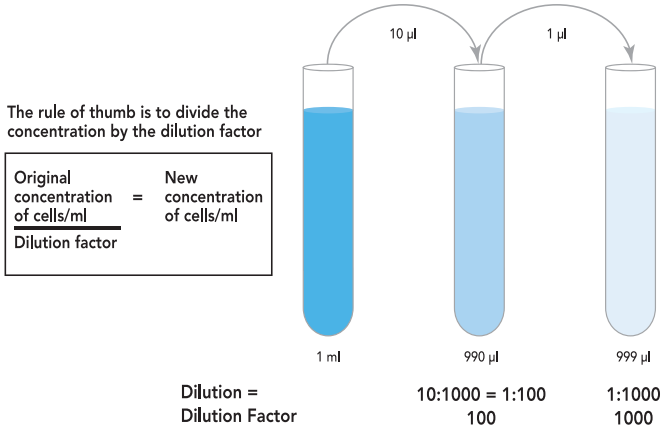
Dilutions

Understanding how to make dilutions is an essential skill for biologists. This skill is used, for example, in making solutions, diluting drugs, diluting bacteria, diluting antibodies, etc. A *simple dilution* is one in which a *unit volume* of a liquid material of interest is combined with an appropriate volume of a *solvent* liquid to achieve the desired concentration. The *dilution factor* is the total number of unit volumes in which your material will be dissolved. The diluted material must then be thoroughly mixed to achieve the true dilution. For example, a 1:5 dilution (verbalize as "1 to 5" dilution) entails combining 1 unit volume of ***solute*** (the material to be diluted) + 4 unit volumes of the ***solvent*** medium (hence, 1 + 4 = 5 = dilution factor). The dilution factor is frequently expressed using exponents: 1:5 would be 5e-1; 1:100 would be 10e-2, and so on.

Example 1: Frozen orange juice concentrate is usually diluted with 4 additional cans of cold water (the dilution solvent) giving a dilution factor of 5, i.e., the orange concentrate represents one unit volume to which you have added 4 more cans (same unit volumes) of water. So the orange concentrate is now distributed through 5 unit volumes. This would be called a 1:5 dilution, and the OJ is now 1/5 as concentrated as it was originally. So, in a simple dilution, *add one less unit volume of solvent* than the desired dilution factor value.

Example 2: Suppose you must prepare 400 ml of a disinfectant that requires 1:8 dilution from a concentrated stock solution with water. Divide the volume needed by the dilution factor (400 ml / 8 = 50 ml) to determine the unit volume. The dilution is then done as 50 ml concentrated disinfectant + 350 ml water.

Let's say you want to perform a *three step* 1:100 serial dilution of a drug (see figure below) Each step in this example uses a 1 ml total volume. The initial step combines 1 unit volume of drug (10 µl) with 99 unit volumes of media (990 µl) = 1:100 dilution. In the second step, one unit volume (10 µl) *of the 1:100 dilution* is combined with 99 unit (990 µl) volumes of media now yielding a total dilution of 1:100x100 = 1:10,000 dilution. Repeated again (the third step) the total dilution would be 1:100x10,000 = 1:1,000,000 total dilution. The concentration drug is now one million times *less* than in the original sample.



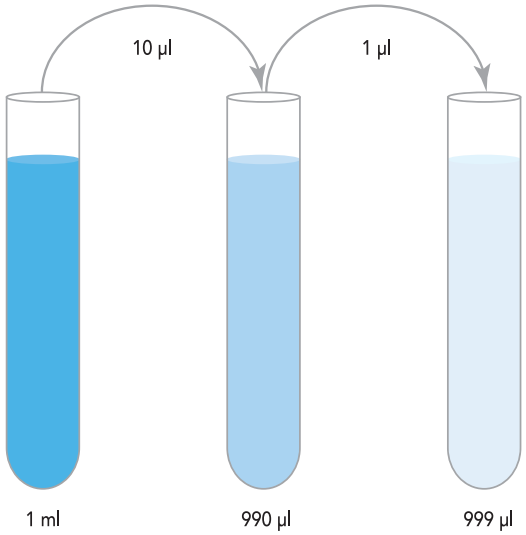
BACKGROUND INFORMATION ON SERIAL DILUTIONS (PAGE 2)

The most common examples deal with concentration of cells or organisms, or the concentration of a solute. The approximate concentration should be known at the start of the experiment before the appropriate number and amount of dilutions can be made. In order to arrive at the desired concentration, use serial dilutions, instead of making one big dilution, in order to finally arrive at the desired concentration. This method is not only cost effective but it also allows for small aliquots (amounts) to be diluted instead of unnecessarily large quantities of materials.

This technique involves the removal of a small amount of an original solution to another container which is then brought up to the original volume using the required buffer or water. In the example below, if you have 1 ml of your original solution and you remove 10 µL and place it in a tube containing 990 µL of water or media you have made a 1:100 dilution. If the original solution contained 5 x 10^8 organisms or cells/ml, we now have a concentration of 5 x 10^6 cells/ml, because we have simply divided our concentration by 100. Now, if we want to dilute this by a factor of 1:1000, we must remove 1 µL of the second solution and place it in a tube containing 999 µL of media. We have now diluted our secondary concentration by 1000, and would then divide our concentration by 1000 to yield a 5 x 10^3 cells/ml.

The rule of thumb is to divide the concentration by the dilution factor

$$\frac{\text{Original concentration of cells/ml}}{\text{Dilution factor}} = \text{New concentration of cells/ml}$$



Dilution =	10:1000 = 1:100	1:1000
Dilution Factor	100	1000

IC_{50} Assay Protocol & Analysis

Objective: To determine the best dose of drug that will obtain an IC_{50} death rate of cancer cells using a colorimetric scale.

Materials (per group):

DAY ONE	DAY TWO
• 1 15 ml conical tube with cells suspended in media (pale yellow in color) • 1 1.5 ml Eppendorf tube containing the drug stock • 6 empty 1.5ml Eppendorf tubes • 1 96 well plate • p200 pipettor with tips • Sharpie Pen	• 1 1.5 ml Eppendorf tube containing the colorimetric reagent • Incubated 96 well plate with treated cells

Protocol:
Day ONE:
1. Create the drug dilutions:
   a. Label the 6 empty1.5ml Eppendorf tubes as follows:

10000nM	1000nM	100nM	10nM	1nM	0.1nM

   b. Add 500µL of cells and media to each of the 6 labeled tubes

   c. Transfer 50µL of drug stock to the 10000nM, mix well, then transfer 50µL from the 10000nM to the 1000nM tube, mix well and repeat the last 4 dilutions in the same manor.

2. Plate the controls (drug stock and cells in media only) and treated drugs in triplicate as follows, 100µL per well:

	1	2	3	4	5	6	7	8
A	Drug Stock Control	Cells in Media Control	10000nM	1000nM	100nM	10nM	1nM	0.1nM
B	Drug Stock Control	Cells in Media Control	10000nM	1000nM	100nM	10nM	1nM	0.1nM
C	Drug Stock Control	Cells in Media Control	10000nM	1000nM	100nM	10nM	1nM	0.1nM

3. Incubate for 24 hours.

Day TWO:
1. Add 10µL of color metric reagent to each well.
2. Record the color change below:

Cell Contents	Drug Stock Control	Cells in Media Control	10000nM	1000nM	100nM	10nM	1nM	0.1nM
Color Change								

3. Color Scale:
   Red: No Cell Proliferation
   Orange: Less than 25% Cell Proliferation
   Yellow: 40-59% Cell Proliferation
   Green: Over 60% Cell Proliferation

Analysis:
1. What does the term IC_{50} mean? In your experiment which drug dose achieved IC_{50}? How do you know?

2. Which wells were the positive and negative controls? Why were positive and negative controls needed?

3. Below are the results of an actual drug trial on KG1 leukemia cells treated with the drug Pazopanib. The results show the % of cells that survived after 48 hours. Create a graph in Excel of the average survival percentage and use the graph to determine the IC_{50} of Pazopanib on KG1 cells. Print your graph and staple it to this paper.

	no drug	0.1 nM	1 nM	10 nM	100 nM	1000 nM	10000 nM
KG1-Trial 1	0.684567	0.337667	0.620767	0.491767	0.320167	0.251966647	0.328667
KG1-Trial 2	0.651067	0.638467	1.718467	0.526767	0.425267	0.23546668	0.108667
KG1-Trial 3	0.701467	0.998267	0.352767	0.961267	0.698967	0.400666638	0.049367

4. You are given a test tube containing 10 ml of a solution with 8.4 x 107 cells/ml. You are to produce a solution that contains less than 100 cells/ml. You are diluting the cells with water. How many 1:100 dilutions must you perform in order to arrive at the desired result? Show all work.

5. You have a microtube containing 1 ml of a solution with 4.3 x 104 cells/ml and you do two 1:100 dilutions. How many cells are in your final solution?

6. Sometimes it is necessary to use one solution to make a specific amount of a more dilute solution. To do this, you can use the formula:

   $V1C1 = V2C2$

   where:
   V1 = volume of starting solution needed to make the new solution
   C1 = concentration of starting solution
   V2 = final volume of new solution
   C2 = final concentration of new solution

   a. How would you make 10ml of a 1:10 dilution of a 1M drug solution (you are diluting the drug with media)?

   b. What would the final concentration of drug be from 1a above?

   c. How would you make 80 ml of a 1:20 dilution of a 1M drug solution?

   d. How would you make 50 ml of a 1:25 dilutions of a 1M drug solution?

Analysis Answer Key

1. What does the term IC_{50} mean? In your experiment which drug dose achieved IC_{50}? How do you know?

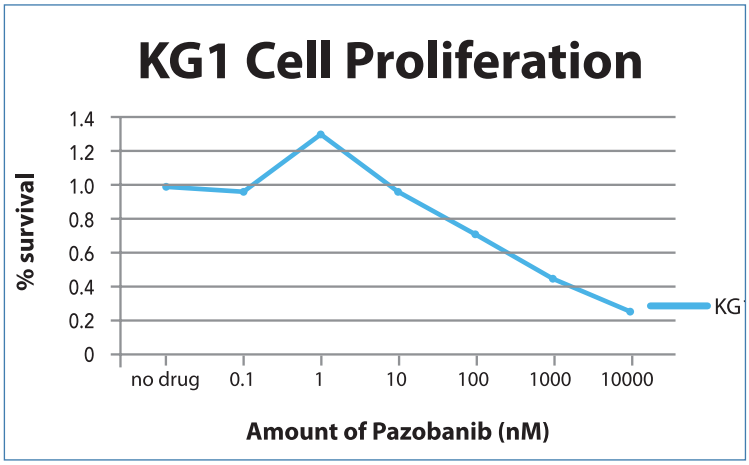
The IC_{50} indicates how much of a particular drug is needed to kill (stop proliferation) in 50% of the cells in a given sample. The 1000nM dose was, indicating 40-59% cell proliferation in that well, or the IC_{50} dose.

2. Which wells were the positive and negative controls? Why were positive and negative controls needed?

The well with drug only was the negative control and was expected to be red since no cells were added. If this well was any other color, it would indicate that there is something wrong with the experiment (contamination, bad reagents etc). The well with the cells only is the positive control and was expected to be green since no drug was added and all the cells were expected to live/proliferate. If the cells only well had been any other color it would have indicated that something was wrong with the experiment (contamination, problems with the cell line, bad reagents etc).

3. Below are the results of an actual drug trial on KG1 leukemia cells treated with the drug pazopanib. The results show the % of cells that survived after 48 hours. Create a graph of the average survival percentage and use the graph to determine the IC_{50} of pazopanib on KG1 cells.

	no drug	0.1 µL	1	10	100	1000	10000
Trial 1	0.684567	0.337667	0.620767	0.491767	0.320167	0.251966647	0.328667
Trial 2	0.651067	0.638467	1.718467	0.526767	0.425267	0.23546668	0.108667
Trial 3	0.701467	0.998267	0.352767	0.961267	0.698967	0.400666638	0.049367



The IC_{50} is approximately 500nM (where the line crosses the 50% survival mark)

4. You are given a test tube containing 10 ml of a solution with 8.4 x 107 cells/ml. You are to produce a solution that contains less than 100 cells/ml. You are diluting the cells with water. How many 1:100 dilutions must you perform in order to arrive at the desired result? Show all work.

You should perform a series of three 1:100 dilutions to yield 84 cells/ml.

1 ml of original solution to 99 ml of water = 8.4 x 105 cells/ml.

1 ml of second solution to 99 ml of water = 8.4 x 103 cells/ml.

1 ml of third solution to 99 ml of water = 8.4 x 101 or 84 cells/ml.

5. You have a microtube containing 1 ml of a solution with 4.3 x 104 cells/ml and you do two 1:100 dilutions. How many cells are in your final solution?

10 µL of original solution to 990 µL of water = 4.3 x 102 cells/ml

100 µL of second solution to 900 µL of water = 4.3 x 101 or 43 cells/ml

6. Sometimes it is necessary to use one solution to make a specific amount of a more dilute solution. To do this, you can use the formula:

$V_1C_1 = V_2C_2$

where:

V_1 = volume of starting solution needed to make the new solution

C_1 = concentration of starting solution

V_2 = final volume of new solution

C_2 = final concentration of new solution

a. How would you make 10 ml of a 1:10 dilution of a 1M drug solution (you are diluting the drug with media)?

1 ml of 1M drug + 9 ml of media

b. What would the final concentration of drug be from 1a above?

V_1 = 1 ml
C_1= 1M
V_2= 10 ml
C_2 =?
Use $V_1C_1 = V_2C_2$ to solve for C_2

C_2 =0.1M

c. How would you make 80 ml of a 1:20 dilution of a 1M drug solution?

V_1 = ?
C_1= 1M
V_2= 80 ml
C_2 =.05M
Use $V_1C_1 = V_2C_2$ to solve for V_1
V_1=0.1M

4 ml of 1M drug + 76 ml of media

d. How would you make 50 ml of a 1:25 dilutions of a 1M drug solution?

V_1 =?
C_1= 1M
V_2= 50 ml
C_2 =.04M (1M/25 = .04M)
Use $V_1C_1 = V_2C_2$ to solve for V_1
V_1=2 ml

2 ml of 1M drug + 48 ml of media

Notes:

Future Battles in the War on Cancer

7

Vocabulary:

Students will define five vocabulary words from each article.

Lesson Summary:

Using a reading guide, students work in groups to read a science article about some aspect of current cancer research and answer questions or write a summary of their article. Students then share their information during a whole class presentation. The articles are all about different types of experimental cancer treatment including drug treatments, vaccines and personalized medicine.

Student Learning Objectives:

The student will be able to...

1. Improve scientific literacy by reading current articles on cancer research.
2. Summarize information from a scientific article in their own words.
3. Orally present scientific information to an audience.

Standards:

SC.912.L.14.6
SC.912.L.16.8
SC.912.L.16.10
SC.912.N.1.1
SC.912.N.1.2
SC.912.N.1.3
SC.912.N.1.4
SC.912.N.1.5
SC.912.N.1.6
SC.912.N.1.7
SC.912.N.2.4
SC.912.N.2.5
SC.912.N.4.1
SC.912.N.4.2

Materials:

- Student Page: Article Reading Guide (Version I, which is more structured or Version II which is designed for more advanced students)
- Teacher Page: Rubric Lesson 7 Presentation of Journal Findings
- Selected articles for each student group (see below for suggestions for both standard and advanced students)

Standard Biology

Griffin, Catherine, "Every Day I'm Alive, It's A MIRACLE." *Good Housekeeping* 252.4 (2011): 59-67, *Academic Search Premier*. Web 21 July 2013.

Grady, Denise. "A Cell Therapy Shows Promise In a Leukemia." *New York Times* 14 Mar. 2013: A1(L). *Academic OneFile*. Web. 20 July 2013.

Hartocollis, Anemona. "Cancer Centers Racing to Map Patients' Genes." *New York Times* 22 Apr. 2013: A1(L). *Academic OneFile*. Web. 20 July 2013.

Harvard University. "New plan of attack in cancer fight: Two-drug combination, under certain circumstances, can eliminate disease." *ScienceDaily*, 19 Jul. 2013. Web. 21 Jul. 2013.

Kolata, Gina. "Tiny Patients, Major Goals." *New York Times* 11 June 2013: D1(L). *Academic OneFile*. Web. 20 July 2013.

KEY QUESTION(S):

- How do you read a scientific article for understanding?
- What does the future of cancer research look like?

TIME ESTIMATE:

- Two 50 minute class periods

LEARNING STYLES:

- Visual and auditory

Lilly Rothman, et al. "The Angelina Effect." *Time* 181(20): 28. *Academic Premier.* Web. 21. 21 July 2013

Mukherjee, Siddhartha. "I'm Sorry, Steve. I Wish We Had Done Better. " *Newsweek* 160.14/15 (2012): 50-53. *Academic Search Premier.* Web. 21 July 2013

Norris, Jeffrey. "Stem Cell Discovery Furthers Research on Cell-Based Therapy and Cancer." *University of California, San Francisco*. University of California, San Francisco, 19 July 2013. Web. 21 July 2013.

O'Connor, Anahad. "New Radiation Therapy Prolongs Prostate Cancer Survival." *New York Times* 17 July 2013: A15(L). *Academic OneFile*. Web. 20 July 2013.

Advanced Biology

Collins, Francis S., and Anna D. Barker, "Mapping the Cancer Genome." *Scientific American Special Edition,* 18.3 (2008): 22-29 *Academic Search Premier.* Web 21 July 2013

Duncan, David Ewing. "Your Cancer, Your Cure" *Discover* 33.9 (2012): 56-61. *Academic Search Premier.* Web. 21 July 2013

Jain, Rakesh K. "Taming Vessels to Treat Cancer." *Scientific American* 298.1 (2008): 56-63. *Academic Search Premier.* Web.21 July 2013

Strain, Daniel. "Crushing Cancer's Defenses."*Science News* 1790.10 (2011): 20-23. *Academic Search Premier.* Web 21 July 2013

Wilson, Claire. "Villages Of The DAMNED." *New Scientist* 218.2912 (2013): 34-37. *Academic Search Premier.* Web. 21 July 2013

Zimmer, Carl. "Studying tumors differently, in hopes of outsmarting them." *New York Times* 27 June 2013: NA(L). *Academic OneFile*. Web. 20 July 2013.

Background Information:

Reading and reviewing other scientific research is critical in both classic "bench research" as well as clinical/translational medicine; however it is a skill that can be frustrating to the novice. In this lesson, students will have guided practice reading introductory articles. The teacher will notice a broad variety of articles suggested for this lesson, to accommodate for a wide range of reading abilities in the class.

Advance Preparation:

1. Teacher should read through the procedure and all of the articles before class.
   NOTE: Selected articles are provided at the end of this lesson for teacher reference only. Copyright laws may prevent the copying and distribution to large numbers of students.
2. Teacher must chose Version I or Version II, based on student need and print enough corresponding article copies for each group, one article per student.
   NOTE: Version II was designed to be done individually, perhaps as homework in an advanced class, which would allow this lesson to be completed in one class period.
3. Print the appropriate Student Page: Article Reading Guide

Procedure and Discussion Questions with Time Estimates:

Day ONE

1. **(5-7 min)** Introduce the class to the activity by saying that they will be reading articles that describe advances in cancer treatment. Remind students that even though great progress has been made in treating and preventing cancer many thousands of people still die. (You may want to refer to the timeline). Show students the following quote (which is on the student worksheet version 1):

   "Well in our country," said Alice, still panting a little, "you'd generally get to somewhere else-if you ran very fast for a long time as we've been doing."

   "A slow sort of country!" said the Queen. "Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

   —Lewis Carroll, *Through the Looking Glass*

Ask students how this applies to cancer research. Guide students to establishing the following:

- Cancer is caused by multiple mutations in DNA. These mutations vary in different types of cancer and from individual to individual who have the same type of cancer.
- Therefore, it is unlikely that scientists will ever find one cure for cancer, and cancer will likely require individualized treatment.
- At the same time scientists are developing new treatments/drugs, new mutations are allowing cancers to evolve and become resistant to therapy.

2. **(30 min)** Pass out copies of the articles to each group (each group will read one article). Students should read the articles and answer the questions on the worksheet.

   a. Circulate around the room to assist students as they read, etc.

Day TWO

1. **(25-30 min)** Give each group 5 minutes to share the content of their articles with the entire class. Allow time for students in the audience to ask the group presenters questions.

   a. If using version II, ensure that students are grouped together based on the articles they read.

2. **(10 min)** Share this passage from *The Emperor of All Maladies* by Siddhartha Mukherjee:
   "Is the end of cancer conceivable in the future? Is it possible to eradicate the disease from our bodies and our societies forever?

   The answers to these questions are embedded in the biology of this incredible disease. Cancer, we have discovered, is stitched into our genome. Oncogenes arise from mutations in essential genes that regulate the growth of cells. Mutations accumulate in these genes where DNA is damaged by carcinogens, but also by seemingly random errors in copying genes when cells divide. The former might be preventable, but the later is endogenous. Cancer is a flaw in our growth, but this flaw is deeply entrenched in ourselves. We can rid ourselves of cancer, then, only as much as we can rid ourselves of the processes in our physiology that depend on growth-ageing, regeneration, healing, reproduction." (page 462)

3. **(3-4 min)** ***Optional*** Read the story of Germaine Berne on pages 467-470 in *The Emperor of All Maladies.* The story illustrates how the Red Queen phenomenon (introduced on Day 1) applies to cancer.

4. **(10-15 min)** Have students complete the same survey about cancer that they completed in Lesson 1. Pass back their original surveys and ask them to compare their answers. Lead a class discussion about what students have learned during the course of the unit.

As a written assignment you may assign a "questions journal" for homework about the five most important things they believe they learned during this unit. You may also ask students to write about ways in which this lesson personally/emotionally affected them.

Assessment Suggestions:

- To assess students understanding of the content in their articles you could collect the article worksheets and/or use the rubric on the following page to grade groups on their oral presentations to the class. We recommend completing one rubric for each student to assess students contribution to the group work in the "collaboration with peers" and "listens to others presentations" categories.
- Collect the students' journal entries to evaluate student learning for the entire unit.

Resources/References

- Mukherjee, Siddhartha. *The Emperor of All Maladies: A Biography of Cancer*. New York: Scribner, 2010. Print.
- NCI's cancer therapy fact sheets: www.cancer.gov/cancertopics/factsheet/
- Explore the Vanderbilt Ingram Cancer Database at mycancergenome.org

Rubric Lesson 7: Presentation of Journal Findings

CATEGORY	4	3	2	1
Content	Shows a full understanding of the topic.	Shows a good understanding of the topic.	Shows a good understanding of parts of the topic.	Does not seem to understand the topic very well.
Time-Limit	Presentation is 5-6 minutes long.	Presentation is 4 minutes long.	Presentation is 3 minutes long.	Presentation is less than 3 minutes OR more than 6 minutes.
Listens to Other Presentations	Listens intently. Does not make distracting noises or movements.	Listens intently but has one distracting noise or movement.	Sometimes does not appear to be listening but is not distracting.	Sometimes does not appear to be listening and has distracting noises or movements.
Vocabulary	Uses vocabulary appropriate for the audience. Extends audience vocabulary by defining words that might be new to most of the audience.	Uses vocabulary appropriate for the audience. Includes 1-2 words that might be new to most of the audience, but does not define them.	Uses vocabulary appropriate for the audience. Does not include any vocabulary that might be new to the audience.	Uses several (5 or more) words or phrases that are not understood by the audience.
Comprehension	Student is able to accurately answer almost all questions posed by classmates about the topic.	Student is able to accurately answer most questions posed by classmates about the topic.	Student is able to accurately answer a few questions posed by classmates about the topic.	Student is unable to accurately answer questions posed by classmates about the topic.
Collaboration with Peers	Almost always listens to, shares with, and supports the efforts of others in the group. Tries to keep people working well together.	Usually listens to, shares with, and supports the efforts of others in the group. Does not cause \"waves\" in the group.	Often listens to, shares with, and supports the efforts of others in the group but sometimes is not a good team member.	Rarely listens to, shares with, and supports the efforts of others in the group. Often is not a good team member.

Total: ____ / 24

Article Reading Guide Version 1

"Well in our country," said Alice, still panting a little, "you'd generally get to somewhere else-if you ran very fast for a long time as we've been doing."

"A slow sort of country!" said the Queen. "Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

—Lewis Carroll, *Through the Looking Glass*

Instructions: Read the article provided and answer the following questions as a group. As you read you may want to underline important information on your copy. All the answers to the questions must be in YOUR own words and NOT copied directly from the article. Be prepared to present the information from your article to the class.

1. Title: _____

   Author/s: _____

   Name of Journal: _____

   Date Published: _____

2. Define at least 5 vocabulary words from your article that you don't know (or, if there are not five that you don't know, choose five that are difficult) and write them with their definitions in the table below:

VOCABULARY WORD	DEFINITION

3. What was the purpose of the study/new clinical trial? Describe the science behind the study/clinical trial.

4. What question(s) were the scientists trying to answer?

5. How did the scientists test/implement the new treatment?

6. What conclusions or new information was learned in this study/clinical trial?

7. What other questions did the article bring up that need to be answered and/or what questions do you have after reading the article?

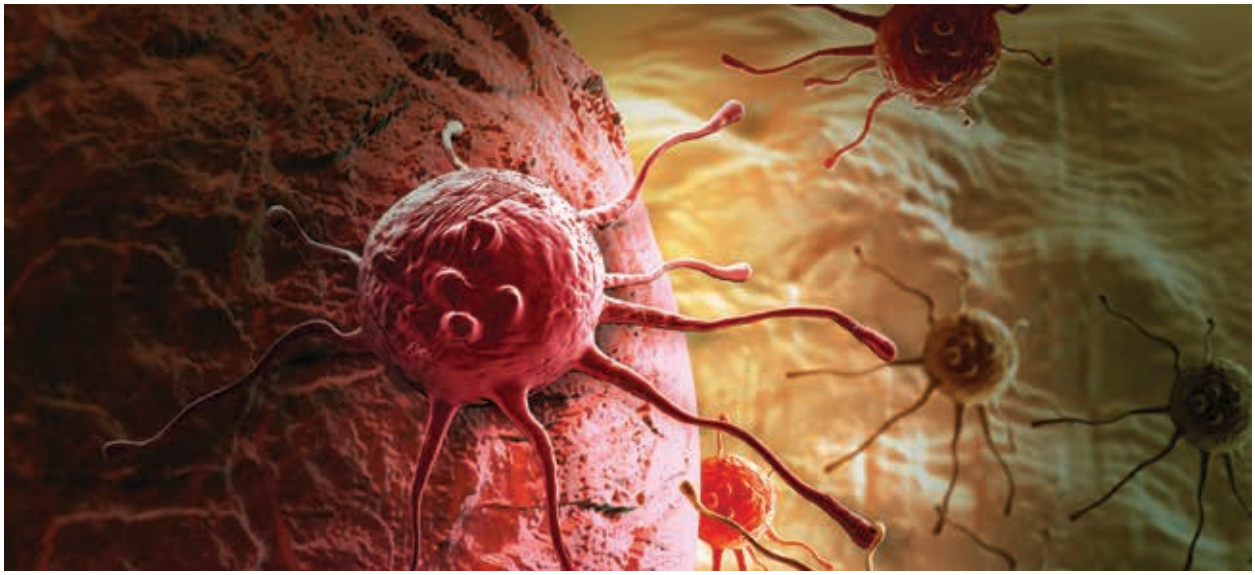
8. List at least two interesting facts your group learned from reading the article.

Article Reading Guide Version 11

"Well in our country," said Alice, still panting a little, "you'd generally get to somewhere else-if you ran very fast for a long time as we've been doing."

"A slow sort of country!" said the Queen. "Now, here, you see, it takes all the running you can do, to keep in the same place. If you want to get somewhere else, you must run at least twice as fast as that!"

—Lewis Carroll, *Through the Looking Glass*



Read the article and then write a summary that includes the following components:

Introduction: Introduce the article by describing or defining the major ideas that relate to cancer treatment covered in the article.

Content Summary: They key word here is *summary.* **Do not copy the content of the entire article.** What was the article all about? What were the main scientific concepts and ideas that were discussed? What was the question(s) the author was investigating? What methods did he/she use? If the article is about clinical trials make sure to specify what phase the clinical trials were in. What evidence was uncovered to support the main body of the article?

Evaluation: Restate the main areas of importance in the magazine article. With your perspective as a biology student, discuss the quality of the article with regard to its relevance, importance, readability, interest level, and scientific content. Explain how this article relates to information you have learned throughout the course of this unit.

You are expected to write using appropriate grammar, sentence structure and formatting. You are also expected to use your own words when summarizing; do not plagiarize!

Notes: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