The War of the 21st Century:
The Cell Cycle, Cancer and Clinical Trials
Authors: Jessica Mahoney & Jennifer Sunderman

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

Please direct inquiries to the Center for Precollegiate Education and Training at cpet@cpet.ufl.edu.

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INTRODUCTION
Cancer is a word that seems to exist in everyone’s vocabulary in the 21st century. We have at least one person in our lives that have 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 are striving to provide students with an opportunity to learn more about the mechanisms of cancer; that cancer is just a mutation of the cell cycle, and how translational medicine is leading the way to new, less invasive, treatments for cancer patients through clinical trials.

AUTHOR’S NOTE
Jennifer Sunderman and I 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 personal experience we can provide to our students and the heart touching stories woven into our material that students would not only be intrigued, they would be whole-heartily engaged in learning the material and perhaps 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 provide student driven, inquiry style material as well.

BIG IDEAS
1-Before drugs can be developed the mechanism of cancer must be understood.
2-Translational medicine is the application of traditional “bench research” to better the human condition and create novel treatments for many diseases, especially cancer.
2-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.
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 (Gap1, 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
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
Quick Check for Understanding: NobelpriZe.org: Control the Cell Cycle

LESSON FOUR: Loosing Control: The Cell Cycle and Cancer
Cell Cycle Interactive Wheel-What’s Gone and What Will that Mean?
Cancer Spotlight: Leukemia

LESSON FIVE: Going to War: Clinical Trials
Students will complete a short webquest to identify different stages of a clinical trial by exploring various ongoing clinical trials available on the ClinicalTrials.gov database

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
Since the 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.

45 minute periods

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<tr>
<th>Week 1</th>
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<th>Day 2</th>
<th>Day 3</th>
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<td>Week 2</td>
<td>Lesson 4 Loosing Control: The Cell Cycle and Cancer</td>
<td>Lesson 5 Going to War: Clinical Trials</td>
<td>Optional, but strongly suggested: Pipette Practice: Battleship on a 96 well plate</td>
<td>Lesson 6 Fighting the Battle: Conducting a Clinical Assay (Running the Lab)</td>
<td>Lesson 6 Fighting the Battle: Conducting a Clinical Assay (Analyzing the Results)</td>
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<td>Week 3</td>
<td>Lesson 7 In the Situation Room: Fighting Cancer in the Future (Analyzing Articles)</td>
<td>Lesson 7 In the Situation Room: Fighting Cancer in the Future (Reporting)</td>
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**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.

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

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

**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)

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

**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.

**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

**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 the mouth and intestines or cause hair to grow.

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

**Cyclin** - a family of proteins that control the progression of cells through the cell cycle by activating Cyclin-dependent kinase (CDK) enzymes.

**Cyclin-dependent kinases (CDKs)** - a family of protein kinases first discovered for their role in regulating the cell cycle

**Cytokinesis** - process by which the cytoplasm divides

**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.

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

**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 precedes cellular division.

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

**IC\textsubscript{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.

**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.”

**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.

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

**Mastectomy** – the 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.

**Metaphase** - second phase of mitosis, chromosomes align along the cell’s equator.

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

**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.

**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.

**P53** - tumor suppressor gene that expresses the protein p53.

**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*.

**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.

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

**Serial dilution** - 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.
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.

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.
## NEXT GENERATION SUNSHINE STATE STANDARDS – SCIENCE

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<td>SC.912.L.14.6</td>
<td>Explain the significance of genetic factors, environmental factors, and pathogenic agents to health from the perspectives of both individual and public health.</td>
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<td>SC.912.L.16.3</td>
<td>Describe the basic process of DNA replication and how it relates to the transmission and conservation of the genetic information.</td>
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<tr>
<td>SC.912.L.16.4</td>
<td>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.</td>
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<td>SC.912.L.16.8</td>
<td>Explain the relationship between mutation, cell cycle, and uncontrolled cell growth potentially resulting in cancer.</td>
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<td>SC.912.L.16.10</td>
<td>Evaluate the impact of biotechnology on the individual, society and the environment, including medical and ethical issues.</td>
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<td>SC.912.L.16.14</td>
<td>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.</td>
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<td>SC.912.L.18.11</td>
<td>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.</td>
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<td>SC.912.N.1.1</td>
<td>Define a problem based on a specific body of knowledge, for example: biology, chemistry, physics, and earth/space science, and do the following:</td>
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<td>SC.912.N.1.2</td>
<td>Describe and explain what characterizes science and its methods.</td>
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<td>SC.912.N.1.3</td>
<td>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.</td>
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<td>SC.912.N.1.4</td>
<td>Identify sources of information and assess their reliability according to the strict standards of scientific investigation.</td>
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<td>Benchmark</td>
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<tr>
<td>SC.912.N.1.5</td>
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<td>Describe and provide examples of how similar investigations conducted in many parts of the world result in the same outcome.</td>
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<td>SC.912.N.1.6</td>
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<td>Describe how scientific inferences are drawn from scientific observations and provide examples from the content being studied.</td>
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<td>SC.912.N.1.7</td>
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<td>Recognize the role of creativity in constructing scientific questions, methods and explanations.</td>
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<tr>
<td>SC.912.N.2.4</td>
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<td>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.</td>
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<td>SC.912.N.2.5</td>
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<td>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.</td>
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<td>SC.912.N.3.5</td>
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<td>Describe the function of models in science, and identify the wide range of models used in science.</td>
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<td>SC.912.N.4.1</td>
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<td>Explain how scientific knowledge and reasoning provide an empirically-based perspective to inform society's decision making.</td>
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<td>SC.912.N.4.2</td>
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<td>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.</td>
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LESSON ONE: CANCER WARRIORS-A PERSONAL STORY OF TRANSLATIONAL MEDICINE

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?

OVERALL 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

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 the 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

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
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 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 there 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 poles. (Note polls are automatically deleted after 30 days)

PROCEDURE AND DISCUSSION QUESTIONS WITH TIME ESTIMATES:
Day ONE:
1. (1-2 minutes) 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 minutes) 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 and 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 minutes) 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 questions to share their responses)

4. (25 minutes) 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 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.

### How To Vote via Texting

**EXAMPLE**

1. Standard texting rates only (worst case US $0.20)
2. We have no access to your phone number
3. Capitalization doesn’t matter, but spaces and spelling do
How To Vote via PollEv.com

TIP  Capitalization doesn’t matter, but spaces and spelling do

Day TWO:
1.  (5-7 minutes) 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 minutes 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 minutes) 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 minutes) 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 minutes) 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
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.

<table>
<thead>
<tr>
<th>STATEMENTS ABOUT CANCER</th>
<th>YOUR RESPONSE (1, 2, 3, OR 4)</th>
<th>CLASS RESPONSE (RECORD THE NUMBER OF STUDENTS WHO RESPONDED WITH EACH NUMBER ABOVE THE NUMBER)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If your parents had cancer, so will you.</td>
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<td>1 2 3 4</td>
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<tr>
<td>2. If you find an abnormal lump on your body, it must be cancer.</td>
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<td>1 2 3 4</td>
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<td>3. It is possible to have cancer without exhibiting any symptoms or warning signs.</td>
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<td>1 2 3 4</td>
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<tr>
<td>4. Young peoples’ lifestyles affect their chances of getting cancer later in life.</td>
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<td>1 2 3 4</td>
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<td>5. Cancer that has metastasized (spread throughout the body) is fatal.</td>
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<td>1 2 3 4</td>
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<td>6. Everyone with the same type of cancer gets the same kind of treatment.</td>
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<td>1 2 3 4</td>
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<tr>
<td>7. The only treatments for cancer are surgery, radiation, and chemotherapy.</td>
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<td>1 2 3 4</td>
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<td>8. Some types of cancer are contagious.</td>
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<tr>
<td>10. Cancer is caused by changes in genetic material.</td>
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<td>11. Tumors must have a blood supply to survive.</td>
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<tr>
<td>12. Only elderly people develop cancer.</td>
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<tr>
<td>13. New cancer fighting drugs move through clinical trials quickly.</td>
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<tr>
<td>14. Many mutations are required for someone to develop cancer.</td>
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<td></td>
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<tr>
<td>15. Once a patient enters remission, they are cured of cancer.</td>
<td></td>
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</table>
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?

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. What is the benefit of having strict protocols during clinical trials if it means some patients must be taken off them, thus losing access to the new treatment procedure?

15. Based on the material presented in Cancer Warrior, what is “translational medicine?”
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.”*

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 that 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.

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 angiogenesis inhibiting molecules.

14. 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? 
   A clinical trial is a highly controlled experiment; you can only test one variable at a time.
In the summer of 1990, Barbara Bradfield, a forty-eight-year-old woman from Burbank, California, discovered a mass in her breast and a lump under her arm. A biopsy confirmed what she had already suspected: she had breast cancer that had spread to her lymph nodes. She was treated with a bilateral mastectomy followed by nearly seven months of chemotherapy. "When I was finished with all that," she recalled, "I felt as if I had crossed a river of tragedy."

But there was more river to ford: Bradfield's life was hit by yet another incommensurate tragedy. In the winter of 1991, driving on a highway not far from their house, her daughter, twenty-three years old and pregnant, was killed in a fiery accident. A few months later, sitting numbly in a Bible-study class one morning, Bradfield let her fingers wander up to the edge of her neck. A new grape-size mass had appeared just above her collarbone. Her breast cancer had relapsed and metastasized—almost certainly a harbinger of death.

Bradfield's oncologist in Burbank offered her more chemotherapy, but she declined it. She enrolled in an alternative herbal therapy program and bought a vegetable juicer and planned a trip to Mexico. When her oncologist asked if he could send samples of her breast cancer to Dr. Slamon's lab at UCLA for a second opinion, she agreed reluctantly. A faraway doctor performing unfamiliar tests on her tumor sample, she knew could not possibly affect her.

One afternoon in the summer of 1991, Bradfield received a phone call from Slamon. He introduced himself as a researcher who had been analyzing her slides. Slamon told Bradfield about Her-2. "His tone changed," she recalled. Her tumor, he said, had one of the highest levels of amplified Her-2 that he had ever seen. Slamon told her that he was launching a trial for a new drug. Bradfield refused. "I was at the end of my road," she said, "and I had accepted what seemed inevitable." Slamon tried to reason with her for awhile, but found her unbending. He thanked her for her consideration and rang off.

Early the next morning, though, Slamon was back on the telephone. He apologized for the intrusion, but her decision had troubled him all night. Of all the variants of Her-2 amplification that he had encountered, hers had truly been extraordinary; Bradfield's tumor was chock full of Her-2, almost hypnotically drunk on the oncogene. He begged her once again to join his trial.

"Survivors look back and see omens, messages they missed," Joan Didion wrote. For Bradfield, Slamon's second phone call was an omen that was not missed; something in that conversation pierced through a shield that she had drawn around herself. On a warm August morning in 1992, Bradfield visited Slamon in his clinic at UCLA. He met her in the hallway and led her to a room in the back. Under the microscope, he showed her the breast cancer that had been excised from her body, with its dark ring-lets of Her-2 labeled cells. On a whiteboard, he drew a step-by-step picture of an epic scientific journey. He began with the discovery of neu (an oncogene found in rats, the human homolog is Her-2)...the struggles to produce a drug, culminating in the antibody (Herceptin) stitched together so carefully...Bradfield considered the line that stretched from oncogene to drug. She agreed to join Slamon's trial.
It was an extraordinary fortunate decision. In the four months between Slamon's phone call and the first infusion of Herceptin, Bradfield's tumor had erupted, spraying sixteen new masses into her lungs.

Fifteen women, including Bradfield, enrolled in Slamon's trial at UCLA in 1992. (The number would later be expanded to thirty-seven). The drug was given for nine weeks, in combination with cisplatin, a standard chemotherapy agent used to kill breast cancer cells, both delivered intravenously. As a matter of convenience, Slamon planned to treat all the women on the same day in the same room. The effect was theatrical; this was a stage occupied a beleaguered set of actors. Some women had begged and finagled their way into Slamon's trial through friends and relatives; other such as Bradfield, had been begged to join it. "All of us knew that we were living on borrowed time," Bradfield said, "and so we felt twice as alive and lived twice as fiercely." A Chinese woman in her fifties brought stash after stash of traditional herbs and salves that she swore had kept her alive thus far; she would take oncology's newest drug, Herceptin, only if she could take its most ancient drugs with it. A frail, thin woman in her thirties, recently relapsed with breast cancer after a bone marrow transplant, glowered silently and intensely in a corner. Some treated their illnesses reverentially. Some were bewildered, some too embittered to care. A mother from Boston in her midfifties cracked raunchy jokes about her cancer. The daylong drill of infusions and blood tests was exhausting. In the late evening after all the tests, the women went their own ways. Bradfield went home and prayed. Another woman soused herself with martinis.

The lump on Bradfield's neck-the only tumor in the group that could be physically touched, measure and watched- became the compass for the trial. On the morning of the first intravenous infusion of the Her-2 antibody, all the women came up to feel the lump, one by one, running their hands across Bradfield's collarbone. It was a peculiarly intimate ritual that would be repeated every week. Two weeks after the first dose of the antibody, when the group filed past Bradfield, touching the node again, the change was incontrovertible. Bradfield's tumor had softened and visibly shrunk. "We began to believe that something was happening here, Bradfield recalled."Suddenly the weight of our good fortune hit us."

Not everyone was as fortunate as Bradfield. Exhausted and nauseous one evening, the young woman with relapsed metastatic cancer was unable to keep the fluids down needed to hydrate her body. She vomited through the night and then, too tired to keep drinking and too sick to understand the consequences, fell back into sleep. She died of kidney failure the next week.

Bradfield's extraordinary response continued. When the CT scans were repeated two months into the trial, the tumor in her neck had virtually disappeared and the lung metastases had also diminished both in number and size. The responses in many of the thirteen other women were more ambiguous. At the three-month midpoint of the trial, when Slamon reviewed the data with Genentech (the drug manufacturer) and the external trial monitors, tough decisions clearly needed to be made. Tumors had remained unchanged in size in some women-not shrunk, but static; was this to be counted as a positive response? Some women with bone metastasis reported diminished bone pain, but pain could not be objectively judged. After a prolonged and bitter debate, the trial coordinators suggested dropping seven of the women from the study because their responses could not be quantified. One woman
discontinued the drug herself. Only five of the original cohort, including Bradfield, continued the trial to its six-month endpoint. Embittered and disappointed, the others returned to their local oncologists, their hopes for a miracle drug again dashed.

Barbara Bradfield finished eighteen weeks of therapy in 1993. She survives today. A gray-haired woman with crystalline gray-blue eyes, she lives in the small town of Pyallup near Seattle, hikes in the nearby woods, and leads discussion groups for her church. She vividly remembers her days at the Los Angeles clinic—the half lit room in the back where the nurses dosed the drugs, the strangely intimate touch of the other women feeling the node in her neck. And Slamon of course. "Dennis is my hero," she said. "I refused his first phone call, but I have never, ever refused him anything since that time." The animation in energy in her voice crackled across the phone line like an electrical current. She quizzed me about my research. I thanked her for her time, but she, in turn, apologized for the distraction. "Get back to work," she said laughing. "There are people waiting for discoveries."

Note: Barbara Bradfield's 10th Anniversary of being in remission is featured on the her2 support group webpage at http://her2support.org/community/member-stories/216-barbaras-10th-anniversary-page
LESSON TWO: PREPARING FOR WAR: A HISTORY OF CANCER

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

OVERALL TIME ESTIMATE:
- Advanced Preparation: 45 minutes (25 minutes to assemble timeline pieces; 20 minutes background reading)
- Student Procedure: One 50 minute period

LEARNING STYLES: Visual, auditory and kinesthetic

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.

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

STANDARDS:
SC.912.L.14.6
SC.912.L.16.8
SC.912.L.16.10
SC.912.N.1.1
SC.912.N.1.3
SC.912.N.1.5
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)

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:
1. Prepare the student timeline cards for each student group. For extended use, consider cardstock and/or laminating.
2. Prepare the wall timeline cards. You may want to print these in color. For extended use, consider cardstock and/or laminating.
3. Make copies of the student worksheet, one per student or student group.
4. 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 minutes) Discuss student responses to journal questions from Lesson One and answer any student questions about Cancer Warrior

2. (2 minutes) 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 minutes) Once students are assembled in groups of 2-4 and settled, distribute one envelope of time line cards to each group.

3. (15-20 minutes) 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. (20 minutes) 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... 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.

EXTENSIONS:

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

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 a rare kind of cancer called a gastrointestinal stromal tumor (GIST). The story ends with the author thoughts on our struggle against cancer and could lead to some interesting class discussions. The story is on pages 467-470 of the book.

RESOURCES/REFERENCES:


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 woman'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.
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.

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.

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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 woman'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.
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.

460-377BCE
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.

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.

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Name: ________________________________  
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<table>
<thead>
<tr>
<th>Date</th>
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</tr>
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<tbody>
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<tr>
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<tr>
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</tr>
<tr>
<td>1890</td>
<td>Surgeons begin performing radical mastectomies.</td>
</tr>
<tr>
<td>1896</td>
<td>High doses of radiation are used to treat tumors.</td>
</tr>
<tr>
<td>1937</td>
<td>The National Cancer Institute is created.</td>
</tr>
<tr>
<td>1938</td>
<td>Scientists begin studying the use of chemicals (chemotherapy) as a treatment for cancer.</td>
</tr>
<tr>
<td>1948</td>
<td>Dr. Sydney Farber creates the Jimmy Fund, a cancer advocacy organization.</td>
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<td>1950s</td>
<td>Studies linking smoking and lung cancer are published.</td>
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<td>Nixon declares a &quot;War on Cancer&quot; and signs the National Cancer Act.</td>
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<td>1976</td>
<td>The first oncogene (gene that can cause cancer) is discovered.</td>
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<tr>
<td>1981</td>
<td>A study showing that simple mastectomies are just as effective (and have a lower rate of mortality) as radical mastectomies is published.</td>
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<tr>
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<td>Year</td>
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LESSON THREE: KEEPING IT ALL IN CHECK: THE LIFE OF A CELL IN THE CELL CYCLE

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?

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

LEARNING STYLE(S): Visual, auditory and kinesthetic

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

Cyclin - a family of proteins that control the progression of cells through the cell cycle by activating Cyclin-dependent kinase (CDK) enzymes.

Cyclin-dependent kinases (CDKs) - a family of protein kinases first discovered for their role in regulating the cell cycle

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 envelop reforms, chromosomes uncoil and spindle fibers disassemble.

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.

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.

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

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/Markers
- Teacher Answer Key (Completed Cell Cycle Diagram)

BACKGROUND INFORMATION:
The three following webpages were used to prepare this lesson. A surface review of each one should be sufficient for the instruction of the lesson:
The Cell Cycle
The Eukaryotic Cell Cycle and the Genetics of Cancer by Phillip McClean
Cell Cycle, on Wikipedia (correct citations present and verified)

ADVANCE PREPARATION:
1. Review background information about the cell cycle and checkpoints
2. Print student handouts
3. Transfer large, blank cell cycle 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 the blank cell cycle diagram onto a white board or smart board for class discussion.

PROCEDURE AND DISCUSSION QUESTIONS WITH TIME ESTIMATES:
1. (Before class starts) Pass out large, blank cell cycle and a roll of tape to each student group.

2. (1-2 minutes) 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 minutes) 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. (6-8 minutes) Pass out the second set of labeling cards and give students ~5-7 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 in the right direction if necessary.

5. (10-12 minutes) Pass out the third set of labeling cards and instruct students to correctly place G₀ ("gee-zero") on the diagram (after Gap 1). Allow ~10 minutes 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 if necessary.

6. (8-10 minutes) Finally 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, etc.

7. (5 minutes) Explain to students that collectively the genes that control the checkpoints are referred to as Proto-oncogenes. (Trigger students’ background vocabulary by asking “What type of doctor works with cancer patients?” Answer: Oncologist...aka Onco=Cancer, therefore Proto-Oncogenes mean—roughly—genes that prevent cancer). Students should recall the Src gene (pronounced "sarc" as it is short for sarcoma) from Lesson Two. Another set of genes involved in the control of the regular cell division are the tumor suppressor genes. The most common gene is P53. Studies have found that over 50% of all human cancers have some sort of mutation in the P53 gene segment.
   TEACHER NOTE: The p53 protein senses DNA damage and can halt progression of the cell cycle in G₁ (by blocking the activity of Cdk2). Both copies of the p53 gene must be mutated for this to fail so mutations in p53 are recessive, and p53 qualifies as a tumor suppressor gene.
   a. Encourage students to record this information on the margin of their Student Handout
   b. After the class discussion is complete ensure students leave group diagrams intact and store them for the following day/ Lesson 4.

8. (10 minutes) After review/discussion is over give students ~8-10 minutes to play the NoblePrize.org game: Control the Cycle
   Implementation Note: The game only takes ~4 minutes to play, if all the correct choices are made on the first round, however the timeframe also includes reading the instructions, background information and introduction into how damage to the cell cycle can lead to cancer, the topic for Lesson 4.

ASSESSMENT SUGGESTIONS:
- Student Handout can be collected to access 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.

EXTENSIONS:

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

RESOURCES/REFERENCES:

GROUP HANDOUT: 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.
STUDENT LABELING CARDS: SET ONE—THE BASICS

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

<table>
<thead>
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<th>Cellular Division</th>
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<tbody>
<tr>
<td>Prophase</td>
<td>Metaphase</td>
</tr>
<tr>
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<td>Telophase</td>
</tr>
<tr>
<td>Cytokinesis</td>
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**STUDENT LABELING CARDS: SET TWO-STAGES OF INTERPHASE**

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<table>
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<tbody>
<tr>
<td>• Cells Grow</td>
<td>• Cells Grow</td>
<td>DNA is Replicated</td>
</tr>
<tr>
<td>• Organelles are Replicated</td>
<td>• Cells carry out their normal function, depending on cell type</td>
<td></td>
</tr>
<tr>
<td>• Cells carry out their normal function, depending on cell type</td>
<td>• Cells prepare to divide</td>
<td></td>
</tr>
</tbody>
</table>
STUDENT LABELING CARDS: SET THREE: CHECKPOINTS

Note: Print on colored paper (preferably different from Set One and 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 G₀, or delay division for a short period of time.
- Considers if the environment is suitable for cellular proliferation
- Controlled by Cyclin/CDK interactions

### Post Replication
- Screens DNA for mutations
- Controlled by *chk1* gene
  - Some evidence indicates *BRCA1* tumor suppressor plays a role in the activation of human *chk1*

### Spindle Assembly (SAC)
- Monitors the interaction between improperly connected kinetochores and spindle microtubules
- Controlled by measurement of tension between sister kinetochores

### G₀
- Normal Cell Function until cellular reproduction is required.
Proto-Oncogene

Tumor Suppressor Gene
Spindle Assembly (SA):
- Monitors the interaction between improperly connected kinetochores and spindle microtubules.
- Controlled by the checkpoint of tension between sister kinetochores.

Gap 1 (G1):
- Cells Grow
- Organelles are Replicated
- Cells carry out their normal function, depending on cell type

Restriction Point:
- Determines if a cell should divide, enter G0, or delay division for a short period of time.
- Considers if the environment is suitable for cellular proliferation.
- Controlled by Cyclin/CDK interactions.

Synthesis (S-phase):
- DNA is Replicated

Gap 2 (G2):
- Cells Grow
- Cells carry out their normal function, depending on cell type
- Cells prepare to divide

Go:
- Normal Cell Function until cellular reproduction is required.
LESSON FOUR: LOOSING CONTROL: THE CELL CYCLE AND CANCER

KEY QUESTION(S): When mutations arise in proto-oncopgenes what changes occur in 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? How many mutations might be necessary for cancer to develop?

OVERALL TIME ESTIMATE:
- Advanced Preparation: ~30 minutes:
- Student Procedure: One 50 minute period

LEARNING STYLES: Visual, auditory and kinesthetic

VOCABULARY:
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.

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

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.

LESSON SUMMARY: Videos from National Institutes of Health “Cell Biology and Cancer” curriculum will be used to prompt comparisons of normal cell “behavior” versus a cancerous cell. Students will use knowledge of the cell cycle and checkpoints from Lesson Three to predict how mutations at various checkpoints will affect the progress of a cell through the stages of the cell cycle and cellular division, eventually determining when cancer could develop. Students will also explore the relationships between patients, doctors, bench researchers, drug companies, and the IRB as an individual with relapsed leukemia enters a clinical trial.

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.
3. Identify the relationship patterns between individuals involved in clinical trials.

STANDARDS:
SC.912.L.16.3
SC.912.L.16.4
SC.912.L.16.8
SC.912.L.16.10
SC.912.L.16.14
SC.912.N.4.1
SC.912.N.4.2

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 Scenario Cards
• Computers with internet access
• Clinical Trials Web Cards
• Ball of string

BACKGROUND INFORMATION:
Got the Learn Genetics "Dropping Signals" page at http://learn.genetics.utah.edu/content/begin/cells/signals/ and click on the cancer for different examples of how signals can disrupt the cell cycle and cause cancer.


A very detailed description of the checkpoints of the cell cycle from The National Center for Biotechnology (NCBI) can be found at http://www.ncbi.nlm.nih.gov/books/NBK26856/

ADVANCE PREPARATION:
• Print Student Page: What Happens When Genes Lose Control? (one per student)
• Prepare student scenario cards by printing them on colored paper and possibly laminating for future use.
• Prepare Clinical Trials Web cards by printing them on colored paper, cutting between the “speaker paragraphs” and possibly laminating for future use.
• Download the You Tube video "It's Too Late to Apoptize" if you do not have access to You Tube in the classroom.

PROCEDURE AND DISCUSSION QUESTIONS WITH TIME ESTIMATES:
1. (5-7 minutes) Show the cell cycle animation videos (1-3, 5) from National Institutes of Health “Cell Biology and Cancer” curriculum Student Activities 2-Cancer and the Cell Cycle.
   a. Briefly ask students to summarize each video and address any questions/misconceptions.

2. (10-12 minutes) Pass back group cell cycle diagrams from Lesson 3 and copies of the student page What Happens When Genes Lose Control?
   a. Randomly pass out a student scenario card to each group and instruct students to identify where in the cell cycle, or genes controlling cellular reproduction, their scenario would make a change and what could happen to the cell cycle control after that change occurred, using their completed Cell Cycle Diagrams as a reference.
   b. Students will record the change from the scenario card under the cause column on their What Happens When Genes Lose Control? student page and what the possible outcome of that change is under the effect column. TEACHER NOTE: Essentially the students should determine if the cell cycle is compromised and cancer will develop. See the Teacher Page: What Happens When Genes Lose Control? for more details.
   c. Circulate around the groups, ensuring each group considers all the possibilities their scenario card would provide and nudging them towards the intended outcome if necessary.
   d. If some groups seem to finish faster than others, give them a second card and the “challenge” of layering the two cards together to determine their combined effect on the cell cycle.

3. (5-10 minutes) ask each group to share what was on their card (the cause) and what effect they think it had on the cell cycle. Instruct the rest of the class to record each group’s resulting “cause & effect” on their student page: What Happens When Genes Lose Control?
4. (3 minutes) As a wrap up to this section show students the "It's Too Late to Apoptize Video" at http://youtu.be/mHOX43-4PvE

5. (10-12 minutes) Instruct students to form a circle, facing into the center. TEACHER NOTE: I like to allow my students to sit on top of the desks for this type of activity, but standing is fine too. Pass out the Clinical Trials Web cards randomly to students ensuring that the three “John” cards go to the same student and the cards are equally distributed amongst the students (not all clumped at one end of the circle, for example). Students must figure out 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.

ASSESSMENT SUGGESTIONS:

- Collect Student Page: What Happens When Genes Lose Control?
- Instruct students to create a concept map showing the relationship between the individuals portrayed in the Clinical Trials Web activity.

EXTENSIONS:

- Students research and make career fair posters for members of the Clinical Trials Web activity.

RESOURCES/REFERENCES:

**CELL CYCLE & CANCER SCENARIO CARDS**

**TEACHER NOTE:** you may want to create two “sets” of the scenario cards, to ensure all groups can receive a combination of two “minor” mutations, one major mutation, a minor and a major mutation, etc. Remember, the purpose of this activity to ensure student understanding that one mutation doesn’t necessarily cause cancer. It is a combination of multiple small mutations, one very large mutation or some other combination.

| Minor mutation in the SAC. Tension measurement is still functional. | Major mutation in the SAC. Tension measurement is no longer functional. |
| Minor mutation in the cylcin gene. Gene is still functional | Major mutation in the cylcin gene. Gene is no longer functional |
| Minor mutation in the chk1 gene. Gene is still functional | Major mutation in the chk1 gene. Gene is no longer functional |
STUDENT PAGE: 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 scenario card (the cause).

<table>
<thead>
<tr>
<th>Cause</th>
<th>Effect</th>
</tr>
</thead>
</table>


### TEACHER PAGE: WHAT HAPPENS WHEN GENES LOSE CONTROL?

<table>
<thead>
<tr>
<th>Cause</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor mutation in the P53 tumor suppressor gene. Gene is still functional.</td>
<td>Gene is still functional, so cell cycle will continue at a steady pace, controlled by P53.</td>
</tr>
<tr>
<td>Major mutation in the P53 tumor suppressor gene. Gene is no longer functional.</td>
<td>Gene is no longer functional, so cell division speeds may increase, allowing for cell proliferation with damage in cell size, etc.</td>
</tr>
<tr>
<td>Minor mutation in the Scr proto-oncogene. Gene is still functional.</td>
<td>Gene is still functional, so cells will continue to divide as normal and damaged cells will under apoptosis, as usual.</td>
</tr>
<tr>
<td>Major mutation in the Scr proto-oncogene. Gene is no longer functional.</td>
<td>Gene is no longer functional, so cellular division may speed up, or slow down depending on other environmental factors. Also damaged cells will no longer undergo apoptosis, allowing them to grown and eventually divide as well, creating more damaged cells.</td>
</tr>
<tr>
<td>Minor mutation in the SAC. Tension measurement is still functional.</td>
<td>Chromosomes will continue to split normally into chromatids and cell division will continue, unchanged.</td>
</tr>
<tr>
<td>Major mutation in the SAC. Tension measurement is no longer functional.</td>
<td>Chromosomes will not split into sister chromatids, causing multiploidy cells, which may continue to reproduce and divide, depending on other possible mutations in the checkpoints.</td>
</tr>
<tr>
<td>Minor mutation in the cyclin gene. Gene is still functional</td>
<td>Gene is still functional, no change in the cell cycle.</td>
</tr>
<tr>
<td>Major mutation in the cyclin gene. Gene is no longer functional</td>
<td>Gene is no longer functional; cells might not pause to grow properly during G1 and will continue on in the cell cycle regardless of size and organelle development issues.</td>
</tr>
<tr>
<td>Minor mutation in the chk1 gene. Gene is still functional</td>
<td>Gene is still functional and should continue to check newly synthesized DNA for mutations and ensure the cell is ready to enter cellular division.</td>
</tr>
<tr>
<td>Major mutation in the chk1 gene. Gene is no longer functional</td>
<td>Gene is not functional and will no longer check newly synthesized DNA for mutations allowing the cell to enter cellular division w/ critical DNA mutations.</td>
</tr>
</tbody>
</table>
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 ($45,000 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.

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. (Source)

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 who are not candidates for more chemotherapy or have relapsed after a 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. (Source: Med City News February 24, 2012 http://medcitynews.com/2012/02/sanofis-viehbacher-thinks-big-pharma-will-seek-earlier-stage-deals-heres-why/)

**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.
LESSON FIVE: GOING TO WAR: CLINICAL TRIALS

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?

OVERALL TIME ESTIMATE: One 50 minute period

LEARNING STYLES: Visual and auditory

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 - 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

LESSON SUMMARY: Students complete a webquest to learn about clinical trials as homework the night before the lesson. During class time students research current clinical trials and then practice designing their own clinical trials.

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.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:
• Computers with internet access
• Copies of student webquest (1 copy for each student)
• Copies of clinical trial search worksheet (1 copy per student)
• Copies of Experimental Design worksheet (1 copy per student)

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:

1. Teacher should read through the entire preparation and familiarize themselves with the clinicaltrials.gov site.
2. Make copies of webquest, clinical trial and experimental design worksheets for each student.

PROCEDURE AND DISCUSSION QUESTIONS WITH TIME ESTIMATES:

1. Assign the clinical trials webquest as homework the night before the lesson (or this can be completed in during class time in about 30 minutes)
2. (5 minutes) 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.
3. Distribute Clinical Trial Search Worksheet to each student or student group.
4. (20 minutes) Tell students they will search for clinical trials on line and answer questions on the clinical trial search worksheet (can be completed as a group or individual activity)
5. (25 minutes) Students will practice designing scientific experiments from given scenarios. Complete problem one as a whole class.
Divide the class into four groups and have each group design one phase of the clinical trial.
Discuss the answers as a whole class. Make sure to highlight the goal of each phase of the trial.
Students then complete the remaining two activities in class or as homework for extra practice and to demonstrate mastery.

ASSESSMENT SUGGESTIONS:

- Teachers could collect the wequest worksheet to assess student knowledge of clinical trials.
- Teachers should collect the experimental design worksheet to assess student's understanding of placebos, control groups and the importance of well designed experiments.

EXTENSIONS:

- Students can explore the importance of patient participation in clinical trials using this The New York Times article: [http://www.nytimes.com/2009/08/03/health/research/03trials.html?pagewanted=all](http://www.nytimes.com/2009/08/03/health/research/03trials.html?pagewanted=all)

RESOURCES/REFERENCES:

- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
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.

<table>
<thead>
<tr>
<th>Phase</th>
<th>Description of What Happens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-Clinical</td>
<td>Lab and Animal Studies</td>
</tr>
<tr>
<td>Phase I</td>
<td></td>
</tr>
<tr>
<td>Phase II</td>
<td></td>
</tr>
<tr>
<td>Phase III</td>
<td></td>
</tr>
<tr>
<td>Phase IV</td>
<td></td>
</tr>
</tbody>
</table>

2. List and describe the five different types of clinical trials used in class research.

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.

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

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

Go to [http://clinicaltrials.gov/ct2/info/glossary](http://clinicaltrials.gov/ct2/info/glossary) and define the following terms

Randomized Trial -

Blind -

Double Blind -

Placebo -
Go to [http://www.cancer.gov/cancertopics/factsheet/Information/clinical-trials](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.

   ![Diagram of clinical trial phases]

2. List and describe the five different types of clinical trials used in cancer research.

   **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.

<table>
<thead>
<tr>
<th>Benefits</th>
<th>Risks</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Access to promising new interventions that are generally not available outside of a clinical trial.</td>
<td>• The new intervention being studied may not be better than standard therapy, or it may have harmful side effects.</td>
</tr>
<tr>
<td>• The intervention being studied may be more effective than standard therapy.</td>
<td>• 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.</td>
</tr>
<tr>
<td>• Trial participants receive regular and careful medical attention from a research team that includes doctors, nurses, and other health professionals.</td>
<td>• Health insurance may not cover all patient care costs in a trial.</td>
</tr>
<tr>
<td>• The results of the trial may help other people who need cancer treatment in the future.</td>
<td>•</td>
</tr>
<tr>
<td>• Trial participants are helping scientists learn more about cancer</td>
<td></td>
</tr>
</tbody>
</table>

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 get involved.

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.
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](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?

___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________
___________________________________________________________________________

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

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

2. Design a 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

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

1. What would 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 a 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.

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 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 2\(\mu\)L of pazopanib everyday for one week and the two other cultures will be given 2 \(\mu\)L 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 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? How would you know whether bevacizumab was more effective than chemotherapy alone? Why or why not?

**Independent Variable:** bevacizumab  
**Dependent Variable:** amount of cancer cells in biopsy sample

**Experimental Group (Arm)** Patients that receive 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.
LESSON SIX: FIGHTING THE BATTLES: CONDUCTING A CLINICAL ASSAY

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

OVERALL TIME ESTIMATE:
- Advanced Preparation: ~45 minutes:
- Student Procedure: Two 50 minute periods

LEARNING STYLES: Visual and kinesthetic

VOCABULARY:
Cell Culture Assay- is any method which is used to assess the cytotoxicity (toxicity to cells) of a material. This refers to the \textit{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.

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.

half maximal inhibitory concentration (IC\textsubscript{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.

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.”

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

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\textsubscript{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\textsubscript{50} in a simulated biotechnology assay.
2. Analyze data and graph sample data from an actual IC\textsubscript{50} assay performed in a cancer research lab.
3. Design the next step in the IC\textsubscript{50} experimental process, as if in preparation to take the drug to clinical trial.

STANDARDS:
SC.912.L.16.8
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<sub>50</sub> Assay Protocol & Analysis
- Computer access with Excel

Lab Materials (see advanced preparation for specifics)
- Water (tap is fine) with yellow food coloring (1-2 drops per 15mL water), ~5mL per group in a 15mL conical tube
  - 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), 200μL per group, in an Eppendorf tube
  - This will be referred to as the “drug stock”
- 1:1 ratio of 0.5% methyl red: 0.5% bromothymol blue, 100μL per group, in an Eppendorf tube
  - This is the colorimetric reagent
  - To be used Day TWO Only!
- 1.5mL Eppendorf tube (6 empty tubes per group)
- 96 well plate (1 per group)
- p1000 pipettor with tips
- 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 effectively kill the cells, while reducing side effects. When researchers are testing a new drug in vitro they perform serial dilutions to determine the IC<sub>50</sub> (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-see below for details) to determine the IC<sub>50</sub> of the drug.

Part I Serial Dilutions

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

The technique used to make a single dilution is repeated sequentially using more and more dilute solutions as the "stock" solution. At each step, 1ml of the previous dilution is added to 9ml 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.
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: IC50 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 pmicropipettes, we strongly encourage you to do a practice with colored water, such as the Designer Battleship Plates activity prior to beginning Day ONE of Lesson Six.

Day ONE:
1. (1 minute) Pass out the Student Assay Protocols to each student, who should already be sitting in groups of 3-4.

2. (1-2 minutes) 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 IC50, 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 minutes) Briefly go over the Student Assay Protocols, ensuring students understand the serial dilution process and answer any questions students may have. TEACHER NOTE: See student protocol for specifics.

4. (30-40 minutes) 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 minutes) After each group has finished plating their assay, collect the plate to be “incubated” for 24 hours.

Day TWO:
1. (1-2 minutes) Return the assay plates to each group and provide them with a tube of the colorimetric reagent.
2. (1-2 minutes) 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 minutes) Circulate the room, assisting students as they read the colorimetric scale, determine their IC50 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 Image]

**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 IC50 dose.
Dilutions
Understanding how to make dilutions is an essential skill for scientists, in both research and industry. 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.
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 \(5 \times 10^8\) organisms or cells/mL, we now have a concentration of \(5 \times 10^6\) 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 \(5 \times 10^3\) cells/mL.
**Objective:** To determine the best dose of drug that will obtain an IC\textsubscript{50} death rate of cancer cells using a colorimetric scale.

**Materials** (per group):

<table>
<thead>
<tr>
<th>Day ONE:</th>
<th>Day TWO:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - 15mL conical tube with cells suspended in media (pale yellow in color)</td>
<td>1 - 1.5mL Eppendorf tube containing the colorimetric reagent Incubated 96 well plate with treated cells</td>
</tr>
<tr>
<td>1 - 1.5mL Eppendorf tube containing the drug stock</td>
<td></td>
</tr>
<tr>
<td>6 empty 1.5mL Eppendorf tubes</td>
<td></td>
</tr>
<tr>
<td>1 - 96 well plate</td>
<td></td>
</tr>
<tr>
<td>p1000 pipettor with tips</td>
<td></td>
</tr>
<tr>
<td>p200 pipettor with tips</td>
<td></td>
</tr>
<tr>
<td>Sharpie Pen</td>
<td></td>
</tr>
</tbody>
</table>

**Protocol:**

**Day ONE:**

1. Create the drug dilutions:
   a. Label the 6 empty 1.5mL Eppendorf tubes as follows:
      10000nM, 1000nM, 100nM, 10nM, 1nM, 0.1nM
   b. Add 500\mu L of cells and media to each of the 6 labeled tubes
   c. Transfer 50\mu L of drug stock to the 10000nM, mix well, then transfer 50\mu L 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, 100\mu L per well:

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Drug Stock Control</td>
<td>Cells in Media Control</td>
<td>10000nM</td>
<td>1000nM</td>
<td>100nM</td>
<td>10nM</td>
<td>1nM</td>
<td>0.1nM</td>
</tr>
<tr>
<td>B</td>
<td>Drug Stock Control</td>
<td>Cells in Media Control</td>
<td>10000nM</td>
<td>1000nM</td>
<td>100nM</td>
<td>10nM</td>
<td>1nM</td>
<td>0.1nM</td>
</tr>
<tr>
<td>C</td>
<td>Drug Stock Control</td>
<td>Cells in Media Control</td>
<td>10000nM</td>
<td>1000nM</td>
<td>100nM</td>
<td>10nM</td>
<td>1nM</td>
<td>0.1nM</td>
</tr>
</tbody>
</table>
3. Incubate for 24 hours.

Day TWO:
  1. Add 10μL of color metric reagent to each well.

  2. Record the color change below:

<table>
<thead>
<tr>
<th>Cell Contents</th>
<th>Drug Stock Control</th>
<th>Cells in Media Control</th>
<th>10000nM</th>
<th>1000nM</th>
<th>100nM</th>
<th>10nM</th>
<th>1nM</th>
<th>0.1nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Color Change</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 percentage 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.

<table>
<thead>
<tr>
<th>KG1-Trial</th>
<th>no drug</th>
<th>0.1 nM</th>
<th>1 nM</th>
<th>10 nM</th>
<th>100 nM</th>
<th>1000 nM</th>
<th>10000 nM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>0.684567</td>
<td>0.337667</td>
<td>0.620767</td>
<td>0.491767</td>
<td>0.320167</td>
<td>0.25196647</td>
<td>0.328667</td>
</tr>
<tr>
<td>Trial 2</td>
<td>0.651067</td>
<td>0.638467</td>
<td>1.718467</td>
<td>0.526767</td>
<td>0.425267</td>
<td>0.23546668</td>
<td>0.108667</td>
</tr>
<tr>
<td>Trial 3</td>
<td>0.701467</td>
<td>0.998267</td>
<td>0.352767</td>
<td>0.961267</td>
<td>0.698967</td>
<td>0.400666638</td>
<td>0.049367</td>
</tr>
</tbody>
</table>
4. You are given a test tube containing 10 mL of a solution with $8.4 \times 10^7$ 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 $4.3 \times 10^4$ 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:

$$V_1C_1 = V_2C_2$$

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)?

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?
TEACHER: IC\textsubscript{50} ANALYSIS ANSWER KEY

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

The IC\textsubscript{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\textsubscript{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\textsubscript{50} of pazopanib on KG1 cells.

<table>
<thead>
<tr>
<th></th>
<th>no drug</th>
<th>0.1 µL</th>
<th>1</th>
<th>10</th>
<th>100</th>
<th>1000</th>
<th>10000</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trial 1</td>
<td>0.684567</td>
<td>0.33767</td>
<td>0.620767</td>
<td>0.491767</td>
<td>0.320167</td>
<td>0.251966647</td>
<td>0.328667</td>
</tr>
<tr>
<td>Trial 2</td>
<td>0.651067</td>
<td>0.638467</td>
<td>1.718467</td>
<td>0.526767</td>
<td>0.425267</td>
<td>0.23546668</td>
<td>0.108667</td>
</tr>
<tr>
<td>Trial 3</td>
<td>0.701467</td>
<td>0.998267</td>
<td>0.352767</td>
<td>0.961267</td>
<td>0.698967</td>
<td>0.400666638</td>
<td>0.049367</td>
</tr>
</tbody>
</table>

The IC\textsubscript{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 $8.4 \times 10^7$ 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 = $8.4 \times 10^5$ cells/mL.
   1 mL of second solution to 99 mL of water = $8.4 \times 10^3$ cells/mL.
   1 mL of third solution to 99 mL of water = $8.4 \times 10^1$ or 84 cells/mL.

5. You have a microtube containing 1 mL of a solution with $4.3 \times 10^4$ 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 = $4.3 \times 10^2$ cells/mL.
   100 µL of second solution to 900 µL of water = $4.3 \times 10^1$ 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:
   \[ V_1 = \text{volume of starting solution needed to make the new solution} \]
   \[ C_1 = \text{concentration of starting solution} \]
   \[ V_2 = \text{final volume of new solution} \]
   \[ C_2 = \text{final concentration of new solution} \]

   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?
      \[ V_1 = 1 \text{mL} \]
      \[ C_1 = 1 \text{M} \]
      \[ V_2 = 10 \text{mL} \]
      \[ C_2 = ? \]

      Use \[ V_1C_1 = V_2C_2 \] to solve for \[ C_2 \]
      \[ C_2 = 0.1 \text{M} \]

   c. How would you make 80 mL of a 1:20 dilution of a 1M drug solution?
      \[ V_1 = ? \]
      \[ C_1 = 1 \text{M} \]
      \[ V_2 = 80 \text{mL} \]
\[ C_2 = .05M \]
Use \[V_1C_1 = V_2C_2\] to solve for \[V_1\]
\[V_1 = 0.1M\]

**4mL of 1M drug + 76mL of media**

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

\[V_1 = ?\]
\[C_1 = 1M\]
\[V_2 = 50mL\]
\[C_2 = .04M\] (1M/25 = .04M)
Use \[V_1C_1 = V_2C_2\] to solve for \[V_1\]
\[V_1 = 2 mL\]

**2mL of 1M drug + 48mL of media**
LESSON SEVEN: FUTURE BATTLES IN THE WAR ON CANCER

KEY QUESTION(S): How do you read a scientific article for understanding? What does the future of cancer research look like?

OVERALL TIME ESTIMATE: Two 50 minute class periods

LEARNING STYLES: Visual and auditory

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 (Pick from 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
- Copies of the following articles:
  - "A Triumph in the War Against Cancer" Smithsonian Magazine, May 2011
  - "Unraveling Complex Genetic Stories in Cancer Cells May Lead to Personalized Treatment" Science News, September 24, 2011
  - "Everyday I'm Alive It's A Miracle", Good Housekeeping, April 2011 (available on Academic Search Premiere)
  - "Taming Vessels to Treat Cancer", Scientific American, January 2008
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 minutes) 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 minutes) 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 minutes) 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 minutes) 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 minutes) 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 minutes) 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.
   a. 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:

- NCI’s cancer therapy fact sheets: www.cancer.gov/cancertopics/factsheet/
- Explore the Vanderbilt Ingram Cancer Database at mycancergenome.org
**TEACHER PAGE: RUBRIC LESSON 7 PRESENTATION OF JOURNAL FINDINGS**

Name ____________________________________

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

Total ____________/24
"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

<table>
<thead>
<tr>
<th>Vocabulary Word</th>
<th>Definition</th>
</tr>
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<tbody>
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</table>
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.
"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!
Vaccine approval offers hope while other armies muster
Twirling globs of white blood cells circle a tumor like a Greek
army ready to lay siege. These cells are used to winning—they
take down baddies such as viruses and bacteria on a daily basis.
But cancer cells are not an ordinary enemy. Like Troy, they set
up hefty barricades against attack, often killing white blood cells
or turning them off on the spot. Too often, the immune system
loses this Trojan War.

But recent advances in therapeutic cancer vaccine research may provide the immune system
with an offensive edge. Such therapies aren't the same as the shots kids get before starting
school to prevent measles or polio. Nor are they like antiviral vaccines, such as Gardasil, that
stave off infections which can lead to cancer. Therapeutic cancer vaccines wouldn't prevent
cancer, they would treat it: training the immune system to turn its forces on a tumor already in
the body with the skill of Achilles and the strength of Ajax.

At least that has been the hope. For about a decade, large clinical trials of cancer vaccine
candidates have turned out mostly disappointing. But now a handful of new therapies are
showing signs that the cancer vaccine effort could be on the brink of big breakthroughs.
"The whole field is a lot more encouraged now," says Jay Berzofsky, chief of the National Cancer
Institute's Vaccine Branch in Bethesda, Md. "It warrants a lot more investment."

After a long search, scientists have hit on a few possible vaccines that seem to do some good. In
2010, the U.S. Food and Drug Administration gave the final OK to its first cancer vaccine, a
prostate cancer therapy called Provenge.

A second treatment now in large clinical trials could revive fading hopes for a melanoma
vaccine. At the same time, many scientists now acknowledge that vaccines probably can't do
the job alone. Two new therapies, which aren't vaccines but do duck tumor defenses and
ultimately spur on the immune system, show promise in their own right and may make natural
allies for cancer vaccines.

Though the gains have yet to match many doctors' hopes, Provenge and other immune-
energizing drugs have given terminal cancer patients months of life as part of clinical trials.
"That's when you know the idea is no longer just an attractive idea," says Glenn Dranoff, an
oncologist at the Dana-Farber Cancer Institute in Boston. "Now, you have proof."
Coley's vaccine
The proof may be new, but the idea behind cancer vaccines is not. A New York City surgeon named William Coley was enthralled in the late 1800s by the story of a male cancer patient who came down with a severe infection, then saw his tumor shrink dramatically. Coley decided to put the power of the fever to the test, injecting cancer patients with shots of killed pathogens, including strep bacteria. The strange thing: In many patients, it worked.

"These were patients with advanced inoperable cancer," says epidemiologist Stephen Hoption Cann of the University of British Columbia in Vancouver. "They would be considered, by and large, incurable by today's standards."

Still, Coley's findings didn't gain much traction; instead radiation and chemotherapy became the hot treatments in oncology. But by the 1980s and '90s, researchers were frustrated because such therapies couldn't slow many malignant diseases. More and more teams turned to Coley's old battle plan.

The current thinking is that infections kick the immune system into overdrive. White blood cells go after pathogens in force, causing a lot of collateral damage to tumors in the process. Today's proposed vaccines are better sharpshooters than Coley's original cocktail, targeting tumors specifically or at least limiting the damage in healthy organs. Some vaccines include whole cancer cells killed with radiation, while others contain a brew of proteins native to tumors. A few package such proteins into viruses.

To rev up the body to attack, many of these new vaccines focus on activating immune players called dendritic cells. Among other roles, these spy cells gather intelligence on potential baddies, from free-floating proteins to whole parasites. These spies return worrisome finds to a type of white blood cell called T cells. T cells, the soldier cells, then divide rapidly and go on the offensive, looking for cells or substances that match the spies' intel.

But because cancer cells grow from normal tissue, they often look like good guys. To clue the spy cells in to big tumors, oncologists need to fix the intel.

Provenge and beyond
And that's exactly what the team that designed the cancer vaccine Provenge did. Doctors prepare the vaccine cocktail by taking dendritic cells and similar immune players directly from a patient and mixing them with proteins that sit atop prostate cells, says Philip Kantoff, an oncologist with Dana-Farber. The mixture goes back into the patient's bloodstream where, scientists think, the dendritic spies present the prostate proteins to immune soldier cells. That convinces the immune system to treat the prostate cells as an enemy, like it would a common virus. Vaccine researchers had previously tried this strategy and a range of others with little success. But Provenge differed from the long list of misfires in one key respect: "It actually worked," Kantoff says.
In a Phase III trial—a large, controlled study, often the last step before FDA approval—Kantoff and his colleagues dosed 330 prostate cancer patients with customized versions of Provenge. The team also treated 167 patients with a placebo. Patients received traditional therapies before and after vaccine treatment.

Individuals given Provenge survived for a median of about four months longer than placebo patients, nearly 26 months from when they enrolled in the study instead of about 22 months. The vaccine is obviously doing something right, Kantoff says. Curiously, though, tumors appeared to grow or spread equally fast regardless of the treatment, an observation Kantoff attributes to a monitoring failure.

The team published its results in July 2010 in the New England Journal of Medicine, and Provenge got the nod from the FDA later that year.

Before Provenge, the prospects for cancer vaccines looked grim, says Guido Forni, an immunologist at the University of Turin in Italy. "The field was very depressed." But today, he says, it's a different story. "Many, many people who were skeptical of vaccines are now inspired by this research to work again."

But despite the advances, the benefits have been modest, Forni acknowledges. Provenge is better than chemotherapy alone, which gives about a two- to three-month bump to survival, but not by much. Vaccines like Provenge also rely on a patient's own cells, and that customization can get pricey, says Leisha Emens, an oncologist at Johns Hopkins University. Next-generation treatments that tip off spy cells in the body with general ingredients from the lab could be thriftier options, she says.

One of many new therapies that takes this approach has its sights set on skin cancer. Every year, 132,000 people worldwide develop malignant melanoma, according to a World Health Organization estimate. And for many the outlook is poor. Advanced melanoma sufferers survive for a median of only six months from diagnosis. Today, "the melanoma vaccine situation is pretty barren," says Jeffrey Weber, a melanoma specialist at the Moffitt Cancer Center in Tampa, Fla.

Weber, however, has some hope for the MAGE-A3 vaccine, a drug developed by the pharmaceutical company GlaxoSmithKline that he has worked with in the clinic. The treatment is a one-size-fits-all cocktail of flags mimicking proteins found on tumor cells (but not normal tissue) mixed with a few immune-boosting chemicals. Though the company has focused largely on melanoma and lung cancer, the same protein flags sit on a laundry list of other cancer cells, says Vincent Brichard, head of GlaxoSmithKline's Belgium-based immunotherapeutics team. That means, if it works in further studies, the vaccine could one day treat a range of diseases including liver and bladder cancer.
Unlike Provenge, GSK's shot hasn't proved itself on the big stage. In a preliminary trial including 182 patients who underwent lung tumor removal surgery, tumor recurrence was delayed by 33 percent in MAGE-A3 recipients compared with those given placebo. But the improvement could have been due to chance. Brichard will be better able to evaluate the drug's potential for success during two ongoing Phase III trials—one for melanoma and one for lung cancer—that look at thousands of patients. Early trials have already unearthed an encouraging detail, says Brichard. A suite of genes in tumors may reveal which patients will respond well to the vaccine and which won't. These cues could help oncologists tailor therapies on a patient-by-patient basis, often considered the "Holy Grail" of medicine, he says. Assuming the genetic signatures stack up in future studies, that sort of predictive power would make any vaccine researcher salivate.

So far, few melanoma vaccines have lived up to expectations, says Yvonne Saenger, a melanoma specialist at the Mount Sinai School of Medicine in New York City. MAGE-A3 may or may not be different, she says. She is waiting to see the Phase III results before weighing in. Even vaccines that end up getting the FDA's approval can do only so much, Weber says. "Getting a vaccine alone to work in metastatic melanoma, I don't think it's going to happen," he says.

One big problem may be that tumors are just too good at rebuffing attacking white blood cells. And as the legendary Greeks learned, if you can't overcome Troy's defenses, you might as well go home.

**Breaking barricades**

During their day-to-day surveillance, white blood cells cull the low-hanging fruit well--cancer cells that readily give up their identities or that lack good defenses. But some cells avoid attack, and they can grow into tumors. The National Cancer Institute's Berzofsky compares the immune system's task to that of the Department of Homeland Security: "You can stop 99 percent of the terrorists. But it's the 1 percent that get through that kill you."

Often cancer cells escape the siege by taking advantage of the body's hesitancy to attack its own cells. Despite the best laid plans in a healthy body some white blood cells do wind up targeting healthy lungs, skin or liver. When that happens, the immune system sets off fail-safes that silence or kill outright the rogue white blood cells. Many cancers call off attacks by triggering the same fail-safes. And that's just the start: Some tumors are downright devious, surrounding themselves with minefields laced with anti-immune chemicals. "Tumors feather their own beds," Berzofsky says.

Cancer vaccines need a Trojan Horse to overcome these barriers. Enter ipilimumab. This drug snaps onto and turns off a type of immune protein called CTLA-4. In healthy people, CTLA-4 is a godsend because it's a natural brake on immune attacks, says Steven O'Day, director of the Melanoma Program at the Angeles Clinic and Research Institute in Santa Monica, Calif. This protein pops up on top of soldier immune cells when the cells go into battle mode. If a passing spy cell grabs onto the protein, it acts like a kill switch on the soldier cell. That's perfect for viral
infections, O'Day says. Soldier cells can hit cold and flu viruses fast and hard, then, as part of the immune system's checks against collateral damage, dial back when the job is done. But such short skirmishes don't often work on tumors. "Here you're trying to build an army of T cells, basically, to go into battle," O'Day says. "It can take anywhere from three to six months." Ipilimumab's trick is to keep immune cells going.

In a recent Phase III trial in patients with advanced melanoma, ipilimumab seemed to give soldier cells that much-needed breathing room, says O'Day, one of the study coauthors. Among nearly 700 patients, those that got ipilimumab survived for a median of 10 months after enrollment in the study, while patients not receiving the treatment survived for just over six, the team reported last year in the New England Journal of Medicine. But even more exciting, O'Day says, about 20 to 25 percent of patients survived for much longer --two years and counting. Ipilimumab seems to be a rarity, a drug that actually slows down melanoma.

But the drug has its downsides. In the absence of CTLA-4, many immune cells don't know when to quit. In the Phase III trial, 10 to 15 percent of patients on ipilimumab developed severe immune side effects from diarrhea to skin rashes, and seven patients died as a result. Preparation and careful monitoring in the future should keep such ill effects in check, Saenger says.

Ipilimumab received the thumbs-up vote from the FDA in March 2011. And that's a big deal, says Suzanne Topalian, a melanoma specialist at Johns Hopkins. "But at the same time, we all realize thatipi is a starting point," she says. Future work will focus not only on better drugs but also on drugs that work as part of a multifront war.

Data from mouse studies suggest ipilimumab, now marketed as Yervoy, could help next-gen vaccines slip past cancer walls, says Topalian, who has helped conduct clinical trials on ipilimumab. "A vaccine is going to focus the immune response," she says. "But these other maneuvers are going to enhance the immune response above a threshold that's needed for clinical activity."

Early data suggest medications that target a kill switch called PD-1, similar to CTLA-4, could pair well with vaccines and have fewer side effects, Topalian says. So far, though, successfully mixing and matching vaccines with such kill-switch blockers remains little more than an attractive idea. O'Day's team tested ipilimumab alongside a cancer vaccine--the gp100 vaccine --that hadn't received FDA approval. Ipilimumab, however, seemed to do better on its own. Some doctors, including Topalian, suggest that gp100 may not be ideal, but think that newer pairings will succeed where this run failed.

And traditional drugs and treatments such as chemotherapy may work along with vaccines to make for a one-thousand-ship army. "Everyone is now on this bandwagon of developing combination therapy," Topalian says.
Still, it may take years for patients to see the full fruits of this research, just as it has already taken years to see a cancer vaccine that holds promise. "It's still hard because it's still just a long path," Saenger says. "You see a patient that has melanoma now; it's still very difficult." But she says there is a lot of room for hope.

A motley army now appears to be mustering. As more and more possible treatments trickle into the market, deciding which troops to send in to which patients, says O'Day, will make the fight against cancer more of an art.

*Trove of Trials*
A number of possible vaccines for a variety of cancers are currently in clinical trials. Some are shown below, but more can be found online at clinicaltrials.gov

<table>
<thead>
<tr>
<th>Drug</th>
<th>Company/Institution</th>
<th>Type of cancer</th>
<th>Phase</th>
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<tr>
<td>NY-ESO-1 peptide vaccine</td>
<td>National Cancer Institute</td>
<td>Melanoma</td>
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<tr>
<td>PROSTVAC</td>
<td>BN ImmunoTherapeutics</td>
<td>Prostate</td>
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<td>ADXS11-001</td>
<td>National Cancer Institute</td>
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<td>Lucanix</td>
<td>NovaRx Corporation</td>
<td>Non-small cell lung</td>
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<td>BiovaxlD</td>
<td>Biovest International</td>
<td>Non-Hodkin's lymphoma</td>
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<td>Stimuvax</td>
<td>EMD Serono</td>
<td>Non-small cell lung</td>
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<td>Autologous tumor lysate-pulsed DC vaccine</td>
<td>UCLA</td>
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<tr>
<td>Allogeneic GM-CSF-secreting vaccine</td>
<td>Johns Hopkins</td>
<td>Breast</td>
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*How Does the Cancer Vaccine Work?*
1. Though approaches vary, the aim of cancer vaccines is to provoke the body to attack tumor cells.
2. Specific flags, or antigens, sit atop tumor cells.
3. Scientists mix those flags with a person's own spy cells.
4. The spy cells, sometimes dendritic cells, take up the flags.
5. The activated spy cells are injected back into the body.
6. The spy cells display the flags, alerting the body's T cells.
7. The T cells proliferate and attack cancer cells.
Unraveling Complex Genetic Stories in Cancer Cells May Lead to Personalized Treatment
By Tina Hesman Saey
Science News September 24th, 2011; Vol.180 #7

Tumors are ugly. But the staff at Massachusetts General Hospital takes a snapshot of almost every one that crosses the doorstep. These snapshots are not photographs, but are rather whole rap sheets on the genetic deformities that twist normal cells into cancerous ones. In a laboratory tucked within the labyrinth of corridors connecting the hospital's many buildings, researchers punch tiny cores no bigger than a grain of rice from tumor samples. Those cores are handed off to robots and tested for 110 mutations that commonly strike 15 genes important in cancer. Across the country, doctors at the Oregon Health & Science University in Portland use another method for testing tumors. The staff there looks for 643 different mutations in 52 genes in solid tumors, such as those of lung and colon cancer, and screens blood or bone marrow from leukemia patients for 370 mutations across 31 genes. Though the tests don't reveal everything that has gone wrong to lead to a patient's tumor, they may point to mistakes that drive the cancer. "They're the original 'stomp on the gas pedal' type of mutations," says Christopher Corless, a pathologist who directs the tests at Oregon.

Efforts under way at these two cancer centers are creating some of the first ripples in what many scientists predict will be a growing wave of genetic testing of tumors. Traditionally doctors order tests to see if just one of a small handful of genes is broken, and such tests have been used widely for the treatment of only breast cancer and a few other cancer types. But that piecemeal approach is giving way to more comprehensive probes of cancer's molecular workings.

Big cancer centers and clinical labs at university-affiliated hospitals around the country are now adopting tumor-testing programs similar to those in Massachusetts and Oregon. Even though the wave has yet to swell outside of academic centers to smaller community hospitals and doctors' offices, some clinicians are already finding troublemaker genes and drugs that can counteract them. Scientists are taking the process many steps further in the lab, deciphering a tumor's complete genetic instruction book. Having such information, at least in the case of one man with a rare cancer, has helped uncover unexpected cancer drivers and tailor patient care. Such comprehensive testing is beginning to change the way many doctors and researchers think about cancer. Soon tumors may be diagnosed and treated much like an infectious disease. Just as identifying the bacteria or virus responsible for an infection helps doctors prescribe the right
medication, finding the mutations behind a tumor could lead to treatments that target and knock out cancer cells while sparing healthy ones.

Where a quick-and-easy cure isn't possible, cancer could be transformed into something akin to chronic infections like HIV or hepatitis C. "We're trying to convert all of cancer to what we did for HIV," says David Ryan, an oncologist at Massachusetts General Hospital, in Boston. With cancer, "You hear this constant, 'I'm going to beat it, I'm going to beat it, I'm going to beat it.' Well, HIV never goes away. You still have to take the medicines, but you can live with it."

Live (longer) with it
Pharmaceutical companies have a couple of success stories that suggest Ryan's vision may not be far-fetched. A drug called Gleevec has extended by years the lives of people with one form of leukemia. That drug stops the cancer-promoting action of specific proteins that help tell a cell when to grow and divide.

Some cancer-causing mutations switch these proteins, known as tyrosine kinases, to a permanent "on" position, like the accelerator pedal in a car getting stuck to the floor. Gleevec helps pull back on the throttle, slowing or stopping the cancer's growth. Other drugs (erlotinib, gefitinib, cetuximab) block the action of a tyrosine kinase called the epidermal growth factor receptor or EGFR, which turns on cell growth programs. Genetic mutations that keep the protein permanently active or that cause too much of it to be produced can lead to lung cancer. Despite these signs that targeting specific genes and their products can help fight cancer, only about 5 percent of all cancer patients have benefited from genetic testing thus far, estimates Daniel Haber, a cancer geneticist at Mass General who counts the development of erlotinib as the happiest experience of his research career. Yet the number of beneficiaries may be about to grow.

Researchers have recently learned that between 40 and 60 percent of melanomas and 7 to 8 percent of all cancers have accelerator-sticking mutations in a gene called BRAF that codes for another growth-control molecule. The most common of the mutations changes one link in the amino acid chain that makes up the BRAF protein, a switch from valine to glutamic acid. A study published in the New England Journal of Medicine last year showed that an experimental drug known as vemurafenib could melt away many melanoma tumors that had spread throughout the body by inhibiting the activity of the mutant BRAF protein. The drug, now approved by the U.S. Food and Drug Administration, has stopped tumor growth for more than seven months in patients with the mutation, extending their lives. Other drugs are buying cancer patients even more time. Drugs that combat EGFR abnormalities have given lung cancer patients as long as 30 months from diagnosis. Standard chemotherapy typically offers only 12 months, says William Pao, director of personalized cancer medicine at the Vanderbilt-Ingram Cancer Center in Nashville.

"That's a big difference if they want to see their kid graduate or another baby being born," Pao says.
A case of cancer

"Magical" drugs like these are still wishful thinking for most patients, though, says John Iafrate, a molecular pathologist at Mass General and a pioneer of the hospital's tumor snapshot program. The search for anticancer medications that pinpoint specific genetic defects reminds him of the early days of antiretroviral therapy for HIV. Attacking one tumor process may not be enough to completely eliminate the cancer, he says, just as the antiretroviral drug AZT wasn't able to control HIV infections on its own.

To leap forward, scientists have to find out what makes each person's cancer tick, so they can go after it with the right drug combination. Iafrate and others are testing a few dozen genes known to be important in many different cancers. But that approach offers limited information -- and in some cases can even mislead doctors.

That's what happened in the case of a 78-year-old man with a very rare tumor on his tongue. Doctors treating the British Columbia man had his tumor tested for a small number of mutations, finding that the tumor cells made twice as much EGFR protein as normal cells do. A drug prescribed to combat the change proved futile; the cancer spread to the man's lungs. At that point, the clinicians decided they needed help. They turned to Steven Jones and his team at Canada's Michael Smith Genome Sciences Centre at the British Columbia Cancer Agency in Vancouver. Jones' team deciphered the complete genetic blueprint of one of the lung tumors. In a study published last year in Genome Biology, the researchers described the genetic mess: 7,629 genes were duplicated, triplicated or more; at least four chromosomes were missing huge chunks of DNA; and four genes contained mutations that would alter protein products. Also, 1,078 genes had higher-than-normal activity, while 1,986 others were less active than normal.

Compiling the data turned out to be the easy part. Figuring out which of these myriad abnormalities were responsible for the man's cancer required "quite a lot of computational gymnastics," Jones says. "There is no computer program that you just put your data in and it spits out what's causing the problem."

It took "15 people in a room scratching our heads and consulting the literature" to conclude that a gene called RET and its cronies were probably driving the tumor's runaway growth, Jones says. RET produces a protein that helps cells decide when it is time to grow and differentiate. Other mutations in known cancer genes probably goaded further growth and made the tumors immune to the first drug.

With that info, the doctors put the man on a drug that inhibits the RET protein and other growth-promoting proteins. After about a month of treatment, the lung tumors had shrunk by 22 percent. But after four months on the drug, the tumors began to grow again, so doctors tried two other drugs. Those drugs bought the man another three months before the cancer started progressing yet again.
Researchers examined the genetic blueprints of the treatment-resistant cancer and found nine new mutations that weren't in the original tumor or the man's normal DNA. And other bits of DNA continued to be added and lost as well. Jones and colleagues speculate that only a carefully concocted cocktail of drugs could have stopped the cancer, which ultimately led to the man's death.

Too little, too late
The case highlights how having a tumor's complete genetic profile -- what scientists call a genome sequence -- can change patient care. But the study is also an exception. Most studies catalog a tumor's genetic changes long after it has been removed from the body, when it is far too late to influence treatment, says Elaine Mardis, a genome scientist at Washington University School of Medicine in St. Louis.

Genome sequences aren't often used during early treatment because it can take months to prepare samples, compile the genetic blueprints and then analyze the results. In a study published in the April 20 Journal of the American Medical Association, Mardis and her colleagues showed that they could find the source of a patient's leukemia in just seven weeks, a short enough time to affect treatment.

Still, Pao says clinical tests shouldn't take much longer than a week or two. And besides costing valuable time, the bill for a complete genetic blueprint can be substantial. Some companies estimate that it costs $5,000 to $6,000 to assemble a tumor's whole genome.

Mark Boguski, a pathologist at Harvard Medical School, thinks it's a bargain. "If I had cancer and $10,000, I'd have two choices: Take a cruise and check off my bucket list, or get my genome sequenced," he says. "I'd get my genome sequenced, no question."

But there are additional costs in the bioinformatics. Cancer databases that might help in interpreting genetic details usually don't present information in clinically useful ways, Pao says. Even for a doctor who has a patient's cancer genome in hand and knows all the mutations, it is incredibly hard to extract meaning from the alphabet soup of genetic errors. Pao and his Vanderbilt colleagues have built a new database that may help doctors decide which of the many mutations in a cancer cell are important, and which drugs to prescribe.

Right now, every time scientists compile a person's genetic information, they have to sift through a mountain of data to find the changes that are driving that person's cancer. "Every case is a research project," Boguski says.

Spotting the drivers
Jerry Shay, a cell biologist at the University of Texas Southwestern Medical Center at Dallas, once wondered whether churning out reams of genetic data was even worthwhile. "I started this thinking that we'd show most of this stuff was rubbish, and we were wasting money sequencing cancer genomes," he says. "I'm a complete turnaround."

Shay's original problem with most cancer genome studies was that they came up with exhaustive lists of all the ways that cancer cells are messed up and then somebody had to make a rather subjective decision about which of those abnormalities was important. Instead of guessing, he and his colleagues decided to ask colon cancer cells.
Previous studies had estimated that 151 genes play a role in colon cancer. Only eight to 15 were thought to really drive the tumor -- causing its out-of-control growth. The vast majority of mutations were thought to have happened incidentally and were like passengers on a runaway bus.

Shay's team grew cells from the lining of the colon in lab dishes and then introduced mutations in two genes frequently involved in cancer, p53 and KRAS. But cells with mutations in either of those genes grew fairly normally, the researchers reported in the July Cancer Research. Then the researchers used a genetic trick to start knocking out each of the 151 genes one by one from colon cells that already carried either the p53 or KRAS abnormalities.

Instead of a bus with a few drivers and lots of passengers, Shay's team found that 65 of the presumed passengers were anything but backseat drivers. Those mutations had a hand either directly on the wheel or were involved in biological processes with genes that did, encouraging the colon cells to grow like tumors. Of those, 49 sparked cancerlike behavior when paired with either p53 or KRAS mutations.

If the study were a Dr. Seuss book about colon cells, it might be called "Oh, the Places You'll Go Wrong!" There could be 50 to 100 paths that lead a colon cell to cancer, not just eight to 15 as other researchers had thought, Shay says.

"The idea that cancer cells accumulate a lot of incidental mutations that don't mean much is not well-founded," he says. "It's just not as simple as we'd like to think."

Finding so many genes steering cancer could be good news for treatment. Right now, there is no way to stop KRAS once it has run amok. But the right drugs might persuade a codriver to hit the brakes, Shay suggests. He says more tests are needed to determine if other cancers also have many drivers.

**Personal touch**

After compiling genetic blueprints of more than 400 tumors from 20 different types of cancer, Mardis and her colleagues have discovered that genome sequences can point to more than just a cancer's driving mutations.

One thing Mardis and her collaborators have learned is that tumors are not monolithic entities. They contain many groups of cells, some with mutations that might render them immune to chemotherapy or targeted drugs. Even if such cells make up only 10 percent or less of a tumor, they could still cause the tumor to spread or cause a recurrence at the original tumor site. Mardis wants to determine just how many cells' DNA needs to be thoroughly looked at to identify all the problem mutations.

"We're not going to learn that information until we just go ahead and do it," she says. Moving genetic testing forward may also one day help reveal whether precancerous cells are going to turn into cancer, saving some people from unnecessary surgery while allowing others
to shut down cancer before a tumor revs up. "People don't really understand just how personalized cancer care is going to become," Mardis says.

The personal touch is still on the horizon, though. Despite decades of openly declared war on cancer, researchers are still in the early phase of learning about the genetics behind the disease.

When it comes to cancer, says Ryan, doctors are in the same position they were in when he started working in 1988 at Columbia College of Physicians and Surgeons in New York City. "HIV was rampant. Every night I was on call we'd admit 10 people, and seven to eight of them had HIV." Once the protease inhibitors came out in the mid-1990s, the university hospital no longer needed a floor for AIDS and tuberculosis. "It's gone," he says. "That's what we want for cancer."

**Tumor testing dreams**

Though some patients do benefit from drugs that target specific cancer-causing mutations, in most cases a tumor's underlying mutations are unknown. Someday, researchers hope, comprehensive genetic tumor testing (steps depicted below) will become cheap and fast enough to influence patient care, providing every cancer sufferer with personalized treatment.

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1. Extract genetic information from multiple cells in a tumor, as well as healthy cells in the same patient for comparison.
2. Decipher the genetic blueprint, identifying mutations and sites where genes are lost, inserted, duplicated or otherwise modified.
3. Using online databases of known cancer-related genes, catalog the modifications and try to pinpoint the troublemakers.
4. Deliver a cocktail of drugs that target the potentially troublesome genes and protein products.
5. Assess the patient's health. Switch up the drug cocktail as needed, or get new genetic information as the tumor cells change over time.
A Triumph in the War Against Cancer

By Terence Monmaney
Photographs by Robbie McClaran
Smithsonian magazine, May 2011

There’s a photograph of LaDonna Lopossa that helps tell the story. She’s all smiles, lying on the grass in a vaguely Betty Grable manner atop her own cemetery plot. The portrait was her husband’s idea—in their decades together it seems George, a.k.a. Mr. No Serious, never saw a gag he didn’t like—but it was LaDonna who came up with the cheesecake pose.

“OK,” George had said, “now take off your shirt.”

“George!”

Click.

On the one hand it’s a silly snapshot of a 60-year-old woman in a cardigan and sensible sandals in Winlock, Washington, one sunny day in May 2000. On the other hand it’s a glimpse of a possible future in which science has solved a fearsome problem. For this is how LaDonna and George faced her lethal cancer, not just whistling past the graveyard but clowning around in the middle of it.

Three months before, LaDonna was lying in a hospital bed in Olympia about to draw the curtain. There was a lot to let go of: four grown children, several grandkids, friends at church, a good marriage. (Never mind that as she lay there George was loudly telling the nurses he was going to hit the bars to find another wife, which she understood as his oddball effort to ease her mind.) She was ready to leave everyone and all those things and more because of the pain.

Her spleen, normally tucked beneath the lowest left rib and no bigger than a peach, was so engorged with white blood cells it was the size of a cantaloupe. She could hardly walk. Her skin

Oncologist Brian Druker developed a new treatment for a deadly cancer, leading to a breakthrough that has transformed medicine.
was ghostly, her blood dangerously short of red cells. To breathe was a chore. Regular vomiting. Stabbing aches deep in her bones, where the marrow was frantically cranking out white cells, or leukocytes. Recurring fevers. And cold, strangely, unnervingly COLD: she was freezing under the hospital blankets.

She was too old and too sick to undergo a bone marrow transplant, a grueling, highly risky treatment for her blood cancer, chronic myeloid leukemia (CML). She had already tried the other standard CML treatment, regular doses of the powerful compound interferon. But it so intensified her nausea, fevers and bone pain she abandoned the medication, come what may. With nothing left in their leukemia-fighting arsenal, the doctors were down to Dilaudid, a derivative of morphine, the narcotic painkiller. It was calming, it was comforting and for a patient in her condition it was, of course, the end.

George had given away most of her belongings and had reserved a U-Haul truck to cart his stuff to Southern California, where he would move in with one of their sons. The music for her funeral was chosen, including “Because I Have Been Given Much,” to be sung by the grandkids. When the hospital recommended moving LaDonna to a hospice, George took her home instead and followed her doctor’s advice to summon the children; Terry, Darren and Stephen flew up from the Los Angeles area, and Kelly drove over from her place in Winlock. One by one they went into the bedroom, sat at LaDonna’s bedside and said goodbye.

CML is one of the four main types of adult leukemia, but it is not common, striking 5,000 people in the United States each year. As a rule, it is fatal, with most patients dying within five years of being diagnosed. The first phase, a stealthy explosion of otherwise normal white blood cells, can last months or years; patients are often alerted to the condition by a routine blood test. If the disease goes unchecked, the white cells become increasingly abnormal, issuing helter-skelter from particular stem cells in bone marrow called myeloid cells; such leukocytes burst capillaries, overwhelm organs and suffocate tissues by crowding out oxygen-carrying red blood cells.

Chromosomes Accidentally Cross Paths CML arises when a stem cell errs during division. Instead of the 23 chromosome pairs being accurately duplicated, bits of No. 9 and No. 22 chromosomes change places, creating an aberrant “Philadelphia chromosome” bearing a mutant gene.
The disease’s course is exceptionally predictable, physicians say, but its clockwork nature has also provided scientists with an opportunity: prying into the molecular gears and springs that propel CML, they understand it better than any other cancer. Once, in early December 1999, George was driving to see LaDonna at the hospital in Olympia and stopped at a Safeway to buy a newspaper. Mr. No Serious is an avid reader, had even briefly run a bookstore with LaDonna, and he devoured the paper in her hospital room. As it happened, an experimental leukemia treatment was then making headlines. “Leukemia Pill Holds Promise,” the Associated Press reported, saying CML patients “had normal blood counts within a month of beginning treatment.” The study was then underway at the Oregon Health & Science University (OHSU) in Portland.

George hurried out of the hospital room to find LaDonna’s oncologist.

Target for Intervention

A Drug That Strikes the Target The mutant gene manufactures a renegade enzyme of the same name, BCR-ABL. It spurs runaway white blood cell division, or leukemia.

A steep, winding, tree-lined road leads to the main campus, which is perched near the summit of 574-foot-high Marquam Hill and on foggy days appears to float above the city like a castle in a fairy tale. Another route up to OHSU is the Portland aerial tram: two Swiss-made gondola cars of gleaming steel soar on cables high over Interstate 5, whizzing people back and forth between the west bank of the Willamette River and a hospital platform perched closer to the edge of a cliff than disembarking heart patients might wish it to be.

Brian Druker arrived at OHSU in 1993, years before the tram would be built and the hall-of-fame mural in the adjacent passageway would include a picture of him. Tall, as lanky and lightfooted as a greyhound, soft-spoken, Druker was 38 and had just spent nine years at the Dana-Farber Cancer Institute, part of Harvard Medical School, in Boston. “I saw cancer as being a tractable problem,” he recalled of the research path he chose after finishing medical school at the University of California, San Diego. “People were beginning to get some hints and some clues and it just seemed to me that in my lifetime it was likely to yield to science and discovery.” At Dana-Farber, Druker landed in a laboratory studying how a normal human cell gives rise to
runaway growth—malignancy. Among other things, the lab focused on enzymes, proteins that change other molecules by breaking them down (gut enzymes, for example, help digest food) or linking them up (hair follicle enzymes construct silky keratin fibers). Enzymes also figure in chain reactions, with one enzyme activating another and so on, until some complex cellular feat is accomplished; thus a cell can control a process such as growth or division by initiating a single reaction, like tipping the first domino. Under the lab’s chief, Thomas Roberts, Druker mastered numerous techniques for tracking and measuring enzymes in tissue samples, eventually turning to one implicated in CML.

Working out the details of why this particular enzyme is the key to CML had involved hundreds of scientists around the world—research that would lead to several Nobel Prizes—but here’s basically where Druker started:

First, all CML patients have the renegade enzyme in their white blood cells. Second, the enzyme itself is the product of a freakish gene, called BCR-ABL, formed during a single myeloid stem cell’s division and thereafter transmitted to billions of descendants: the tips of two chromosomes, those spindly structures that store DNA, actually swap places, causing separated genes called BCR and ABL to fuse (see illustration). The new mutant BCR-ABL gene sits on a peculiar chromosome discovered in 1960 by scientists at the University of Pennsylvania. This “Philadelphia chromosome,” visible through a microscope, is CML’s hallmark.

Third, the BCR-ABL enzyme is the evil twin of a normal enzyme that helps control the production of white blood cells. But like a switch stuck in the “on” position, the mutant spurs the wild proliferation that is leukemia.

You didn’t have to be a Harvard doctor to see that a single enzyme that causes a fatal leukemia was, as researchers say, an attractive target for intervention. And, indeed, scientists were then setting out to find or invent compounds that could block the BCR-ABL enzyme.

Druker and his Boston co-workers, using specially designed antibodies, developed a new way to measure the enzyme’s activity—a tool that would prove invaluable to evaluating potential CML treatments. A necktie-wearing physician among jean-clad PhDs, Druker was racing competitors at other research centers to find a drug that suppresses cancer by disabling a critical enzyme and spares healthy tissues in the bargain. By tradition, cancer treatments carpet-bombed the body with powerful drugs, killing healthy and cancer cells alike—“cytotoxic chemotherapy,” doctors call it. The alternative, targeted therapy, would fight cancer better with less collateral damage, or at least that was the notion that often kept Druker in the lab until 11 p.m.

Then things began to fall apart. “My marriage had broken down. I wasn’t what you would call a devoted husband. I was a devoted researcher and scientist and physician. And that took a toll.” (Druker and his wife split after two years of marriage and were later divorced.)

Still, with a score of published studies and a nifty enzyme-measuring technique to show for his
efforts, Druker thought he was ready to move up the Harvard ladder from instructor to assistant professor. “I sat down with the head of medical oncology at Dana-Farber,” Druker recalled. “He looked over my résumé and said, ‘I just don’t think this work is going to go anywhere here.’”

Translation: “I was told I had no future at Dana-Farber.”

“It was awful,” he recalled. “I was depressed. But it forced me to really say, Do I believe in myself? Am I going to make it, make a difference?”

Growing Concern

Asked to describe Druker’s approach, one scientist said it boiled down to “perseverance and stubbornness in not letting go of an idea.”

“I think intrinsically he’s a shy person,” said another. “But on this” — cancer therapy — “he’s like a crusader.”

“He takes everything that is complicated, shoves it in his mind and outputs the simplest possible interpretation and intervention.”

“When you ask a question, there’s silence in the room, almost uncomfortable silence, and you’re, like, did he even hear me? He thinks things through before giving an answer.”

“He lets the science do the talking.”

Druker grew up the youngest of four children in St. Paul, Minnesota, and attended public schools, excelling at math and science. His father was a chemist at 3M whose work on printing processes was patented. His mother was a homemaker who got involved in school-board politics and ran unsuccessfully for the state legislature. After graduating with a chemistry degree from UC San Diego, he stayed on, and in 1978, his first year in medical school, he wrote a 16-page paper hinting at a future he would help create. Written in longhand with blue ink on lined notebook paper and titled “Cancer Chemotherapy,” it concluded that, someday, when the action of cancer drugs is “understood in biochemical terms the field of cancer chemotherapy should make advancements far beyond the progress already made.”

After the Dana-Farber Cancer Institute gave him the bum’s rush, Druker marshaled new resolve.

“When I moved here to Oregon, my goal was to identify a drug company that had a drug for CML and get that into the clinic,” he said.

He’d previously met Nick Lydon, a biochemist at the Swiss pharmaceutical firm Ciba-Geigy (which would merge with Sandoz in 1996 to form Novartis). Lydon had collaborated with Roberts, Druker’s former lab chief. “I called my friend Nick at Ciba-Geigy and he said, ‘We have what you’re looking for.’” It was called STI571. Company chemists had synthesized it and other compounds while searching for a new anti-inflammatory drug, but they had learned it could also
block the activity of enzymes in a test tube. Still, they hadn’t quite decided what to do with the compound.

In August 1993, Druker received his first batch of liquid STI571 and another candidate compound from Switzerland. Using the enzyme-measuring tool he’d helped develop, he confirmed that STI571 strongly inhibited the BCR-ABL enzyme, which belongs to a class of enzymes known as tyrosine kinases; the other compound did so only weakly. He also poured minute amounts of STI571 into a tray of thimble-size containers that held fluid and live white blood cells derived from a CML patient. Druker had hoped the cells’ growth would slow or stop. Even better, the cells died. Moreover, a large amount of STI571 given to healthy cells in a dish did no harm. “Brian’s contribution was critical,” Lydon recalled, in convincing the company to “move in that direction.”

But, of course, the road to dashed hopes is paved with experimental drugs that looked terrific in a test tube but failed in human beings. Skeptics pointed out that hundreds of different types of tyrosine kinase enzymes are at work in the body, and, they added, wouldn’t a drug that blocked one also block many others and wreak physiological havoc? “There were many naysayers who argued that it would be impossible to develop specific protein kinase inhibitors” for treating cancer, Tony Hunter, a biochemist at the Salk Institute in La Jolla, California, wrote in the *Journal of Clinical Investigation.*

Scientific ideas don’t take root like dandelion seeds wafted onto fertile ground. They need advocates, people who want to win. Druker plugged away, doing more experiments, such as inducing a form of CML in laboratory mice and subjecting them to STI571. It all but eliminated the animals’ disease. “I was putting in probably 60 to 80 hours a week,” recalled Druker, who in his scant free time competed in bicycle races, a sport that demands a high tolerance for pain and a sense of when to break out of the pack. “My life in those days was I’d work [in the lab], work out, eat and sleep.” What was driving him, he said, were CML patients who were dying.

By 1997, having published numerous studies with co-workers in Portland and Switzerland, Druker believed the compound was ready to be tried in human beings. Novartis disagreed. For one thing, when dogs had been given the drug in intravenous form, it tended to cause blood clots at the end of the catheter. Novartis chemists spent months reformulating the liquid drug as a pill. But when the researchers gave large doses to dogs, the animals showed signs of liver damage. Some company officials, Druker recalled, advised dropping the project altogether. But the canine liver damage didn’t faze him; chemotherapy, after all, is destructive. “We knew how to give people toxic cancer drugs,” he said.

The next thing Druker did may not have been illegal, but it certainly wasn’t kosher. He bypassed Novartis and went straight to the Food and Drug Administration to see if he’d accumulated enough data to start a human trial. “I called up the toxicologist at the FDA and said, ‘Here’s the problem.’ And he said, ‘My goodness, you have a ton of data, we would probably accept this application.’” Druker then told Novartis what he’d done. “I got myself in some hot water
because I’d gone behind their back.”

Finally, in June 1998, with FDA permission to proceed, Druker administered STI571 to a human being, a 68-year-old Oregon man with CML. “It was almost anticlimactic,” Druker recalled, “in that we’d been ready in November 1996 and here it was over a year and a half later.”

He had recruited two eminent oncologists to help run the clinical trial, Moshe Talpaz at the M.D. Anderson Cancer Center in Houston and Charles Sawyers at UCLA. All the CML patients enrolled in the three cities had undergone interferon therapy and either had failed to improve or had relapsed. None was eligible for a bone marrow transplant.

Gradually increasing the STI571 dosage, the physicians observed by around six months that astronomical white blood counts of nearly 100,000 cells per cubic millimeter were falling to less than 10,000, well within normal. Analysis of one of the first patients’ white blood cells found no signs of the Philadelphia chromosome, suggesting the leukemia had been stopped at the source. More impressive, whatever trace of the BCR-ABL gene remained had ceased copying itself. “That’s when we knew we had something the likes of which had never been seen before in cancer therapy,” Druker said.

As word spread on the Internet, other CML patients wanted in. Druker pressed Novartis to produce more of the drug. But Novartis wasn’t ready. The drug was difficult to make, Daniel Vasella, then the Novartis chief executive officer and now chairman of the board, would recall in his book about the drug, Magic Cancer Bullet. “Nor was [the drug] a high priority, given the small number of CML patients,” he added. Plus, proving that it was both safe and effective would require a substantial investment. “A severe side effect could develop in one out of 1,000 patients and that would be the end of the trial,” he wrote.

In September 1999, Druker got an e-mail from a 33-year-old CML patient in Montreal, Suzan McNamara. She’d been on interferon, which had suppressed her disease for nearly a year, but now it was roaring back, and she wanted to join an STI571 trial. “I was sick to the point where I could barely leave my house,” she recalled to me.

Druker phoned her the next day and said it would be months before she could enroll in a study—Novartis had not committed to producing more STI571. But, he added, the company might move more quickly if it heard directly from patients.

McNamara and a friend used an Internet site to create a petition requesting that the drug be made more widely available; thousands of CML patients endorsed it. She sent it to Vasella with a letter saying, “We have viewed with growing concern our belief...that the supply of the drug has not been sufficient to expand the trials as fast as the evidence to date would warrant.”

“The letter could not be ignored,” Vasella has said. The company increased STI571 production.

The honor of announcing the early clinical results fell to Druker. In New Orleans on December 3,
1999, he told an auditorium full of hematologists that all 31 patients in the study responded favorably to STI571, with the white blood cell counts of 30 falling to normal within a month. The pill’s side effects—upset stomachs, muscle cramps—were what oncologists term “mild to moderate.” Druker says he doesn’t remember the standing ovation.

The findings were “a molecular oncologist’s dream come true,” wrote Harold Varmus, who now heads the National Cancer Institute and was awarded a Nobel Prize for research that laid some of the groundwork for STI571’s success. The drug, he recalls in his 2009 book, *The Art and Politics of Science*, was “the best evidence to date that the most fundamental aspects of cancer research had dramatic benefits for patients with cancer.”

CNN, the *New York Times*, “Good Morning America” and the Associated Press covered the breakthrough cancer pill.

**Wave of the Future**

After LaDonna Lopossa and her children said their goodbyes in February 2000, she eked out a few more days and made it to an appointment at OHSU. LaDonna’s oncologist and George had managed to get her into the second phase of the STI571 trial, which would enroll some 500 new patients at a dozen medical centers worldwide. She shuffled into the clinic on George’s arm.

“What have we gotten ourselves into?” one of the nurses said, meaning LaDonna’s death, which appeared imminent, would count as a black mark against the drug. Her white blood count exceeded 200,000, more than 20 times normal. “There were no two ways about it,” Druker said.

“You looked at her and she was in trouble.”

They examined her and gave her an STI571 pill. She threw it up.

The next morning, George and LaDonna awoke in her sister’s apartment in Portland and George made LaDonna a banana milkshake. Later that day, the STI571 pill stayed down. And the next, and so on.

“Within three weeks her spleen was back to practically normal,” Druker said. “She was feeling great. White count had come down. A Lazarus-like effect. It was truly miraculous.”

It was in May of that same year that LaDonna and George visited the cemetery in Winlock to place flowers on her mother’s gravesite, which is next to the plot LaDonna had bought for herself. “I’m supposed to be in that grave,” she said to George.

“Well,” he said, “since you’re not, why don’t we take a picture?”

By the late winter of 2001, Druker and his collaborators had pooled much of their STI571 data: in roughly 95 percent of patients, white blood cell levels had returned to normal, and in 60 percent the Philadelphia chromosome was not detected. The company submitted the results with its
new-drug application to the FDA, which it approved in two and a half months—to this day the fastest drug review in the agency’s history.

Ten years ago this month, the U.S. government announced that the drug, which Novartis named Gleevec in the North American market (Glivec in Europe), would be available to CML patients. It was a defining moment. The previous century of cancer treatments—intermittently successful, based on trial-and-error testing, almost always agonizing—would be known to experts as “before Gleevec.” From then on was “after Gleevec,” the era of targeted therapy. At a Washington, D.C. press conference on May 10, the Secretary of Health and Human Services, Tommy Thompson, called the drug a “breakthrough” and “the wave of the future.” The then director of the National Cancer Institute, Richard Klausner, described it as “a picture of the future of cancer treatment.”

Today, Suzan McNamara would agree that future is good. When she first traveled to Portland in 2000 to take part in the Gleevec study, she recalled, “I went there with half my hair, and anorexic, and couldn’t even walk up a flight of stairs. And I came back in one and a half months 20 pounds heavier and full of life.” Her next steps were to attend McGill University, study leukemia therapies and earn a PhD in experimental medicine. Now 44, she lives in Montreal and works in Ottawa for Health Canada, a federal agency. Still on Gleevec, she runs several miles a few times a week. “I’d go more if I wasn’t so lazy,” she said. In January 2010 she wed her longtime boyfriend, Derek Tahamont, in Hawaii. “He stood by me through the whole illness and everything,” she said. “We decided to hop on a plane and get married on a beach, just the two of us. It was perfect.”
Gleevec has encouraged people to think cancer is not always a deadly invader that must be annihilated but a chronic ailment that can be managed, like diabetes. In follow-up studies led by Druker, some 90 percent of newly diagnosed CML patients who began taking Gleevec had survived five years. “I tell patients how optimistic I am about their future,” Druker said. “We’re projecting for Gleevec that average survival will be 30 years. Someone who’s diagnosed at 60 can live to 90, and die of something else.”

Back when LaDonna Lopossa was 60, she recalled, Druker said he would keep her alive until she was 70. Then she reached that milestone. “I meant when I turned 70,” he joked to her then. LaDonna, now 71, and George, 68, live in Battle Ground, Washington, a rural town 24 miles north of OHSU, where LaDonna remains under Druker’s care. The Lopossas live in a bungalow in a state-subsidized senior-citizen housing complex across the street from a family that keeps hens in the yard and lets George grow herbs. A framed magazine ad for Gleevec featuring LaDonna hangs on a living room wall. Two portraits of Christ grace a dining room wall. George, who is quick to say he’s not religious—“nobody knows what Jesus looked like,” he quipped of LaDonna’s iconography—has his own den, where he watches “Family Guy.”

LaDonna volunteers at the North County Community Food Bank down the street, at the Mormon church she belongs to and, by telephone, she counsels people newly diagnosed with CML for the Leukemia and Lymphoma Society. One of her biggest challenges these days, she said, is convincing patients to keep taking Gleevec; they haven’t endured the symptoms of fulminating CML and some find the drug’s side effects annoying.

Gleevec held LaDonna’s CML at bay for seven years, at which time her disease became resistant to the drug. Fortunately, medical scientists and drug companies had developed two new CML drugs, each disabling the BCR-ABL enzyme in a different fashion and compensating for a type of Gleevec resistance. Sprycel didn’t help LaDonna, but Tasigna did—for about two years. Now she’s on her fourth targeted CML drug, bosutinib, which is still experimental. “Her leukemia is the best controlled it’s ever been since I have taken care of her in the past 11 years,” Druker said.

*Personalized Oncology*

Seated at the small round conference table in his small corner office high on Marquam Hill, Druker said he was still studying CML, hoping to understand how to eliminate every last mutant stem cell, and he was also trying to apply “the Gleevec paradigm” to other leukemias. A bright yellow bicycle-racing jersey worn and autographed by the Tour de France champ and cancer survivor Lance Armstrong hung framed on the wall. It was a clear day and the great vanilla ice-cream scoop of Mount St. Helens was visible out the window facing north and the storybook white triangle of Mount Hood could be seen through the window facing east. The guy who didn’t have the right stuff to be a Harvard assistant professor is today the director of OHSU’s Knight Cancer Institute, named after Phil Knight, the founder of Nike and a Portland native, and his wife, Penny, who in 2008 pledged $100 million to the facility. “Brian Druker is nothing short of a
genius and a visionary,” Phil Knight said at the time.

The honors have poured in, including the field’s top U.S. prize, the Lasker-DeBakey Clinical Medical Research Award, which Druker shared in 2009 with Lydon and Sawyers. Of his many appearances in the news media none would change his life more than a story about him in People, “The Miracle Worker,” published in February 2001. The magazine had sent a reporter named Alexandra Hardy to interview the dragon-slaying physician at the hospital in the clouds. The two were married in 2002 and are parents to Holden, Julia and Claire. Said Druker: “I have the ability now to focus on family as a priority. I couldn’t have done that 10 or 15 years ago.”

To some observers, the Gleevec fable soon lost its luster. “Wonder Drug’ for Leukemia Suffers Setback,” the Wall Street Journal reported in 2002 once some patients became resistant to the drug or could not tolerate it. Also, it seemed researchers were slow to produce other drugs targeted to tame other cancers, calling the strategy’s promise into question. A Time reporter blogged in 2006 that Gleevec was a “Cinderella drug”—a glass slipper that fit a singular candidate. Sawyers said he got tired of researchers saying Gleevec was a one-off, a lucky shot. The drug’s cost has been controversial since Day 1. A year’s supply in the United States now runs about $50,000, or around $140 per daily pill. That is twice the original cost, which Vasella had defended as “high” but also “fair,” because the drug gives patients a good quality of life and the company’s revenue underwrites research on other drugs. (Asked about the reasons for the price increase, a Novartis spokeswoman declined to comment.) In any event, a drug that Novartis balked at developing because the market was too small is now a blockbuster. In 2010, Gleevec generated $4.3 billion in worldwide sales—the company’s second-highest-grossing drug. To be sure, Novartis has provided free or discounted medication to low-income patients. In 2010, the company assisted some 5,000 U.S. patients by donating to them $130 million worth of Gleevec and Tasigna, also a Novartis drug.

But patients, doctors and others have long complained about Gleevec’s price. In her 2004 book, The Truth About the Drug Companies, Marcia Angell, former editor of the New England Journal of Medicine, suggested Novartis was “gouging” patients on Gleevec. Recently, physicians have reported that patients stopped taking Gleevec because they could not afford it, despite the company’s assistance program.

Druker, who said his lab has received Novartis research funding but neither he nor OHSU has ever earned Gleevec royalties, deprecates the cost. “It should be an affordable price, which would be in the $6,000 to $8,000 a year range,” he told me. “The company would still have plenty of profits.” He went on, “Many cancer drugs are now priced well out of the realm of affordability. As a health care industry, we’re going to have to tackle and deal with that.”

There will be plenty to deal with: it appears Gleevec was not merely a lucky shot. Just the fact that scientists quickly designed new drugs to cope with Gleevec resistance shows they increasingly know what they’re doing, said Sawyers, now at Memorial Sloan-Kettering Cancer Center. He led a group that was the first to explain resistance and was involved in Sprycel’s development. “Why am I so optimistic?” he said. “We know the enemy and we know how to
vanquish it.”

Indeed, several enzyme-targeted cancer therapies won FDA approval in Gleevec’s wake, including drugs against particular forms of lung cancer and pancreatic cancer. And researchers say they’re heartened by treatments well along in clinical trials. Some melanoma patients whose disease is caused by a known genetic mutation appear to benefit greatly from an experimental drug called PLX4032. Sawyers is studying a form of prostate cancer spurred by a mutant hormone receptor, and he said clinical tests of a drug (called MDV3100) targeted against it are “exciting.” One pharmaceutical-industry analysis estimates that drug companies are currently developing and testing nearly 300 targeted molecular cancer therapies à la Gleevec.

Arul Chinnaiyan, a research pathologist specializing in cancer at the University of Michigan Medical School, in Ann Arbor, is frank about Gleevec’s influence. “We’re trying to franchise its success,” he said of his attempts to apply the targeted-therapy approach to solid tumors, which are more complex than CML. Each type of solid tumor may be driven by multiple errant enzymes and receptors—protein structures that transmit chemical messages—and the variety of mutations might vary person to person. Chinnaiyan himself has discovered two different mutant gene fusions analogous to BCR-ABL that appear to drive many prostate cancers. “The thought is if we know these are the molecular lesions, we’ll be able to match the drug or combination of drugs appropriately,” Chinnaiyan said.

I got a sense of what he calls “personalized oncology” one day in a brew pub in Ann Arbor. Across the scarred wooden table eating a bacon cheeseburger and sipping ale was Jerry Mayfield, 62, a former Louisiana state trooper. Diagnosed with CML in 1999, Mayfield was told at the time by his hematologist that he had two to three years to live. Mayfield asked if there were experimental drugs to consider. The doctor said no. Mayfield checked the Internet, learned about STI571 and, having taught himself computer programming while manning the night desk at police headquarters in Monroe, created a Web site, newcmldrug.com, to inform other patients. If he’d listened to his hometown doctor, Mayfield said, “without question I would not be here today.”

He still runs his Web site, and these days lives in Bloomington, Illinois. He was in Ann Arbor to see Talpaz, who had collaborated on the initial Gleevec clinical trials in Houston but had moved to the University of Michigan. He has taken care of Mayfield for more than a decade,
administering targeted therapies in succession as Mayfield became resistant or could no longer tolerate them: Gleevec, Sprycel, Tasigna, bosutinib and now ponatinib, yet another experimental kinase-blocking CML drug racing through clinical trials.

Mayfield is “a poster boy for CML therapy,” Talpaz told me. “He’s doing extremely well.” Over the pub’s blaring music Mayfield said of his BCR-ABL gene, “I had the G250E mutation—have the G250E mutation—which is why I became resistant to Gleevec.”

His remark sounded like something out of a time machine programmed to years or decades from now, when people will nonchalantly talk about their deadly genetic mutations and the drugs that stymie them. It’s an image Druker often conjures. “In the not-too-distant future,” he wrote when accepting the Lasker-DeBakey Award, “clinicians will be able to thoroughly analyze individuals’ tumors for molecular defects and match each person with specific, effective therapies that will yield a durable response with minimal toxicity.”

Mayfield has never been treated by Druker but has consulted him. “I was sitting in my local oncologist’s office one day ten years ago, and my cellphone rang,” Mayfield said. “It was Dr. Druker. I’d sent him an e-mail. I was stunned. I told my oncologist, ‘It’s rude to answer this call but this is my hero.’ He’s such a kind and gentle and dedicated man, not the least bit arrogant. He has saved so many lives. Everybody in the country should know his name. He’s the kind of idol we should have, instead of sports stars.”

Mayfield’s Web site has an “appreciation album” dedicated to Druker, filled with tributes from CML patients. Snapshot after snapshot shows people smiling in bright sunlight—hiking, planting trees, drinking champagne—people who felt moved to say they owed him, well, everything. They submitted dozens of poems and limericks, such as this one by a patient named Jane Graham:

THERE ONCE WAS A DOCTOR NAMED BRIAN
ON WHOSE RESEARCH WE ALL WERE RELYIN’
HE KNEW WE WERE ILL,
SO HE MADE US A PILL,
AND NOW WE’RE NOT PLANNIN’ ON DYIN.’

Contrary to Expectations
Druker met with LaDonna Lopossa in the examining room where he sees study patients every Thursday. George, who says LaDonna has an “unsinkable-Molly Brown quality,” had driven her down from Battle Ground for her checkup. She sat in a chair while Druker, wearing a loose-fitting dark blue suit, leaned against the edge of an examining table. “I wouldn’t be here without you,” LaDonna said (possibly for my benefit).

“Well, you’re here,” Druker said. “You’re doing well.”
“I’m, like, dancing-in-the-streets well.”

“Great. Any problems?”

“No. I just have a rash.”

“When did that start?”

“About ten weeks ago.”

He asked about the rash, and later I would leave the room so he could examine her.

“You still working at the food bank?” he asked.

“I’m doing one day a week.”

“How’s that going?”

“Terrific.”

“How’s your energy?”

“My energy is low. But my brain is active.”

“You’re just doing spectacularly, leukemia-wise.”

“I know it. I can feel it.”

“What else? Questions for me?”

“I’m going on a trip tomorrow.”

“To?”

“San Diego and Knott’s Berry Farm with all my grandkids.” She updated their progress, and Druker recited their ages, as if to check that he had the facts right. When he addresses scientists at professional conferences, he often shows photographs of LaDonna and her grandchildren. Contrary to all expectations, he says, she is getting to watch her great-grandchildren grow up.

“I have such a wonderful life,” LaDonna said, tearing up. “And I didn’t want it. I told my doctors, ‘Don’t do any more to me.’”
Dabbing her eyes with a tissue, she mentioned her first visit to the clinic, in 2000, when she’d barely made it through the door. “That was a long time ago,” she said to no one in particular.

Then, to Druker, she said, “But it’s gone fast, hasn’t it?”

“Hasn’t it?” he said.

“When you’ve almost died you get a different perspective on life,” says Lopossa, at her home with her husband, George. “You have more appreciation for what we have.”
A revolutionary new drug saved Maggie Barbieri -- and may soon help millions of other cancer patients, too.

One night in April 2005, Maggie Barbieri awoke with a burning pain on the right side of her groin. She'd been bothered by a lump there on and off for the past year and a half, but hadn't gone to the doctor. She felt healthy, was in good shape, and figured it was just one of those things that happen after you turn 40. Plus, she was too busy. Maggie and her husband, Jim, a middle school teacher, had two children -- a daughter, Dea, 11 at the time, and Patrick, then 6. In addition to all the kid activities -- among other things, she coached Patrick's T-ball team -- Maggie worked full-time as a freelance textbook editor. And, fulfilling a lifelong ambition to write a novel, she had completed two mysteries. Both had been accepted by a major publisher.

Now, though, the pain in her groin scared her, and she quickly made an appointment. It was a hernia, her internist said -- not a big deal, but it did have to be repaired.

A few weeks later, Maggie had the procedure in a hospital near her Croton-on-Hudson, NY, home. In the recovery room, light-headed from the anesthesia, she was goofing around with Jim when her surgeon came in. "Something very serious has come up," she said. "You have a melanoma tumor."

"It was as if all the air had been sucked out of the room," says Maggie. "I sobered up immediately."

Maggie is fair-skinned, blue-eyed, and of Irish descent -- "a typical melanoma candidate," she says. But no one in her family had ever had the disease. Plus, she'd had no idea that melanoma could show up as a lump below the skin -- she'd only heard about dark spots or moles on the skin.

The most likely scenario, the doctor told her, was that she'd had a skin lesion that had gone unnoticed, then disappeared -- but not before sending malignant cells elsewhere in her body.
The lump in her groin was a lymph node that had been invaded by the cancer. The surgeon, seeing what was going on, had simply closed the incision without removing the lump.

"I knew that people whose melanoma is caught early have a better chance of beating it," Maggie says. But she also knew that for anyone whose cancer had spread, the outlook was usually pretty dire. Hers was Stage III; Stage IV was the deadliest.

Maggie put on her clothes and, as she walked out of the recovery room, glanced at the nurses. "We had been joking a half hour before," she says, "and now they looked devastated."

At home, she saw that the contracts for her two novels had arrived in the mail. Overwhelmed with her news and this irony, she got into her pajamas, took a painkiller, and went to sleep until her kids came home from school. Patrick was too young to understand much of what was happening, but Dea began to cry. Her aunt, Jim's stepsister Mary Beth, who was very close to the family, had recently finished treatment for breast cancer. "We'll get through this like Mary Beth has gotten through it," Maggie reassured her daughter.

Inwardly, though, she was terrified. Later that night, sitting at the dining room table with Jim, she pulled out the contracts. "I don't think I should sign these," she told him. She knew there was a real possibility she wouldn't live long enough to see the project through. "But Jim encouraged me to think of the contracts as a sign that my future held good things," Maggie says.

About a week later, she went to see the cancer specialist recommended by a colleague of her surgeon's -- Anna Pavlick, D.O., an oncologist at New York University Langone Medical Center. "So this is a sucky poo-poo diagnosis!" Dr. Pavlick blurted out as she walked into the room.

"Jim and I burst out laughing," says Maggie. "It was such a welcome moment of levity." And they were even more comforted when Dr. Pavlick added, "We can fix this."

But Maggie faced a rough 10-month regimen: intravenous chemo to shrink the tumor, then surgery to remove it, followed by oral chemo and radiation. Only 24 to 59 percent of Stage III melanoma patients survive 10 years, but Dr. Pavlick didn't dwell on statistics. "I knew she would do everything in her power to help me get better," Maggie says. "I left her office feeling more hopeful."

That night, Maggie's parish held a prayer service for her. Sitting in the church surrounded by about 150 people -- some of whom she didn't even know -- Maggie felt deeply comforted. "It was such an outpouring of love," she remembers. "I said to my husband, 'I'll have to be a lot nicer.'"

The treatment was difficult, but Maggie and Jim tried to keep their routines. "I had a family," Maggie says. "I had to cook dinner, do laundry. I didn't want to give in to just being a cancer patient." Continuing to work on her fiction was crucial. The heroine of her series, Murder 101, is
a college professor who solves mysteries. "Her life is nothing like mine," Maggie explains. "She's a babe, she's single, and she will not get cancer." Writing about her, she says, "helped me get completely out of my own head and escape into another world."

After her final round of chemo in March 2006, Maggie was starting to feel more like herself again, and she and Jim began planning a trip to Bermuda to celebrate. One day, though, she discovered a lump on her rib cage. "I went into a panic," she says. She immediately called Dr. Pavlick's office and spoke to a nurse-practitioner, who asked if the lump was soft or hard. But Maggie was so hysterical, 'T couldn't even tell," she says. A few days later, she saw Dr. Pavlick, who reassured her the lump was a harmless growth called a lipoma. But then, during the exam, she found about a dozen tiny black-and-blue marks on Maggie's leg and groin.

"Maggie, I'm so sorry," Dr. Pavlick said. "This is new tumor." In fact, each tiny mark was a separate melanoma.

"I went cold, sitting there in a state of shock and staring at her," Maggie recalls. Then she burst into tears. "This can't be happening. I have to be here. I have to be here for my kids," she sobbed as Dr. Pavlick sat next to her on the examining table and put her arms around her. "Just breathe," Dr. Pavlick said gently. "Just breathe."

Over the next few weeks, dozens more of the tiny tumors appeared. Then, several months later, a CT scan revealed the cancer had spread to her liver. The cancer was now Stage IV, at which survival rates drop to 10 to 15 percent.

The first time his wife was diagnosed, Jim recalls, he didn't cry. But when he called his mother to tell her the cancer had come back, he couldn't stop the tears. "Saying it out loud made it sink in," Jim says.

Dr. Pavlick quickly put together a plan, getting Maggie into a clinical trial of a drug called sorafenib, which was being tested in melanoma patients. "When I'm told there's nothing else, I'll have to make my peace with that," Maggie remembers thinking. But until then, she would do whatever she could to survive.

Luckily, the family could go ahead with the Bermuda trip. In her sun-protection outfit -- cotton pants, a long-sleeved T-shirt, sunglasses, and a hat -- "I looked like a beekeeper," says Maggie. But the trip helped her gather strength for the ordeal ahead.

She needed it. Later that summer, she developed blisters on her feet so severe that she couldn't walk -- a side effect of the sorafenib -- and she had to go off it. She was worried, but Dr. Pavlick told her there might be another experimental drug they could try. First, though, Maggie would need a few weeks' "washout period" to get the sorafenib out of her system.
In the fall, Dr. Pavlick left for a vacation in Italy to celebrate her 10th wedding anniversary. It was the first trip she'd taken in a long time, and she promised her husband she would stay off her BlackBerry. Every now and then, though, she took a quick peek at her e-mail. One day, in Rome, she got a message saying that the clinical trial in which she hoped to enroll Maggie and four other patients was about to close.

Promise or no promise, she had to get Maggie into the trial. She locked herself in the hotel bathroom and e-mailed furiously, directing her staff to get consent forms to Maggie and the other patients immediately.

The new drug that Dr. Pavlick was so excited about, tremelimumab, is a form of immunotherapy. Rather than destroying both cancerous and noncancerous cells, as chemotherapy does, tremelimumab helps a patient's T cells -- the workhorses of the body's immune system -- attack the cancer more vigorously.

Researchers have been trying for decades to develop drugs like this one, and their work is finally beginning to pay off. About 20 percent of advanced melanoma patients in clinical trials have responded well to tremelimumab and a similar drug, ipilimumab: Their cancers have stopped growing or have shrunk dramatically. Even more striking, in about 2 percent of these patients, the cancer has disappeared completely. But there's no way to identify those people ahead of time; patients just have to start the drug and hope.

Maggie had her first infusion of tremelimumab in early November 2006. A couple of weeks later, while volunteering at a local soup kitchen, she noticed that the tumors in her left groin had gotten bigger -- they were hot, swollen, and painful. But when she went in for her regular appointment a few days later, Dr. Pavlick was thrilled. "I went into the happy dance," she says. "Maggie thought I'd lost my mind."

The pain, heat, and swelling signaled that Maggie's immune system had mounted a fierce attack on her tumors. The drug was working.

Six months later, after Maggie had two more treatments, there was more evidence. She was lying on the examining table in Dr. Pavlick's office when the nurse-practitioner said, "Oh, my God! The hair on your leg is white."

"We like that, too!" Dr. Pavlick said as she came into the room. For reasons that researchers don't fully understand, when patients have a complete response to tremelimumab or ipilimumab, their hair turns totally -- and permanently-white. "So I found a wonderful hair colorist," Maggie says. "I went from being someone who got maybe two haircuts a year and pulled my hair back into a ponytail when it got too long to being a serious beauty salon attendee."
These **drugs** can also have riskier side effects, including life-threatening inflammation of the bowel. Even so, they and other new melanoma treatments (see "New Drugs, Real Hope," page 62) represent stunning progress, **cancer** experts say. "I've been treating patients with metastatic melanoma for 25 years," says Lynn Schuchter, M.D., of the University of Pennsylvania Abramson **Cancer** Center. "This is completely different. Now, when we see our patients, we’re crying joyfully."

Maggie continued to get infusions of tremelimunab every three months, and had her last of 10 treatments in February 2009. A scan at that time showed that every tumor in her body had disappeared. She's remained **cancer**-free since then, and is likely to stay that way. "Patients who achieve a complete, durable response to this therapy do not relapse," Dr. Pavlick explains. What's more, if Maggie's melanoma were ever to recur, she would be treated with tremelimunab again. "There is no downside to this," says Dr. Pavlick.

In the past few years, Maggie has taken a trip to Paris, bought herself a "wildly impractical" sports car, and written three more books. She is, she says, "hypervigilant" about the sun. When she goes swimming or kayaking, she wears long swim tights that have an SPF of about 50, and a swim shirt or UV-protective jacket. "These are easier for me because they’re idiot-proof -- I don't have to worry about missing any spots with sunscreen," says Maggie. She also dons a hat and sunglasses.

Of the five Stage IV melanoma patients Dr. Pavlick enrolled in the tremelimunab trial, Maggie is the only one who is still alive. She is a gifted writer, but still Maggie struggles to put the experience into words. She knows, above all, that she is profoundly fortunate. "It sounds so trite," she says. "But every day I'm alive, it's a miracle."

**NEW DRUGS, REAL HOPE**

Melanoma, unlike many other forms of **cancer**, has been stubbornly resistant to breakthroughs; once the disease spreads, survival rates drop significantly. But several promising treatments may be available soon.

Using the body's immune system A **drug** very similar to the one Maggie Barbieri took -- ipilimumab -- was the first treatment shown to lengthen the lives of people with metastatic melanoma. In a large 2010 study at 125 centers, "ipi" (as even doctors call it) extended survival of advanced melanoma patients by nearly four months. More striking, 24 percent of patients were alive after two years, compared with 14 percent not on the **drug**. Using the immune system and its T cells to fight **cancer** holds tremendous promise, researchers say. "T cells can find tumor cells wherever they are," explains James Allison, Ph.D., chairman of immunology at Memorial Sloan-Kettering **Cancer** Center. "And since the **drugs** treat the immune system and not tumor cells, they can potentially be used against any kind of **cancer**."

Going after a tumor's genes A second approach, known as targeted therapy, may prove even more helpful. The best known **drug** of this kind, called PLX4032 ("plexi"), targets a specific genetic mutation found in about half of melanoma tumors. In January, an early report on a
large trial found that plexi boosted overall survival and the length of time before patients' tumors began to progress again. But for the vast majority, the cancer does recur.