

# YOUR WORLD

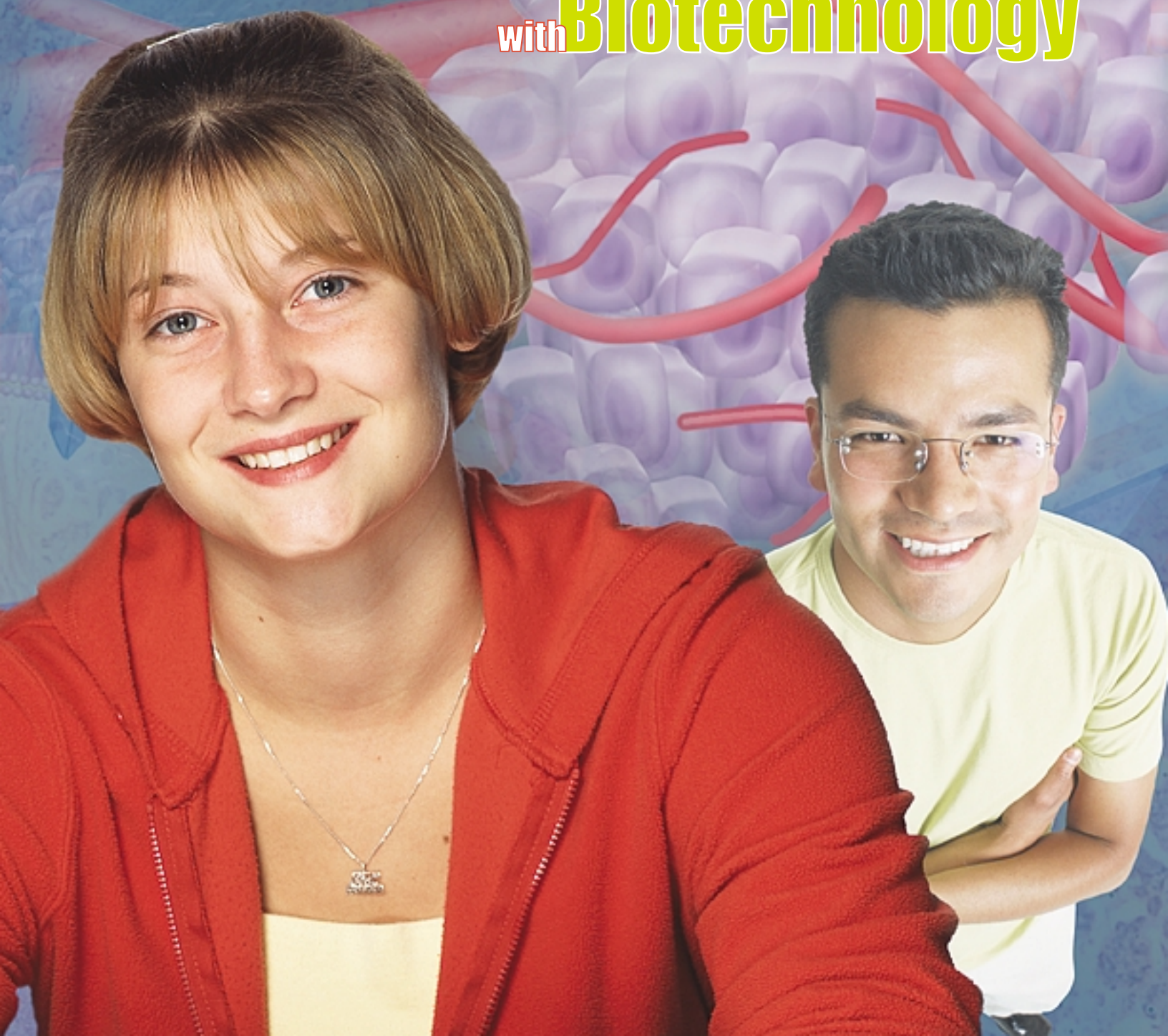
**Biotechnology & You**

A magazine of biotechnology applications in healthcare, agriculture, the environment, and industry.

**bi** Biotechnology  
INSTITUTE

Volume 11, Issue No. 1

## Fighting Cancer with **Biotechnology**





# A Life-Threatening Disease

## Cancer Basics

- Cancer is a disease of altered (mutated) genes: Mutated genes cause cells to grow out of control and destroy tissues or organs.
- There are more than 200 different kinds of cancer.
- Cancer risks increase with age (with a lifetime's accumulation of exposure to risk factors that contribute to cancer).
- More than 40 percent of the U.S. population will get cancer in their lifetime.
- About 1.2 million Americans will be diagnosed with cancer and 500,000 will die of it this year.
- Cancer rates have gone up in the last 50 years, possibly because of our longer life-span, increased tobacco use, sun-tanning, heavy alcohol drinking, and high-fat diets.
- **Oncology** is the study of cancer. (The word "onco" means tumor or mass in Greek.)
- **Chemotherapy** is a treatment that damages or kills fast growing cells such as cancer cells.



When Anna turned 15 and went to her yearly check-up, she mentioned to her doctor that she felt weak and had a tightness in her chest. Her comment signaled the beginning of a life changing event for her and her family – the fight against cancer.\*

An X-ray showed a hazy mass near her lungs, but the image didn't tell much about what was going on inside her body. The doctor scheduled Anna for a biopsy, which is the surgical removal of a piece of tissue from the suspicious area. The specialist who examined the cells under the microscope thought they looked like cancer. But what kind? Her age helped narrow the diagnosis. It was the "cancer of young adults" – Hodgkin's **lymphoma**, a cancer of the lymphatic system. The lymph system drains white blood cells from tissues and carries them to the spleen and glands (nodes), where the cells activate to fight off infections.

Nobody was concerned when Anna had swollen glands recently. Glands always swell to fight off mild infections. Now it was clear that this was not your everyday swelling. It was the result of rapidly growing cancer cells crowding out normal cells. Worse, the lymph system distributes white blood cells

\*Anna is a fictionalized person, but the situations presented in this magazine are very real.

## Contents...

The Making of a Cancer .....	4
A Cancer Turns Deadly .....	6
Sun and Smokes .....	8
Colon Cancer's Jump Start .....	10
Leukemia and a Magic Bullet .....	12
<b>Profile:</b> Sir David Lane and the p53 Gene .....	14
<b>Something You Can Try:</b> Detecting a Cancer Risk Factor .....	15
Resources .....	16

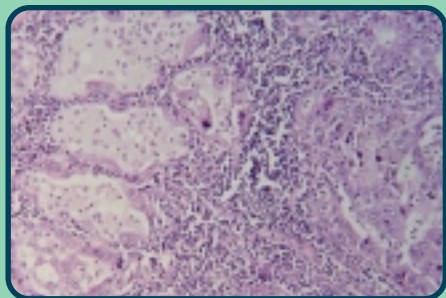


Image provided by AMGEN.


*Lung cancer cells: Doctors can tell by looking at abnormal cells that they are cancerous, but they cannot always determine the specific type of cancer. Genetic analysis will provide a new type of "microscope" for studying cancer.*

throughout the body. Thus, cancer could now be anywhere.

Anna's plans for summer camp came to a screeching end. Her brother's upcoming football championship faded from importance. Her parents felt paralyzed. She envied her friends' fuss over what to wear to the dance. Would she even live to see another dance?

Several decades before, the diagnosis of cancer was almost a certain death sentence. By the time it was found, it had usually spread to other sites in body. Today, however, almost 70 percent of childhood and young adult cancers are cured, thanks to new tools of biotechnology. Biotechnology is producing methods to detect cancer earlier and to diagnose it more accurately. It is also leading to more effective treatments with fewer side effects.

Despite these advances, there is still a long way to go to cure cancer. Doctors struggled to determine the exact form of Anna's lymphoma and how to treat it. Her treatment lasted over a year and required more courage than she could have imagined. The drugs made her so sick she wondered if the cure was worse than the disease. She made many friends at the cancer center, each with a unique and challenging story.

In this issue of *Your World*, you will follow what Anna learned about our new understanding of cancer as a disease of altered genes and how that understanding is leading to new treatments and hope. 


### Dear Readers,

The Biotechnology Institute is pleased to present the fall 2001 issue of *Your World*. I hope this issue will help spark your curiosity about biotechnology's impact on us all, and especially its role in treating and curing cancer.

Cancer kills as many as 500,000 Americans every year. Among today's students are the scientists, doctors, and technicians of tomorrow whose discoveries will take us closer to success in preventing, treating, and curing this disease. This issue can help inspire these students and inform all students about behaviors that increase their risks for many types of cancer.

The Biotechnology Institute publishes *Your World* for teachers and students in middle and high schools across the country and, increasingly, throughout the world. I welcome your comments about the magazine and the Institute.

We are especially grateful to Dr. Samuel Waksal, President and Chief Executive Officer of ImClone Systems Incorporated, for his interest and his company's sponsorship of this issue of *Your World*. Sincerely,

  
Paul Hanle, President

The Biotechnology Institute would like to thank the Pennsylvania Biotechnology Association, which originally developed *Your World*.

## YOUR WORLD

Biotechnology & You

Volume 11, Issue No. 1

Published by:

Jeff Alan Davidson - BioSciEd

In Partnership with:

Biotechnology Industry Organization (BIO)  
Neo/SCI Corporation  
Pennsylvania Biotechnology Association

Writing by:

The Writing Company,  
Cathryn M. Delude and  
Kenneth W. Mirvis, Ed.D.

Design by:

Snavelly Associates, Ltd.

Illustrations by:

Neo/SCI

Science Advisor:

Sridhar Ramaswamy, M.D.,  
Dana-Farber Cancer Institute/Harvard  
Medical School and Whitehead / MIT  
Center for Genome Research

Reviewers:

Shanny L. Dyer, Ph.D.

Gloria A. Seelman, M.A.,  
Instructional Specialist

William Sheridan, M.D.,

Vice President, Product Development,  
Amgen, Inc.

The Institute acknowledges with deep gratitude the financial support of ImClone Systems Incorporated in producing this issue.



**ImClone Systems  
Incorporated**

## Biotechnology INSTITUTE

The Biotechnology Institute (BI) is a national non-profit entity based in Washington, DC, and dedicated to education and research about biotechnology. Our mission is to engage, excite, and educate people about biotechnology's potential to solve human health and environmental problems. *Your World* focuses on biotechnology issues and brings scientific discoveries to life for 7<sup>th</sup> to 12<sup>th</sup> grade students. We publish issues on different topics each fall and spring. Please contact Jeff Alan Davidson, Publisher, for information on subscriptions (individual, teacher, or library sets). Some back issues are available.

For more information:

Jeff Alan Davidson, Publisher  
1524 W. College Avenue, Suite 206  
State College, PA 16801  
800-796-5806

JeffDavidson@cs.com  
[www.BiotechInstitute.org](http://www.BiotechInstitute.org)

Copyright 2001, BI. All rights reserved.

### Peak Performance by Mandy Blumenshine

Sixteen, driving, friends, fun, life guarding, swim team, prom, limp, ouch, physical therapy, x-ray, leg, tumor, brace, crutches, Denver, life threatening, limb salvage, amputation, death, life, hospitals, what, scared, biopsy, pathology, doctors, nurses, Broviac, blood, drugs, bone scan, CAT scan, MRI, stop, enough, fear family, support, waiting, results, why, oncologist, osteogenicsarcoma, protocol, photographer, Katy, pictures, chemotherapy, Adriamycin, Cisplatin, vomit, sick, blonde, hair loss, bald, cry, attitude, hats, scarves, pediatrics, third floor, new friends, Jason, Marco, Jovannah, surgery, four hours, 100% tumor kill, wake up, pain, good news, save leg, total knee replacement, scar, recovery, healing, no crutches, no brace, two legs, two feet, standing, walking, chemo finished, alive, growing hair, high school, graduation, college, pre-med, doctor, me, healthy, life guarding, friends, fun eighteen. I am a survivor of cancer.

Mandy Blumenshine wrote this award-winning poem in 1995 after her two year struggle with cancer. She now has a son and is pursuing her medical degree. The photograph at left was taken by the fellow cancer survivor "Katy" (Tartakoff) mentioned in the poem, who is now a professional photographer.





# The Making of a Cancer

What are three genetic malfunctions that lead to cancer?

After Anna recovered from the shock of learning she had cancer, she wanted to know why. What had gone wrong in her body?

Anna's doctors told her that they had only recently been able to answer that question. Throughout history, cancer seemed chaotic. There are so many types that behave in such different ways. Is it one disease or hundreds? Sometimes it seems to run in families. Sometimes it seems caused by exposure to outside agents like radiation, toxins, or a virus. Other times it just appears mysteriously.

A unifying explanation came when scientists could examine chromosomes and genes. They observed that cancer cells had abnormal-looking chromosomes. Some chromosomes had swapped sections. Others were duplicated or deleted. Eventually scientists realized that cancers arise when certain genes on these chromosomes are **mutated**, causing a change in the DNA. DNA is the molecule that "spells out" the genetic information that tells your body how to grow and operate. These **mutations** (DNA changes or "misspellings") can happen during your lifetime, or you can inherit them from your parents.

Genes are like little computer programs written in the code of DNA. They give the cell the instructions to make RNA and eventually proteins. The cell uses proteins for its own structure or to create its products, like mucus, insulin, or hormones. A DNA mutation can alter a protein, which can change the way the cell behaves. Scientists saw that cancer cells have many mutations, and they suspected that these mutations might be in the genes that control cell growth.

## Accelerator Genes: "Grow and Divide"

Normally, cells send out growth signals that say, "Cells! We need more of you. Divide!" Cells in healthy tissues send out these signals for many reasons. Perhaps a baby needs to build more bone and muscle. Perhaps you need to heal a cut on your hand. Cells send out signals (called growth factor proteins) that travel to other cells near and far. When a growth signal lands on the

right "antenna" (called a **receptor**) on the outside of a cell, it sets off a chain reaction of events. These events make their way to the nucleus, the home of the chromosomes and genes. A different gene controls each step in this chain. These growth signals become inactive when the tissue doesn't need more cells. However, if genes involved in this signaling pathway mutate, they allow too many growth signals to reach a cell. The cell divides too rapidly, and cell growth "accelerates" out of control. The mutated genes that cause this growth acceleration are called **oncogenes**. Oncogenes encourage the growth of a mass of cells that can become a cancerous tumor. (You will read about two oncogenes, *src* and *ras*, in later articles.)

## Brake Genes: "Stop Growing"

Scientists observed that certain genes other than oncogenes were deleted in cancer cells.

The loss of those genes seemed to accelerate cell growth. They theorized that those lost genes might be "brake" genes that

b) The "brake" (tumor suppressor) genes fail to stop the signal pathway.



normally slow down cell division. When you were a baby, your cells needed to divide rapidly. As you reach adulthood, however, most of your cells are actually resting. They only divide to replace lost or damaged cells.

To keep cells in a peaceful, restful state, a set of brake genes slow or stop the cell division. They also jump into action if an accelerator gene goes too fast. These genes are called **growth suppressor** or **tumor suppressor genes**. Just as accelerators can get stuck in the “on” position, however, the brakes can fail. When brake genes are mutated, a cell accelerates its drive towards cancer. (You will find two of these brake genes in the article on colon cancer on page 10.)

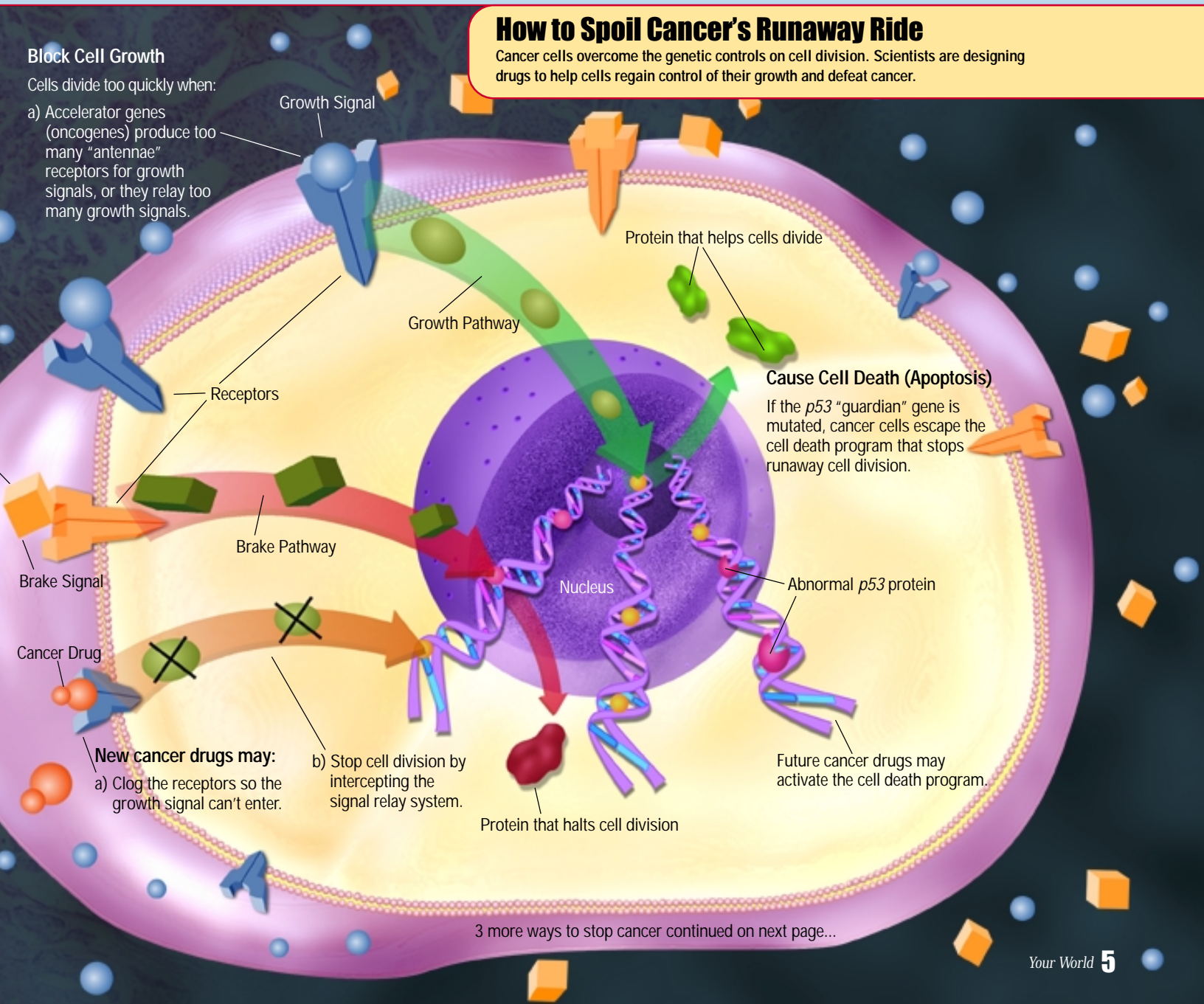
### Guardian Gene: “Repair or Die”

Cleverly, cells are equipped to deal with such damage. They have a “fail safe” program masterminded by a “guardian” gene. This guardian, called **p53**, normally works as a building inspector

for the chromosomes. (You will meet this gene several times in this magazine.) When **p53** sees damage, it calls in a repair crew. If the damage is too great to repair, it starts a cell death program: it orders the cell to kill itself, and the cell obeys! In that way, the tissue neighborhood remains safe. (Programmed cell death is a natural part of life. It is called **apoptosis**, the Greek word for a tree shedding its leaves.) Unfortunately, mutations occasionally cripple the guardian itself. In fact, many cancers have a damaged **p53** guardian gene – and a disabled cell death program. Any cell that escapes the guardian gene’s control has a big advantage over the well-behaved, slowly dividing healthy cells.

### Cancer’s Genetic Program Takes Over

Anna’s doctors explained that this model of cancer genetics has not been described for every cancer type. Still, these ideas likely underlie all cancers. As Anna would learn, other mutations allow cancer to become aggressive and take over a tissue. ❏



### How to Spoil Cancer’s Runaway Ride

Cancer cells overcome the genetic controls on cell division. Scientists are designing drugs to help cells regain control of their growth and defeat cancer.

3 more ways to stop cancer continued on next page...



What genetic mutations help a cancer become malignant and deadly?

# A Cancer Turns Deadly

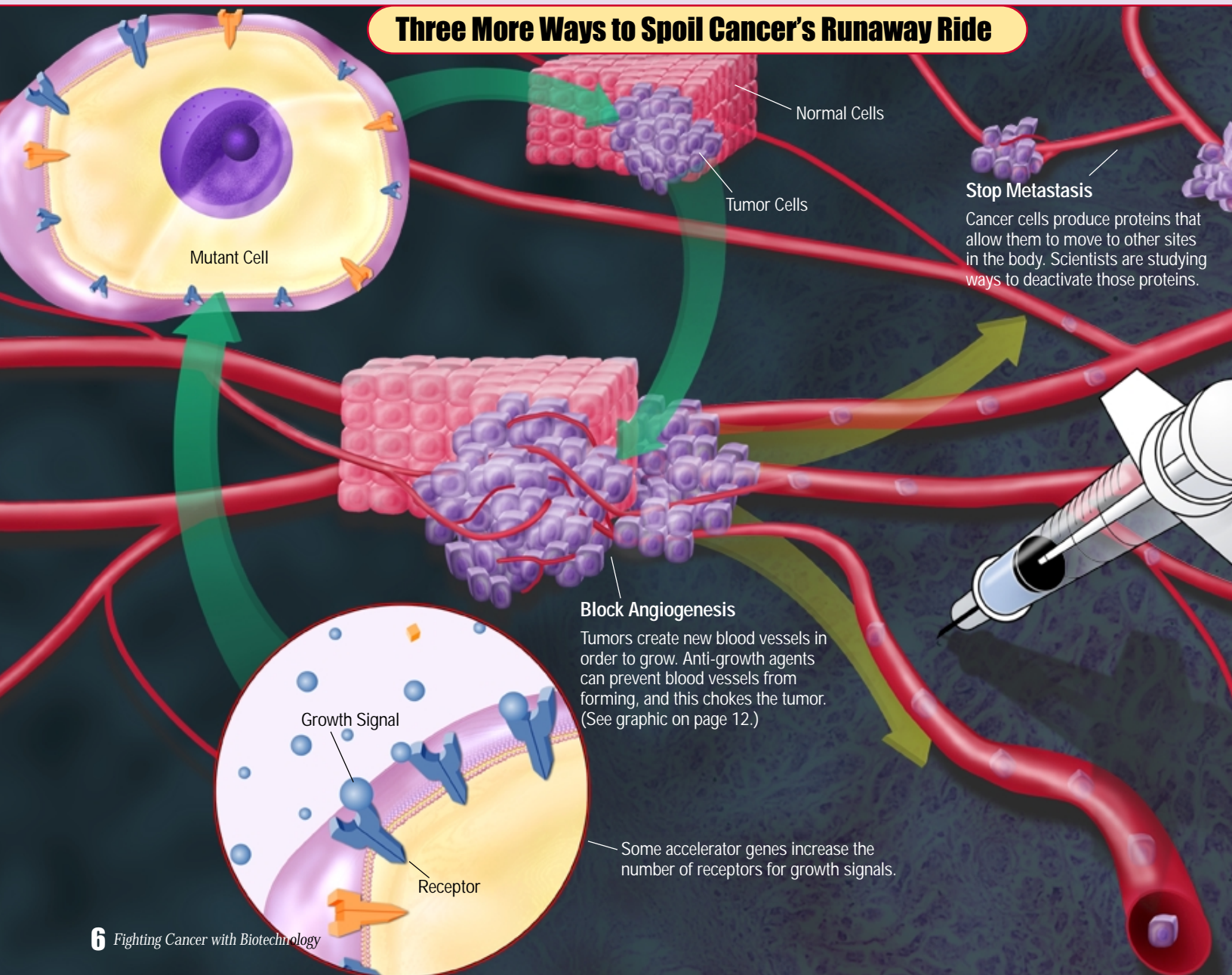
As Anna explored the genetics of cancer, she learned more about how cells normally function. Cancer has to overcome many built-in protections that keep cells from going astray.

## Evading the Spell Checker

Any gene can become mutated quite easily. The wonder is that all cells don't become cancerous. First of all, daily living is hard on cells. Sunshine mutates DNA in your skin cells. Many chemicals

that you meet while breathing, eating, and moving, can also mutate DNA. So can certain viruses. Cells that suffer the most frequent damage, like those on your skin or in your intestines, divide frequently to replace the damaged cells. Each cell division carries a risk. Before dividing, the cell makes a copy of your 23 chromosome pairs. Together, the 23 chromosomes contain 3 billion DNA "letters." Could you copy that many letters without a mistake? Cells can't either. So, they come equipped with spell checker genes. These DNA repair genes can also correct the mutations that happen through daily living. In most cases, they

## Three More Ways to Spoil Cancer's Runaway Ride



### Stop Metastasis

Cancer cells produce proteins that allow them to move to other sites in the body. Scientists are studying ways to deactivate those proteins.

### Block Angiogenesis

Tumors create new blood vessels in order to grow. Anti-growth agents can prevent blood vessels from forming, and this chokes the tumor. (See graphic on page 12.)

Some accelerator genes increase the number of receptors for growth signals.

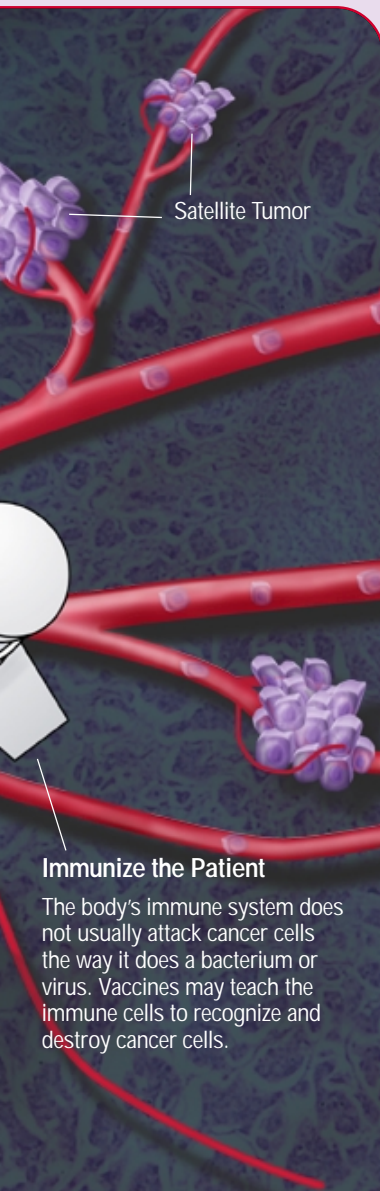




succeed. Sometimes, however, the repair genes themselves are damaged. When they can't correct mistakes, more mutations sneak in unchecked.

## Fixing the Frayed Shoelaces

It's a fact that life always ends in death. That fact holds for the whole organism and for its individual cells. When a cell gets too old to function properly, it puts the organism in peril. Cells have a handy system for knowing when to die. It is a mechanical wearing down of an essential part: the **telomeres**, which are the tips of the chromosomes. They are like the plastic tips of shoelaces, keeping the laces from fraying. Every time a cell divides, it wears down the tip a bit. After many divisions, the tips are too short and they fall apart. Then the chromosomes decay – and the cell collapses. The shortening tips act like counters, ticking off the time to death. Even a cell with a jammed accelerator and broken brakes will die when the telomeres fray. To become cancerous, the cell must keep the tips intact. Somehow it turns on a gene that has been turned off since infancy. This gene produces a protein (called **telomerase**) that rebuilds the telomeres. Thus, the cell can divide indefinitely, becoming “immortal.” Immortality coupled with a racing accelerator creates a dangerous situation: an unruly mass of cells that have broken free of the tissue's control.



## Thirsty for Blood

An immortal clump of cancer cells (a **tumor**) has free reign to grow. Eventually, though, it will meet a limit when it runs out of food and oxygen. To continue to grow, the tumor needs a blood supply. So, it hijacks one. A pediatric surgeon, Judah Folkman, discovered that tumors send out growth signals to nearby blood vessels. The blood vessels then create new vessels for the tumor, tricking the body into supporting the cancer. This process is called **angiogenesis**. (“Angio” means blood and “genesis” means beginning. In fact, cancer gets its name because



**Charles Darwin based his theory of evolution on the idea of “the survival of the fittest.” Species that are more successful at reproducing in a particular environment become more dominant. Do cancer cells behave in a Darwinian fashion in the body's “environment”?**

of the blood vessels radiating out from a tumor like the arms of crab: “Cancer” means “crab” in Latin.) Scientists have found several proteins that promote this blood supply. They have also found other “brake” proteins that slow down the growth of blood vessels. These anti-growth proteins may someday lead to drugs that can choke a tumor to death.

## An Invasion

Most cancers could be cured – if surgeons could remove the entire tumor. But once a tumor has a blood supply, it usually has more ambitious plans: an invasion. It chews through the walls of the surrounding tissue and destroys the organ's vital function in the body. Then, some cancer cells become mobile. They travel through blood and the lymphatic systems to other organs, where they try to set up camp. For instance, lung cancer cells may try to colonize the brain. This spreading is called **metastasis**, and it makes cancer truly deadly.

## A New Task for Drug Designers

Anna feared that cancer is just too clever to defeat! Her doctors, however, are hopeful. They believe it will be possible to intercept the malfunctioning genes and kill the cancer cells, without harming healthy cells way that the current chemotherapy does. (See illustrations on pages 4 through 7.)

**Career Center:** Molecular biologists compare how genes and proteins interact in healthy cells and cancer cells.

# Cancer

## and the Environment:

### Sun and Smokes



Why is cancer usually a disease of "old age"?



Anna's cancer was probably the result of several mutations, although what they are and how she got them is still unclear. However, scientists think many people get cancer because of specific things they do. Now Anna worries about her friends who take risks with cancer.

In most cases, no single event causes cancer. Getting cancer is considered to be a long, drawn-out process over the course of a lifetime. But lifestyle choices can speed it up.

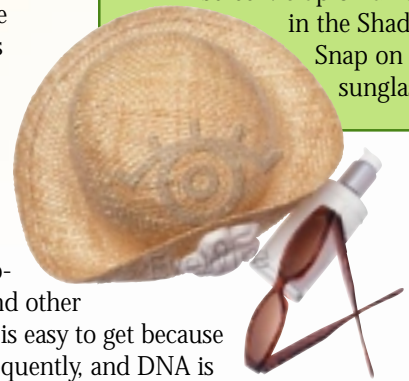
### No Such Thing as a Healthy Tan

A friend who works as a lifeguard came to visit Anna. He was proud of his tan. The nurses told him how they used to see just older people with skin cancers. A long lifetime of exposure to the sun's ultraviolet rays caused their cancer. Now the nurses see people in their twenties with skin cancer, even the most deadly kind: **melanoma**. Our culture idealizes life in the sun, and it encourages us to show more bare skin. We put more of ourselves more directly – and more frequently – in the line of fire of the sun's harmful rays.

Sunshine's ultraviolet rays (UV) damage DNA in the skin cells. The skin's outer layer (epidermis) has three layers. Flat, scale-like cells (*squamous*) produce the keratin that protects your body. They lie over round cells (*basal*) that cover the cells (*melanocytes*) that produce the brown pigment melanin. Sunlight can damage all three cells to cause three types of cancers: *squamous*, *basal*, and *melanoma*. The first two cancers cause ugly growths on the skin, but they are slow growing and treatable with surgery. Melanoma, however, is very aggressive. It quickly invades the layer of skin (*dermis*) that contains blood and lymphatic vessels. It uses those vessels to gain access to the entire body and scatter cancer cells throughout (metastasis).

### Skin Cancer Prevention: Slip-Slop-Slap-Shade-Snap

When your shadow is shorter than you are, the sun is strong enough to damage your skin. Slip on a shirt. Slop on sun-screen. Slap on a hat. Sit in the Shade. Snap on sunglasses.



### Divide and Be Conquered

In a resting cell, the chromosomes' DNA is tightly wound and protected. When cells divide, the DNA unwinds so it can be copied. In its unwound state, it is an easy target for ultraviolet light, chemicals, and other menaces. Skin cancer is easy to get because skin cells divide so frequently, and DNA is damaged most easily during cell division.

### A Smoking Epidemic

Two other friends came to visit Anna. They smelled of cigarettes, and a nurse told them an interesting story. Back in 1919, a doctor in a St. Louis hospital invited an entire medical class to watch an autopsy of a man who died of lung cancer. Lung cancer was so rare that the doctor thought the students might never see another case. He was wrong! Lung cancer became increasingly

Think about it!

Smoking-related diseases have personal, social, and economic costs. We could prevent 30% of all cancer if people stopped smoking. Why is it legal?

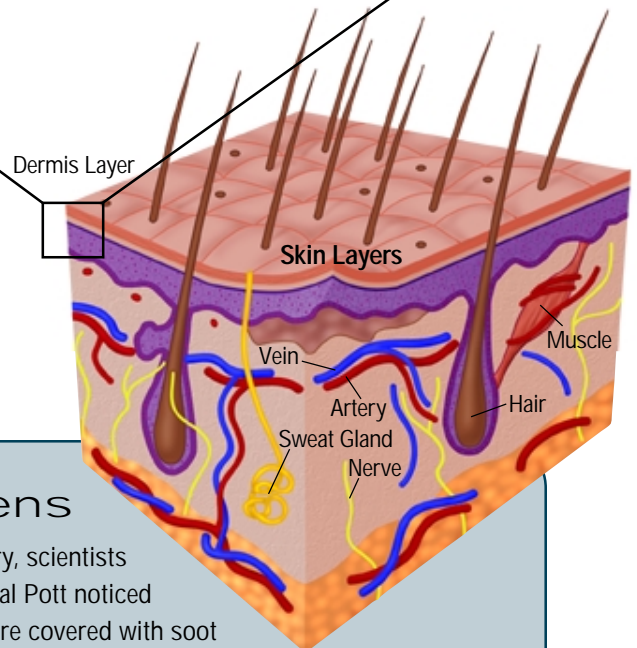
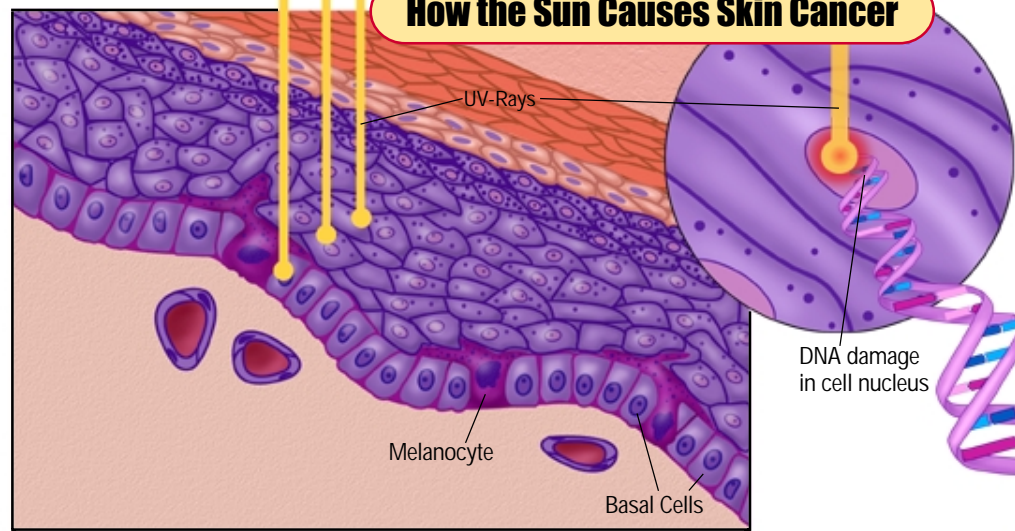


## How the Sun Causes Skin Cancer

common. It now accounts for 30 to 40 percent of all cancer deaths. That sharp increase followed a new invention for smoking tobacco in 1912: the cigarette. Previously, natives in the Americas had smoked tobacco, and Sir Walter Raleigh introduced it to Europeans in the 1600s. However, early tobacco was too strong to inhale. The milder form in cigarettes allowed people to suck the smoke deep into their lungs.

No one knew then – as we do now – that cigarette smoke contains dozens of **carcinogens**, chemicals that can cause cancer. One of those chemicals mutates the *p53* gene so it can no longer destroy abnormal cells. Normally, our lungs are rarely exposed to such an onslaught. But with each drag, a smoker adds another risk of damaging a lung cell's DNA.

Cases of lung cancer rose much higher in men than in women for the first part of the twentieth century because it was not “ladylike” to smoke. After WWII, more women began smoking. Now they have caught up with men in lung cancer. Today, every young medical student sees too many encrusted lungs ravaged by cancer. 🙄



**Career Center:** Epidemiology, the study of how a disease occurs in a population, was – and still is – essential in identifying causes of cancer.



## Chimney Sweeps and Chickens

Why do some people get cancer and others don't? Throughout history, scientists struggled with conflicting clues. In 1775 the English physician Percival Pott noticed that many chimney sweeps got a rare form of cancer. The sweeps were covered with soot containing chemicals that somehow damaged their cells. Thus, cancer seemed to be caused by outside agents. Over time, a variety of chemicals, X-rays, and even foods were added to the list of carcinogens.

In 1886, Hilario de Gouvea, a Brazilian doctor, reported that an eye cancer (retinoblastoma) seemed to be inherited in certain families. This clue that some cancers seemed hereditary contradicted the evidence that it was caused by chemicals and other agents.

In the early 1900s, a scientist named Peyton Rous studied chickens with a cancer called sarcoma (a tumor in a bone or muscle). He realized the tumors carried a virus that caused cancer when it infected other chickens. That really confused the theory of cancer! Was it infectious, hereditary, or caused by carcinogens?

In the 1970s, U.S. scientists Harold Varmus and Michael Bishop discovered that the chicken tumor has a mutated form of a gene that controls cell growth. They theorized that the mutated gene acts like an accelerator oncogene when the virus introduces it into a normal cell, thus causing cancer. This gene is closely related to a human gene that controls cell growth. Other scientists showed that people who seem to “inherit” cancer actually inherit faulty genes involved in cellular growth. Thus, studying the genetics of cancer unifies all the conflicting clues. Cancer is caused by an enemy within our own cells.



London chimney sweep at the dawn of the 20th century

Why do some cancers seem to "run in families"?

# Cancer and Heredity: Colon Cancer's Jump Start

One of the families Anna met was particularly unlucky. A thirty-year-old woman had colon cancer, which is usually a disease of older people. Even worse, her mother and her brother died of colon cancer in their 40s.

Cancer of the large intestine (colon) begins when small growths called **polyps** form in the lining of this tissue. After many years, polyps can grow into cancerous tumors. They interfere with regular bowel functions and can spread to nearby organs, such as the liver. Although it is an ugly disease, colon cancer is a good example of the multi-step breakdown of genes that control cell division. Scientists Bert Vogelstein and Kenneth Kinzler broke colon cancer's process into four steps:

**First Mutation:** A growth suppressor gene (*APC*) on chromosome 5 is destroyed in one cell. Without this brake, that cell divides too much, but otherwise looks normal.

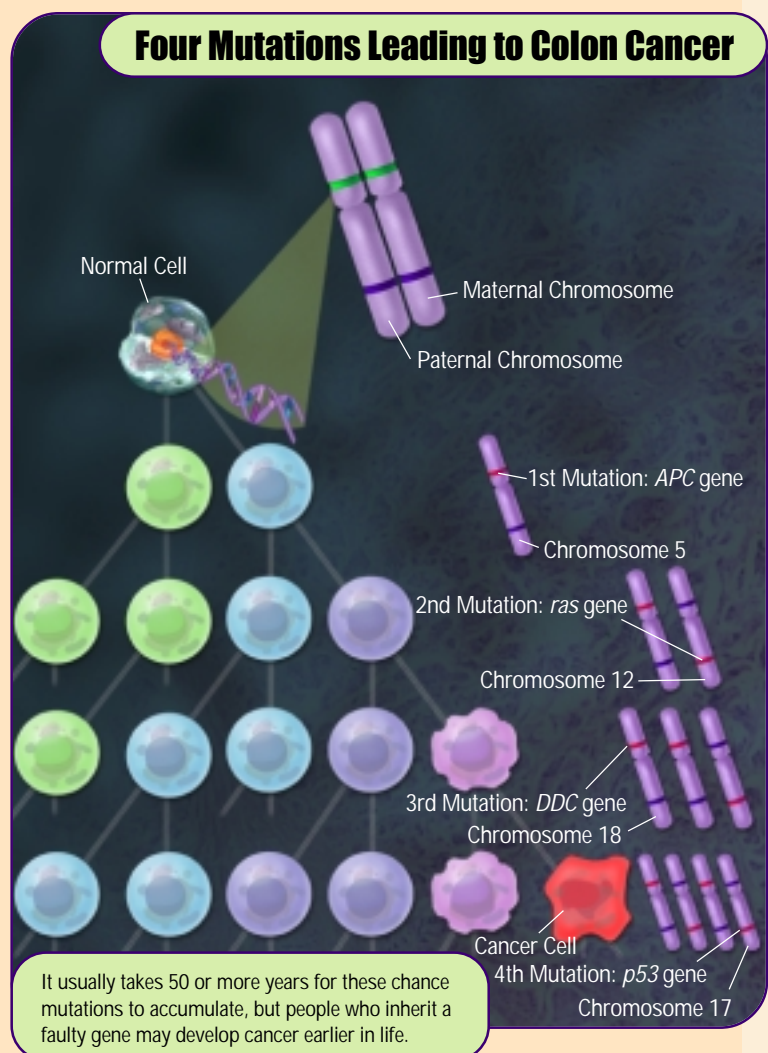
**Second Mutation:** In one of that cell's offspring, a gene on chromosome 12 for a growth signal (*ras*) mutates into an oncogene. Normally, *ras* sits under the cell membrane waiting for a growth signal. The mutant *ras* doesn't wait for signals from outside the cell. It produces its own signal. Cells divide rapidly into a tiny mass called a "polyp."

**Third Mutation:** In one of the polyp's cells, another growth suppressor gene, *DDC* on chromosome 18, is knocked out. The polyp grows into a tumor with cells that begin to look and act abnormal.

**Fourth Mutation:** A tumor cell suffers a one-letter spelling mistake in the "guardian" *p53* gene on chromosome 17. Their offspring collect new mutations. Cells become immortal and then spread throughout the body.

The chance of getting each hit is small. That's why it usually takes 50 years or more for colon cancer to develop – if you get it at all. However, in about 10 percent of colon cancer cases in the U.S., people are born with one hit. They inherit a gene that is already mutated, so they get colon cancer at much younger ages.

## Four Mutations Leading to Colon Cancer





## An Inherited Risk


When you think of a hereditary disease, you may think of cystic fibrosis, sickle cell anemia, or Downs syndrome. In these, a specific genetic mutation directly causes the disease condition. Cancer is not like that. When a cancer is “hereditary” one of the genes responsible for controlling cell growth starts out mutated. You don’t have to wait for some environmental factor to mutate it. You are already one step down the road, so you need one less “hit” to get cancer. If you never encounter the other hits, however, you don’t get it.

Understanding cancer requires studying how cells interact and communicate with each other in the living body. Some scientists estimate that cells in a tissue may send and receive as many communication signals as the population of New York City each day.

In the case of colon cancer, some families inherit a faulty version of the APC growth suppressor gene (step 1). While they are still young, their colons become blanketed with small polyps, each of which carries the risk of becoming cancerous. Other families inherit a damaged DNA repair gene called *MSH*. Normally, this gene catches DNA spelling errors. The mutated gene, however, lets the spelling errors pass, so mutations build up in the cells.

When a person inherits one of these faulty genes, every cell has it. However, only the colon cells activate it. Every colon cell has the faulty gene, so the chances are higher than normal for other mutations to happen.

## An Ounce of Prevention

Most colon cancers are not caused by inherited genes. For most of us, lifestyle matters more than genes. For example, Americans, who love beef burgers, are ten times more likely to get colon cancer than Africans, who eat mainly fruits and vegetables. Diet, exercise, alcohol consumption, and smoking all influence your risk of getting colon cancer – and many other cancers and diseases. 



**What can you do to prevent cancer? Regular exercise and a diet with plenty of fruits and vegetables seem to keep the doctor away. Obesity seems to increase the risk of many forms of cancer (such as colon, breast, and ovarian), as well as diabetes, arthritis, and heart disease.**

## Vaccines: Teaching the Body to Fight its Own Cancer

In a way, the simplest way to fight cancer would be a vaccine that triggers the immune system to kill cancer cells. Vaccines work by alerting the immune cells to fight off a foreign invader. Since cancer is an invader from within, our immune system has trouble recognizing it as a danger. However, in the 1890s, the New York City surgeon William B. Coley discovered that the body’s immune cells can be coaxed to attack its own cancer cells. He noticed that cancer patients who got bacterial infections were sometimes cured of cancer. He injected tumors with bacteria, and the tumors shrank! The bacteria activated the immune system, which fought the cancer along with the infection. Recently, scientists have used the products of an activated immune system, such as *interleukins*, to treat some cancers. Unfortunately, interleukins also make patients very sick. Scientists want to kill cancer but spare the person. They are identifying proteins that cancer cells have on their surface, but that normal cells don’t make. Then they produce an antibody (which carries a poison) that will lock on to those specific proteins. When injected into the patient, the antibody vaccine homes in on just the cancer cells and leaves the rest of the body healthy. One vaccine technique stimulates the immune cells to recognize the cancer cells as a danger. Another technique is to remove some cancer cells, manipulate them in the lab to make them more visible to the immune cells, and then reintroduce them into the patient as a vaccine. Scientists see vaccines as part of their future collection of cancer fighting drugs. (See next article.)

# Cancer Drugs

## Leukemia and a Magic Bullet



One little boy in Anna's cancer center had a very rare and deadly form of leukemia. He became part of a new cancer treatment that gave everyone hope.

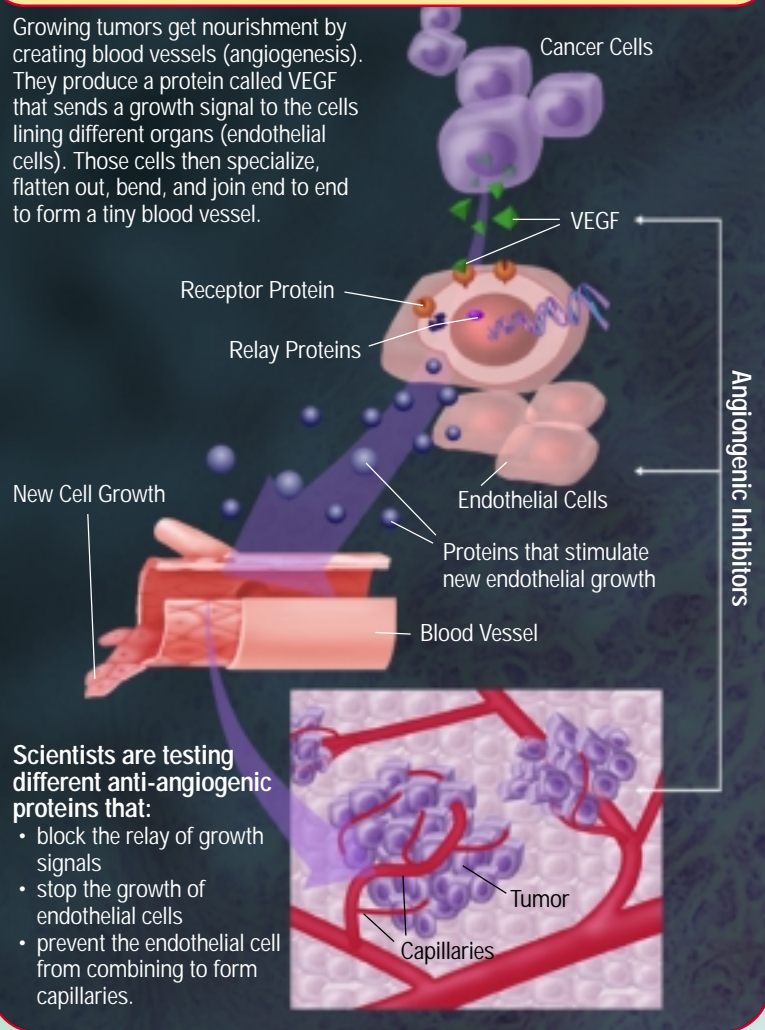
drug in the early stage of testing. Patients urgently lobbied the drug company to do a large-scale trial. Normally, drug companies can't afford large-scale programs for a rare disease like CML. They were mainly doing this early trial to test a new concept: rational drug design. (See below.) The company agreed, and the results were amazing. The little boy is back outside playing baseball, and many other patients seem cured.

In 1845, a biologist named Rudolf Virchow examined a dying patient and saw what looked like pus in her blood. He was really seeing an excessive number of large, abnormal white blood cells. The disease became called leukemia. ("Leuko" means white and "[h]emia" means blood in Greek.) Blood cells are made from immature **stem cells** in the bone marrow, the spongy tissue inside bones. These cells are called stem cells because many types of cells can arise or stem from them. There are many different types of leukemia. Some are **chronic** (slow-growing) and others **acute** (fast-growing). Leukemia prevents stem cells from maturing into the many specialized white cells that fight off infections. Like in all cancers, the cancerous cells crowd out the normal ones. The body doesn't produce enough red blood cells that carry oxygen throughout the body or the platelets that heal cuts and bruises. Unlike most cancers, leukemia doesn't form a solid tumor. In a sense, the "pus" in the blood vessels is the tumor.

Most childhood leukemia is the acute kind, which is usually treatable today. That's why it was so sad when the little boy got Chronic Myelogenous Leukemia, or CML, which is very hard to treat. His parents joined an internet support group. They learned about a new

### Blocking New Blood Vessels (Anti-Angiogenesis)

Growing tumors get nourishment by creating blood vessels (angiogenesis). They produce a protein called VEGF that sends a growth signal to the cells lining different organs (endothelial cells). Those cells then specialize, flatten out, bend, and join end to end to form a tiny blood vessel.



Scientists are testing different anti-angiogenic proteins that:

- block the relay of growth signals
- stop the growth of endothelial cells
- prevent the endothelial cell from combining to form capillaries.








How can understanding cancer genetics help create better drugs?

## Rational Drug Design



Most chemotherapy drugs were developed in a hit-or-miss way. If they work, no one knows exactly how, except that they kill rapidly dividing cancer cells. Unfortunately, they also kill many healthy cells. They leave the patient weak, nauseous, temporarily

bald, and prone to other diseases. As scientists learn how cancer reprograms the signals inside healthy cells, they can see how to beat cancer at its own game. The drug Glivec™, which was developed to fight CML leukemia, is an example of this new kind of “smart” drug.

First, scientists realized that CML happens when chromosomes 9 and 22 swap sections. They pinpointed that swap in the middle of a growth signal gene called *abl* on chromosome 22. That swap turns the *abl* gene into an oncogene that stays “on” continuously. Then scientists looked for a small molecule that could slip into the mutated *abl* protein and jam it. Eventually, they found just the molecule and used it to create the drug Glivec. The drug stops the *abl* protein from sending out the

“Grow!” signal, so the cancer cells stop dividing. The molecule fits only in the abnormal *abl* protein and doesn’t harm healthy cells or cause serious side effects.

Unfortunately, patients in the late stages of CML seem better for a few months, but the cancer returns. Some of these advanced cancer cells have an additional mutation that allows them to keep producing the growth signal. These drug-resistant cells begin to take over, and the cancer revives. Now scientists are working on other molecules that will target advanced mutations. They are also working on other “rationally designed” molecular smart bombs for different cancers.


## A New Class System

Leukemia is the center of another breakthrough in cancer research: classification. Doctors mainly classify cancers by the tissue it starts in. Advanced cancers are hard to classify, though, and not all cancers in the same tissue behave the same way. Since cancer is caused by faulty genes, what about identifying cancer by how it behaves genetically rather than by how it looks? If scientists knew which genetic program a cancer cell used, they could select the right treatment program to “debug” it.

To get started in this direction, scientist Todd Golub and

colleagues experimented with two forms of acute leukemia. They created “blind” samples so they wouldn’t know which cell was from which type. They identified the active genes in both cell types and used computers to develop genetic profiles of the two types. They found that those profiles helped them tell the two types apart in other blind samples. Scientists now hope such methods can create a “periodic table” or “global map” of cancer. It will take some very advanced computer and mathematical skills to get there. The pay-offs will be huge: faster diagnosis, more effective treatment, and more cures. 🌐

## A New View of Cancer



Anna could see the day when a teen would tell the doctor about a symptom that might mean cancer. The doctor would take a tissue or blood sample to look for proteins made only by specific cancer cells. Imaging machines would scan the body’s organs in 3-D to pinpoint the location of a tumor. The cells taken from that spot would go under a new kind of microscope: a genetic one. DNA tests would tell doctors exactly which genes were active in the cancer’s program. Then they could select a few “rationally designed” drugs to clog several of cancer’s gears. Those drugs would harm only the cancer cells, leaving the immune cells, stomach lining, intestines, and hair follicles alone. No more vomiting. Goodbye, diarrhea. Hello, hair! Anna feels lucky to be alive, and she’s going to everything to keep cancer from revisiting her. No cigarettes. No tans. Fruit every day. Little alcohol. Exercise. And lots of leaping for joy.

**Career Center:** Bioinformatics combines biology, computers, mathematics, and graphic imaging. It is a valuable key for systematizing the genetics of cancer.



# Sir David Lane and the *p53* Gene

## PROFILE

Cancer is a stubborn, vexing, and very complex disease. If it were not, the long war on cancer might have succeeded by now. David Lane became a knight in the determined battle to understand and defeat cancer. Queen Elizabeth of England bestowed the knighthood on him in 2000 for his discovery of the *p53* gene, which could be a chink in cancer's armor.

**A**s a teenager in England, David planned to concentrate in art courses, but he “fell” into science. He studied microbiology at the University College in London and decided to pursue a career in science. He earned a Ph.D. in immunology and did postgraduate research at the Imperial Cancer Research Fund. “I love finding out how things work,” he said, “and the definitive nature of science, the sense that you are coming up with solutions.”

One solution was to understand better what makes a cell cancerous. He discovered that many cancer cells activate a gene he called *p53* (because it makes a protein with an atomic weight of 53,000). He assumed it was an oncogene that was enabling the cancer's growth. A few years later at the University of Dundee in Scotland, he realized that *p53* acted more like a tumor suppressor gene.

One of his colleagues, Peter Hall, offered himself – or rather his arm – as a guinea pig. They exposed a section of Peter's arm to radiation and then did a biopsy of his skin in the affected and unaffected areas. (DON'T try this at home!) The *p53* gene had turned on in the cells exposed to radiation, a sign that it was trying to repair the damaged cells or suppress their growth. In the ten years since then, research has revealed the critical role of *p53* in “policing” the cell death program of a fatally damaged cell.

Researchers found that *p53* mutates in about half of human cancers, making the tumors aggressive



**Sir David Lane**

*Professor of Molecular Oncology, University of Dundee and Chief Scientific Officer, Cyclacel*

because they have lost the ability to police themselves. This finding sheds light on a previous mystery: Why does radiation and chemotherapy kill some tumors and not others? When these techniques work, it is not because they are directly killing the cancer cells. It is because they damage the cell enough to activate *p53*, which then orders the cell to die. Likewise, when the treatments fail, it is often because the *p53* gene itself is damaged and can't pass out the death verdict to the cell. Knowing whether a patient's tumor has a working version of *p53* can help doctors decide if these painful treatments have a chance of success. This insight may also lead to new cancer treatments. Finding a way to activate a working version of *p53* more directly could spare patients the unpleasant side effects of most cancer therapies. Likewise, injecting the *p53* protein into a tumor that has lost its working version of the gene could improve the treatment's success.

In addition to teaching and researching at the University of Dundee, Sir David Lane heads a company, Cyclacel, that is developing cancer treatments using *p53*. He finds working in science engaging and fun. “We're constantly doing interesting things, and we have the potential to improve human health and understanding. You can travel internationally, network, make great friends, and still do things that are hugely satisfying.”

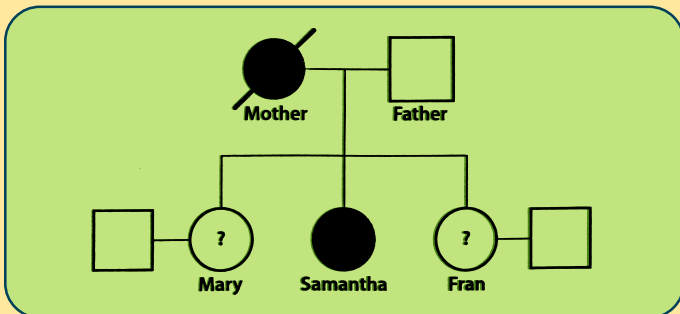


# something YOU CAN Try

## Detecting a Cancer Risk Factor

Biotechnology helps us detect genetic mutations that can lead to cancer and predict the probability of getting some inherited forms of cancer. For example, about five percent of people who get breast cancer have inherited a mutation in a DNA repair gene called BRCA-1. Both men and women with this mutation have a high risk of getting breast cancer.

Mary and Fran's older sister Samantha has been diagnosed with breast cancer at just 45 years of age. Their mother and an aunt died of breast cancer, also in their forties. The sisters wonder if their family carries the BRCA-1 mutation. Here is their family tree:



The sisters go to a genetic counselor to discuss whether they should get genetic testing. The counselor stresses that the test for Samantha would be diagnostic: determining if the BRCA-1 mutation runs in the family. If it does, the test for Mary and Fran could predict the probability that they will also develop cancer. *Predictive tests deal with probabilities, not certainties.* The counselor also discusses the downside of knowing if you carry the gene: there is no prevention, and insurance companies could penalize people with genetic cancer risks. The sisters decide to have the tests, because they want to know their own risks and if they could have passed the gene on to their children. They also hope to keep the results private.

If your teacher has the necessary kit, you can simulate genetic testing. The kit uses a simplified gene technology called gel electrophoresis with wells for holding DNA samples. These samples contain DNA fragments of different lengths, including the simulated BRCA-1 gene mutation. To use the kit:

1) For each sample, use a new micropipette to draw 24  $\mu$ l of the DNA, and deposit it into the wells :

**Well #1:** Normal Control DNA Sample

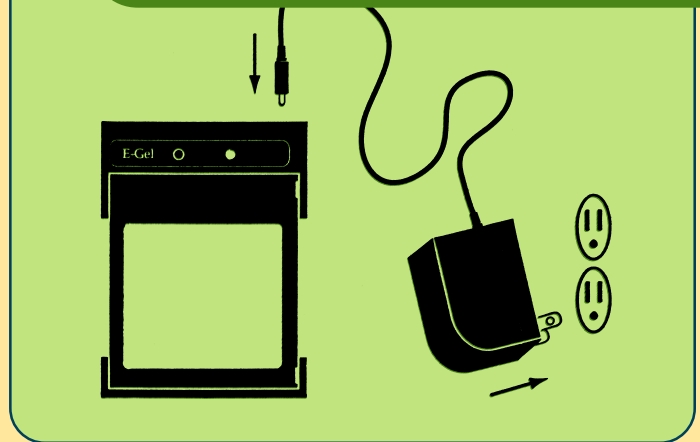
**Well #2:** Mary's DNA Sample

**Well #3:** Samantha's DNA Sample

**Well #4:** Fran's DNA Sample



To complete this activity, a "Gene Technology and Cancer Prediction Kit" and an E-Gel System need to be ordered.



- 2) Run the electrophoresis kit for 35 minutes. The kit applies an electric current through both ends of the gel, creating an electric field. Because DNA is negatively charged, DNA fragments migrate toward the positive pole (opposite the well). The smaller fragments move more quickly, so they travel farther. The DNA fragments will appear as bands arranged according to length, with the smaller pieces closer to the bottom and the larger pieces closer to the top.
- 3) Make an accurate diagram of the patterns of the bands. Measure the migration distance of each band in millimeters (mm) from the bottom of the well to the bottom of the band. Record your results.
- 4) Compare the results for each sister with the normal control.

### Questions:

- 1) Do any of the sisters carry the BRCA-1 mutation?
- 2) What chance does each sister have of passing the mutation to a child?
- 3) Do you think the sisters were wise to have genetic testing?
- 4) Do you think the sisters should have their children tested for the mutation?
- 5) What are their options if they learn they have the mutation?
- 6) What could happen if genetic test results are placed in medical records?



The Biotechnology Institute is a not-for-profit organization dedicated to education and research about the present and future impact of biotechnology. Its mission is to engage, excite, and educate as many people as possible, especially young people, about biotechnology and its immense potential for solving human health and environmental problems. The Institute thanks the following sponsors for financial support of its activities for 2000-2001.

- Abgenix
- Alkermes
- Amgen Foundation
- AVANT Immunotherapeutics, Inc.
- Aventis
- BIO
- Biogen, Inc.
- Centocor
- Connetics Corporation
- Council for Biotechnology Information
- CV Therapeutics, Inc.
- Ernst & Young
- Fisher Scientific International, Inc.
- Genecor International, Inc.
- Genzyme, Inc.
- Inhale Therapeutic Systems, Inc.
- Intermune Pharmaceuticals, Inc.
- Johnson & Johnson
- Kellogg Center for Biotechnology (Northwestern University)
- Edward Lanphier
- MdBio
- Merck & Company, Inc.
- Monsanto Fund
- Walter Moos & Susan Miller
- Neose Technologies, Inc.
- Novartis Foundation
- Ogilvy Public Relations Worldwide
- Onyx Pharmaceuticals, Inc.
- Ortho Biotech
- Pennsylvania Biotechnology Association
- Pfizer, Inc.
- Schering-Plough Research Institute
- Scottish Enterprise
- TheraMed, Inc.
- Utah State University Biotechnology Center
- U.S. Department of Commerce
- U.S. Department of Energy
- Thomas G. Wiggans
- Wyeth-Ayerst Research

This issue sponsored by:



**ImClone Systems Incorporated**  
Targeted Oncology

## Expand Your Knowledge

### Your Personal War on Cancer

- Don't smoke!!!
- Wear hats and sun screen
- Eat fruits, vegetables, and whole grains
- Be careful with alcohol
- Exercise

### Helping Others

- Volunteer
- Raise funds for research
- Study science and become a cancer researcher
- Sign up with a bone marrow donor agency
- Donate hair!



## BiotechInstitute.org

Visit the Biotechnology Institute on-line at [www.BiotechInstitute.org](http://www.BiotechInstitute.org) for student and teacher resources on Biotechnology and Cancer:

- Cancer Education Links
- A Downloadable Crossword Puzzle
- A Teacher's Guide
- Supporting Overheads
- Teacher and Student Surveys

The following issues of *Your World* are available for **free** downloading:

- Exploring the Human Genome (5:2)
- Gene Therapy (4:2)
- Environmental Biotechnology (4:1)
- Industrial Biotechnology (3:1)
- Plant Biotechnology (2:2)
- Molecular Diagnostics (2:1)
- Heath Care, Agriculture, and the Environment (1:1)

### Teachers will find the following useful information:

- How to subscribe to *YourWorld* or order recently published issues,
- A list of all issues published and upcoming issues planned,
- Downloadable Teacher's Guides for all issues,
  - Links to biotechnology education Web sites.

The next issue of *Your World* (11.2) will focus on microbial genomics, including topics on biofilms, environmental remediation, global warming, space, and bioterrorism.



### To Learn More About Cancer

- Lance Armstrong, *It's Not About the Bike: My Journey Back to Life*
- Webster K Cavenee and Raymond L. White, "The Genetic Basis of Cancer," *Scientific American*, March 1995.
- Robert Cooke, *Dr. Folkman's War: Angiogenesis and the Struggle to Defeat Cancer*
- Jerome Groopman, "The Thirty Year's War," *The New Yorker* (June 4, 2001)
- Matt Ridley, Chapter 17 in *Genome: Autobiography of a Species in 23 Chapters*
- Robert Weinberg, *One Renegade Cell*
- Lisa Yount, *Cancer*
- Time* and *Newsweek* cover articles on cancer topics
- American Cancer Society: <http://www.cancer.org>
- National Cancer Institute: <http://www.nci.nih.gov>
- National Childhood Cancer Foundation: <http://www.nccf.org>
- Oncolink: <http://www.oncolink.upenn.edu>
- NOVA's program on Judah Folkman, Cancer Warrior: <http://pbs.org/wgbh/nova/cancer>