EXPLORING

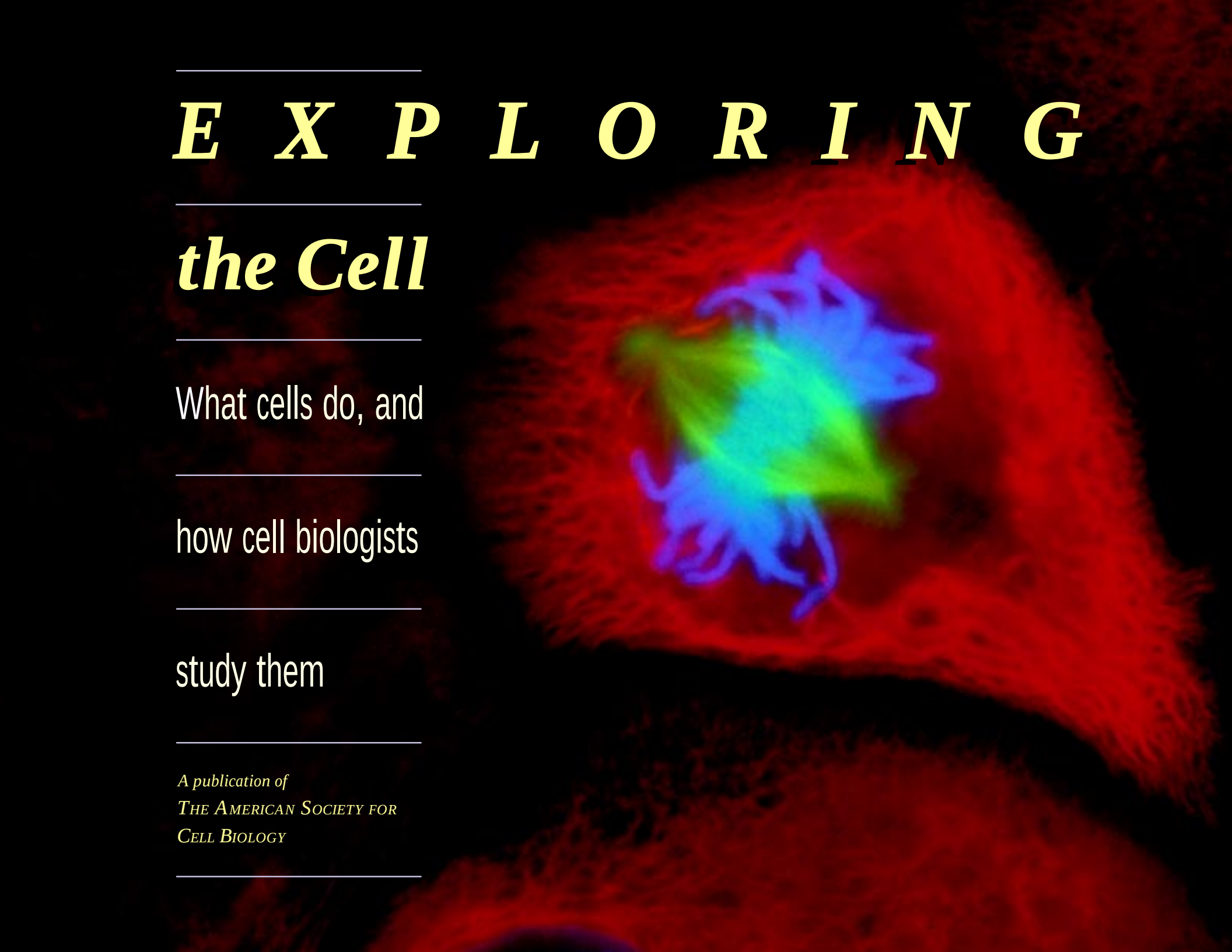
the Cell

What cells do, and

how cell biologists

study them

A publication of
The American Society for
Cell Biology



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For more information about the ASCB, contact the Society at

9650 Rockville Pike

Bethesda, Maryland 20814

301-530-7153; 301-530-7139 (fax);

ascbinfo@ascb.org or www.ascb.org/ascb.

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schmidel.com/bionet.cfm	A guide to biology and chemistry educational resources on the web.
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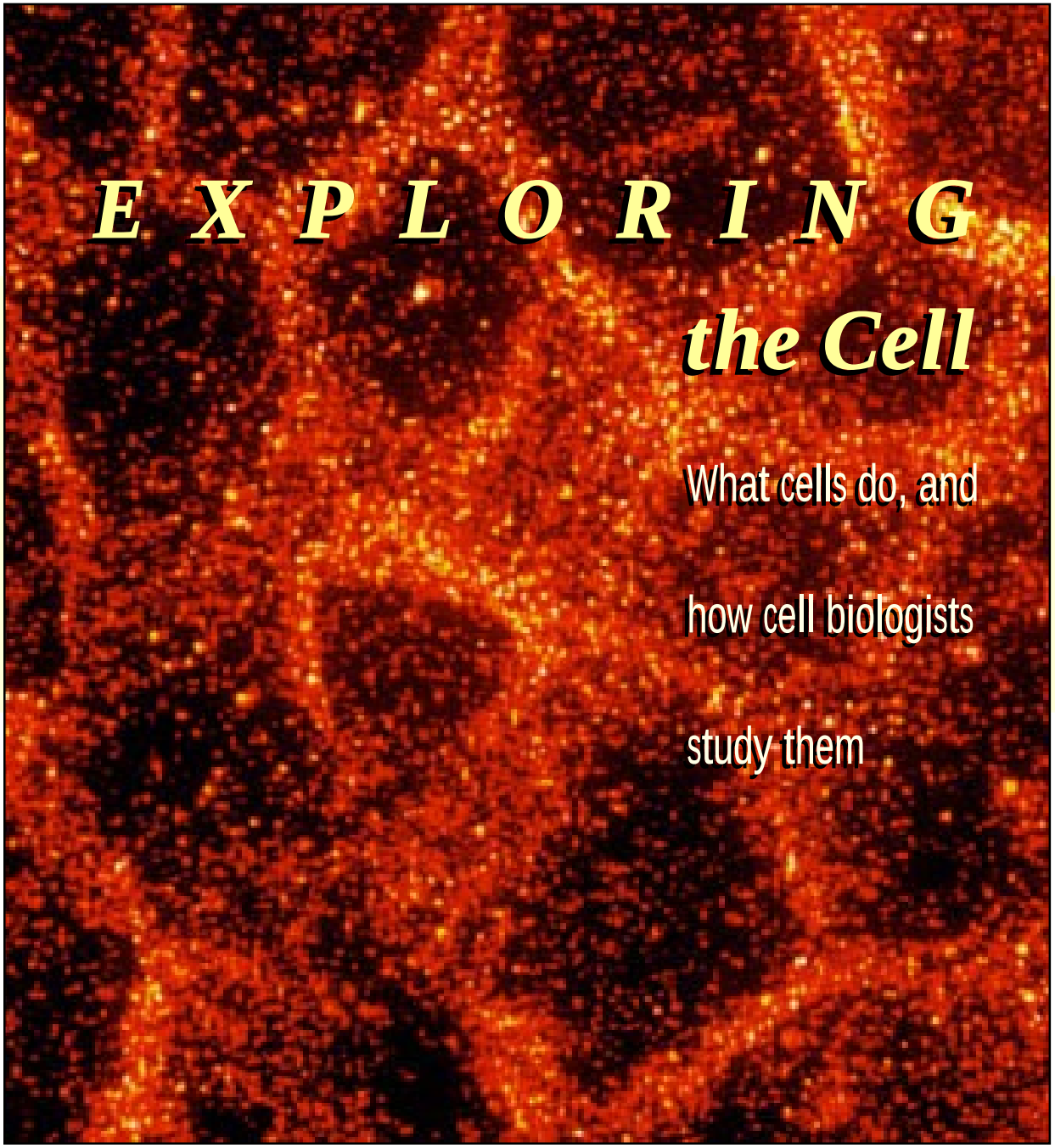
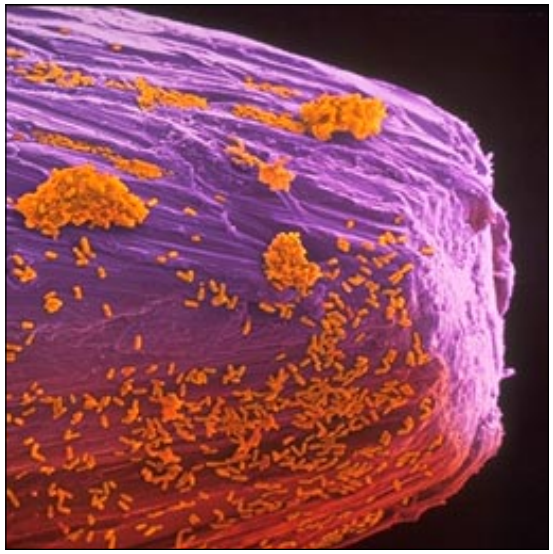
Ultraviolet light triggers DNA damage in skin cells. This causes a protein, CD95, to gather on the surface of the cells, forming the bright red clusters seen here. The clusters send a signal to the cell to commit suicide rather than risk becoming cancerous; see page 16.

Cover photograph:

A cell going through the cell division stage called mitosis. The chromosomes, in blue, have duplicated and are lined up in the middle of the cell by the spindle (yellow). The chromosomes contain DNA, the information store of the cell. Tiny motor proteins in the cell use the tracks of the spindle fibers to distribute one copy of each chromosome to each of the two new cells. The red keratin filaments form a protective cage around the spindle and the chromosomes.





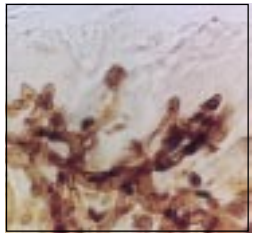
Humans, plants and bacteria are all made from cells.

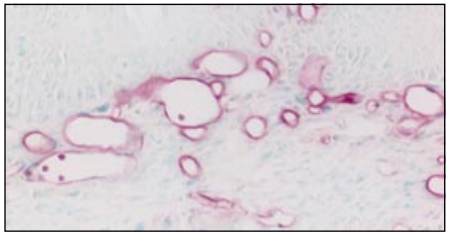
Cell biologists study life's basic unit

Cells are life's basic building block. Cells are small—above we see a few thousand bacterial cells on the point of a pin. But a few trillion human cells together becomes a person who can think, eat and talk. The fate of the cells determines in large part the development, health and lifespan of the person.

Many conditions and diseases start with one cell. Sperm that can't move properly can cause infertility. Arthritis or diabetes can be triggered by **immune cells** that mistakenly attack the body's own proteins. And **cancer** results from cells growing when and where they shouldn't.

Cancerous cells ignore the normal limits on growth. Once the cancer has grown to a certain stage, it needs to attract blood vessels to supply it with food and oxygen and to remove wastes. Shown below at top right is a magnified cross-section of normal skin; the surface of the skin is at top. The top layer of cells is thin and is fed by blood vessels below (in red). At bottom right is a similar section from cancerous cells. The top layer of cells has reproduced aggressively, and has induced the growth of a large number of blood vessels from below (in red, and in brown at bottom left).





A cancer needs food so it attracts its own blood supply

What can a cell biologist do?

An education in cell biology is preparation for many different careers.

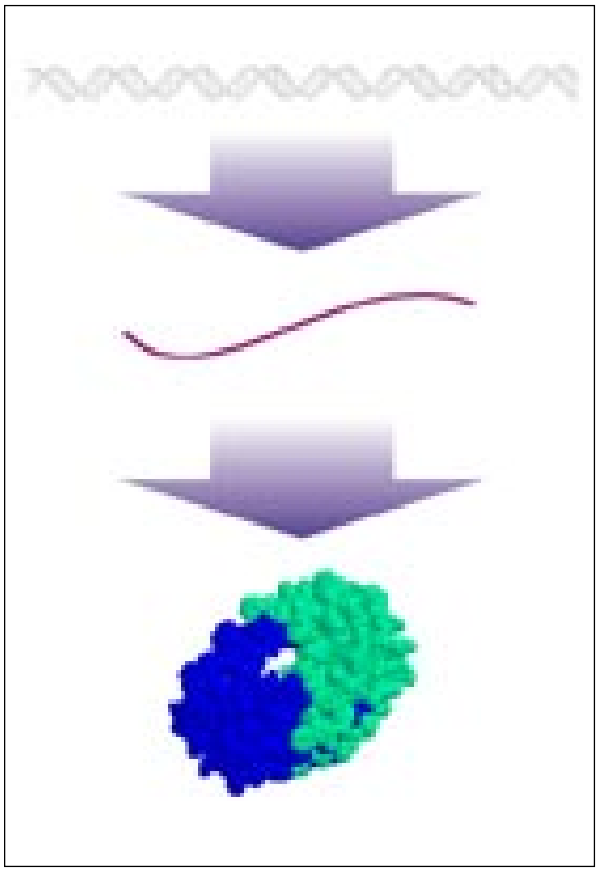
Cell biologists enjoy a range of **careers**, including research in **universities** and **biotechnology** or **drug companies**. Cell biologists are well trained in critical and analytical thinking, skills that are desirable in many professions in addition to research, including education and business.

To become an independent researcher, the first step is an undergraduate degree, commonly in one of the sciences. Next, the student usually pursues a Ph.D., which typically takes about five or six years of courses and laboratory work in several areas. In most Ph.D. programs, the student is supported by grants that are sufficient to live on and to pay tuition; in return the student may help teach undergraduates. Once a scientist has received the Ph.D., 3-6 years of independent post-doctoral laboratory work, under the supervision of a professor, often follows.

Many cell biologists carry out research in biotechnology or drug companies. They use their broad knowledge of how cells work, and of technologies for studying cells, to explore the cell's normal and abnormal function and how to correct its defects. Finding drugs is no longer a question of hit-or-miss, but is highly dependent on understanding the biology of a disease as well as how cells misbehave.

Cell biologists also bring valuable skills and education to teaching (both high school and college), the law (particularly patent law), policymaking (helping government make informed laws and regulations), business and finance (particularly in biotechnology) and writing (for newspapers, magazines, popular books and textbooks).

A parts list



Information is stored in DNA, read into RNA, and converted into protein.

Each cell contains the information to create tens of thousands of proteins.

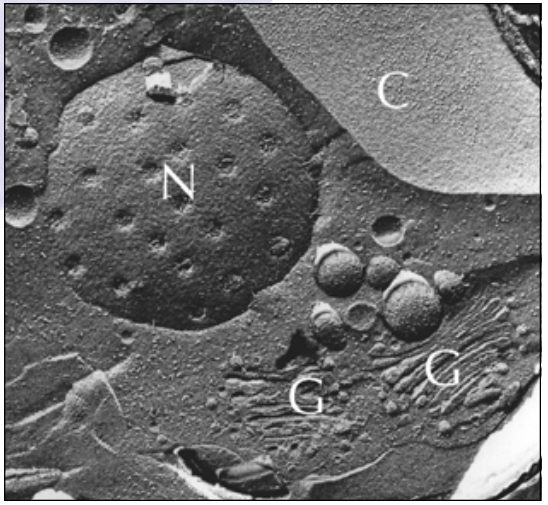
The cell is a self-sustaining machine, and the **information** store that directs the machine's operation is **DNA** (top of diagram on left). DNA is made up of building blocks called **bases**. Each human cell (except older red blood cells) has about six billion bases of DNA. The DNA is organized into genes, which vary in size from a few hundred to over a million bases each. Groups of **genes** are hooked together to make a **chromosome**.

Special proteins select genes to be copied into **RNA** (middle of diagram on left). The RNA is then converted by an established code into **protein** (bottom of diagram on left). With a few exceptions, each gene yields one protein.

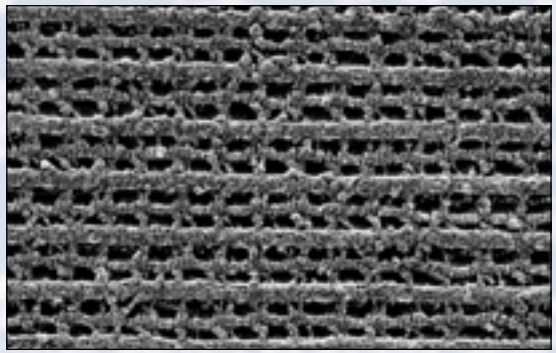
Membranes create compartments.

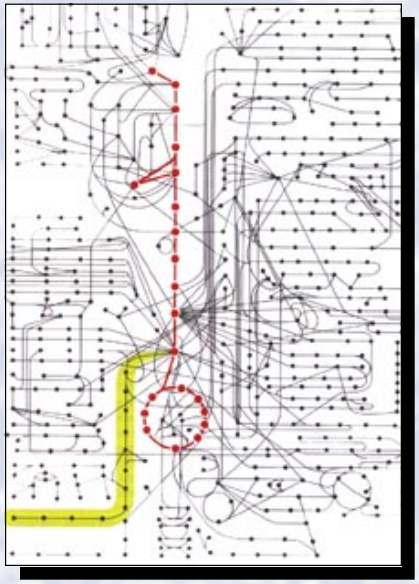
The cell uses membranes to organize and segregate its activities.

Fat is an important component of a cell. The shape of certain fat molecules makes them perfect for making a barrier in the cell. The water-loving ends of these fat molecules stick outward, and the water-averse ends point inward, mixing only with each other. A double layer of fat molecules in this arrangement creates a **lipid bilayer membrane**, which surrounds the cell and acts as its boundary. Lipid bilayers are also used to define the **nucleus** (where the DNA is kept, reproduced and read), the **mitochondria** (where energy is produced), the **endoplasmic reticulum** and **Golgi** (where proteins are sorted so they can be sent to different locations), and the **chloroplast** (where plants harvest light energy and make oxygen).



Above we see part of a green algae cell. The cell has been frozen, opened and viewed with an electron microscope. This reveals the membranes of the nucleus (N, with nuclear pores for moving molecules in and out), Golgi stacks (G) and chloroplast (C).





Proteins do work and provide structural support.

Proteins contract muscles, process food and keep the cell in shape.

Every time you move your finger, trillions of **filaments** like the ones pictured on the top left are sliding over each other. A protein, **myosin**, attaches to one filament, grabs onto the neighboring filament, and pulls. When enough filaments slide in the right direction, a muscle contracts.

Proteins also convert food into usable energy and structural elements of cells. On the lower left is a diagram where each dot is a chemical, and each line is a protein which converts one chemical to another. A central energy pathway is in red, and the pathway for making cholesterol (a part of cell membranes) is in yellow.

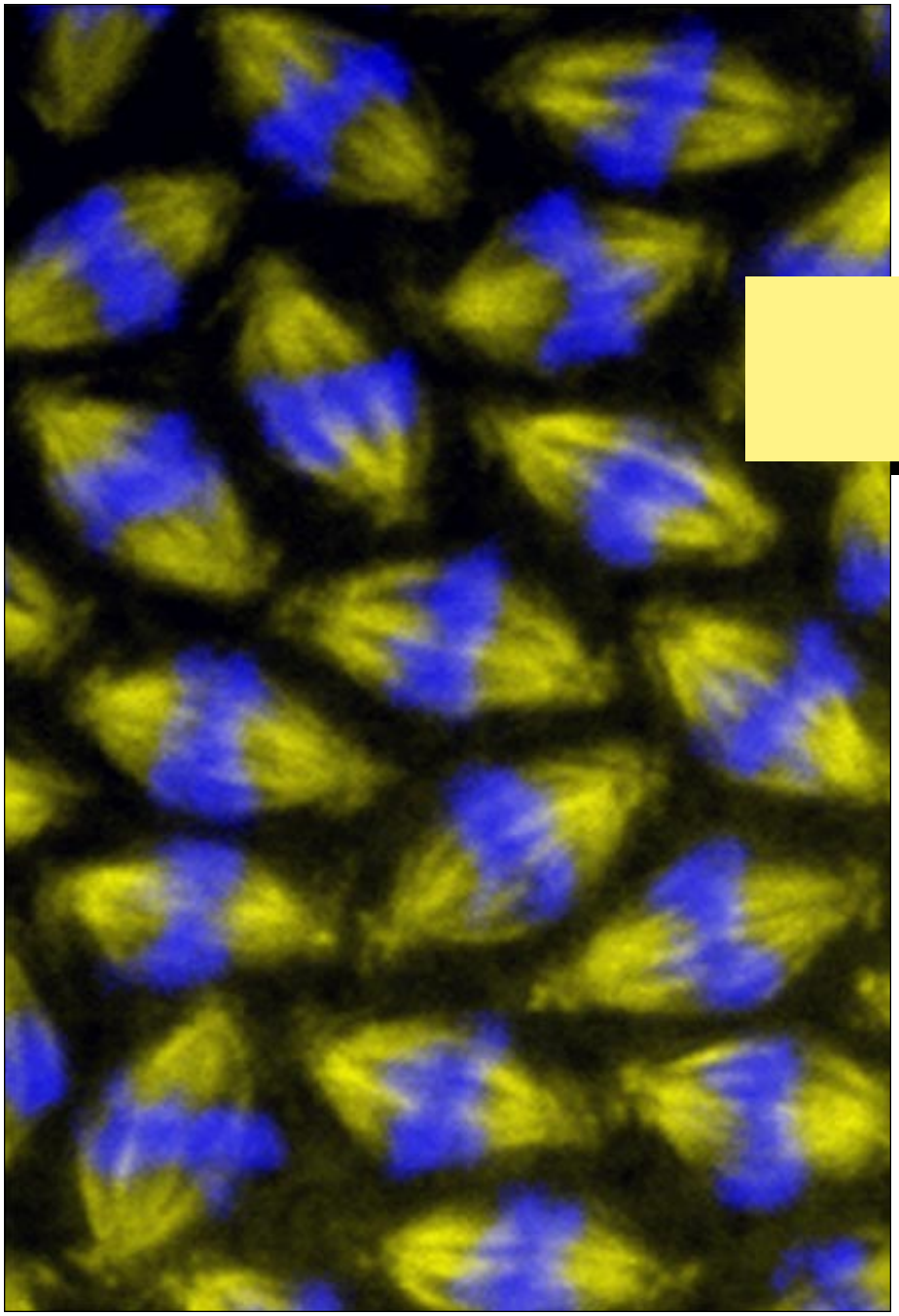
How do we see proteins?

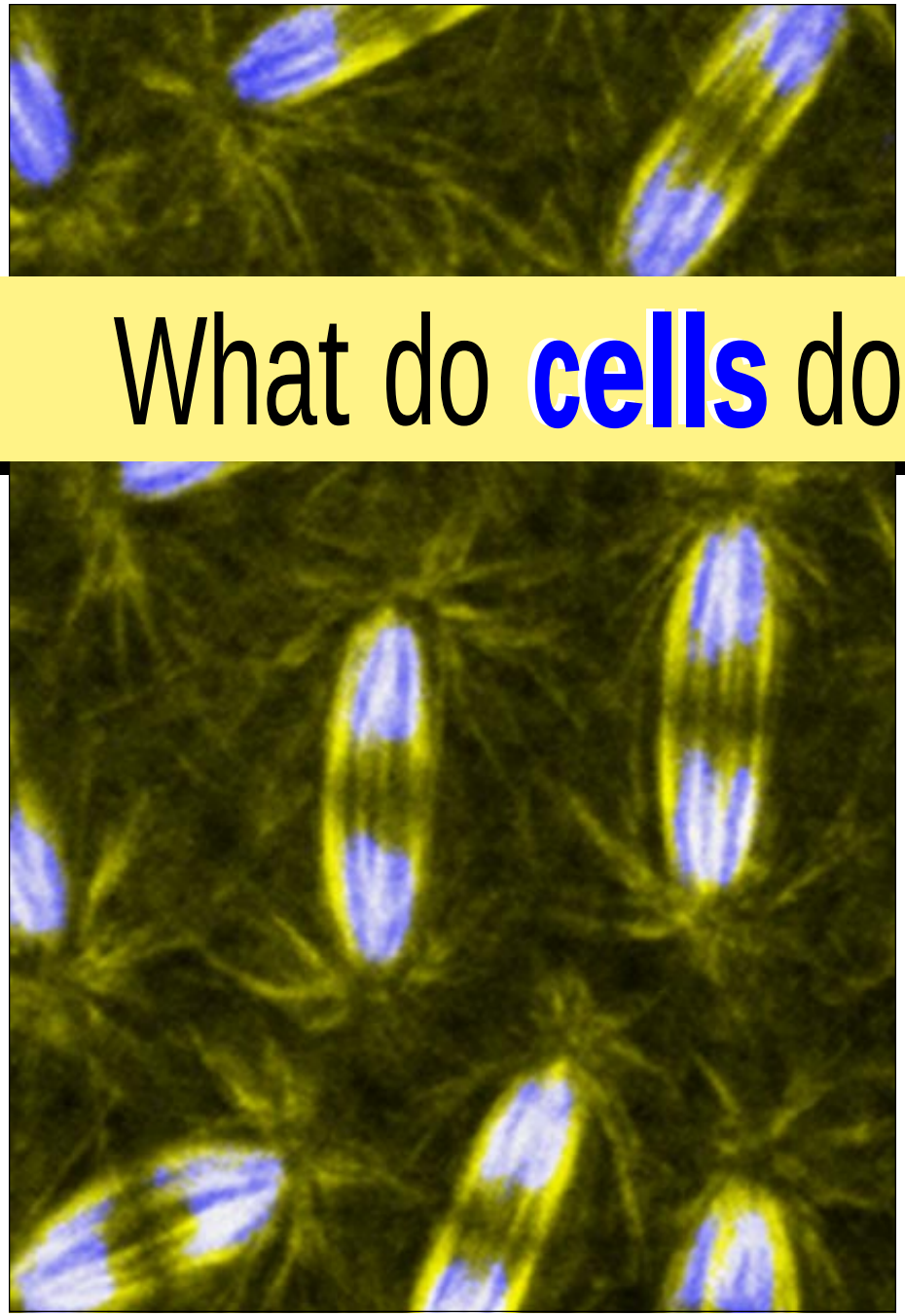
The function of a protein is directly related to where in the cell it resides. Cell biologists use **electron microscopes** to see large protein structures, such as the muscle proteins at the top of the page; for other proteins they use **antibodies**. The protein of interest is injected into a rabbit or mouse. The animal has an immune reaction to the protein, and produces antibodies that specifically attach to the protein. Antibodies normally help to protect against disease. In research, antibodies are collected and purified, and a **fluorescent label** is attached to them. Most of the bright colors in this booklet are based on the fluorescence from labeled antibodies.

Following pages (see also pages 12–15):

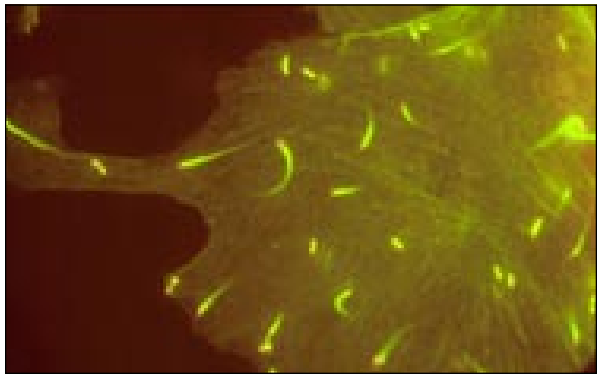
Opposite page, left: Duplicated chromosomes made of DNA (blue) are lined up in the middle of the spindle (yellow). The picture is from a fly embryo, which duplicates its DNA many times before forming cell boundaries around the DNA.

Opposite page, right: The spindles pulling apart the chromosomes.





What do **cells** do?



This bacterium uses the cell's own machinery to move around the cell, spreading infection into neighboring cells.

Cells move

Cruising at the cell's expense.

Listeria monocytogenes is harmless to most people, but it can kill people who are very old or very young and anyone whose immune system is compromised. Once *Listeria* is inside a human cell, it makes a single protein that recruits human proteins. These proteins form a tail behind the **bacterium.** The tail is visible above as a green streak; the *Listeria* are the faint red blobs at one end. More tail material is constantly forming where the tail meets the bacterium, driving the bacterium forward. The force of the tail can launch the *Listeria* into a neighboring human cell, spreading the infection.

The proteins in the *Listeria* tail are not made by the human cell for the benefit of *Listeria*—they are essential to the normal movement of the human cell, when they are not being co-opted by *Listeria*. By studying how *Listeria* uses these proteins, scientists can better understand how human cells move.

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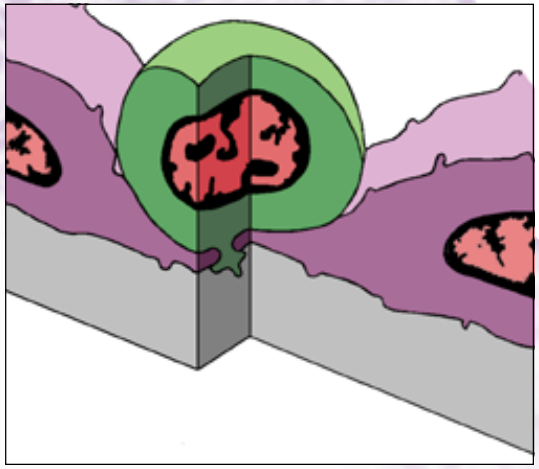
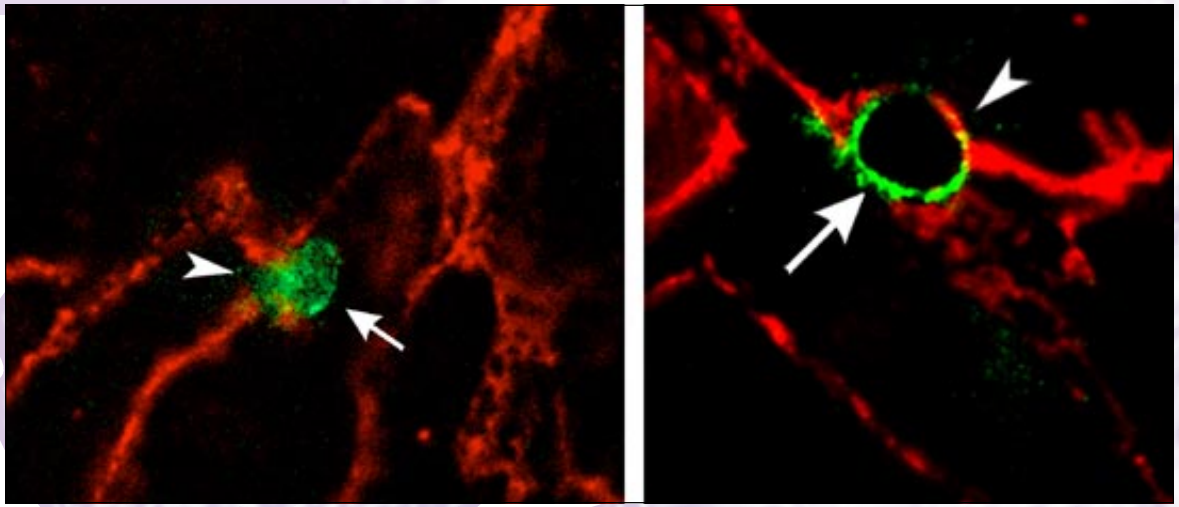
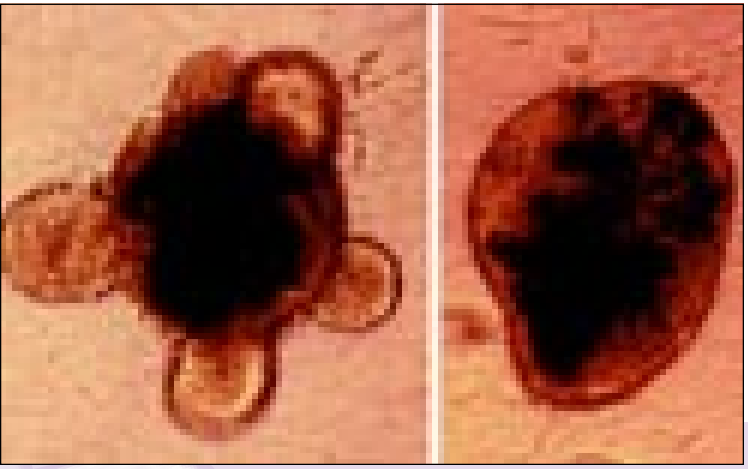
Let me out!

Cells that line blood vessels form a tight seal to keep blood in. But when there is an infection in surrounding tissues, the cell lining yields to immune cells that need to escape.



The body responds to the first signs of **infection** by attracting immune cells from the blood to the site of infection. The immune cells (seen above and below in green) must squeeze between the cells that line the blood vessel walls (seen in the diagram at top right in purple and red.). In the image above, a sticky molecule on the immune cell is stained green. At first it appears only at the point of the cell that is pushing between the blood vessel cells (left image; viewed from above), but later the immune cell opens this gap so that the whole cell can move through and into the tissue beyond (image on right).





Clear a path—here comes the pancreas.

These cells are destined to make a pancreas, but only if they can make themselves a space in the surrounding web of proteins.

Between cells, there is a tangled protein mesh that supports cells: this is called the **matrix**. But when cells want to move, the matrix gets in the way. The cells at top left are moving into an artificial matrix. If they were in the body, this would result in the formation of small groups of clustered cells, called **islets**, that make up part of the pancreas. The cells make space to move by chewing up the matrix. In the image above (right panel), the protein that performs this function has been blocked, and the cells no longer move.

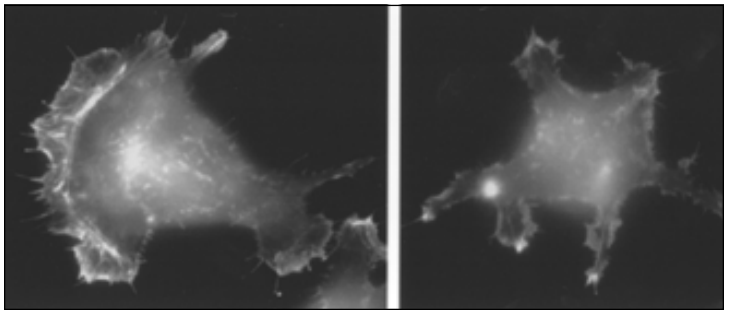
Cancerous cells move abnormally.

Cancer cells become a threat once they can move, and spread.

Cancer cells are normal cells that have gone through a series of changes that make them grow uncontrollably. One of the changes is the ability to move at will, disregarding the controls that limit the movement of normal cells. Mobility allows cancer cells to find places to grow where they have a supply of food and oxygen.

A colon cancer cell is shown below (left panel), moving from right to left. The large fan and spikes on the left of the cell are reaching out for new footholds. **Actin**—the protein identified in white—will help pull on these footholds so the cell can move.

A series of **signals** in the cell must be triggered for the cell to move. In the colon cancer cell, one of those requirements is the destruction of a small chemical called **cyclic AMP**. When the cell is prevented from consuming this chemical, as in the cell on the right, the cell can no longer form a fan, so it does not move. If this inhibition could be developed without toxic side-effects, it might be used as an anti-cancer drug.



Profile of a postdoc: NEDRA WILSON.

How do algae know when to stop making their tails?

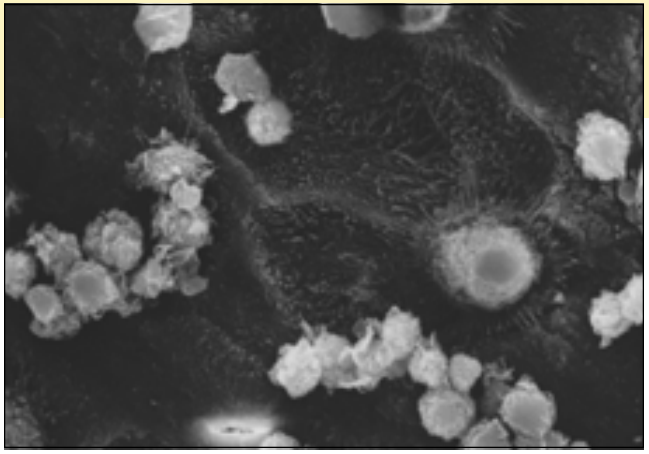
Growing up in Muskogee, Oklahoma, Nedra Wilson was not obsessed by science. But she was intrigued by the medicine that her aunt, a doctor, was practicing in Africa. “Every year she would bring back pictures of people with weird diseases,” remembers Wilson.

Science took center stage when Wilson did her first laboratory work as an undergraduate at Northeastern State University at Tahlequah, Oklahoma, home of the Cherokee Nation. As a member of the Cherokee Nation, Wilson taught high school students in the community, and still returns every year for the national Cherokee holiday.

The next step was a Ph.D. at the University of Texas Southwestern Medical Center in Dallas, and intense study of green algae called *Chlamydomonas*. In Texas, Wilson used the algae to study how two cells can merge, or fuse, such as when a sperm and egg meet, or when a virus invades a cell. Wilson used the algae because she could isolate the part of its cell that fuses, to understand which proteins make the membranes merge, and how they do it.

In her postdoctoral work at the University of Minnesota, St. Paul, Wilson is looking at another part of *Chlamydomonas*—the propeller-like tails, or flagella that move the algae around. Wilson is studying several mutant algae that make flagella that are two or three times longer than normal. By observing the mutants, she hopes to understand how the algae turn the flagella-making apparatus on and off, and how it can sense when the structure is long enough.

Cells eat



Cells that eat bones.

A protein that makes this bone-eating cell hyperactive can cause osteoporosis.

To keep our **bones** strong, much of our bone mass must be recycled every year. The process requires a finely-tuned balance of bone-eating (resorption) and bone formation. Too much **resorption** can result in **osteoporosis**, which causes bones to become brittle, a particular problem for old people.

Resorption is performed by **osteoclast** cells, such as the large spiky cell pictured above. These cells make a tight seal with the bone, into which they release acid and proteins that consume bone proteins, resulting in a cavity in the bone.

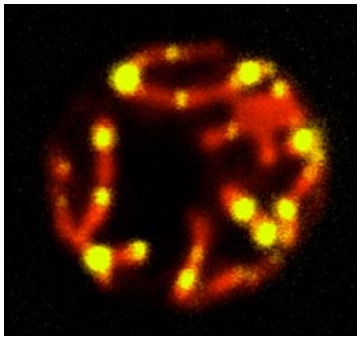
The body makes proteins that both increase and decrease the activity of the osteoclasts. **OPGL** is a protein that turns on osteoclasts. When there is no OPGL, osteoclasts make an occasional, isolated groove in the bone (bottom left). But when OPGL is added to a mixture of bone and osteoclasts, the osteoclasts produce clusters of cavities (bottom right).

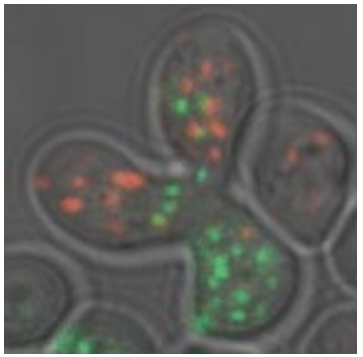
A protein called **OPG** turns off OPGL, and slows down the effect of osteoporosis in mice. OPG is currently in human trials for the treatment of osteoporosis.

Building the power generator.

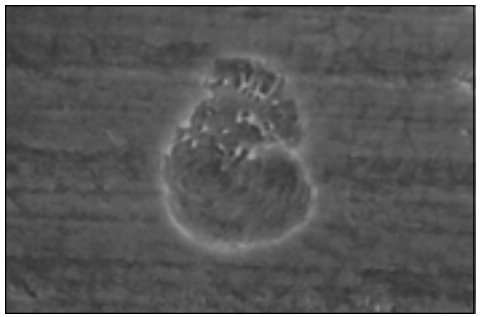
Mitochondria—the compartments that turn food into energy—have special mechanisms for joining together and splitting apart.

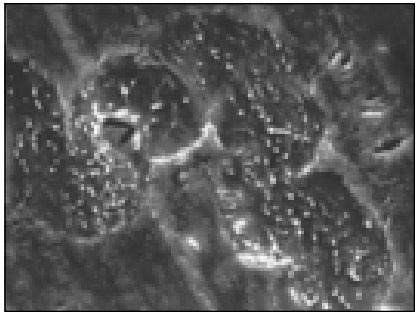
Mitochondria are surrounded by **membranes**, which they use to generate energy for the cell. The cell must control when the membranes join to form one mitochondrion, and when they split apart to form many. In **baker's yeast**, shown directly below, the mitochondria join together; multiple copies of DNA (yellow spots) are in a single large mitochondrion (continuous red ribbons). When this cell reproduces, at least two separate mitochondria must form so that each new cell gets a mitochondrion.





The defective cells shown on right are mating (like a sperm joining with an egg). The cell on the left, with its red mitochondria, has joined with the cell on the right, with its green mitochondria. But these defective cells have formed a new daughter cell, above, with a mixture of red and green mitochondria. Normally the mating cells would fuse their mitochondria together and we would see one large yellow ribbon (in fluorescence, red and green combine to make yellow). Identifying the gene that causes this defect can contribute to understanding how membranes are normally joined together.





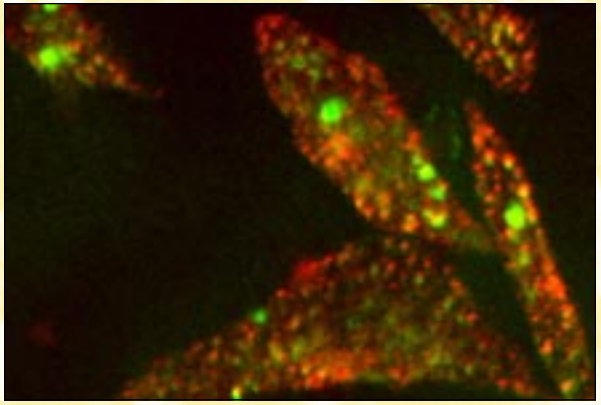
The many mouths of the cell.

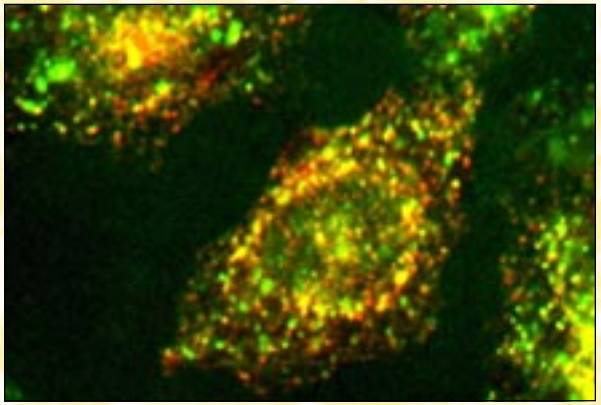
Food enters cells by more than one route.

For most **food** molecules, the membrane that forms the outside of the cell is a barrier. Some food molecules can travel through special holes in the membrane—protein channels designed specifically for them. Other food molecules are brought in using **vesicles**.

The cell gets around the membrane barrier by producing proteins that transport specific chemicals. In the images at right, a protein specific for **glucose** (a sugar) is in green, and a protein that transports **iron** is in red. The green protein forms a channel through the membrane to allow glucose into the cell, but excludes other chemicals. The red protein protrudes from the membrane and latches onto iron. The protein and its cargo then enter the cell in a vesicle that pinches off from the outer membrane.

When the cell wants to reduce the amount of glucose entering the cell, it removes the glucose channel from the membrane. The channel enters the cell in a vesicle. The bottom image is of cells at 37° C (98°F) —red and green proteins have mingled together in this import system so the predominant color is yellow (red combines with green to make yellow). The top image shows the cells at 15°C (59°F). At this temperature, the pinching-off process occurs, but the mingling process does not. With this trick of temperature, we can see that the cell initially brings the glucose channel and iron into the cell by two distinct routes, rather than channeling the transport proteins together. This may allow the cell to fine-tune the amount of transport of the two cargoes independently.



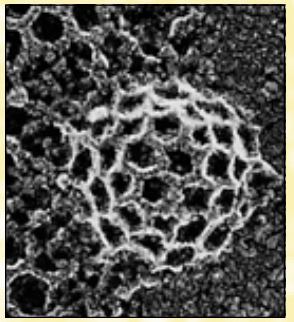


The protein that wrings necks.

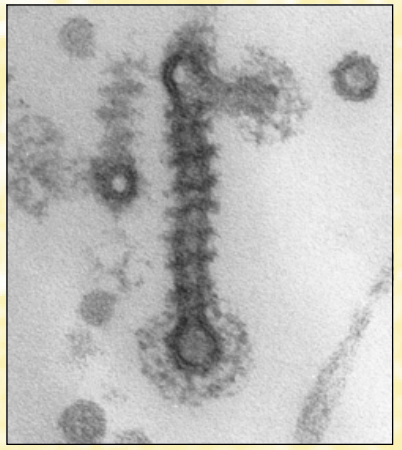
Dynamin can self-assemble into a spiral. Constriction of the spiral pinches off membrane packages that enter the cell.

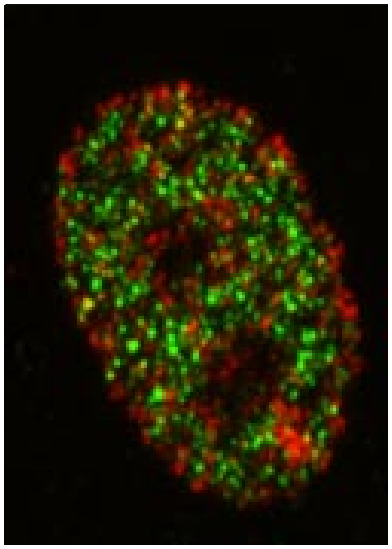
Vesicles are bubbles of membrane that start off as an indentation in the main cell membrane. This indentation protrudes into the cell and eventually becomes a bubble. Once the bubble is inside the cell, what was outside the cell is now inside the bubble.

The membrane is first curved inward by the assembly of multiple copies of a protein called **clathrin**. Molecules of clathrin bind to the membrane and to one another. As the clathrin proteins move into place next to each other, they naturally form a curve (top image at right).



To finish off the bubble, a protein called **dynamin** forms a spiral around the neck (bottom image). As the spiral tightens, it pinches off the neck, leaving a complete bubble that can move around inside the cell.



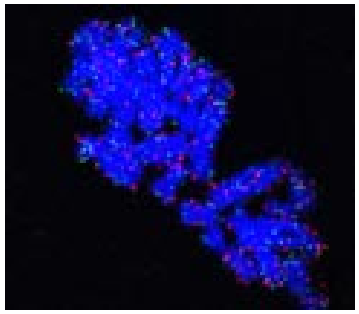


Copying DNA requires organization and planning.

Every one of the billions of bases of DNA must be copied once and only once every time the cell divides. The cellular mechanism that copies DNA does not work randomly, but instead copies particular sections in a particular order.

Cells reproduce

By attaching fluorescent molecules to bases, the building blocks of DNA, we can see where and when DNA is made. In the image above, bases labeled green and red were added at different times. The green DNA was made early in cell division, and the red DNA was made four hours later. The patches are distinct and, by molecular standards, large. Each one consists of about two million bases of DNA.



In the image on the left, the cell has progressed to the stage just before it will split into two. The DNA has folded itself into sausage-shaped chromosomes, but the areas of green and red are still intact and distinct.

Particular areas of DNA are copied at the same relative time (early or late), and in the same relative location in the cell, in multiple successive rounds of cell duplication. Scientists do not yet know how the DNA reorganizes itself after each cell division, nor how it remembers its place in the waiting line for duplication.

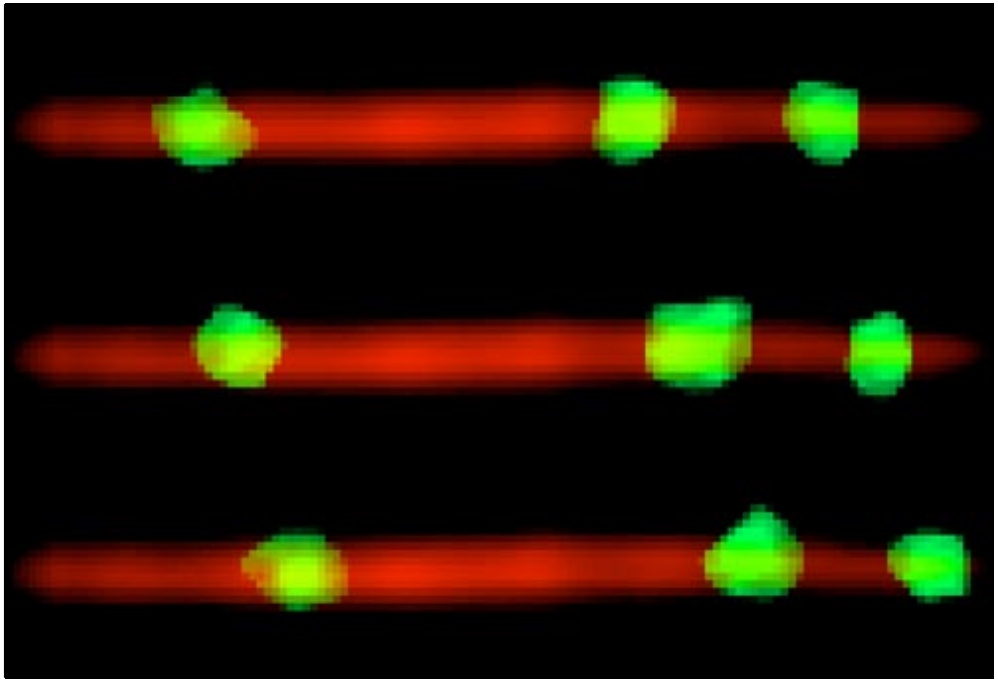
The world's tiniest motor in action.

Chromosomes and other cargoes are carried around the cell by tiny molecular motors.

Once the DNA has been duplicated and packaged into chromosomes, a network of fibers called the **spindle** grabs onto the chromosomes. **Motor proteins** walk along the fibers (called **microtubules**) and carry the chromosomes into opposite regions of the cell, to become incorporated into two new cells.

The picture below shows a time sequence of three individual motor proteins (in green) moving along a single microtubule track (in red). The motors are moving from left to right, and the images are taken at one-second intervals, from top to bottom. The motors are moving at approximately one millimeter per hour, which is fast for a cell. At that rate the motor can go from one end of the cell to the other every one to two minutes.

Only very recently have scientists been able to see individual proteins like this. The method for seeing the motors is called **total internal reflection microscopy**. This method bends the light sharply



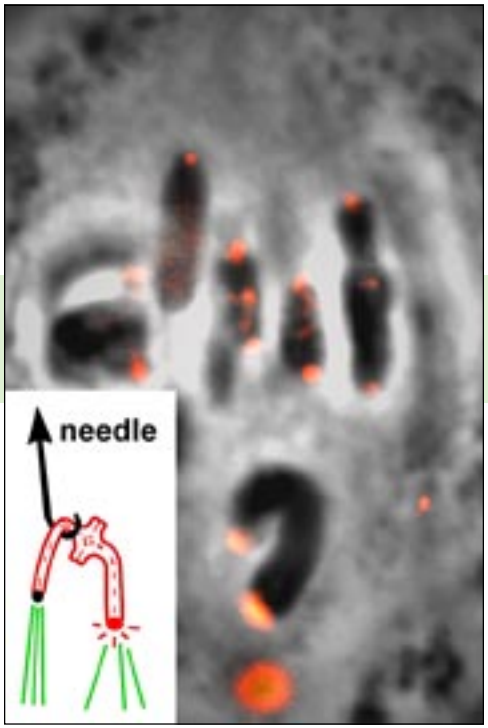
as it enters the sample, so that the light merely grazes the surface before bouncing back out. Thus only a thin layer of the sample is lit up, and there is almost no background fuzz from out-of-focus objects. With the power to see the movement of individual proteins, scientists can learn which parts of the motor protein are needed to keep the motor from falling off the tracks, and what determines whether the motors go forward or backward.

A traffic light for the cell.

On the chromosome at the bottom of this image, there is a bright red dot that is telling the cell to stop dividing. Why and how?

In this grasshopper sperm cell, most of the duplicated chromosomes (visible as black sausage-shaped objects in the image on the right) are lined up ready to be pulled apart into two new cells. The spindle will pull one chromosome from each pair upward, and the other downward. (Barely visible in this image, the diamond-shaped spindle runs from the top to the bottom of the picture.) The chromosomes line up in the middle of the cell so that each end of the spindle can grab one chromosome of each pair.

But in this cell there is one chromosome pair—the one at the bottom of the image—that is lost. Both ends of the chromosome pair are attached to the same end of the spindle. If cell division proceeds, the cell at the bottom will get two copies of the chromosome and the cell at the top will get none. To prevent this, the cell has a mechanism to pause until the wayward pair of chromosomes finds its way back to the middle of the cell.



How does the cell know that one of its chromosomes is lost? In other words, how is the lost chromosome different?

One difference is how the chromosomes are attached to the spindle. The chromosome pairs in the middle of the cell have one chromosome attached to each end of the spindle, so the spindle pulling creates tension across the pair. But for the lost chromosome pair, both chromosomes are attached to the same end of the spindle (the bottom). There is no tension.

What might detect the lack of tension? One possibility is the protein identified in red. The identity of this protein is not known, but clearly the red mark is much more distinct on one end of the lost chromosome pair. This could be what is telling the cell to stop.

The red mark is very bright only on one chromosome of the lost chromosome pair because the researchers are tugging on the other end with a tiny glass needle (not visible, but diagrammed in the lower left of the picture). The tugging mimics attachment to the other end of the spindle, but the pulling is directed so that there is tension only at one end of the chromosome pair. This turns off one protein, but leaves the other one on.

If the cell detects where its chromosomes are by a lack of tension, there are probably proteins that can detect the level of tension. Now we have to find those proteins.

Profile of a graduate student: PAUL MADDOX.

Sometimes the best experiment is simply looking.

Paul Maddox is a graduate student at the University of North Carolina, but his schedule is more like that of a business executive. After flying in from Argentina, he is taking off the next day for the Woods Hole Marine Biological Laboratory in Massachusetts. In both places he is teaching others the fine art of looking, using hi-tech microscopes.

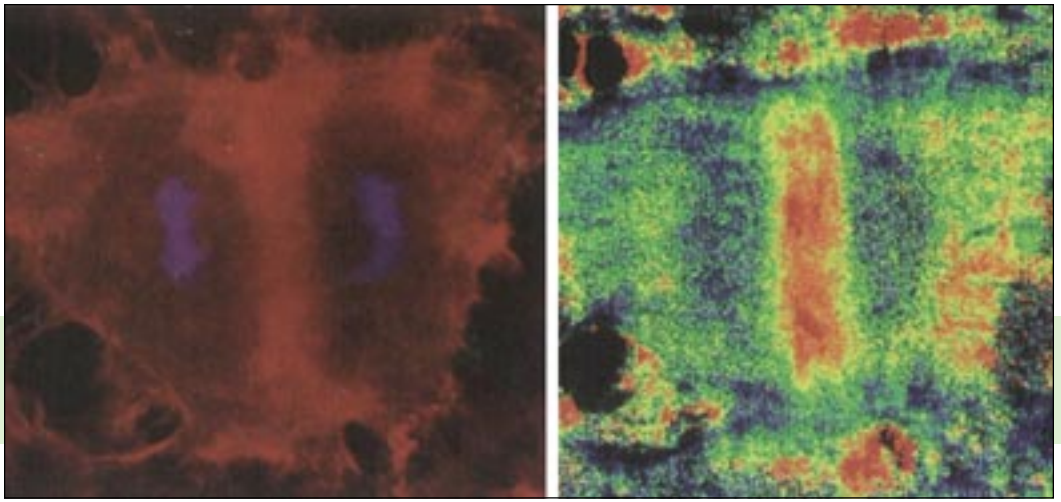
Maddox grew up in Asheville, North Carolina. He enrolled at UNC intending to major in physics, but an introductory biology course convinced him to switch to biology. A course in his senior year called "Unsolved Problems in Cell Biology" stimulated him to do research. Cell reproduction in particular caught his attention in this course. "There was a vast array of old information describing it, and a bunch of hypotheses," he says. "The questions had been out there for ages, and there were still no answers."

Maddox is trying to get those answers by direct observation. His latest success came from looking closely at mating yeast cells. The cells make tracks of microtubule fibers to bring the contents of the two cells together once the cells have fused. Maddox found that these microtubules are attached to parts of the cell, but that the microtubules change in length by adding and subtracting. How is the attachment maintained even as parts of the track come on and off? Maddox can now tackle this by looking for yeast mutants that fail to maintain the attachment.

Maddox aims to lead a laboratory one day, but he is taking one step at a time. "My first goal is to finish my degree," he says. In the meantime, the student life suits him well. "It's great," he says. "I get paid to play around all day."

How to cut one cell into two.

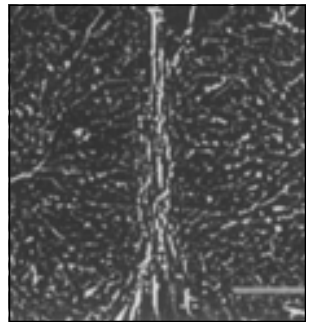
Once the DNA and other contents of the cell have been duplicated and moved to opposite ends of the cell, the middle of the cell pinches together to make two new cells. No leaking is allowed.



The image at top left shows a cell with two copies of DNA (in dark blue) separated to the right and left, with a broad band of red between them. The red is **actin**, a protein that forms cable-like structures. A muscle protein called **myosin** attaches to the actin cables and slides them past each other, resulting in an effect similar to a string around the center of a balloon. The effect on the cell is to cleave it into two **daughter cells**.

For this process to work, the actin tracks need to run parallel to one another, and to run around the cell (from the top to the bottom of these images), producing a ring of ever-decreasing diameter.

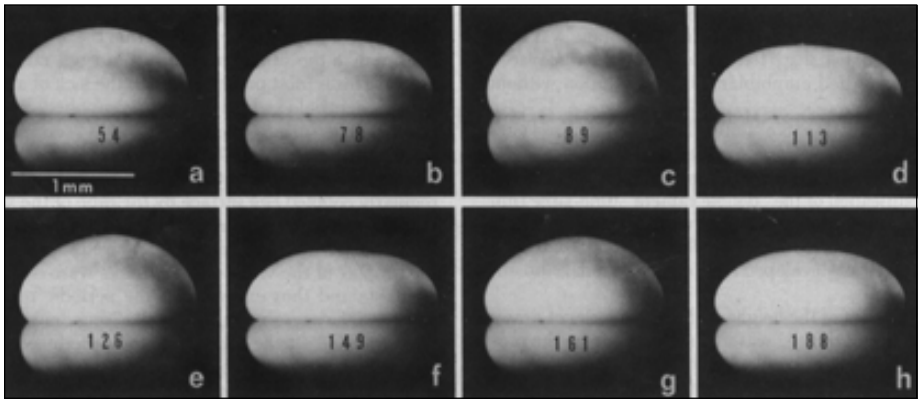
In the image at top right, polarized light has been used to show that the actin in the middle of the cell runs from top to bottom (in red), whereas the actin in the adjacent areas runs from left to right (in blue). The actin in blue may be lined up in this way because it is moving into the middle of the cell to help divide the cell.



The image on the right shows the alignment of the actin fibers from top to bottom.

The cell that won't stop bouncing.

Look carefully and you will see that the cell on the right is alternately rising and falling over time. This betrays the presence of an internal clock, now known to control the division of all cells with a nucleus.



Fertilization of an egg by a sperm sets in motion a rapid series of **cell divisions**. The cell pictured on the right is a frog egg that has been pricked with a needle. This tricks the egg into thinking that the sperm has arrived, which signals the cell to divide. But without the sperm there is neither the full set of DNA to make two new cells, nor the apparatus to divide the DNA. No cell divisions take place.

But that does not stop the cell from trying. Before every cell division, the cell squeezes itself. This helps form the machinery that divides the cell in two. In the unfertilized egg above, the division does not take place, but the squeezing does. It can be seen as the cell alternately rises up (as in (a), (c), (e) and (g)) and then relaxes again (as in (b), (d), (f) and (h)).

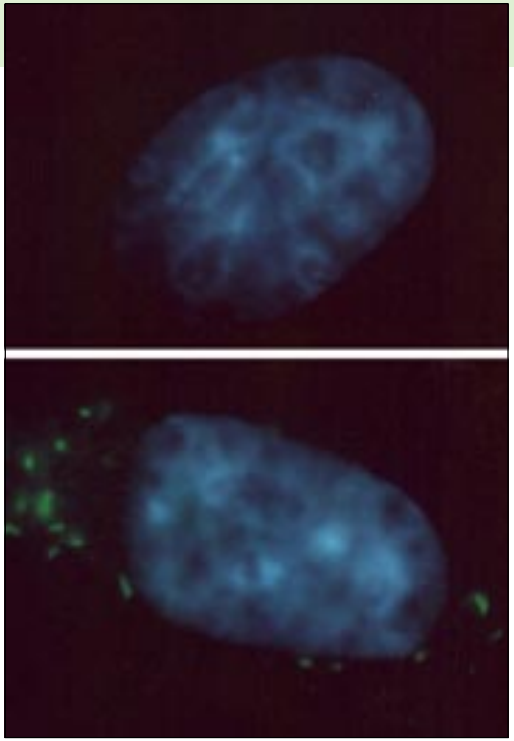
The egg's movement betrays a **clock** that is ticking inside the cell. This clock is driven neither by the nucleus nor the DNA, normally thought of as the director and producer of the cell. Instead, a set of proteins cyclically turn each other on and off, and these proteins determine the timing of cell division.

Making something out of nothing.

Some of the structures in cells resemble houses or skyscrapers in their complexity. How does the cell make these structures?

The green blobs in the lower half of this figure to the right are **peroxisomes**, which the cell uses to break down **toxins** (including alcohol) and fats. The cell's DNA is shown in blue.

For the most part, new peroxisomes are made by enlarging existing peroxisomes, but sometimes they have to be made from scratch. How does this happen? The cell's DNA contains instructions for making all cellular structures, but we know very little about how the DNA directs the creation of something as large and complex as a peroxisome.

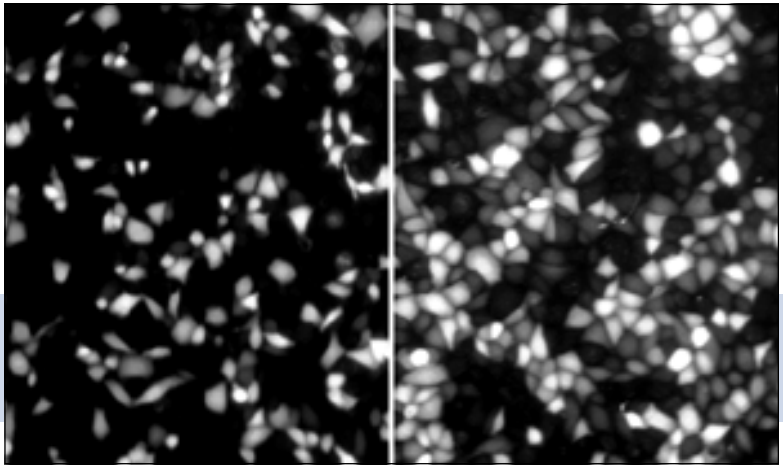


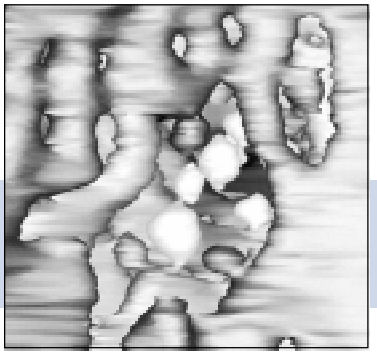
The cell at the top of the color figure below has no detectable peroxisomes because it comes from a patient with **Zellweger syndrome**, a defect of the DNA resulting in the inability to make peroxisomes. Victims of this syndrome suffer massive brain, kidney and liver problems, and die soon after birth.

With the addition of a single protein, called **Pex16**, to the defective cell, peroxisomes are formed (bottom image). The new peroxisomes have a membrane coating and multiple proteins organized to do different tasks. To construct this complex system, Pex16 grabs existing proteins that are floating around inside the cell. How this process gets started is not known.

To heal we must communicate.

As cells move into a wound to repair it, they communicate to coordinate their actions.

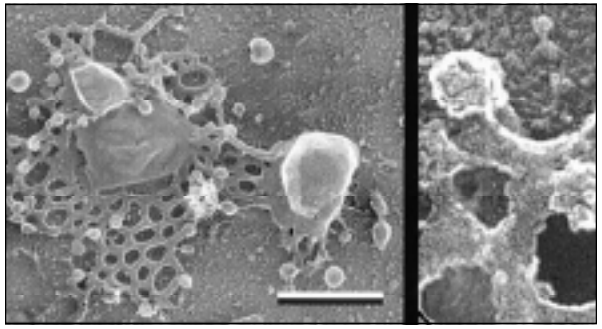




Cells communicate

A break in the skin quickly becomes besieged by cells. The first to arrive are individualistic explorers which scout the damaged territory. They leave behind a substance called **laminin 5** to guide the cells that follow. That second wave of cells has a different task: to form a protective barrier for the wound. To do that, they open up channels between themselves so they can communicate and coordinate. It is the laminin 5 that instructs them to create the channels.

How do we know that this is the function of laminin 5? On the left of the top center photo a few fluorescent cells have been mixed with non-fluorescent cells. Growing on a substance called **collagen**, the fluorescent cells remain distinct and the dye does not spread to the neighboring cells. But when the same cell mixture grows on laminin 5 (right of image), the laminin 5 triggers the cells to form channels, called **gap junctions**, between one another. The dye flows from one cell to another through these junctions.



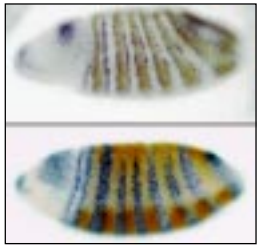
Meet the mail-room of the cell.

Many proteins in the cell are devoted to telling other proteins where to go.

The cell has multiple compartments for generating energy, destroying waste, and processing incoming signals. Each compartment has its own set of proteins to carry out its own particular mission. How do the proteins reach their correct destinations?

Many of the proteins are shuttled around in small bags called **vesicles**, shown in the images above, with a close-up shown on the right.

The **Golgi** system is a major sorting site; in the image above we see a three-dimensional reconstruction of its complex architecture. The Golgi is a series of large, interconnected tubes, with smaller vesicles moving among them. Deciphering how certain proteins direct the vesicle traffic is an ongoing task.



How (not) to make a fly.

In this cluster of young cells there is the promise of a head and tail, wings and legs. But first there are a huge number of different genes that must turn on and off. The end result—a fruit fly.

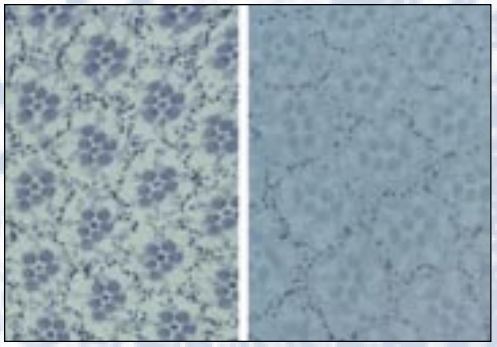
Fly larvae come in segments, but fly eggs do not. The first signs that segments are developing are the bands of protein seen in the normal fly embryo in the top image directly above. These proteins will direct the development of a segment so that it has a front and a back, and forms the correct part of the fly body.

The proteins have unusual names—Fushi-Tarazu (in brown), Wingless (in blue), and Even-Skipped (not shown here, but normally present in the white stripes of the top image). Fushi-Tarazu is not made in the white stripes at least in part because Even-Skipped turns its gene off. The Wingless gene is turned off by both of the other proteins, so Wingless is made only in thin stripes between the two.

Scientists work out how one protein controls another by altering the order in which the proteins are made by the embryo. In the bottom image, a gene called **runt** has been artificially turned on throughout the embryo. Runt protein turns off the Even-Skipped gene, so the bands of Fushi-Tarazu and Wingless expand. These aberrations in protein location translate into disorganization of the segments of the larvae, and the larvae die even before they get a chance to turn into a fly.

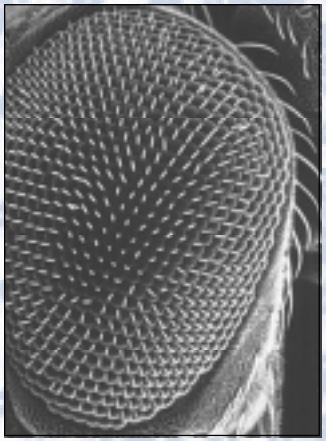
What does this fly see, and why should we care?

Without a gene called Sevenless, a fly can't see ultraviolet light. But it can tell us something about ourselves.

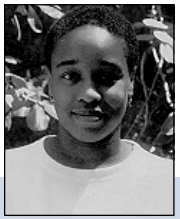


The fly eye is beautiful. Each cluster of **photoreceptor cells** (dark circles in the image to the right) is arranged in a single **ommatidium** (small domes in the top image). The clustered pattern is repeated perfectly, approximately 800 times.

How is this pattern created? Researchers approached this question by looking for flies unable to make the seventh photoreceptor (**R7**) at the center of each cluster. This is easily done, because flies without R7 do not sense **ultraviolet light**. The flies that lack R7 (bottom right) have a defective gene, sensibly called "Sevenless." The defect blocks signals in the eye that normally create R7.



One may wonder why scientists bother to study how signals in the fly eye create the seventh photoreceptor in each cell cluster. The reason is that many of the proteins that direct fly eye development also control cell reproduction, and therefore cancer, in humans. It is much easier to find the genes first in flies, and then use that knowledge to find the human counterpart. Once we know how these proteins work together, it may be possible to design drugs that stop the proteins and the cancer.



Profile of a young professor: SYLVIA SANDERS.

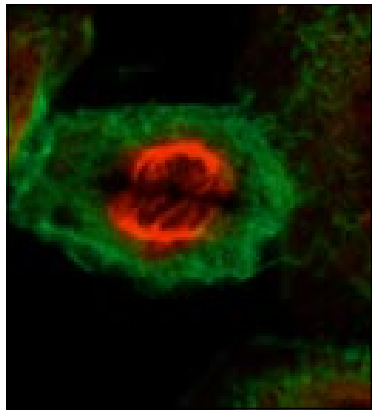
The mysteries of baker's yeast are unfolding.

Sylvia Sanders, an Assistant Professor of Biology at the Massachusetts Institute of Technology, grew up in Lawrence, Kansas, and stayed there for her undergraduate degree at the University of Kansas. She toyed with becoming a teacher, physician, and engineer before settling on biochemistry in college.

From Kansas she moved to the University of California at Berkeley. Her Ph.D. work at Berkeley involved how proteins get sent out of the cell. Sanders and her colleagues used genetics to find mutants of brewer's yeast that couldn't export proteins, and biochemistry to work out how the normal versions of those proteins worked. She found that a group of proteins formed a hole in one of the cell's membranes, allowing them to travel from one compartment to another.

Since then, Sanders has stayed with yeast, but turned to a different biological question. "What we want to know," she explains, "is how the cell can organize structures at the right time and the right place." The structure that Sanders focuses on is called the bud site. It defines the place on the mother yeast cell where a new yeast cell (the "daughter") will be created. Part of the answer, it seems, is that special proteins pick up on the remnants left from the creation of the last daughter, and these proteins then determine where the next daughter is created.

Sanders is making an important transition from bench scientist to principal investigator. "I like what I'm doing," she says. "I like interacting with the graduate students, and planning experiments. Teaching graduate students, and seeing them progress, is really fun."



Keep that protein in place, or you're dead.

Faced with the possibility of a defective cell division, the cell prefers to commit suicide.

The **spindle** is the structure that pulls the chromosomes apart and places them into two daughter cells during division. If the spindle isn't working properly, new cells may get too many or too few chromosomes. This can lead to uncontrolled cell reproduction (i.e., cancer).

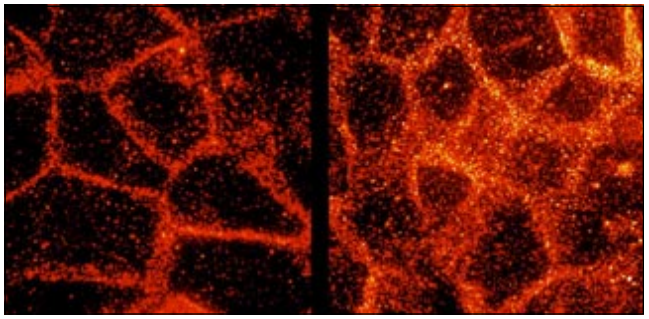
To prevent uncontrolled cell reproduction, the cell puts a protein appropriately called **survivin** on the spindle (seen directly above in red). Only if **survivin** is in place on an intact spindle is the cell allowed to divide. If the spindle is disrupted, the survivin signal doesn't get through and the cell destroys itself. Unfortunately, some cancer cells make excess survivin, which may allow them to survive and reproduce even when their spindle is not working properly.

Sunburnt cells commit suicide.

Skin cells damaged by ultraviolet (UV) light will kill themselves rather than risk becoming skin cancer.

UV light from the sun damages DNA. When repairing the DNA, the cell sometimes introduces mistakes, called **mutations**. Those mistakes can allow a cell to grow uncontrollably and form a skin cancer.

In normal skin cells (left of image, below), a protein called **CD95** (red dots) is spread along the



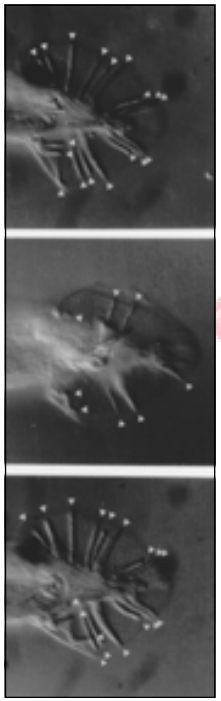
cell surface. When the same cells are exposed to a large dose of UV light (right part of image, above), the cells detect the DNA damage caused by the UV, and react by grouping the CD95 molecules in clusters. The clusters, visible as brighter red dots, signal the cell to commit suicide.

The worm with fewer tail fins.

The shape of this worm can be manipulated by turning suicide genes on or off.

A normal male worm (top, right) has eighteen protrusions on his tail, called **rays**. He uses them to find a mate.

A worm protein called **Ced9** protects the ray cells from dying—the worm in the middle has less Ced9 and fewer rays. But **cell death** requires the active participation of other proteins also, including **Ced4**. A worm that cannot make either Ced4 or Ced9 regains its full complement of rays (bottom image).



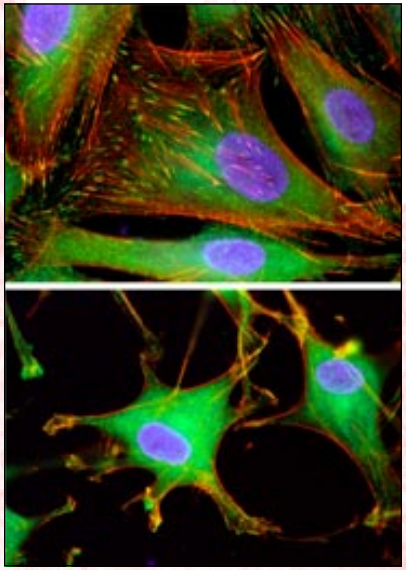
A worm can survive absent a few appendages because he still has some functional Ced9. But if there is no Ced9, only a few cells survive and the worm dies as an embryo. Thus the worm is programmed to self-destruct unless something—like Ced9—tells it that it shouldn't. Humans, too, have their own versions of both Ced4 and Ced9.

A cell that sticks is a cell that lives.

Cells can grow only when they are stuck to certain proteins.

The cells in the top part of the composite image on page 17 are thriving. Cables of actin (red) help attach the cell to sticky proteins outside the cell through connection points called **focal contacts** (yellow-green spots). This allows the cell to spread out, and gives it a signal that it is growing in the right place, near other cells.

Cells die



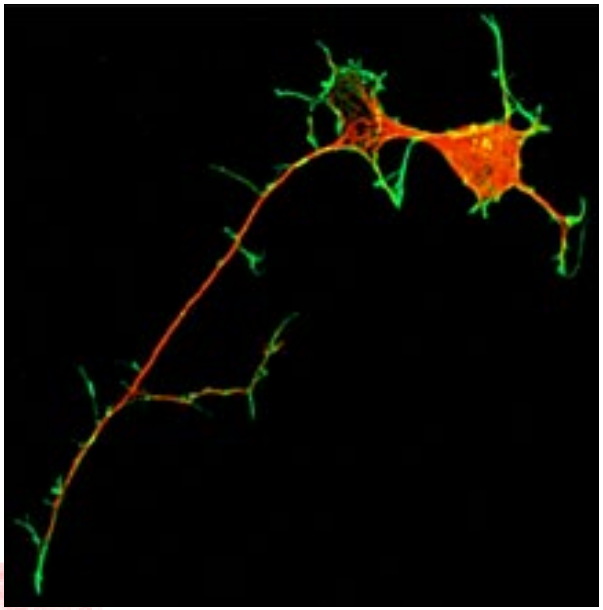
When there are no sticky proteins around (bottom image of composite), there are few actin cables, no focal contacts, and no survival signals. The cells begin to commit suicide. Their DNA (blue) shrinks and breaks down, and within a day, about 80% of the cells will be dead. This suicide mechanism prevents cells from growing where they are not needed, or where other cells are not present to monitor their actions. Cancer cells often lose such controls over their growth.

Wandering is not tolerated.

Nerve cells have to undergo a long and complex journey from the spinal cord to the skin and organs. Those that get lost will die.

The photo shows a **nerve cell** that was taken from a chick embryo ten days after fertilization. The large **cell body**, which contains the DNA, normally lies in the **spinal cord**. The thin **axon** (nerve cell) grows to reach the skin, muscles or organs to detect pain, heat, touch or vibration.

Only about half of the nerve cell axons will reach their destination successfully. The axons are guided in their long journey by proteins made at various landmarks along the way; these proteins are also necessary for the cell's survival. If the axon gets lost, the cell no longer gets its supply of the survival protein, and the cell dies.



Profile of a scientist in biotechnology: ANU SRINIVASAN.

Manipulating cell death may save lives.

It was no surprise that Anu Srinivasan became a scientist. "My family is full of bookworms," she says. "We have enough Ph.D.s to field a cricket team."

Srinivasan grew up in Madras, India, and came to the University of Michigan to do her Ph.D. Her Ph.D. project was a combination of math and biology. She used mathematical descriptions of the properties of atoms to get at the details of a biological process: the generation of oxygen by plant photosynthesis.

Srinivasan's work on how and why cells commit suicide led to her position at Idun Pharmaceuticals, Inc., in La Jolla, California. Idun was formed in 1993 with the aim of finding anti-cell-suicide drugs to treat human diseases.

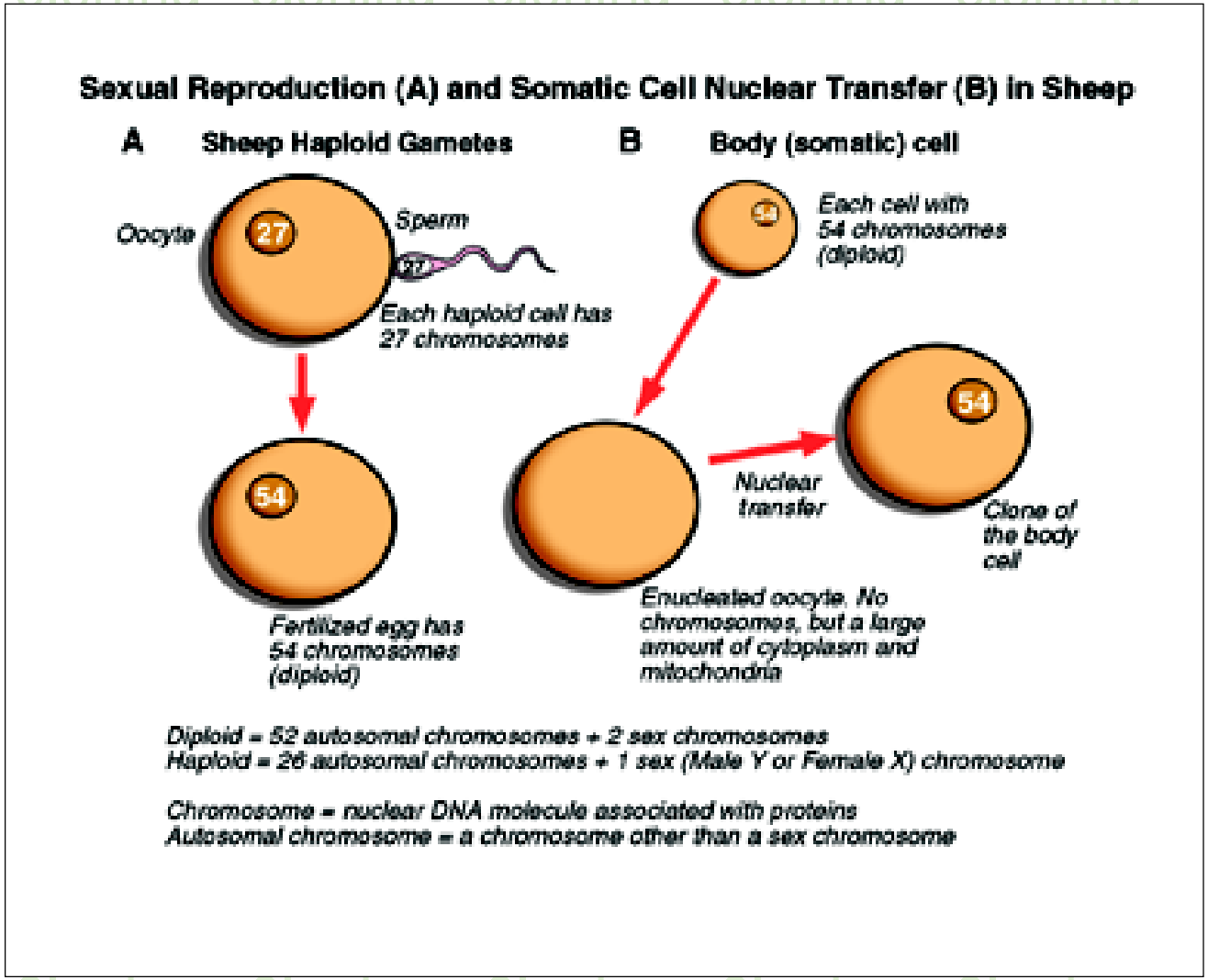
At Idun, Srinivasan uses experiments in culture cell dishes as models for human diseases. For example, heart attacks or strokes cut off the blood supply to an area, starving tissue of nutrients and oxygen. Srinivasan can mimic the same situation in a culture dish by growing cells in low-nutrient, low-oxygen conditions. A drug that helps these cells to survive may help cells that are at risk after a heart attack or stroke.

Some cell death from heart attacks, stroke and neurodegenerative diseases like Alzheimer's may be avoidable. The body reacts to these assaults by sacrificing any cells that are challenged, even if rehabilitation of these damaged cells might be better for the individual.

In a sense, cancer cells present the opposite challenge: they keep growing despite a poor blood supply, DNA damage, or other insults that would cause normal cells to commit suicide. Scientists like Srinivasan and companies like Idun hope to gain insights into both kinds of cellular misbehavior by manipulating cell suicide with drugs.

Cloning

The word **"cloning"** can make us think of science fiction and the creation of multiple identical human beings. But the recent scientific advance made when Scottish scientists "cloned" the sheep Dolly is exciting because of what it can mean for medical care. Before the Dolly experiment, scientists had believed that once a cell started to develop into its specialized form — for example, as part of the heart or the kidney — it lost its ability to reproduce itself and to become any other sort of cell. The Dolly experiment showed otherwise. Now scientists are using the same technique used to clone Dolly — called Somatic Cell Nuclear Transfer Cloning — to try to make healthy hearts and kidneys, and other organs as well, to replace defective tissues in people who are sick.



The Importance of Animals to Research

There are striking similarities between the physiological systems of humans and various species of animals. For example, much of what we know about the immune system has come from studies with mice, and much of what we know about the cardiovascular system has come from studies with dogs.

Research results from animals also provide the information necessary to design human trials that must be completed for legal approval of new devices, drugs or procedures. It is important to be able to gauge how a new drug or procedure will affect a whole biological system before using it on humans. This is critical for scientific and medical as well as ethical reasons. In fact, virtually every major medical advance of the last century is due, in part, to research with animals.

For more information about the role of animals in scientific and medical research, see the Foundation for Biomedical Research website at www.fbresearch.org

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Education and career resources for cell biology and related careers

www.ascb.org/ascb	The American Society for Cell Biology
bio.com/	Bio Online includes a career center and profiles of biotechnology and drug companies.
www.wisc.edu/cbe/cels/edulinks.html	Education links provided by life sciences professional societies through the Coalition for Education in the Life Sciences.
nextwave.sciencemag.org/	Career resources for all scientists complied by the American Association for the Advancement of Science (AAAS) and *Science* Magazine.
www.accessexcellence.org	Access Excellence is a site with biology teaching resources.
www.nih.gov/nigms/about_nigms/more.html	The National Institute of General Medicine Sciences provides funding and information through the Division of Minority Opportunities in Research.
www.nsf.gov/home/ehr/start.html	The National Science Foundation provides educational materials and funding for all levels of science education.
www.nabt.org	The National Association of Biology Teachers (NABT).
www.nsta.org	The National Science Teachers Association (NSTA).
www.abanet.org	The American Bar Association, with information on law education and schools.
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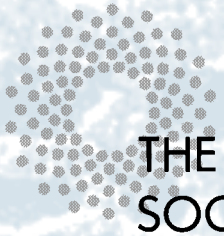
www.picasso.ucsf.edu/~cerpa/patent.html	Career opportunities in patent law.
www.nbif.org/career/career.html	Biotechnology and general biology career information from the National Biotechnology Information Facility (NBIF).
www.nasw.org/	The National Association of Science Writers.
natsci.ucsc.edu/acad/scicom/SciWriting.html	The science writing course at the University of California, Santa Cruz is one of the few journalism programs devoted to science.
www.nas.edu.nrc/	The National Research Council (NRC), a part of the National Academy of Sciences (NAS), complies reports on scientific issues of public importance, and offers internship programs.
www.aaas.org/	The Public Policy Fellowships granted by the American Advancement of Science (AAAS) offers opportunities to get started in science policy.
biodidac.bio.uottawa.ca/	A bank of digital resources for teaching biology.
firstmarket.com/fitzroy/	Undergraduate research projects in biology.
www.internets.com/mednets/sbiology.htm	Links to searchable biology databases.
www.cellbio.com/education	Gateway to cell & molecular biology educational resources.
www.internets.com/mednets/biologyass.htm	Links to Biology Associations.
www.biology.arizona.edu/cell_bio/cell_bio.html	An online interactive resource for learning biology from the University of Arizona.
www.mblab.gla.ac.uk/%7Ejulian/Dict.html	The Dictionary of Cell Biology.
www.os.dhhs.gov/	The Department of Health and Human Services directs biomedical research at the NIH, CDC and FDA. Also contains information for children.
www.nih.gov/	The National Institutes of Health funds biomedical research.
www.nlm.nih.gov/	The National Library of Medicine allows you to search for information about biomedical research.
www.doe.gov/	The Department of Energy funds research regarding energy, some of which relates to biomedical research.
www.nasa.gov/	The National Aeronautics and Space Administration (NASA) provides information on science in space.
www.nih.gov/	The Food and Drug Administration (FDA) ensures that food and drugs are safe for the American people.
www.whitehouse.gov/WH/EOP/OSTP/html/OSTP_Home.html	The Office of Science and Technology Policy is the office at the White House that coordinates all federal policy with regard to science.
bioethics.gov/cgi-bin/bioeth_counter.pl	The National Bioethics Advisory Commission conducts studies on issues of bioethics including cloning, stem cell research and human subjects for research.
www.faseb.org/	The Federation of American Societies for Experimental Biology (FASEB) provides a series of articles called Breakthroughs in Bioscience which are illustrated essays that explain recent breakthroughs in biomedical research and how they are important to society.
www.bio.org/	The Biotechnology Industry Organization (BIO) provides information about the biotechnology industry.
www.phrma.org/	The Pharmaceutical Research and Manufacturers of America provides information about the pharmaceutical industry.
www.exploratorium.edu/learning_studio/	The Exploratorium's Learning Studio is an experimental multimedia and communications lab offering the chance to participate in experiments online.
stone.web.brevard.k12.fl.us/mentornet/mentor.html	Find an online mentor to help guide your journey through the biological sciences.
whyfiles.news.wisc.edu/	The science behind the news stories.
www.madsci.org/	The MAD Scientist Network, based at Washington University Medical School in St. Louis, is a collective cranium of scientists providing answers to your questions and an opportunity to participate in experiments.



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9650 Rockville Pike
Bethesda, MD 20814-3992
ascbinfo@ascb.org
www.ascb.org/ascb

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For more information about the ASCB, contact the Society at

9650 Rockville Pike

Bethesda, Maryland 20814

301-530-7153; 301-530-7139 (fax);

ascbinfo@ascb.org or www.ascb.org/ascb.

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www.furman.edu/~snyder/careers/careers.html	Provides links to sites with information on career planning for anyone interested in broad aspects of biologically oriented careers.
www.primex.co.uk/iob/d31.html	The Institute of Biology has produced a set of careers literature to help school and college students discover the range of careers open in biology.
www.microscopy-uk.org.uk/mag/indexmag.html	Interactive magazine introducing students to instrumentation.
www.studyweb.com/	Commercial site has organized over 63,000 URLS of educational and classroom importance.
www.ed.gov/free	Internet teaching resources aimed primarily at the K-12 audience, from 49 federal agencies. Animations, interviews and tutorials.
www.stanford.edu/group/Urchin/index.html	Over 150 web pages for high school biology teachers.
www.sciencenet.org.uk/index.html	All areas of science are covered with a strong focus on biology and medicine.
vector.cshl.org/dnaftb	Geared towards people without a scientific background.
www.tulane.edu/~dmsander/garryfavweb.html	A general virology resource.
science-education.nih.gov/homepage.nsf	Web site for high school students and teachers.
www.nhgri.nih.gov/DIR/VIP	Site has a glossary of 150 genetic terms with illustrations and audio tracks where various scientists at NIH describe the sense of the term.
pbs.org/wgbh/aso/tryit/dna/#	DNA workshop.
www.hoflink.com/~house/index.html	800 web resources for Biology teachers and students.
www.cotf.edu	Bioblast - NASA funded multimedia project for teachers and students.
www4.nas.edu/beyond/beyounddiscovery.nsf	National Academy of Science case studies of recent technology and medical advances.
www.classroom.net/home.asp	Adventure learning programs with interactive expeditions.
www.biologylessons.sdsu.edu	Biology lessons and teacher guides.
www.microbeworld.org	Facts, stories and vivid images. Links to microbe.org that helps students explore the mysteries and wonders of microbes.
www.hhmi.org/GeneticTrail/	Blazing a genetic trail. Families and scientists joining in seeking the flawed genes that cause disease.
schmidel.com/bionet.cfm	A guide to biology and chemistry educational resources on the web.
www.ncsu.edu/servit/bodzin/	A resource for primary, secondary, and university science educators. Links to other science web sites.