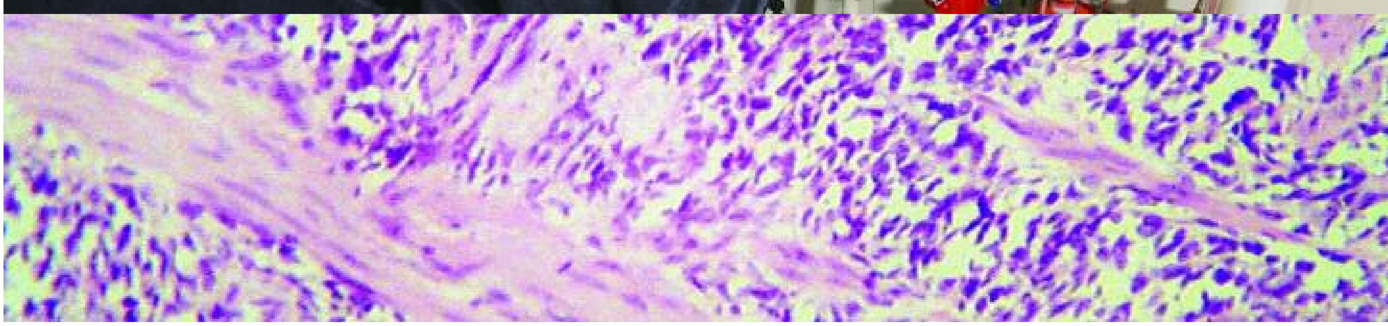
Hunting a Killer



BY ALISA ZAPP MACHALEK

A serial killer is on the loose, and scientists are hot on the trail.

That's because this killer is cancer, and among its pursuers is Yuri Lazebnik, 47, a cell biologist at Cold Spring Harbor Laboratory on Long Island, New York.

As a forensic scientist uses fingerprints and bloodstains, Lazebnik uses tools of cell biology to uncover the roots of cancer and help contribute to a cure.

From Russia With Drive

Lazebnik grew up in St. Petersburg, Russia, raised by a single mother in a house that faced the department of mathematics and mechanics at the nearby university. When the students threw out parts of old computers or bits of broken machinery—knobs, switches, cables, and the like—Lazebnik and his friends would scamper over the fence, retrieve the discarded treasures, and transform them into rocket ships.

To earn money during college and graduate school at St. Petersburg State University, he held various odd jobs, working as a photographer, electrician, night-time store manager, and operator in a coal heating facility. At one point he even served as a cleaner of agricultural irrigation channels, which he remembers as backbreaking work that "involved a nice mixture of lumberjacking and ditch-digging."

One job that shaped the course of Lazebnik's career was working as a technician in a hospital.

"That's where you see the other side of life—people dying," he recalls. He was particularly moved by people who had cancer, especially kids.

Lazebnik resolved to study cancer and immigrated to the United States to do so.

Guided By Surprise

"The most exciting phrase to hear in science, the one that heralds new discoveries, is not 'Eureka!' (I found it!) but 'That's funny…'"

—Isaac Asimov

The hallmark of cancer is its ability to spread. Rather than staying within their home tissue, cancer cells move aggressively into neighboring tissues, damaging or shutting down vital organs and often leading to death if left untreated.

"You have the potential to discover something that could turn around your entire view of the world."

Like many cell biologists who studied cancer in the early 1990s, Lazebnik initially focused on cell division, or mitosis, which goes haywire in cancer.

But a strange sight almost immediately pulled him in another direction. As he peered at dividing cells through a microscope, one of them looked "funny" to him. Its nucleus, normally a smooth, oval-shaped structure, looked like a bunch of grapes or a cluster of darkly colored plastic beads. He knew that whatever he was seeing, it wasn't mitosis.

As it turned out, Lazebnik had witnessed apoptosis, or cellular suicide. Our bodies use this process during normal development to sculpt the shape of our fingers and toes and streamline nerve connections in our brains. Apoptosis is also how the body removes old, worn-out cells throughout our lives.

At the time, few researchers studied apoptosis, and Lazebnik thought those who did were crazy, as most "rational" people didn't believe in apoptosis then, he says.

Nonetheless, Lazebnik followed the trail of where his research led him. Today, some 90,000 scientific papers have been written about apoptosis, and 10,000 new ones are published each year.

Demonstrating Death

As an expert in the field, Lazebnik frequently speaks about apoptosis, both to researchers and to nonscientists. His talks are peppered with analogies, including a scene from the James Bond movie *The Spy Who Loved Me*, old film clips of an aikido master (see sidebar, page 13), and illustrations of bombs, collapsing houses, and a shark sliced up with its pieces rearranged.

Lazebnik saves his most vivid analogy for teaching high school students about proteases, the knifelike enzymes that carve up cells during apoptosis. In this demonstration, he first removes a scalpel from his right

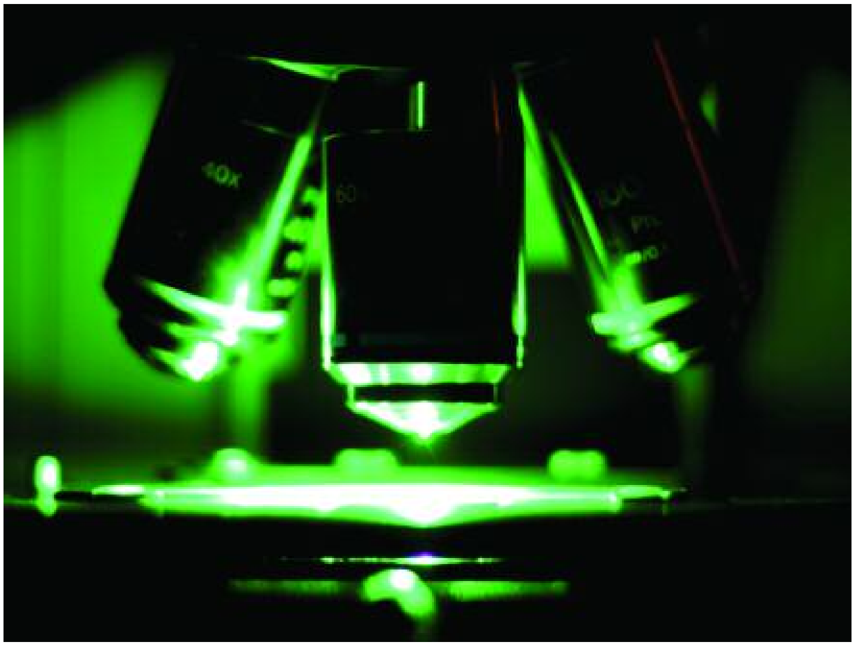
Lazebnik grew up in the Russian city of St. Petersburg.

pocket and shows it to the students. Then he extends his left arm and draws the knife straight across it.

Students gasp, but there's no blood. That's because the scalpel comes with a protective plastic sheath over the blade. Similarly, all cells contain proteases but keep them tucked away until they're needed, Lazebnik explains.

Next, he dramatically snaps off the protector. Every eye is locked on him as he raises the naked blade.

After a pause, he continues, "I take a piece of paper and slice it into many pieces. This shows the students what proteases do during apoptosis. The idea is impregnated into their minds."



By using a microscope to look at cells that have been marked with fluorescent dyes, Lazebnik is studying the roots of cancer.

Fusion Confusion

A few years ago, biology stumped Lazebnik again. As before, finding the answer set him on a new research path.

The surprise finding was originally made by a high school student, David Rubenstein, who was working in Lazebnik's lab for a few months as part of Cold Spring Harbor Laboratory's Partners for the Future program, which Lazebnik directed for several years.

This program gives high school seniors a taste of the real world of biomedical research and helps debunk stereotypes about scientists.

For Rubenstein, it worked.

"I was very surprised seeing the head of the lab in a T-shirt and jeans," he says. *(He and others concede that, at one time, Lazebnik did have hair rather like Albert Einstein's.)*

Rubenstein set up what everyone in the lab thought would be a simple experiment. The results were anything but routine. Two human cell types—a cancer-prone type and a normal cell type—looked like they had somehow merged or fused together. Rubenstein's mentor, Dom Duelli, a postdoctoral researcher in the lab, was skeptical.

"At first I didn't believe him at all," Duelli confesses. "I thought he messed something up."

But Rubenstein repeated the experiment and got the same results, convincing Duelli and the others that he had stumbled across something else "funny."

To figure out what was going on, Lazebnik curled up with his computer to absorb everything that had been published about cell fusion.

He learned that the body keeps a tight rein on the process. In fact, there are only five known examples of healthy cell fusion: fertilization (when a sperm and an egg fuse), formation of part of the placenta, muscle development, bone remodeling, and a type of immune response.

And, Lazebnik learned, except for fertilized eggs, fused cells don't continue to divide—in stark contrast to tumor cells, which do so wildly.

Most telling of all, says Lazebnik, is that when healthy cells accidentally fuse, their reproductive lives screech to a halt—a clear demonstration of how seriously the body takes abnormal cell fusion.

Yet as is often the case, cancerous and cancer-prone cells play by different rules. Rather than avoiding cell fusion, these cells readily merge together and then continue to reproduce—at least in the tissue culture dishes Rubenstein and researchers worldwide use for lab experiments.

"It's called spontaneous cell fusion," says Lazebnik, "which basically means we have no clue [why] it happens."

The real question is: Does it happen in tumors inside people? And, if so, could it be a key to why tumors are so tough to kill?

Viral Culprits

If cancer cells were all the same, we'd have cured the disease long ago. Instead, they vary widely. Even a single tumor can contain a mish-mash of abnormal cells with unpredictable characteristics.

Fusion, which scrambles together different cell types, could cause the strange diversity within tumors, says Lazebnik. As he puts it, "It's like the merging of two companies—you could end up with something completely different in the end."

What makes cells fuse?

To find an answer, Lazebnik and Duelli thoroughly examined the genes and molecules in the fused cells. They discovered that, at least in this case, the culprit was a tiny particle squirted out by the cancer-prone cells. This particle seems to be the virus that causes an AIDS-like disease in monkeys.

The same virus is found in people, but doesn't cause disease. And it's not there alone. There's a family of viruses residing within us so commonly that the viral genetic material intertwines with our own, composing at least 8 percent of our genomes.

Yet just because these viruses are common and don't appear to cause disease doesn't mean they're harmless, cautions Lazebnik. The monkey virus clearly makes human cells fuse in plastic lab dishes, and no one really knows what trouble that might stir up.

Finding a virus that triggers cell fusion isn't new; a number of viruses can do this. In fact, large masses of merged cells, known as syncytia, are typical of infectious diseases like measles and mumps and are also seen in some types of cancer.

But syncytia don't continue to divide. They eventually die and are reabsorbed by the body.

Occasionally, only two or three cells fuse, rather than the hundreds typical of syncytia. In rare cases, these small masses survive and multiply. That's when the trouble starts, explains Lazebnik. The fused cells tend to develop genetic changes, or mutations, that are caused by the haphazard bumping and shuffling of the many different sets of chromosomes within them. Some of these mutations can chart a course toward cancer.

Whether any of that happens—and whether the mass eventually develops into cancer—depends on chance and time, Lazebnik says.

Questions Continue

All of this raises some sobering questions, says Lazebnik.

Do viruses cause some of our cells to fuse? Does cell fusion cause, or contribute to, cancer?

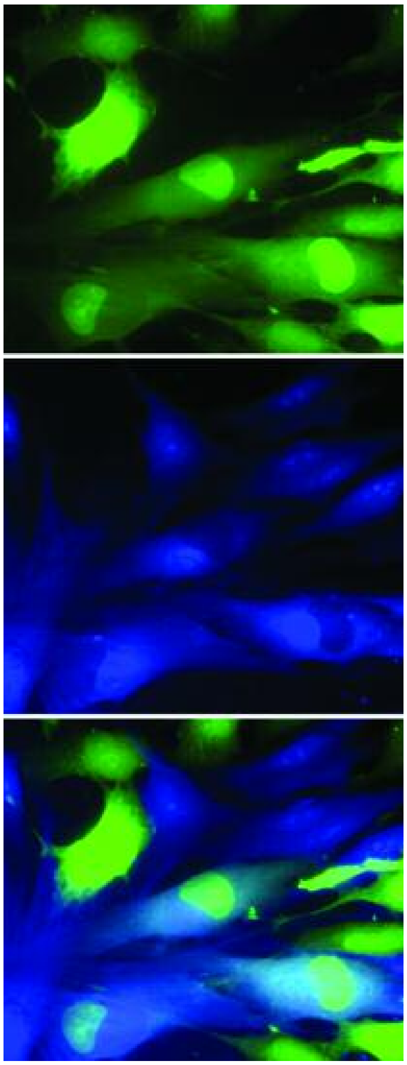
No one knows yet.

Scientists do know that at least 10 percent of cancers are caused, at least in part, by viruses. One example is human papillomavirus (HPV), which causes virtually every case of cervical cancer. Also, hepatitis B and C are strongly associated with liver cancer, and Epstein-Barr virus (which causes mononucleosis or "mono") is linked with some types of lymphoma.

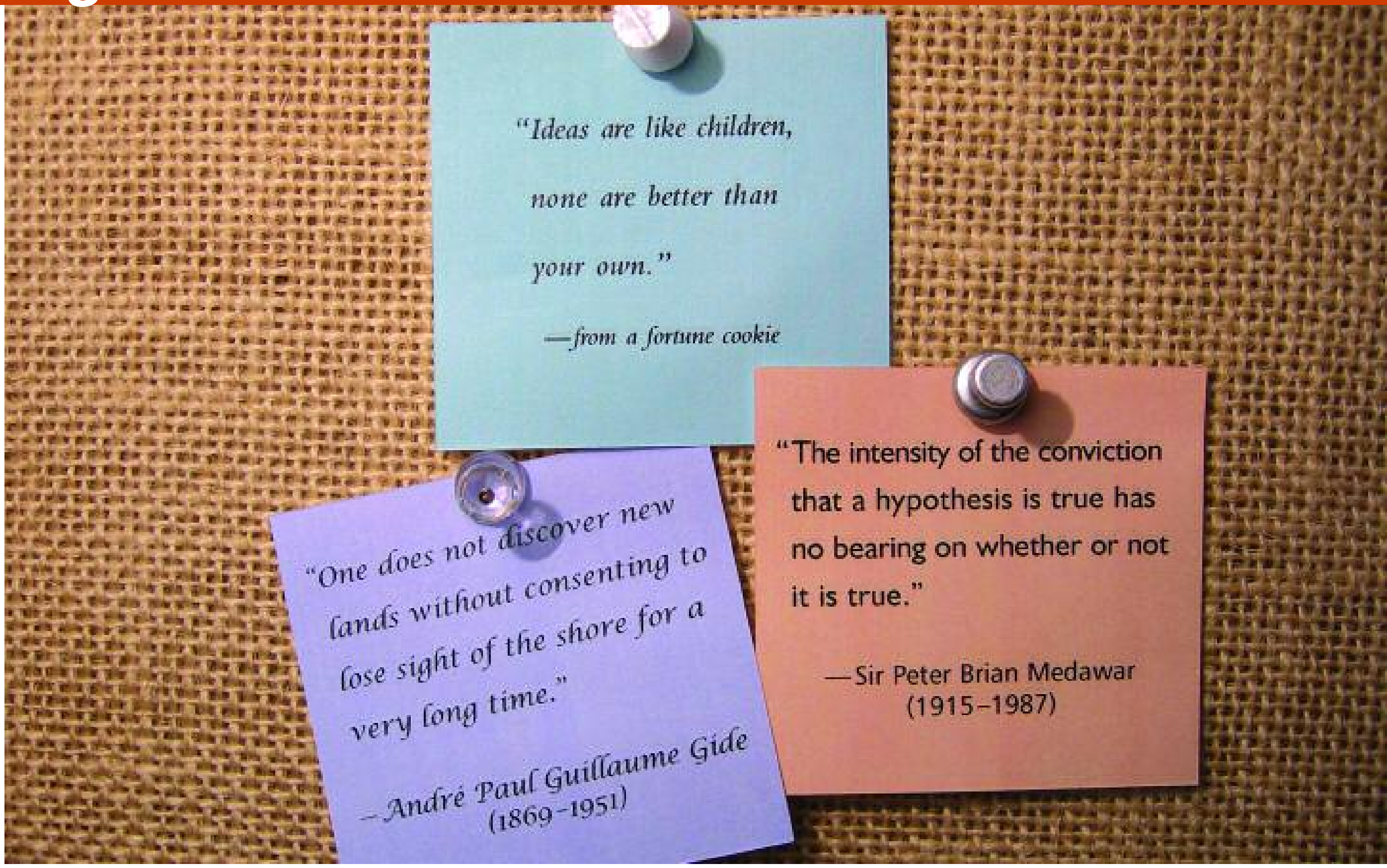
If a virus causes a type of cancer, scientists may be able to prevent that cancer by developing a vaccine against the virus. The first vaccine of this sort targets hepatitis B. It has dramatically reduced the incidence of liver cancer.

Another vaccine, against HPV, was approved by the Food and Drug Administration in June 2006 to prevent cervical cancer.

But viruses aren't the whole story. Only a few of the people infected with these viruses actually get cancer. Even in the case of HPV, only 1 or 2 percent of those with the virus develop invasive cervical cancer.



Researchers label cells with different fluorescent dyes, then mix the cells. Those that contain both blue and green color have fused.



Quotations on the wall of Lazebnik's lab inspire students and other researchers.

So which other factors contribute to cancer? Lazebnik's data point to cell fusion.

This raises a concern about the notion of using viruses as vehicles to deliver genes or medications to specific tissues. The strategies rely on cell fusion, which might lead to bigger problems than the therapies were designed to solve, he says.

"I was very surprised seeing the head of the lab in a T-shirt and jeans."

As he seeks to understand the connections between cell fusion, viruses, and cancer, Lazebnik is in what he calls a "scientific wilderness." Although only a few other researchers are investigating whether cell fusion can contribute to cancer, Lazebnik is quick to point out that the idea is more than 100 years old. He cites papers published in 1887 and 1911 that propose the theory.

Although he admits that not all unusual ideas are correct, he also notes that some of the best ideas in science took years before they were commonly accepted. And he rattles off example after example.

Stories and Histories

It's not only scientists whose ideas were scandalous at first that interest Lazebnik. He seems almost as well versed in the history of science as in science itself, flitting easily between quoting the ancient Greek philosopher Heraclitus, referencing the 17th-century mathematician and physicist Christiaan Huygens, and citing the 1914 paper on the cellular origin of cancer by developmental biologist Theodor Boveri *(which, Lazebnik points out, is sometimes still available—used—on the Internet)*.

Lazebnik's habit of quoting scientists, historians, and philosophers has infected his lab. Taped to walls are strips of paper containing many famous—and infamous—quotations.

After struggling with a series of experiments, one student working in the lab taped this note to her laboratory bench:

"Success consists of going from failure to failure without loss of enthusiasm."

—Winston Churchill

The next day, she added another strip of tape, similar to a quote commonly attributed to Albert Einstein:

"Insanity: doing the same thing over and over again and expecting different results."

If a pithy quote won't do the trick, Lazebnik pulls out a parable, often one from folklore. In one story, two frogs are trapped in a carafe of milk. One frog immediately dies in despair. The other keeps trying to escape. Eventually, the frog feels something hard under him and is able to jump out of the carafe. With his tireless jumping, he had churned the milk into butter. The moral? *Never give up.*

Even the way Lazebnik describes his interest in science is steeped in story. For example, he relates how the ancient Greeks observed that when amber is rubbed with a dry cloth, it becomes charged with an unknown force—now called static electricity—that attracts lightweight objects like dried leaves or bits of paper. The term *electron* is the Greek word for *amber*, he explains.

"What's out there that's comparable to the power of electricity, that we see every day, but that remains hidden?" Lazebnik asks.

That's what he's after. It's what keeps his passion for science alive.

"You have the potential to discover something that could turn around your entire view of the world."

And maybe in the process, you'll hunt down a serial killer. ■

Killing Cancer With Aikido

合氣道

A black-and-white silent film shows an unfurnished room, in the center of which stands a petite, bald-headed Japanese man in his 80s. Suddenly, someone rushes at him from behind. The old man nimbly grabs the attacker's wrist and *swoosh!* The assailant's body slices through the air in an arc of black and white, then thuds on the padded floor. The elderly man, who never even turned to face his much younger opponent, remains standing.

Next, two assailants charge the man. He seizes their wrists, fashions a pretzel by twisting one opponent's head through the arms of the other, then flings them both to the ground.

A moment later, seven attackers engulf the man. The black-haired mob sways like a drunken beetle, then collapses. One figure remains standing: the wizened master, his arms outstretched, while a jumble of limbs in white tunics and black pants lies at his feet.

Those are scenes from a movie showing Morihei Ueshiba, who founded the martial art, aikido, in the 1940s.

JUN AKIYAMA, WWW.AIKIWEB.COM

"Ueshiba was a very tiny guy, even by Japanese standards—about 100 pounds and 5 feet tall. Yet what he could do is just incredible," marvels Yuri Lazebnik, a cell biologist and aikido aficionado.

Lazebnik plays the movie clip during his scientific talks as a visual metaphor for his research approach. He explains that aikido focuses on harnessing the power of your opponents and using it against them.

"By subtle moves and turns, a little person can make a big one flip over," he says. "This is very similar to what we're doing with oncogenes [genes that, when mutated, promote cancer]. Oncogenes have an energy that causes cells to grow and spread throughout the body as cancer. We're trying to reroute this energy to kill the cancer instead."

Lazebnik, who has studied martial arts for more than 20 years, recently earned his first belt in aikido. Aside from cultivating discipline, aikido inspires him by the way its masters appear to steer the laws of physics.

To him, this demonstrates not just one aspect of aikido, but a guiding life principle.

"If you gain and develop skills, you can make things happen that you didn't think were possible."—*A.Z.M.*