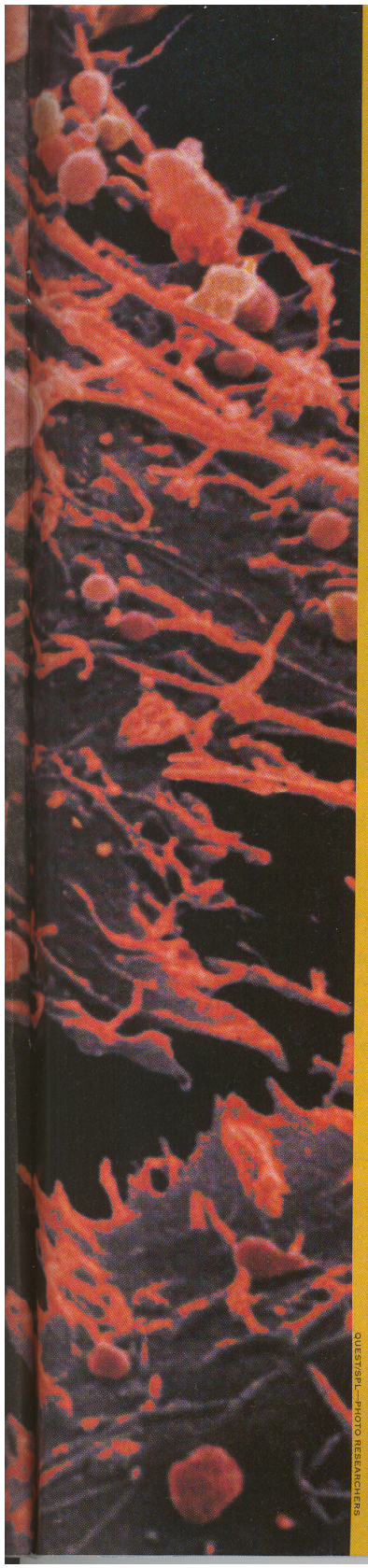
MALIGNANCY:
If left unchecked, a tumor cell—like this magnified breast-cancer cell—will multiply wildly, tear into surrounding tissue and make its own blood supply



QUEST/SPL—PHOTO RESEARCHERS

CANCER UPDATE

NEW HOPE FOR CANCER

This little pill targets cancer cells with uncanny precision. Is it the breakthrough we've been waiting for?

By **MICHAEL D. LEMONICK** and **ALICE PARK** SAN FRANCISCO

By February of last year, Victoria Reiter, 63, figured she had only a few months to live. A writer and translator living in Manhattan, she was suffering from chronic myeloid leukemia, an especially deadly form of blood cancer. The only treatment available was interferon, an immune-system booster that wasn't really working and that made her violently ill. Reiter had spent most of 1999 in bed, too sick to read, to walk, to do much of anything—although she had managed to put together lists dividing her possessions between her two daughters.

Then she went on an experimental drug called Gleevec, and within weeks everything changed. "All my energy started coming back," she says. "Suddenly I could read. I could take a walk." By August, tests showed her bone marrow was clear of leukemia cells; in December, she took up the Argentine tango. She still has the lists

of what her daughters will get, but, she exults, "They're not going to get it yet!"

For Bob Ferber, a Los Angeles prosecutor specializing in animal-abuse cases, the Gleevec experience was very much the same. Less than two years ago, he was lying in a hospital room considering suicide to escape the pain radiating from his bones. "From crawling across the floor on my knees to go to the bathroom, I'm now back at work," says Ferber, 48. "I go to the gym. I'm volunteering for an animal-rescue group. I have a girlfriend. It's the dream of any cancer patient in the world to be able to take a pill that works like this. It's truly a miracle."

That's a tempting way to look at it, anyhow. Gleevec is effective enough that the U.S. Food and Drug Administration approved it in record time two weeks ago—even as researchers announced that it also works against a rare form of stomach cancer. The drug doesn't help everyone, and it can have side effects, including nausea, muscle cramps and skin rash. Moreover, nobody is claiming that it actually cures cancer. Patients may have to continue taking the drug, probably for the rest of their lives, and unless Gleevec is used in combination with some other drugs, it is likely their cancer will come back.

Despite all these caveats, Gleevec is still a breakthrough—not only for what it does but, more important, for the revolutionary strategy it represents. A full 30 years have passed since President Richard Nixon declared war on cancer and called for a national commitment comparable to the effort to land on the moon or split the atom. But over those three decades, researchers have come up with one potential miracle cure after another—only to suffer one disappointment after another. Aside from surgery, which almost invariably leaves behind some malignant cells, the standard treatment for most cancers continues to be radiation and chemotherapy—relatively crude disease-fighting weapons that have limited effectiveness and leave patients weak and nauseated.

Along the way, though, scientists have amassed a wealth of information about how cancer works at the molecular level, from its first awakening in the aberrant DNA of a single cell's nucleus to its rapacious, all-out assault on the body. Armed with that information, they have been developing a broad array of weapons to attack the disease every step along the way. Many of these therapies are just beginning to reach clinical trials and won't be available to save lives for years to come. If you have cancer today, these treatments are likely to come too late to help you. But, says Dr. Larry Norton, a medical director at Memorial Sloan-Kettering Cancer Center in New York City: "I think there is no question that the war on cancer is winnable."

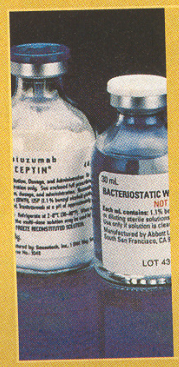
That sentiment was pounded home last week at the annual meeting of the American Society of Clinical Oncology in San Francisco, where a record 26,000 cancer specialists from around the world briefed each other on the good news starting to pour out of their laboratories. Unlike chemo and radiation, which use carpet-bombing tactics that destroy cancer cells and healthy cells alike, these new medicines are like a troop of snipers, firing on cancer cells alone and targeting their weakest links.

Some of these therapies prevent a class of chemicals called growth factors from reaching a tumor, blocking signals that would otherwise instruct the cell to grow out of control. Others tip the delicate balance that every cell maintains between life and death, driving cancerous cells to self-destruct. Still others block enzymes that cancer cells use to chew openings in normal tissues and give themselves room to expand. And, most famously, the class of compounds known as angiogenesis inhibitors keep tumors from building new blood vessels to supply themselves with food and oxygen. Three years ago, Nobel laureate James Watson, co-discoverer of the structure of DNA,

was quoted as saying Dr. Judah Folkman, the Harvard researcher, would use these inhibitors to "cure cancer within two years."

He later claimed that he had been misquoted—and no wonder. Scientists who know anything about cancer are exceedingly cautious about using the *C* word. That's partly because it too easily raises false hopes and partly because doctors are increasingly convinced that a cure is not the only way to beat cancer. Instead, experts believe, by throwing a series of monkey wrenches into the cancer cell's machinery, the new therapies could transform cancer from an intractable, frequently lethal illness to a chronic but manageable one akin to diabetes and high blood pressure. Says

WHAT'S AVAILABLE NOW



HERCEPTIN

Action: Antigrowth

Target cancer: Breast cancer

Manufacturer: Genentech

Side effects: Fever and chills; in rare cases, heart problems and potentially fatal allergic reactions

Cost: About $700 for a week's worth of injections. In clinical trials, the median time on Herceptin was 36 weeks. Total cost: $25,000

RITUXAN

Action: Targeted cell destruction

Target cancer: Non-Hodgkin's lymphoma

Manufacturer: Genentech/IDEC

Side effects: Fever and chills; in rare cases, low blood pressure and potentially fatal allergic reactions

Cost: $10,000 for the full four-week treatment. Retreatment is possible for relapse. Total cost: $10,000-$20,000

JAN SONNENMAIR—AURORA FOR TIME

"This drug is the magic pill people have dreamed of. It's given me the ability not just to survive but to have my life back."

—BOB FERBER, CANCER SURVIVOR

Dr. Leonard Saltz, a colon-cancer specialist at Memorial Sloan-Kettering: "I don't think we're going to hit home runs, but if we can get a series of line-drive singles going and put enough singles back to back, we can score runs."

Four years ago, for example, researchers at IDEC Pharmaceuticals in San Diego, Calif., hit just such a line-drive single with Rituxan, the first drug that successfully targeted proteins on cancer cells. Scientists had learned over the years that cancer cells are studded with an unusually large number of receptacles that compounds essential for survival, including growth factors, can plug into and fuel the cells' growth. Rituxan is a monoclonal antibody, a molecule specifically engineered to fit into the receptacles on non-Hodgkin's lymphoma cells and, in this case, single out the cancer cell for destruction by the immune system. Back in the early 1980s, monoclonal antibodies were hyped in the media as "magic bullets" that would wipe out cancer.

That proved far too strong a claim, but monoclonal antibodies have finally begun to live up to more modest expectations. Rituxan was the first, but just a year later, the same approach led to Herceptin, a drug that keeps growth factors from feeding certain kinds of breast-cancer cells. Such targeted treatments are effective only when the appropriate target exists. Herceptin, for example, latches onto a receptor known as HER2, which is abnormally abundant in only about 30% of breast-cancer tumors. A biopsy can tell doctors whether a patient is likely to respond to Herceptin, but they'd hoped to find a molecule that would plug into a growth-factor receptor more prevalent in cancer cells.

Sure enough, they found one. Dr. John Mendelsohn, then at the University of California, San Diego, and now president of the M.D. Anderson Cancer Center in Houston, had been focusing since 1981 on a receptor called EGFR, which is host to a protein called epidermal growth factor (EGF). It's a close cousin to HER2, and Mendelsohn and his team know that it is present in a huge variety of tumors; two-thirds of all cancer types, in fact, are blanketed with EGF receptors. In 1984 Mendelsohn and his team showed in mice that blocking the EGF receptor with a growth-factor decoy prevented a cell from growing and dividing.

Making a drug out of that decoy would prove tricky, since the receptor, like HER2, also shows up on noncancerous cells. Researchers are now learning, however, that normal cells are more adept than cancer cells at finding other growth factors on which to rely when EGFR is blocked. But when Mendelsohn applied for his first grant from the National Cancer Institute in 1983, he was rejected. "Nobody thought it would work," he says. The following year he turned to philanthropic sources for re-

CAMPATH

Action: Targeted cell destruction

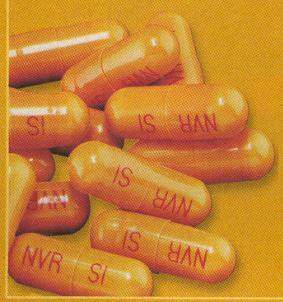
Target cancer: Chronic lymphocytic leukemia

Manufacturer: Millennium/Ilex

Side effects: Fever and chills, infections and sometimes severe anemia; in rare cases, potentially fatal allergic reactions

Cost: A pricing plan has not yet been released for the infusions, which are delivered three times a week for as long as 12 weeks

GLEEVEC



Action: Antigrowth

Target cancer: Chronic myeloid leukemia

Manufacturer: Novartis

Side effects: Swelling, cramps, nausea and in some cases severe anemia. It's too early for researchers to determine whether there are long-term safety problems

Cost: $2,400 for a month's worth. No one is sure, but treatment could be three years to a lifetime. Total cost: $86,000

search dollars. Last year he wowed colleagues with a compound called IMC-C225, which proved effective in treating colon tumors in a small number of patients.

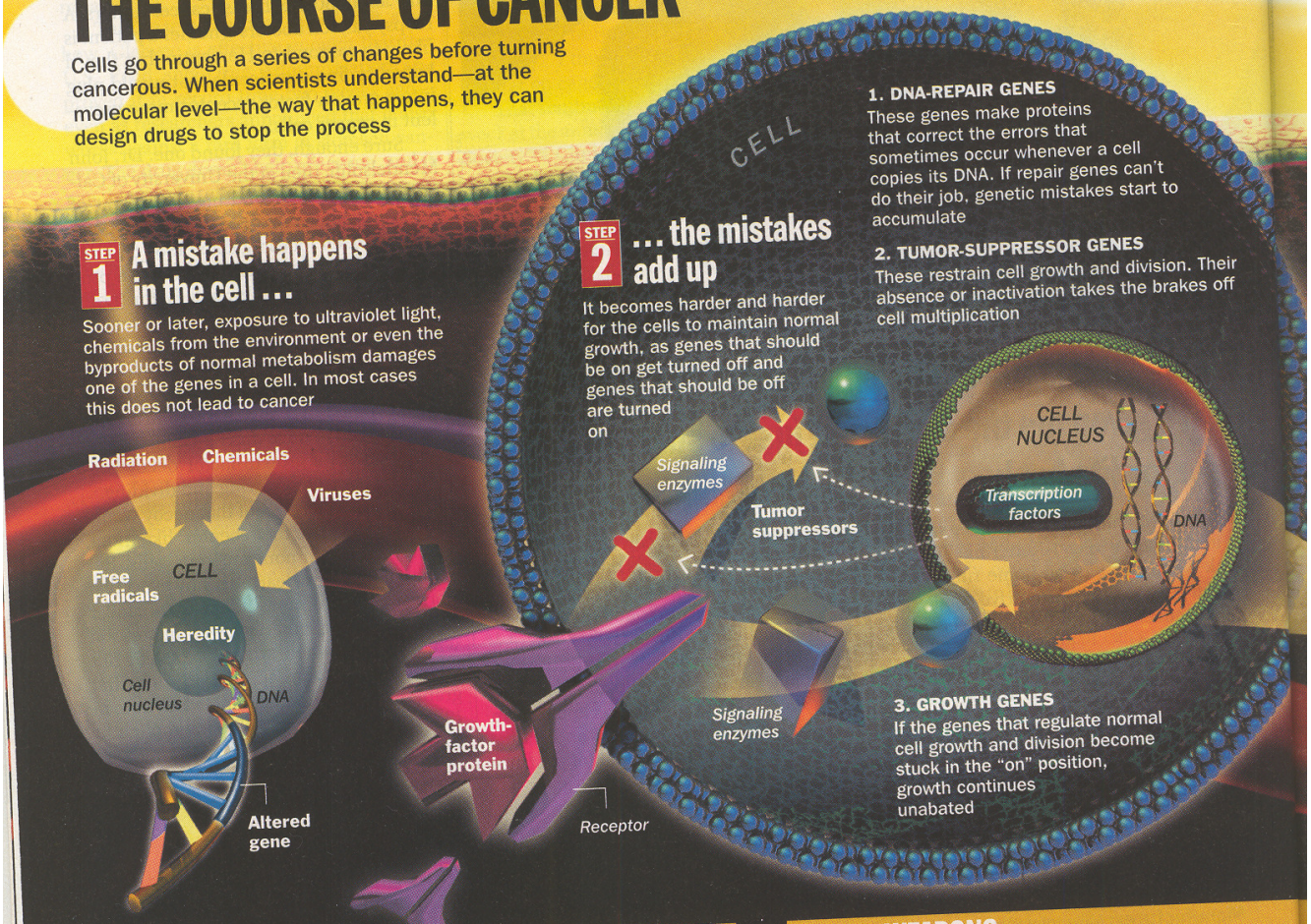
Then just this year researchers at Sloan-Kettering showed that the drug could dramatically boost the effectiveness of standard colorectal-cancer chemotherapy, shrinking tumors in more than a fifth of otherwise hopeless cases. Says Sloan-Kettering's Saltz: "The fact that we got a 20% response rate is staggering." What is happening, he surmises, is that the growth-factor inhibitor weakens the tumor enough for chemotherapy to finish it off.

Buoyed by those results, Saltz will begin testing IMC-C225 in less advanced patients this summer. And because combination therapy seemed to work so well, he is combining the EGFR inhibitor with not one but two chemotherapy agents to pack a triple punch.

Those are only two drugs that keep EGF from doing its job. Gleevec, which reversed Reiter's and Ferber's leukemia so dramatically, is another; so is Tarceva, a drug from OSI Pharmaceuticals in Uniondale, N.Y., which is showing promise against some lung tumors as well as head and neck cancers. Neither of these compounds keeps EGF from docking with cells; instead, each worms its way inside the cells, where it intercepts growth messages percolating in from the surface. Astra Zeneca,

THE COURSE OF CANCER

Cells go through a series of changes before turning cancerous. When scientists understand—at the molecular level—the way that happens, they can design drugs to stop the process



TARGETS OF OPPORTUNITY

Using new insights into how cancer develops, a new generation of drugs is emerging that attacks the disease at earlier and earlier stages

STEP 2 WEAPONS

CANCER PREVENTION
At this stage your best bet is to **eat right, quit smoking** and **avoid sunburns.** Antioxidants like **vitamin E** and drugs like **celecoxib** may also help

STEP 3 WEAPONS

ANTIGROWTH
Herceptin and **Gleevec** are among the first in a generation of new drugs that aim to block the biological signals that promote cancer-cell growth

CELL SUICIDE
Cancer cells don't just grow too much. They refuse to die. Experimental drugs like **Genasense** activate different pathways of cell destruction

headquartered in London, is testing a similar compound, Iressa, against some lung, stomach and prostate cancers.

And that's just the start. Gleevec, Tarceva and Iressa all break one of the most common signaling pathways by blocking an enzyme known as a tyrosine kinase. But the message that encourages a cancer cell to grow involves hundreds of biochemical signals that can travel by hundreds of different pathways. Each of those pathways represents a target, a link that could be interrupted with the properly designed drug.

Another reason cancers grow inexorably is that unlike normal cells, which die a natural death after a fixed number of divisions, cancer cells live forever. Scientists have been looking for compounds that will rewire tumor cells so they will know when it's time to go. The research is still in its early stages, but scientists in several labs have started looking at a group of enzymes called caspaces; inhibiting these enzymes disrupts the process of DNA repair that occurs each time a cell divides.

In Cambridge, Mass., Millennium Pharmaceuticals is focusing on proteins called proteasomes, which evidently play a role in giving cancer cells unnaturally long lives. The company is in Phase II trials with LDP341, a proteasome-inhibiting substance that is showing promise against multiple myeloma and chronic lymphocytic leukemia. Phase I studies on the top five solid tumors (breast, pancreatic, prostate, lung and colon) are under way, and at this point the inhibitor seems to be working—at least in mice.

By far the most celebrated of the new cancer fighters are the antiangiogenesis drugs. Like monoclonal antibodies before them, these compounds, which keep tumors from growing their own blood supplies, were briefly touted as magic one-shot cancer cures—although Folkman, who pioneered the field in the 1970s, was always circumspect about making premature claims. "I think the antiangiogenesis field got some unfair negative publicity," says Saltz. "Our expectations were too high, but there is a lot of brilliant science behind it."

Indeed, while the execution has proved difficult, the idea is very simple. Tumors, like any other cells, need oxygen and nutrients to survive. At first they eat their way through healthy tissue, looking for blood vessels to tap for these essentials.

STEP 3 ... the cells turn cancerous

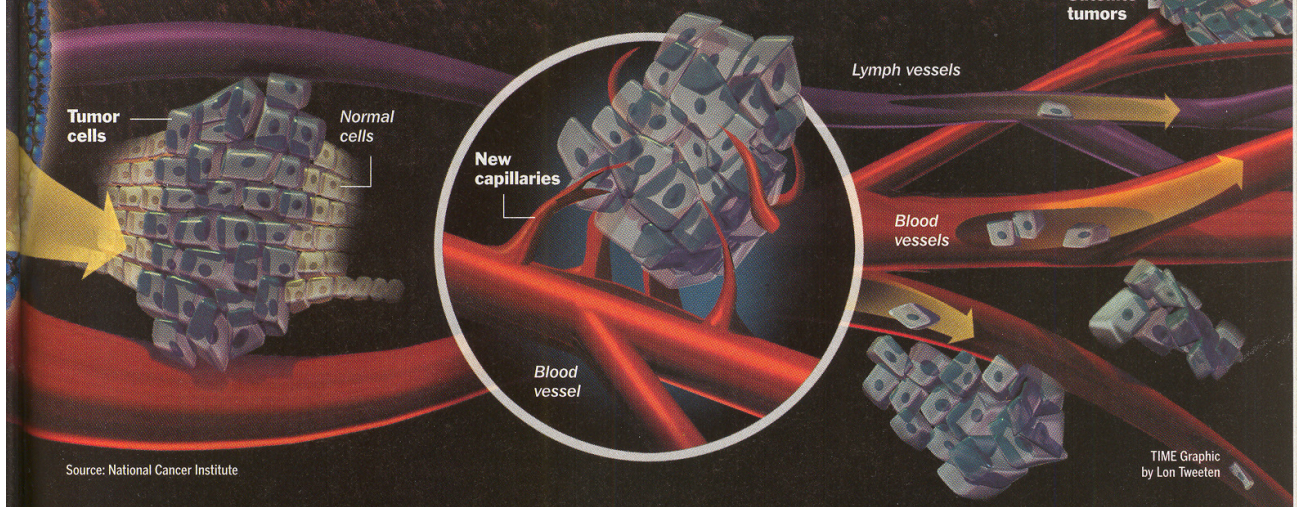
Free of normal restraints, the now malignant cells break all the rules. They divide uncontrollably, become less attached to their neighbors and invade the space occupied by normal cells

STEP 4 ... the tumor's appetite grows

In a process called angiogenesis, malignant cells secrete chemicals that attract and promote the formation of new blood vessels. With a steady supply of nutrients, the tumor can grow without limits

STEP 5 ... the cancer spreads

Pieces of the tumor break off and, in a process called metastasis, migrate through the blood and lymphatic systems. Eventually the runaway cells colonize other parts of the body and give rise to distant tumors



Source: National Cancer Institute

TIME Graphic by Lon Tweeten

STEP 4 WEAPONS

IMMUNE BOOSTER
Cancer cells somehow evade the immune system. Vaccines like **GVAX** and **Virulizin** goad white blood cells into attacking them

MICRORADIATION
Combining the specificity of a monoclonal antibody with the lethality of a radioactive isotope, **Bexxar** targets cancerous lymphoma cells

ANTIANGIOGENESIS
In clinical trials, **Neovastat, semaxanib** and other agents attack the tumor's blood supply in an effort to choke off the flow of nutrients

STEPS 4 AND 5 WEAPONS

SURGERY
Early detection leads to less invasive operations and more cures

CHEMOTHERAPY
Though less toxic than before, these poisons kill both healthy and cancerous cells

RADIATION
Even though radiation beams are localized, they still kill lots of healthy cells

ACID TEST: Cancer cells face new drugs in the lab

COLIN CUTHBERT/SPL—PHOTO RESEARCHERS

Eventually, though, they start to grow their own capillaries and vessels, like oil companies eager to guarantee a steady flow of crude.

Folkman's insight was to look for substances that prevent tumors from building those pipelines. This approach worked beautifully in mice. Now more than 50 angiogenesis inhibitors are being studied in humans with a wide range of cancers; a dozen are in the final stages of testing. Thus far, only a tiny number of human patients treated with these compounds have seen their tumors shrink or disappear. Clinicians are nonetheless encouraged; while angiogenesis inhibitors don't make cancer go away, they do appear to slow tumor growth. And that means they may work best in conjunction with some of the other new treatments to batter cancer from several directions at once.

"We've seen results in very few patients yet," says Folkman. "But we have seem some patients with stable disease. We have seen some patients whose tumors have stopped growing. And we have seen some patients whose tumors slowly regressed. I think the approach is promising, but we are still learning."

While many scientists focus their attention on potential weaknesses in the cancer cell, others are concentrating on the flip side—recruiting the body's immune system to seek and destroy the renegade tissues. So far, this approach has proved less successful, largely because no matter how badly they are misbehaving, tumor cells are purely homegrown and thus presumed innocent by the immune system. When it finally catches on that something is wrong, it's usually too late.

Eight years ago, there were 124 medicines in the research pipeline being tested as potential anticancer agents. Today there are 402

That problem may not be insurmountable, as scientists at last week's clinical-oncology meeting made clear. The trick, it turns out, may be to put aside 99% of the immune system and focus on dendritic cells, a tiny but especially sensitive population of white blood cells that act as sentries to warn against invaders of all kinds. Scientists at California-based Cell Genesys, for example, have taken tumor cells from a number of cancers, genetically engineered them to pump out a hormone that stimulates production of a host of immune cells, and vaccinated late-stage lung-cancer patients with the mixture to boost chances that dendritic cells would sound the alarm against the tumors. In the latest study, three of 22 patients saw their tumors disappear completely, and four saw them stop growing.

Researchers at Stanford University have harvested dendritic cells from advanced-cancer patients, exposed the cells to potent growth factors, added tumor-specific proteins to sensitize them and reintroduced the mixture into patients as a vaccine. Of 12 patients with advanced colorectal and lung cancer, two watched their tumors shrivel away, and another is still tumor free a year after receiving the vaccine.

Whether you're talking about conventional therapy or one of these promising new approaches, experts agree the earlier you catch a cancer, the better your chances of controlling it. And thanks to a growing understanding of the cancer cell's natural life cycle, doctors are learning how to detect the disease at its very earliest stages. One well-known example is the prostate-specific antigen (PSA) test, which identifies a protein secreted by abnormally growing prostate cells before any symptoms appear. (The test is not perfect, however, since PSA is also secreted, albeit in smaller amounts, by benignly growing prostate cells.)

Researchers such as Dr. David Sidransky, an oncologist at Johns Hopkins University, are searching for diagnostics that will pick up other cancers in their preliminary stages. Others are focusing on an even earlier stage, trying to lower the risk of developing cancer to begin with. Here the most exciting work centers on the cycooxygenase inhibitor called COX-2. This pain reliever was originally developed to clamp down on inflammation as aspirin does but without aspirin's tendency to eat through the lining of the stomach.

It turns out that COX-2 inhibitor drugs also have anticancer effects, reducing the number of precancerous polyps in patients with a hereditary form of colon cancer, perhaps through antiangiogenesis. Scientists are currently studying its effect on noninherited colon cancers. And because the receptor for COX-2 is overexpressed on a range of human cancer types, the hope is that COX-2 inhibitors may be useful in preventing a wider range of cancers, including head and neck, bladder, non–small cell lung and breast cancers.

As promising as these therapies are, there remain many questions for researchers to answer. Among the most important: Which treatments should be given to which patients? Says Sidransky: "Within five years, it might be almost impossible to bring a drug forward without having a test to help doctors decide whom the drug is for."

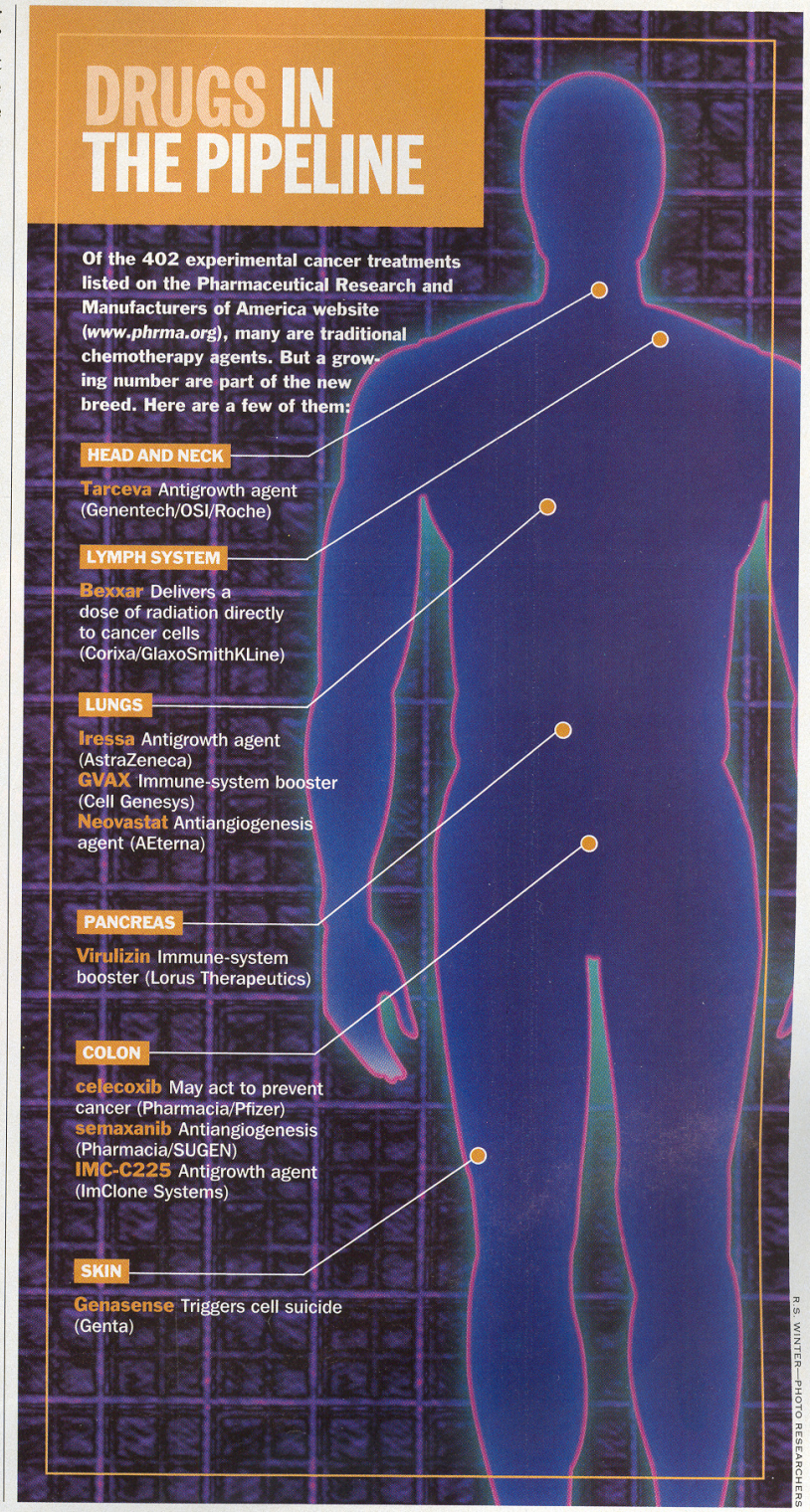
Eventually, the goal is to detect precisely which molecular processes have gone wrong in an individual patient's cancer. Rather than being identified as lung cancer or breast cancer or kidney cancer,

tumors will be tagged as EGFR positive, for example, or COX-2 positive. "The dream," says M.D. Anderson's Mendelsohn, "is that if Mrs. Smith gets a breast biopsy, we'll be able to say, 'Here are the four genes that are abnormal in her tumor,' pull open a drawer, pick out the antibodies or small molecules designed against the abnormal products of those genes, and give her a cocktail targeting the genes that caused her cancer."

That dream comes at a price. Staying on Gleevec, for example, may end up costing patients like Victoria Reiter as much as $2,400 every month—nearly $30,000 a year—for the rest of her newly prolonged life. While the National Cancer Institute funds basic research into cancer biology, the bulk of drug development is done by for-profit pharmaceutical firms. These companies claim that it costs them between $500 million and $1 billion to bring a single new medicine to market—partly because it can take 15 years for the exhaustive testing in animals and humans required by U.S. law and partly because for every medicine finally approved by the FDA, 5,000 others fail somewhere along the way. The drug companies count on that one success to pay for the 5,000 failures. Meanwhile, pharmaceutical firms are under attack both for allegedly conspiring to keep cut-rate competitors out of the market and for profiting handsomely from basic research that was originally funded by the taxpayers.

Now that Gleevec has been taken off the experimental list, insurance companies will probably pick up the tab. Cancer most often strikes the elderly, however, and Medicare's role in paying for prescription drugs is still undecided. President Bush's drug plan would add $153 billion for Medicare drug benefits through 2011. Democrats call the amount "inadequate," and even congressional Republicans agree it is not enough. The final numbers will be hammered out later this year.

At least the drug companies and politicians have something to argue about. Given the painfully slow development of effective cancer treatments over the past three decades, the flood of positive results reported at last week's oncology conference was especially gratifying. "Cancer treatment has always been a satisfying profession," says Dr. Michael Gordon, a cancer specialist at the University of Arizona. "But now it's truly exciting. I've been wondering to myself about where I will be in 20 to 25 years, and I'm thinking that I might just be out of a job. And that will be great." ***—With reporting by Dan Cray/Los Angeles and Christine Gorman/New York***



R.S. WINTER—PHOTO RESEARCHERS