There is new ammunition in the war against cancer. These are the bullets.

Revolutionary new pills like Gleevec combat cancer by targeting only the diseased cells. Is this the breakthrough we've been waiting for?
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 Cleevec, 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 ex- 
ults, "They're not going to get it yet!"

For Bob Ferber, a Los Angeles prose- 
cutor 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 
young 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 ap- 
proved 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, 
obody 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 combi- 
nation 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 revolu- 
tionary 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, re- 
searchers 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 con- 
tinues 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 
marshed 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 rapa- 
cious, all-out assault on the body. Armed 
with that information, they have been de-
veloping 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 Mem- 
orial 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 Fran-
sisco, where a record 26,000 cancer spe-
cialists from around the world briefed each 
other on the good news starting to pour out 
of their laboratories. Unlike chemo and ra-
diation, 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 bal-
ance 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 tu-
mors 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 in-
hbitors to "cure cancer within two years."

He later claimed that he had been mis-
quoted— and no wonder. Scientists who 
know anything about cancer are exceed-
ingly 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 ill-
ness to a chronic but manageable one akin 
to diabetes and high blood pressure. Says
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 EGF, 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 blanketeted 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 EGF 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-
search dollars. Last year he vowed 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 EGFR 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 EGFR 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.

**STEP 1**

A mistake happens in the cell...

Sooner or later, exposure to ultraviolet light, chemicals from the environment or even the byproducts of normal metabolism damages one of the genes in a cell. In most cases this does not lead to cancer.

- **DNA-REPAIR GENES**
  These genes make proteins that correct the errors that sometimes occur whenever a cell copies its DNA. If repair genes can’t do their job, genetic mistakes start to accumulate.

- **TUMOR-SUPPRESSOR GENES**
  These restrain cell growth and division. Their absence or inactivation takes the brakes off cell multiplication.

**STEP 2**

...the mistakes add up

It becomes harder and harder for the cells to maintain normal growth, as genes that should be on get turned off and genes that should be off are turned on.

- **GROWTH GENES**
  If the genes that regulate normal cell growth and division become stuck in the “on” position, growth continues unabated.

**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.

**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.

**STEP 3 WEAPONS**

**CELL SUICIDE**

Cancer cells don’t just grow too much. They refuse to die. Experimental drugs like Gensem refuse to destroy 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 caspases; 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.
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 seen 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.

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 cyclooxygenase 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 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