no helmet, no gloves,

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man, you can dream.

COROLLA

How to tell the hype from the hope
A SPECIAL REPORT
Last week's breathless reports of an imminent cure were, of course, too good to be true. Still, these are exciting times in cancer research.

By CHRISTINE GORMAN

UNLESS YOU HAVE GONE through the experience yourself, or watched a loved one's struggle, you really have no idea just how desperate cancer can make you. You pray, you rage, you bargain with God, but most of all you clutch at any hope, no matter how remote, of a second chance at life.

For a few heady days last week, however, it seemed as if the whole world was a cancer patient and that all humankind had been granted a reprieve. Triggered by a front-page medical news story in the usually reserved New York Times, all anybody was talking about—on the radio, on television, on the Internet, in phone calls to friends and relatives—was the report that a combination of two new drugs could, as the Times put it, "cure cancer in two years."

In a matter of hours patients had jammed their doctors' phone lines begging for a chance to test the miracle cancer cure. Investors scrambled to buy a piece of the action, turning the shares of a little company called EntreMed into the most volatile stock on Wall Street. Cancer scientists
Then preliminary reports indicated that a drug called tamoxifen—and offering perpetuating the second major medicine everyone knew about their research Viagra all over again, without the jokes, generating a new round of headlines. Scientists at the National Cancer Institute announced that they were halting a clinical trial the last week, even the most breathless talk-show hosts had learned what every molecule, called angiostatin and endostatin, and the only cancers they have cured so far have been in mice. By the middle of the year this is a case of science journalism has been a history of curing cancer research has been a history of curing cancer treatments made possible by what they’ve learned about how genes and cancer cells work at the molecular level, the fruits of which are already being delivered to human patients (see following story).

How did a story about preliminary data on laboratory animals spiral so completely out of control? The key is Kolata’s piece in the Times and the prominent placement her editors gave it. “Within a year,” he began, “if all goes well, the first cancer patient will be injected with two new drugs that can eradicate any type of cancer, with no obvious side effects and no drug resistance—in mice.” It was a sentence that couldn’t help grabbing readers’ attention—despite those critical two words, “in mice”—and holding it throughout the rest of the story.

Apart from certain omissions, there was nothing factually inaccurate in what Kolata wrote. Folkman, in his statements, went out of his way to downplay his findings. But his carefully cautious tone was completely overshadowed by the quotes Kolata attributed to a host of other scientists and the adjectives they used to describe Folkman’s work. His results were “remarkable,” “exciting” and “wonderful.” Dr. James Pridal of the National Cancer Institute said he and his colleagues were “electrified” and “almost overwhelmed” by the data.

The quote that nailed the story, however, and put it on the front page, was the one attributed to James Watson, co-discoverer of the DNA double helix and one of the most famous scientists in the world. “Judah,” he is supposed to have said, “is going to cure cancer in two years.” That was all the endorsement most journalists needed to hear. The Times wielded so much influence as the paper of record—and has a reputation for being so conservative in its news judgment—that few reporters could justify holding their own stories while checking out all the details. And even those who did produce more balanced pieces only seemed to reinforce the impression that something really big had happened. Wire service ticked off the highlights. Television anchors and radio announcers provided the sound bites. And the tabloids dutifully served up the tellall stories of cancer patients desperate to try anything.

Most people thought they were hearing about a breakthrough, in fact, Folkman’s work on angiostatin and endostatin had been reported months before in scientific journals and just a few weeks ago in Business Week. A November article in Nature briefly boosted EntreMed’s stock 25%, to $11.25 a share. But of course that was nothing compared with last week, when the stock rocketed past $40 before eventually dropping to $33.35 at Friday’s close.

As the week wore on, further complications emerged. In a letter to the Times, Watson denied his remarks. “I sat next to [Kolata] at a meeting at UCLA six weeks ago,” he told Times. “She never took any notes.” He says he did not tell her that cancer would be cured in two years, although he did communicate his excitement about Folkman’s research.

Kolata stood by her story—as did the Times. “We are entirely comfortable with the coverage and the placement of the article,” says Nancy Nielsen, a spokesperson for the newspaper. As for Watson’s quotes: “We don’t get into a quarrel with a respected scientist, but we are careful in the accuracy of our story.”

But things soon got worse for Kolata. On Wednesday the Los Angeles Times suggested that her enthusiasm for Folkman’s work might have been influenced by a potential conflict of interest. She had refused, in fact, the urging of her agent John Brockman, dashed off an e-mail message that Brockman had given to the right publisher, he worth a cool $2 million. But after meeting with her editors on Tuesday, Kolata quashed any idea of writing a book. “I did not plan a book,” she says, “I did not write anything that anyone could remotely consider to be a proposal, and any idea was immediately withdrawn.”

Then the New York Post reported that Folkman would share in a $1 million book deal with Random House. Flat wrong, says Random House. It is true that the publisher has tapped science writer Robert Coxe of Newsday to produce a book about Folkman’s life and cancer research and that Folkman has agreed to cooperate with the project. But the scientist won’t get any money from the deal.

What he will get is some hard-won recognition for having single-handedly created the field of angiogenesis. Back in the 1970s, when conventional wisdom among cancer researchers was that most tumors are caused by viruses, Folkman was...
pursuing his own, very different insight. He noticed that when cancer cells are still tiny—only a millimeter or two across—they don't need any blood vessels to survive. In pursuing his own, very different insight. tiny-only a millimeter or two across—they in order to grow to life-threatening size, how much people all over the world will be able to see new blood vessels. every day. He was almost too successful. Everywhere he looked—from cartilage to the body also relies on angiogenesis to heal wounds. The body also relies on angiogenesis to make new blood vessels during wound healing. That's a particular concern of people with diabetes, whose cuts and abrasions—particularly in their feet—often take a long time to close, leaving them vulnerable to infection. Fortunately, for them, they can use a new prescription cream, the first angiogenesis product to win fda approval, that stimulates the body's repair processes and helps those tiny capillaries in their toes and feet to grow.

The truth is she's got a point. But the only way to give the drug to all the women we might want it is to take some away from the trials. While that might save some people's lives (perhaps at the expense of someone else's), it could delay further a process that's one potentially.
Armed with such knowledge, younger researchers think they can improve on Folkman's techniques. They prefer a more targeted approach: selectively attacking the various molecules and biochemical signals involved in building a new blood vessel. For instance, researchers at Ixsys, a biotech company in San Diego, have developed an artificial antibody that dissolves the bio-chemical glue that holds a tumor's capillar­ies together. Indeed, one of the patients in their safety study exceeded all expectations when two of the tumors in his abdomen shrank 70%. "I've been on the drug now for over a year," says Barry Bieco, a college professor from Illinois who is suffering from a rare sarcoma. "I have more energy than I did just nine months ago, and I've gained back a lot of weight."

Other researchers are zeroing in on different targets. Some are looking at a spe­cialized growth factor called VEGF (for vascular endothelial growth factor) that so far has been found only in the blood vessels that feed tumors. One synthetic molecule, being tested at UCLA prevents VEGF from stimulating new growth by elbowing it aside and taking its place in the cell's receptors. Safety studies in more than 30 pa­tients have so far not revealed any major side effects, although their tumors' growth was only slowed, not halted. Dr. Joseph Folkman, who se lab relies on Jack Jack­son Laboratory in Bar Harbor, Maine, the world's most famous mouse-breeding facility. Each year the lab ships out some 3 million mice from more than 1,700 stocks, including so-called designer mice with genes added or deleted so that they more closely "model" human disease. Among its customers is Folkman, whose lab relies on Jackson's best-selling C57Bl/6J, or "Black 6" (cost: $8.15 to $10.85 a piece, de­pending on age). It's not always a good thing. In his labs at the University of California, San Fran­cisco, he is genetically altering mice to provide better models for studying leukemia and neuroblastoma, the most common tumor in children under 5. But genetic alterations go so far as to cause "hunting syndrome." The syndrome is still a legitimate issue."

Other researchers are more than willing to accept in their search for a cancer cure.

When designing and built the all-new Seville STS, it was with some admiration for our overseas competition. The Germans, for example, have long been known for their engineering and performance. So, we des­igned our new car to rival the best of Stuttgart and Munich. Its 300-hp Northstar System has more power than the most powerful E-Class Mercedes. It bested the BMW 540i in an independently run slalom for speed and agility. We even had our cockpit judged against the E420 and 540i on twenty-nine different ergonomic and interior convenience measures. We won on twenty-two. When the testing was over, we knew we'd achieved our goal: a Cadillac that rivals the best in the world. And with the incredible power and control of our all-new STS, they now have cause for some admiration for us. Because the STS isn't just new. It's what's next.

**THE ALL-NEW SEVILLE STS IT'S WHAT'S NEXT...**
**Checklist OF CANCER TREATMENTS**

For years doctors and cancer patients had only three options: surgery, radiation and chemotherapy. But that's starting to change, as a new generation of more sophisticated treatments moves out of the lab.

<table>
<thead>
<tr>
<th>TREATMENT</th>
<th>TARGET</th>
<th>HOW THEY WORK</th>
<th>STATUS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anti-angiogenesis</strong></td>
<td>Multiple</td>
<td>A growing tumor requires plenty of nutrients, and to make sure it gets them it must secrete factors that stimulate the growth of new blood vessels. A number of agents can block this process—at least in animals.</td>
<td></td>
</tr>
<tr>
<td><strong>Anti-metastatic</strong></td>
<td>Multiple</td>
<td>What kills most cancer patients is not the primary tumor but its metastatic spread. Scientists have identified a class of enzymes that enables cancer cells to enter the bloodstream by dissolving tissue and boring holes through capillary walls. New drugs could keep cancer cells confined to one spot.</td>
<td>Human tests have just begun</td>
</tr>
<tr>
<td><strong>Anti-oncogenic</strong></td>
<td>Multiple, including breast, colon, pancreatic and lung</td>
<td>Tumors do more than just promote growth factors that circulate in the bloodstream; they also make factors that suppress immune system activity. Many tumors, for example, have been found to contain mutations in the RAS oncogene, and companies are racing to develop drugs that inhibit this growth-promoting activity.</td>
<td>Human tests are in early stages</td>
</tr>
<tr>
<td><strong>Chemoprevention</strong></td>
<td>Breast, head and neck</td>
<td>Many breast cancers depend on the female hormone estrogen to stimulate their growth. Tamoxifen, which acts as an antiestrogen in the breast, has been shown to prevent the development of this form of cancer. Preliminary evidence suggests that a new compound, raloxifene, as well as similar agents that can inhibit the production of estrogen, can prevent recurrence of certain breast and neck cancers.</td>
<td>Tamoxifen has been approved as a treatment for breast cancer risk reduction, as a treatment for osteoporosis</td>
</tr>
<tr>
<td><strong>Gene Therapies</strong></td>
<td>Multiple, including breast, ovarian and small-cell lung cancers</td>
<td>In tumors, genes that are supposed to serve as checks on runaway cellular growth are often so damaged that they stop functioning. Scientists hope to correct this problem by engineering viruses that can &quot;inject&quot; cancerous cells with healthy tumor-suppressor genes. Preliminary evidence suggests that this approach can sometimes cause tumors to stop growing and even shrink in size.</td>
<td>Testing in humans has just begun</td>
</tr>
<tr>
<td><strong>Chemotherapy</strong></td>
<td>Multidose</td>
<td>Non-Hodgkin's lymphoma, breast, colon, melanoma</td>
<td></td>
</tr>
<tr>
<td><strong>Monoclonal Antibodies</strong></td>
<td>Non-Hodgkin's lymphoma, breast, colon, melanoma</td>
<td>Like miniature guided missiles, these biological constructs home in on specific proteins displayed on the surface of cancer cells. By blocking strategic sites, monoclonals can interfere with a tumor's ability to absorb growth factors from the bloodstream. They can also carry radioactive and chemical toxins that directly destroy malignant tissue.</td>
<td></td>
</tr>
<tr>
<td><strong>Radiation Therapies</strong></td>
<td>Multiple, often prostate and solid tumors in internal organs, lymphomas</td>
<td>Radiation destroys cancer cells but can damage healthy ones as well. Using 3-D computer images and new delivery techniques like radiation &quot;sensitizers&quot; and &quot;seeds&quot;, doctors can aim doses with microscopic precision, sparing healthy tissue.</td>
<td></td>
</tr>
<tr>
<td><strong>Surgical Procedures</strong></td>
<td>Multiple</td>
<td>Doctors are always looking for ways to make this standard treatment more effective and less traumatic for the patient—for example, by removing part rather than all of a breast or providing surgery with other treatments. One promising new technique is &quot;cytolytic mapping,&quot; in which surgeons use dyes and radioactive tracers to have them more selective in removing tumors.</td>
<td></td>
</tr>
<tr>
<td><strong>Vaccines</strong></td>
<td>Melanoma, breast, colon, ovarian, pancreatic and many others</td>
<td>Malignant growths have a deadly knack for skirting around the body's immune system. But scientists are finding that by vaccinating patients with antigens derived from tumors, they can sometimes get white blood cells into attacking cancerous tissues.</td>
<td></td>
</tr>
</tbody>
</table>

**WHO'S WHO IN ANGIOGENESIS**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Who's Working on It</th>
<th>How It Works</th>
<th>Source</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vargametast</td>
<td>British Biotechnology and the NCI; Sugen and ULLA</td>
<td>Needed to build tumor blood vessels, synthesized in the lab</td>
<td>Synthesized in the lab</td>
<td>Being tested in breast-cancer patients</td>
</tr>
<tr>
<td>SU5416</td>
<td>Sugen and ULLA</td>
<td>Prevents a tumor blood-vessel growth factor from binding to its receptor</td>
<td>Synthesized in the lab</td>
<td>Being tested for safety in patients</td>
</tr>
<tr>
<td>Nevastatin</td>
<td>Antennax Laboratories</td>
<td>Blocks activity of enzyme involved in the growth of tumor blood vessels</td>
<td>Derived from a new chemical source</td>
<td>Human studies to begin this fall</td>
</tr>
<tr>
<td>Combretastatin</td>
<td>Oncogene</td>
<td>Blocks tumor blood-vessel cells</td>
<td>Oligonucleotides derived from a new chemical source</td>
<td>Safety tested for lung, breast, prostate-cancer patients</td>
</tr>
<tr>
<td>TNP-470</td>
<td>University of Texas Southwestern and LEX Oncology</td>
<td>Attaches to blood vessels and prevents them from being destroyed by the body</td>
<td>Synthesized in the lab</td>
<td>Still being studied in animals</td>
</tr>
<tr>
<td>Angiostatin and milostatin</td>
<td>Children's Hospital and EnteralMed</td>
<td>Somewhat blocks the growth of tumor blood vessels</td>
<td>Oligonucleotides derived from a new chemical source</td>
<td>First human trials expected within a year</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Zeneca will evaluate</td>
<td>Mechanism unknown; may block growth of tumor blood vessels</td>
<td>Synthesized in the lab</td>
<td>New trials to block blood vessels may begin shortly</td>
</tr>
<tr>
<td>TNP-470</td>
<td>TAP Pharmaceuticals</td>
<td>Blocks enzyme that instructs tumor blood-vessel cells to divide</td>
<td>Oligonucleotides derived from a fungus</td>
<td>Being tested in patients</td>
</tr>
</tbody>
</table>

**THE BEST PREVENTION**

Changes in lifestyle—chief among them quitting smoking—can remove risk factors that cause cancer in the first place. Other commonsense advice: exercise regularly, don't drink heavily, avoid overexposure to the sun, go light on fats, serve salmon instead of stearic and eat plenty of fruits and vegetables.
Molecular Revolution

By CLAUDIA WALLIS

LAST WEEK'S MIRACLE-IN-MICE MAY have launched a thousand premature hopes, but there's no doubt in the minds of cancer researchers today that a new era is dawning in the treatment of the U.S.'s No. 2 killer. Three decades ago, the federal government's "War on Cancer" undertook basic discoveries about the ways broken-down genes lead to malignancies. Now that work is beginning to pay off. "The black box that was the cancer cell has been opened," says Dr. Bert Vogelstein, a world-renowned investigator of cancer genes at the Johns Hopkins University in Baltimore, Md. "At first, we felt a tremendous amount of hope, probably for the first time in the history of cancer treatment.

In pharmaceutical-company research departments and academic labs around the country, scientists are feverishly at work on drugs that target the products of specific genes—the very genes that make a cell cancerous. The hope is that these treatments will be more effective, longer lasting and far less toxic than traditional chemotherapy and radiation—treatments that inspire dread so deep that they are almost as feared as cancer itself.

"Because of the early success with chemotherapy in some forms of leukemia and lymphomas," says Dr. Dennis Slamon, of the Revlon/UCLA Women's Cancer Research Program, "we have been shaving at cancer that way for 25 years. We didn't make any significant inroads, and in some cases, we ended up killing people. Now we are beginning to look specifically at what's broken in a cancer cell and trying to target that.

What's broken in cancer cells is genes, usually genes that control some aspect of cell growth and division. Hundreds of genes play a role in this process, and more than three dozen have been identified as playing a role in cancer. Some are accelerators, telling cells to grow, grow, grow. Others put the brakes on growth. Some regulate steps in cell division to make sure that DNA is copied correctly from mother to daughter cell. Some play executioner, killing mutant cells in which the copying has gone awry. Cancer is caused by errors in these genes, usually multiple errors. Though some of these errors may be inherited, most are acquired through years of living. Sunlight, cigarette smoke, environmental toxins and aging itself help these errors accumulate.

Since every gene holds the recipe for a vital protein, corrupt genes mean corrupt proteins: too much of one protein, too little of another, or a misshapen protein that doesn't function properly. The new generation of cancer drugs takes aim at these defective proteins, blocking them, disrupting them in myriad ways. Unlike old-fashioned chemotherapy drugs, the new substances don't poison the tumor—an approach that usually causes collateral damage to healthy cells. Instead, they aim to halt the processes that make a cancer cell act like a cancer cell in the first place.

Barbara Bradfield, 55, is living proof that this can work. A home turned home in La Cañada Flintridge, Calif., Bradfield is one of the lucky cancer patients who have already benefited from the new generation of gene-based treatments. She was 47 years old when she discovered a large lump in her breast. Tests showed that the malignancy had spread to her lymph nodes. Bradfield got the works: a car accident—and she never wanted to face chemo again. "I thought I was probably going to die, and I didn't want to die bald and throwing up." As it happened, Bradfield's tumor cells had a characteristic presence in about 30% of breast-cancer cells: too many copies of a gene known as HER-2/neu. This gene makes a protein that helps relay the signal telling cells to divide. Having too much of it is associated with an especially rampaging, hard-to-treat cancer. Once this form of breast cancer metastasizes, a patient typically has just six to 12 months to live.

Bradfield's doctor put her in touch with UCLA's Slamon, who was testing a brand-new antibody that targeted the HER-2/neu protein. Although Slamon was using the antibody in combination with chemotherapy—and Bradfield was loath to go back to chemo—the combined therapy proved miraculous in her case. Between small tumors in her lungs melted away. By 1993 she was in remission, and still is. "I got to be at my son's wedding," she recalls. "The gift is that I'm here!"

"In my daughter's last year of life, she had a characteristic present in about 30% of breast-cancer cells: too many copies of a gene known as HER-2/neu. This gene makes a protein that helps relay the signal telling cells to divide. Having too much of it is associated with an especially rampaging, hard-to-treat cancer. Once this form of breast cancer metastasizes, a patient typically has just six to 12 months to live. Bradfield's doctor put her in touch with UCLA's Slamon, who was testing a brand-new antibody that targeted the HER-2/neu protein. Although Slamon was using the antibody in combination with chemotherapy—and Bradfield was loath to go back to chemo—the combined therapy proved miraculous in her case. Between small tumors in her lungs melted away. By 1993 she was in remission, and still is. "I get to be at my son's wedding," she recalls. "The gift is that I'm here!"

"The antibody is not a panacea. It didn't work as well for Bradfield's fellow guinea pigs in the initial study. But results of a just completed trial with 470 women do show it
to be a significant improvement over chemotherapies for women with this advanced form of breast cancer. The details of the study were presented by Slamon this Saturday at a meeting in Los Angeles of the American Society of Clinical Oncology.

Manufactured by Genentech under the name Herceptin, the drug is on a fast track for approval by the FDA, perhaps before year’s end.

Herceptin, if approved, will join the family of drugs called growth-factor inhibitors. Unlike chemotherapy agents, these drugs are “cancer cells” and are “cancer proteins,” observes Slamon. "We saw the backlog everybody is talking about. We have now.”

The episode is typical of the biotech industry, where each of some 300 public companies, including Bristol-Meyer Squibb, Johnson & Johnson and Schering-Plough, are testing similar drugs. “We think the odds are that if you have a stock on a hunch, rumor, hope, or dream, you’re going to be left out,” notes Entremed, which has poured $85 million into developing Herceptin. “With Entremed, many placed buy orders for last Monday morning’s "at the market," with no taking that the market price can only thudded sevenfold without a posted trade. The pros know. They use the backing of buy orders that had built up the week before. Another information edge the pros enjoy is "real-time" stock quotes from CNBC, and quotes on most free Websites, are de­livered by a variety of data services. But it is now that you can kill a stock when it is falling a point every 60 sec.

Yet the biotech industry has 600 drugs in advanced de­velopment, vs. maybe 20 for each big drug company.

Biotech companies are notorious for moving ahead with tests too quickly. With this stock, that doesn’t account for this huge disparity.”

But some other things have changed, a lot. The overall market has roared ahead while biotech stocks barely budged, creating a steady wider gap in value. And the biotech industry has had more time to mature. It will probably take a few more years to be in the right stocks.

The risk is especially acute in the complex world of biotechnology, where each of some 300 public companies, including Enzymediate, is trying to have one or more products in clinical research. Those claims make terrific investment pitches, and on the heels of a successful new drug launch—Pfizer’s Celebrex, for example—investors can get, uh, excited. The reality, though, is that maybe 10% of to­day’s biotech companies will ever bring a blockbuster drug to market and will enrich shareholders. But ca­sual investors face long odds trying to be in the right stocks.

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