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May 3, 1998

# Two Drugs Eradicate Tumors in Mice

By GINA KOLATA

Within a year, 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.

Some cancer researchers say the drugs are the most exciting treatment that they have ever seen. But then they temper their enthusiasm with caution, noting that the history of cancer treatments is full of high expectations followed by dashed hopes when drugs with remarkable effects in animals are tested in people.

Still, the National Cancer Institute has made the drugs their top priority, said Dr. Richard Klausner, the director. Klausner called them "the single most exciting thing on the horizon" for the treatment of cancer.

"I am putting nothing on higher priority than getting this into clinical trials," Klausner said. The mouse studies are "remarkable and wonderful," he said, and "very compelling." But he pointed out that the studies were in mice and so, in humans, he said he wanted to emphasize "the if's."

The new drugs, angiostatin and endostatin, work by interfering with the blood supply tumors need. Given together, they make tumors disappear and not return.

Dr. James Pluda, who is directing the cancer institute's planned tests of the drugs in patients, said he and others at the institute were "electrified" when they heard the drug's discoverer deliver a lecture about the newest results. "People were almost overwhelmed," Pluda said. "The data were remarkable."

Although the discovery of the drugs, and some of their effects, have been reported over the past few years, Pluda said that "if people understood how many steps ahead" the research was compared to what had been published, "they'd be even more in awe."

But Dr. Jerome Groopman, a cancer researcher at the Harvard Medical School, was wary. "We are all driven by hope," Groopman said. "But a sober scientist waits for the data." And until the drugs are given to humans, he said, the crucial

data simply do not exist.

So far, the drugs are the only ones ever tested that can seemingly eradicate all tumors in mice, even gigantic ones, equivalent to a two-pound growth in a person. The best that other cancer drugs have done is slow the growth of these large tumors. Mice are the traditional test animals in cancer research.

But even the drugs' discoverer, Dr. Judah Folkman, a cancer researcher at Children's Hospital in Boston, is cautious about the drugs' promise. Until patients take them, he said, it is dangerous to make predictions. All he knows for sure, Folkman said, is that "if you have cancer and you are a mouse, we can take good care of you."

Other scientists are not so restrained. "Judah is going to cure cancer in two years," said Dr. James Watson, a Nobel laureate who directs the Cold Spring Harbor Laboratory, a cancer research center on Long Island. Watson said Folkman would be remembered along with scientists like Darwin as someone who permanently altered civilization.

The long trail to the discovery of the new drugs began more than 30 years ago when Folkman became obsessed by what many saw as a quixotic notion: that cancers cannot grow beyond the size of a pinhead unless they have their own blood supply. If he could block a tumor's blood supply, he reasoned, the tumor should shrink to a minuscule size.

The first major break in the efforts came a decade ago when Folkman and his collaborators found drugs that did what he envisioned. He called them anti-angiogenesis drugs because they stopped the process of developing new blood vessels, or angiogenesis. They slow tumor growth in animals but do not eradicate the tumors. Early results in patients indicate that the drugs may slow human cancers, too. Dozens of companies are now developing such drugs.

The results with these weaker drugs were "a proof of principle," said Dr. Bart Chernow, a professor of medicine and dean for research and technology at the Johns Hopkins University School of Medicine. Chernow is a founder of Entremed, a company in Rockville, Md., that was formed to make and market angiostatin and endostatin as well as some of the weaker drugs that can slow cancer growth.

But the real breakthrough -- and the two new drugs -- came from Folkman's efforts to understand a peculiar phenomenon that has been known to cancer surgeons for 100 years: sometimes a patient will have a single tumor, with no evidence whatsoever of metastases, the satellite cancers that can pepper a patient's body. A doctor will remove the tumor and all will seem fine. But then, a few months later, a whole series of metastases will appear, grow, and kill the patient.

In 1989, Folkman proposed a reason for the effect, which he wrote on a large white board in a room where his laboratory group had its weekly seminars. Is it possible, he asked, that a tumor could be making both stimulators and inhibitors

of blood vessel growth? If so, the inhibitors might travel through the bloodstream, squelching metastases. When the large tumor was removed, it would no longer be a source of inhibitors, allowing the tiny metastases to proliferate.

Folkman tried to get one of his doctoral or post-doctoral students to work on that idea. "Each Friday, at our meeting," he said "I would say, 'Here's a great experiment.' But no one wanted to work on it." It seemed too wild, Folkman said, too unlikely to result in findings that would end up in a scientific journal, a major goal of young scientists.

Then, in 1991, a post-doctoral student, Michael O'Reilly, decided to take on the challenge. O'Reilly focused on a particularly deadly mouse cancer that grows to the equivalent of a two-pound tumor in a person.

As long as mice had the large tumor, they had no signs of metastases. But five days after the tumors were surgically removed, metastases invariably sprang up in the animals' lungs. Within 15 days, the animals would be dead, their lungs packed with large red tumors, like grapes.

Eventually, after arduous work in collaboration with chemists, O'Reilly discovered that the large tumors made a substance that stymied the growth of other tumors. This substance showed up in the animals' urine, but was present in such minute quantities that O'Reilly had to collect 10 quarts of mouse urine to obtain 30-thousandth of an ounce of the mysterious substance. It turned out to be a piece of a larger and very common protein, plasminogen, that the body uses in blood clotting. Folkman named it angiostatin.

Apparently, cells can use the plasminogen gene for two purposes: they can use it at its full length to make plasminogen, or they can use just a piece of it and make angiostatin. Plasminogen does nothing to stop tumor growth. The question was, would angiostatin?

Folkman and O'Reilly discovered that angiostatin also appears, in minute quantities, in human blood. Using outdated human blood discarded by the Red Cross, they extracted enough angiostatin to treat mice. Then they began their experiment.

They had 20 mice with large tumors on their backs. The investigators removed the tumors and then injected half of the mice with angiostatin each day and the others with salt water, as a comparison.

After 15 days, the researchers killed the mice and cut them open. As more than a dozen scientists gathered around a table in the laboratory, O'Reilly opened the first mouse. It had huge tumors filling its lungs. Then Folkman checked a notebook to see what the animal had received: salt water. They looked at the next mouse. No tumors. Folkman checked to see the treatment: angiostatin. And so it went. All 10 of the mice that had been injected with angiostatin were free of cancer. All 10 of those that had been received salt water had huge new tumors.

The room was buzzing, the scientists were grinning. Folkman said. Everyone in the room knew what the results meant, and they were elated. They responded, he said, like men at a football game. "Everyone clapped O'Reilly on the back," Folkman said.

Then the researchers found a second protein fragment, secreted by tumors, that also squelches metastases, Folkman said. It was a piece of a different protein, collagen 18, that is in all blood vessels but by itself has no effect on cancer. They named the collagen fragment endostatin.

"It was even more potent than angiostatin," Folkman said. If he gave it to a mouse with a huge tumor, he said, the equivalent of one weighing a pound and a half in a human, endostatin would shrink the cancer down to a microscopic size.

Moreover, tumors never became resistant to endostatin, said Folkman, who added that he had given the drug to mice with large tumors and they had shrunk to almost nothing. He stopped the drug, he said, and the tumors grew back. Then he gave the drug continuously for the rest of the animals' lives. The tumors remained small and harmless and the animals remained healthy.

Dr. Robert Kerbel, a cancer researcher at Sunnybrook Health Science Center in Toronto, said he was not surprised that the cancers never became resistant to endostatin. Tumors become resistant to chemotherapy drugs, Kerbel said, because cancer cells constantly reshuffle their genetic information. The result, he said, is that the tumors spin off mutant cells that resist the drugs and, ultimately, the tumors grow back, invulnerable.

But, Kerbel said, angiostatin and endostatin do not act on tumors. Instead, they act on normal blood vessels that feed tumors. And normal cells, he said, do not reshuffle their genes and so do not develop drug resistance. That is why chemotherapy drugs continue to devastate normal cells -- causing bone marrow suppression, loss of hair, nausea and vomiting -- even when the cancer cells have grown impervious to their effects, Kerbel said.

Then Folkman discovered that he could actually obliterate tumors in mice with his new drugs. He gave endostatin and angiostatin together, treating mice for 25 days. To his surprise, Folkman said, "there was no tumor left -- we couldn't even find it with a microscope." The tumors, he said, "were eradicated."

And the drugs seem to have no side effects, at least in mice, something that Folkman acknowledges is hard for researchers to believe. But, he said, he had given mice up to four times the doses needed to eliminate cancer and could not find any adverse effects. These two human proteins may be, he said, "exquisitely aimed -- we do not know why -- at cancer."

In contrast, Folkman said, mice become very ill when they receive commonly used chemotherapy -- their hair falls out, they bleed, they refuse to eat.

For the past four years, Folkman said, he and his colleagues have found that all tumors responded to the drugs in the same way. Even leukemia, a blood tumor, responds, he said, because it turns out that leukemia needs to form new blood vessels in the bone marrow to grow. Leukemia tumors grow on these blood vessels, "like berries on a bush," Folkman said, shedding cancer cells into the blood.

But Folkman is the first to urge caution in leaping to conclusions about what might happen when patients try the drugs. "Going from mice to people is a big jump, with lots of failures," he said.

Hopes were high for chemotherapy drugs that worked well in mice but turned out to be less successful in people. Therapies that used the immune system to rid the body of cancer also worked in mice but were disappointing when they were tried in people. Gene therapy treats mouse cancer, but has had limited success in people. From bitter experience, most cancer researchers have learned to be leery of what one called "that four letter word" -- cure.



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21ST STORY of Level 1 printed in FULL format.



June 2, 1997, Monday, City Edition

SECTION: SCIENCE & TECHNOLOGY; Pg. C1

LENGTH: 1168 words

HEADLINE: Tumor-starving drugs show promise

BYLINE: By Richard Saltus, Globe Staff

BODY:

Thirty years after a Boston researcher began to ponder how a tumor induces the body to provide it with new blood vessels that nourish it, the first human trials of drugs based on that observation are suggesting that a new class of non-toxic cancer drugs may be not far off.

Tests with eight drugs, though in their early stages, suggest that they can starve tumors into dormancy by shutting down their blood supply. And ongoing animal experiments with combinations of yet more powerful drugs are raising the stunning prospect of being able to shrink tumors out of existence.

At a time when cancer chemotherapy is drastically limited in its power because of its toxicity and the ability of tumor cells to develop resistance to the drugs, perhaps the most exciting potential of the new compounds is that they have little toxicity and don't evoke tumor resistance.

The long-awaited tests in humans began in 1992, decades after the pioneering Boston researcher, Dr. Judah Folkman, began studying the blood supply solid tumors need to grow. Folkman developed the idea that "angiogenesis inhibitors" - compounds that stop the growth of new blood vessels - could choke off that vital blood supply.

Today eight such drugs are being tested in humans, says Folkman, director of surgical research at Children's Hospital. Some were developed in his lab, and some elsewhere. The results so far are promising, but the value of this approach will be clearer when more potent versions of the drugs, still being tested in lab animals, are tried in humans.

Most likely, two or more angiogenesis inhibitors will be combined in therapy, and they in turn may be combined with conventional chemotherapy drugs, say the researchers.

One combination of two angiogenesis inhibitors, Folkman says, has made large tumors in mice disappear - and the mice remained tumor-free after the drugs were stopped. "We have mice free of tumor and off therapy for almost a year," said Folkman. Such results, he added, were unprecedented.

Folkman and others began formulating this cancer attack strategy in the 1960s, after noticed that blood vessels form in the region of solid tumors, and that those vessels are crucial if the tumor is to stay alive and grow. Eventually, they learned that tumors themselves secrete chemicals that trigger this blood vessel growth, or angiogenesis.

Scientists later found that the tumors also contain substances that can stop angiogenesis. Folkman and others set out to identify the inhibitors, reckoning that they might be the basis of drugs able to render tumors dormant and harmless.

If the researchers are right, angiogenesis inhibitors will have two great advantages over current cancer drugs, says Folkman. First, they have relatively low toxicity, doing far less harm to the patient than drugs now in use. And second, tumors don't seem to become resistant to the inhibitors, as almost always happens with conventional drugs.

"Inducing tumor dormancy might be possible with much less toxicity than with standard treatments," said Lance Liotta, head of the National Cancer Institute's pathology department. "It could be a new approach to treatment, similar to diabetes, epilepsy or hypertension," diseases that can be controlled but are not eliminated.

The drugs now in human testing can halt or shrink tumors but have rarely eliminated them, as the more potent inhibitors in Folkman's latest animal experiments have done. However, he says, one patient in Texas has been free of her original metastatic breast cancer after more than two years on the inhibitors.

Among the most encouraging of the eight inhibitors in human testing is thalidomide, which was widely used in Europe in the 1960s as a tranquilizer and resulted in horrendous birth defects in children of women who took it while pregnant.

Late last week, Boston researchers reported striking results in a very challenging thalidomide test: It halted the growth of lethal brain tumors in half the 32 patients who took it. In four cases, it shrank the tumors.

"Going into it, I thought nothing would work," said Dr. Robert D'Amato, a Children's Hospital researcher who first showed in animals that thalidomide could squelch the growth of new blood vessels. He said "dozens of drugs" have been tried on the fast-growing brain tumors, called glioblastoma multiforme, with little effect. Patients who have the tumors surgically removed usually die within months after the tumor comes back.

Dr. Howard Fine of the Dana-Farber Cancer Institute, a frequent collaborator with the Children's researcher, reported on the thalidomide trials last month at a meeting of the American Society of Clinical Oncology in Denver. "The fact this drug actually shrank malignant brain tumors in some patients, yet it's not a poison, is very important," he said.

In a separate report, other researchers said thalidomide proved effective in treating Kaposi's sarcoma, a skin cancer associated with AIDS.

Dr. Elise Kohn of the National Cancer Institute called the thalidomide findings "important progress," In a telephone interview, Kohn, acting chief of molecular-signalling research in the pathology department, said tests of other angiogenesis inhibitors are also encouraging. "They're showing that this is an important approach to cancer therapy," she said. It's also significant that specialists "have opened up to the idea of using mechanisms other than cytotoxic cell-killing agents in their treatment of cancer."

Kohn is testing an inhibitor called CAI, in combination with the chemotherapy drug Taxol, in patients with a variety of solid tumors. The combination has caused few side effects and has halted the growth of some tumors, she says.

How fast trials of other angiogenesis inhibitors will move from the lab to human testing depends in part on how quickly the drugs can be made in large quantities. Four inhibitors patented by Children's Hospital have already been licensed for development by EntreMed Inc., a Rockville, Md., company that gives Folkman's lab $ 2 million a year for research. At least one of the drugs has been sub-licensed by EntreMed to Bristol Myers Squibb for manufacture. Children's will receive an equity interest in EntreMed under the agreement, says Dr. John Holaday, company president.

He says the firm hopes to submit applications to begin human testing of two of the four inhibitors soon.

Researchers believe combinations of two or more angiogenesis inhibitors will be necessary to obtain the best results. Even so, the drugs now being tested would probably have to be taken for a lifetime to keep a dangerous tumor in check. But Folkman says his success with mice that remained cancer-free nearly a year after the two-inhibitor combination treatment was halted, suggests that humans might need to take the drugs for only a year or so.

"If it was for prostate cancer, for example, you could just be monitored, and if there were signs of the tumor's coming back, you could go back on it," he said.

GRAPHIC: PHOTO, Drugs made tumors in mice disappear, says Dr. Judah Follman.

LANGUAGE: ENGLISH

LOAD-DATE: June 2, 1997

11TH STORY of Level 1 printed in FULL format.


The Boston Globe

November 27, 1997, Thursday, City Edition

SECTION: NATIONAL/FOREIGN; Pg. A1

LENGTH: 970 words

HEADLINE: Scientists say they cut blood supply of tumors

BYLINE: By Richard Saltus, Globe Staff

BODY:

Dr. Judah Folkman and his colleagues at Harvard Medical School say they have permanently eradicated large tumors in mice with a combination of two powerful, natural substances that can choke off the blood supply a cancer needs to grow.

The findings, published today in the journal Nature, are the most dramatic yet in the assault on cancer that Folkman conceived more than 25 years ago. Another specialist in the field said that the results are so compelling that they could "herald a new era of cancer treatment."

Folkman said that in one experiment, several mice that had received transplanted lung cancers were treated just once, for 25 days, with the two substances, angiostatin and endostatin. The tumors regressed completely, and when the mice were killed after 11 months they were found free of tumors. Subsequent tests have produced even longer cancer-free periods, virtually the animals' entire lifetimes.

"No one has ever seen anything like this before - it's a very startling result," said Robert Kerbel, director of cancer biology research at the Sunnybrook Health Science Center in Toronto, in an interview.

The report in Nature is by Folkman along with Drs. Thomas Boehm, Timothy Browder, and Michael S. O'Reilly. The experiments were carried out in the Children's Hospital Surgical Research Laboratory, which Folkman heads.

Angiostatin and endostatin are two of the most recently discovered members of a group of proteins called angiogenesis inhibitors, which block the formation of small blood vessels in the body. If they can successfully be developed as drugs with few side effects, these substances may be an important addition to anticancer weapons.

In addition to the potent combination of angiostatin and endostatin, the Nature report describes experiments using endostatin alone that showed mouse tumors did not develop resistance to the drug even after repeated doses. By contrast, tumors often become resistant - that is, the drugs become ineffective - when conventional chemotherapy agents that had originally been effective are administered again.

While angiostatin and endostatin are too scarce and untried to test in people, the CEO of a Maryland biotech company that is developing them as drugs said they may be ready for initial human testing within two years.

The two proteins, both discovered in Folkman's lab, are part of a chemical system in the body that regulates the growth of new, small blood vessels that occurs during wound healing and at other times.

Folkman's insight, which has inspired an entire field of research, was that solid cancer tumors might be starved into submission by drugs that block the formation of new blood vessels the tumors depend on.

Furthermore, since the drugs attack the blood vessels' endothelial cells instead of the renegade tumor cells themselves, Folkman believed the tumors might be less able to evolve resistance to the drugs.

The reason, he said, is that cancer cells are genetically unstable, meaning they easily mutate, or change, so they can evade the action of the drug attacking them. But the endothelial cells of the blood vessels are more stable and cannot quickly evolve into resistant forms. The new results confirmed that even with long and repeated drug treatment, the tumors remained vulnerable, developing no resistance to the drug.

Kerbel, the Sunnybrook Health Science Center researcher, said "what excites me is that we've always been discouraged by this problem of resistance, and these results provide a glimmer of hope." It was Kerbel who, in 1991, first proposed that angiogenesis inhibitors might not induce tumor resistance.

Kerbel wrote in a Nature commentary accompanying the Folkman report, "The results . . . are unprecedented and could herald a new era of cancer treatment."

The researchers showed that when endostatin was administered to rats with tumors and then halted, the tumors remained vulnerable to the drug throughout several cycles. During periods of treatment, the tumors shrank; when the drug was stopped, the tumors grew large again. But treatment continued to be effective at all times.

Some of the tumors were equivalent to a human tumor weighing more than 3 pounds, Folkman estimated.

In a surprising and unexpected finding, the tumors not only remained vulnerable to the drugs but, after several cycles of treatment, inexplicably became dormant and did not regrow.

This occurred after several cycles of endostatin treatment and, most impressively, after a single 25-day treatment with the angiostatin-endostatin combination.

"That's a big shock," acknowledged Folkman last week during an interview. He said the tumors behave as if they contained some sort of "clock" so that after a given number of treatment cycles, they failed to regrow. But he said he cannot explain the findings yet.

A researcher at the National Cancer Institute, Dr. James M. Pluda, said yesterday, "The observations are remarkable and, although preliminary, have the potential if validated to have a tremendous impact on the therapy of cancer."

Folkman revealed the findings last week during a special lecture at the National Cancer Institute, and Pluda said the NCI "has made the development of

angiogenesis inhibitors an extremely high priority: They're on the front burner."

Development of the inhibitors into drugs is being carried out by Entremed, a Rockville, Md., biotech company that has licensed the patents on angiostatin and endostatin from Children's Hospital.

Entremed CEO Dr. John Holaday said in a telephone interview yesterday that the company, which is partnered with Bristol Myers Squibb in developing angiostatin and with the National Cancer Institute in developing endostatin, hopes to have both drugs ready for initial human trials "in 12 to 18 months."

GRAPHIC: PHOTO, In the journal Nature, Dr. Judah Folkman and his Harvard collegues reported significant advances in attacking large tumors in mice./ GLOBE STAFF FILE PHOTO/BILL GREEEN

LANGUAGE: ENGLISH

LOAD-DATE: November 29, 1997

5TH STORY of Level 1 printed in FULL format.



March 13, 1998

SECTION: Vol 16; No 45; pg 7

LENGTH: 750 words

HEADLINE: Analysts like EntreMed cancer drugs

BYLINE: Matt AndRejczak

DATELINE: Rockville; MD; US; South Atlantic

BODY:

Industry analysts are bullish on EntreMed, a Rockville-based biopharmaceutical company that is developing drugs to prevent cancer cell growth.

Los Angeles-based Seidler Companies recently initiated a "buy" rating on shares of EntreMed, with a 12-month target price range of $ 20 to $ 22 a share.

"We believe that EntreMed may have found the Achilles heel of cancer," the Seidler Co. reported. "Cancerous tumors are dependent on recruiting new blood vessels to grow. The company's drugs have potential to exploit this weakness and overcome factors that limit the efficacy of current cancer treatments."

Meanwhile, Lehman Bros. gave EntreMed a more conservative "venture" rating with a 12-month price target of $ 18 a share. The stock is suited to risk-tolerant investors with well-diversified portfolios, according to the brokerage.

"This could potentially be an interesting story," said Dr. Eric Ende, an analyst at Lehman Bros., "but we want to see some more proof of the concepts."

Lehman's rating indicates that EntreMed's stock could enjoy up to a 40 percent return over the next 12 months. The company's stock has posted a 15 percent return so far this year. Shares of EntreMed closed March 10 up 50 cents at $ 13 a share. Its 52-week high is $ 16 a share; the 52-week low is $ 6.50 a share.

Both research reports said Entre-Med's stock should benefit from positive data generated by clinical trials, additional corporate partnerships and other preclinical trials.

EntreMed is concluding a phase-two trial for thalidomide - an orally administered drug that could help treat certain types of cancers in the brain, prostate and breast. A phase-three trial is expected to commence later this year.

The initial results prompted the Food and Drug Administration to give EntreMed an "orphan drug designation" March 3 for thalidomide as a treatment

for primary brain malignancies.

This designation, which is intended to encourage further testing, would give EntreMed exclusive market rights for the drug over a seven-year period, if the drug is ultimately approved by the FDA.

The designation also makes EntreMed eligible for tax credits to offset some research costs.

"This gives us a secure position for the sales of thalidomide," said Dr. John Holaday, chairman and chief executive officer.

The company - founded in 1991 after receiving $ 18 million from private investors - does not have a product on the market yet.

Analysts predict thalidomide could be commercialized in the year 2000.

EntreMed's strategy is to discover drugs that inhibit the growth of new blood vessels, or antiangiogenesis, which are common factors in a wide range of diseases such as cancer and blindness.

There is where thalidomide comes into the picture. It was introduced in Germany in the 1950s as a sedative to treat morning sickness in pregnant women. It was later banned (and never approved in the United States) because it caused birth defects in newborn babies.

But, after further studies, it became apparent that the birth defects resulted from the drug's inhibitive effect on developing blood vessels.

EntreMed has an exclusive sponsored research agreement with Dr. Judah Folkman, a pioneer in studying the ef-fects of thalidomide as a cancer treatment.

Folkman works for Children's Hospital in Boston, a teaching affiliate of Harvard University.

EntreMed, which raised $ 50 million in its June 1996 initial public offering, is backed by Wendell Starke, chairman of the mutual fund company Invesco Capital Management, and David Bonderman, a majority shareholder of Continental Airlines. Starke serves on EntreMed's board.

EntreMed reported a loss of $ 4.4 million for the first nine months of 1997 on revenue of $ 3.4 million, or 36 cents a share, compared with a loss of $ 3.5 million, or 39 cents a share, on revenue of $ 3.3 million for the same period a year earlier.

There is no debt on the company's balance sheet, which includes $ 46 million in cash. EntreMed spends $ 7 million a year on research and development.

ENTREMED

Business: A biopharmaceutical company that focuses on the role of blood and blood vessels in health and disease. Product candidates focus on next-generation cancer therapeutics.

Headquarters: Rockville

CEO: Dr. John Holaday

Employees: 50

Strategic partnerships: Bristol-Myers Squibb; National Cancer Institute; Children's Hospital in Boston.

Market capitalization: $ 159 million

Shares outstanding: 12.2 million

Exchange/ticker symbol: Nasdaq/

GRAPHIC: Photo; Logo

LANGUAGE: ENGLISH

UMI-ACC-NO: 9881400

LOAD-DATE: April 17, 1998

Business Week

April 27, 1998

SECTION: SCIENCE & TECHNOLOGY; RESEARCH; Number 3575; Pg. 64

LENGTH: 1637 words

HEADLINE: STARVING TUMORS TO DEATH

BYLINE: By Catherine Arnst in New Orleans

HIGHLIGHT:
A new approach cuts off cancer's blood supply

BODY:

Medical researchers searching for a ''magic bullet'' that could treat cancer without poisoning the patient may be on to something. Instead of using chemotherapy or radiation to attack the tumor, they're trying to starve it to death. More than a dozen drugs currently under development have shown remarkable success in treating breast, brain, and lung cancers in mice by blocking blood vessel growth to tumors -- essentially cutting off their life-support system. Even more exciting, some of these compounds have eradicated cancer in mice altogether.

This elegantly simple approach is one of the hottest areas in cancer research, with some 25 pharmaceutical and biotechnology companies around the world working on it. Outfits ranging from drug giants such as SmithKline Beecham, Merck, and Novartis to startups EntreMed, SUGEN, and British Biotech are all testing compounds that block a process called angiogenesis, the growth of new blood vessels. These drugs could address a much broader range of cancers than most existing drugs, which are usually highly toxic and work only against one or two types of cancer. The new drugs -- called angiogenesis inhibitors -- block the chemical signals that tumors send out to attract new blood vessels. Because the signals are the same across a broad range of cancers, the drugs should stop almost any kind of cancer. MEGAMARKET. With more than 1 million new cancer cases diagnosed each year in the U.S., the market for angiogenesis inhibitors could be enormous. The compounds are also being tested against macular degeneration, a common cause of blindness in the aged that occurs when blood vessels grow over the cornea, and which afflicts an estimated 13 million Americans. Wall Street analysts predict that an angiogenesis inhibitor could be the first cancer drug to reach blockbuster status, with annual sales exceeding $ 1 billion.

At least 9 of the 12 or so compounds found to inhibit the growth of new blood vessels to cancer tumors are already in clinical trials. They include the controversial drug thalidomide, marketed as a sedative in the 1960s before it was found to cause horrific birth defects when taken by pregnant women. Researchers discovered in 1992 that thalidomide blocks blood vessel formation, which is why it caused birth defects in the first place -- it cut off blood vessel formation in the fetus. Now, in clinical trials being conducted by the National Cancer Institute, the drug is showing promise against the toughest tumors.

To avoid the problems of thalidomide and other first-generation compounds, the new group of angiogenesis inhibitors targets blood vessel growth more specifically, offering the promise of powerful cancer drugs virtually free of toxic side effects. A recent Lehman Brothers Inc. study that examined a variety of new cancer treatments concluded that angiogenesis inhibitors are the ones likely to ''provide the foundation for cancer therapy in the future.''

The explosion of interest in these drugs was evident at a meeting of the American Association for Cancer Research in New Orleans in March, where researchers presented some 50 papers on the subject, up from a handful a year earlier. Among the most startling was a report by Dr. Erkki Ruoslahti, president of the Burnham Institute, a nonprofit research center in La Jolla, Calif. He described a ''one-two punch'' that knocked out cancer in mice permanently. Ruoslahti's team combined doxorubicin, a widely used chemotherapy drug, with an angiogenesis inhibitor called tumor homing peptide (THP).

The mice implanted with human breast cancer cells that received Ruoslahti's compound, called THP-dox, showed no recurrence of cancer during their lifetimes, while the mice receiving only doxorubicin died either of drug poisoning or tumors that developed drug resistance. ''This is one of the most exciting pieces of work I've seen recently,'' says Donald S. Coffey, professor of oncology research at Johns Hopkins University School of Medicine. ''He really seems to have finally beaten the resistance mechanism.'' THP-dox has been licensed to ILEX Oncology Inc., which is aiming for clinical trials in two years.

Despite these early successes, researchers have a long way to go from mouse to human, cautions Dr. James M. Pluda, senior clinical investigator of the National Cancer Institute's investigational drug branch. ''The field of oncology is littered with the bodies of agents that were the next magic bullet,'' he says. But, he adds, ''I think this form of therapy may be an important weapon in our arsenal against cancer.''

Dr. Judah Folkman of Children's Hospital, Boston, first theorized that cancer tumors depend on angiogenesis 30 years ago. But it is only in the last five years that molecular biologists have been able to isolate the cell mechanisms that trigger the process.

Blood vessels normally have only one big growth spurt, in the fetus. After birth, there are three instances in a healthy person when new capillaries sprout -- menstruation, pregnancy, and wound healing. The big exception is cancer. When rogue cancer cells first emerge in the body, they rapidly divide and form a tumor about the size of a pea -- too far away from the surface of any existing capillary to receive nourishment. This tumor can remain dormant for several years. But at some point it starts sending chemical signals to the endothelial cells that make up blood vessels. In response, new capillaries are formed that reach out to the tumor, carrying nutrients and oxygen. The tumor starts expanding, sending cancer cells along the capillaries until they spread throughout the body. OFF SWITCH. Sometimes, however, that first tumor also sends out signals that suppress the formation of secondary tumors elsewhere in the body. In that case, the tumor applies chemical ''brakes'' that put a stop to capillary growth. Folkman and colleague Michael O'Reilly have isolated two of these primary tumor brakes, proteins called angiostatin and endostatin, and cancer experts say they may be the most powerful angiogenesis inhibitors yet.

Last November, O'Reilly reported that he could eliminate some tumors altogether in mice by using endostatin and angiostatin in combination. But he had only minute amounts of the two proteins, which he had painstakingly isolated from mouse urine. Rockville (Md.)-based EntreMed Inc., which underwrites Folkman's research, has taken a big step toward commercialization, however. The company announced at the recent cancer research meeting that it had successfully produced a bioengineered version of angiostatin, licensed to Bristol-Myers Squibb Co., that will be available in much larger quantities. Kim Lee Sim, senior director of molecular biology at EntreMed, says the recombinant version of angiostatin reduced the number of melanoma tumors in mice by 60% to 80% after 11 days of treatment, and those that remained were tiny. ''We've effectively turned off a switch that the body turned on,'' says EntreMed Chairman John W. Holaday.

To keep that switch off permanently, scientists from Genetix Pharmaceuticals Inc. in Cambridge, Mass., introduced the genes for endostatin and angiostatin into the bone marrow of tumor-infected mice. After 12 weeks, they reported that the mice still carried the proteins and their tumors were reduced dramatically. The gene therapy approach, says Genetix scientist Dr. Robert Pawliuk, empowers the body to make its own cancer-fighting proteins, eliminating the need for daily injections.

There are other angiogenesis inhibitors under development and a steady stream of promising new studies. At the New Orleans meeting, researchers from TAP Pharmaceuticals of Japan reported that their TNP-470 compound prevented the spread of lung and skin cancers in mice during 20 days of treatment. Japanese researchers demonstrated that another inhibitor showed high potency against human stomach tumors that had been implanted in mice. And a team from Monsanto Co. reported on yet another compound as safe and effective against solid tumors in mice.

There were also reports on compounds derived from shark cartilage, a cancer folk remedy long dismissed as ineffective by medical experts. But researchers have found some proteins in shark cartilage that do block blood vessel formation. Bioengineered versions include Neovastat, made by Aeterna Laboratories of Canada; squalamine from Magainin Pharmaceuticals in Plymouth Meeting, Pa.; and Troponin I, from Boston Life Sciences in Boston. All have dramatically reduced the size of tumors in mice without toxic side effects.

A lot of work still needs to be done before the newest angiogenesis inhibitors are proven in humans. Most of them are expected to enter clinical trials later this year, and it will be four or five more years before they could win approval -- if the trials are successful. But researchers say the angiogenesis inhibitors have already had a tremendous impact on the way laboratories are thinking about cancer. ''There are two ways to make an organism extinct. Knock each one out individually or knock out its habitat,'' says Coffey. ''The second way is a lot more effective.'' Someday, researchers hope, that change in thinking will lead to a dramatic change in treatment.

How It Works

Compounds under development attack cancer's life support system rather than the tumors themselves

1. TUMOR cannot expand because the outer cells are not in contact with blood vessels

2. Tumor releases chemical signals called ANGIOGENIC FACTORS that induce new blood vessel growth

3. NEW BLOOD VESSELS deliver nutrients and oxygen, allowing the tumor to grow and spread to other organs

4. ANGIOGENESIS INHIBITORS block growth signals and kill the new blood vessels, causing the tumor to shrink

LANGUAGE: ENGLISH

LOAD-DATE: April 23, 1998

For Norton, the interest is double edged. On one hand, he said, it is good that cancer patients and the public learn about the research, which has been carried out for several years.

But on the other, he worries that cancer patients will put too much stock in a treatment that has not been proved on anything but mice, and often medicines that work on mice do not help humans. Just Monday, he said a patient who had been operated on for breast cancer asked why she should go through post-operative chemotherapy that would help her when the new drug -- she was certain -- would be on the market within a few years.

"This happens every time there is a scientific report about something that has to do with cancer," said Norton, head of the division of medical oncology at Memorial Sloan-Kettering Hospital in Manhattan. "People's expectations get really inflated.

"You have to understand," Norton added. "I am hopeful this is going to turn out to be justified. This is a very exciting idea. Nevertheless we don't have any hard data."

The spike in interest came after an article in The New York Times on Sunday -- followed by other newspaper and television reports -- on the history and progress of the drugs as they are being prepared to go into clinical trials on humans.

Entremed, the company that will produce the drugs, released a statement Monday that it will take between 12 and 18 months before the first stages of the trials begins. With evaluation and further rounds of testing, it could take several years before the drugs are available on the market -- if they become available at all.

Several cancer experts said Monday that the trials could be especially complicated given that the new drugs work on a principle unlike other treatments, like chemotherapy, which attack the tumors themselves and are often accompanied with side effects. Angiostatin and endostatin attack the blood vessels that feed tumors, starving them of the blood they need to grow, and in mice, have done so without the side effects.

The drugs were discovered by Dr. Judah Folkman, a cancer researcher at Children's Hospital in Boston, and even he has urged caution about its promise. But for all the qualifications and warnings about possible failure, hope is rising among cancer patients.

"I'm getting faxes and e-mails," said Dr. Richard Klausner, director of the National Cancer Institute, who called putting the drugs into clinical trials his highest priority. "People want the drug. They're asking me, 'Couldn't we just compassionately release it?' I have to tell them, 'It doesn't exist.' "

"It's such a roller coaster for people whose relatives are dying," he added. "It's

very difficult to maintain understanding when something is available in animals but not in people."

On Long Island, where the rates of breast cancer are higher than average, Francine Kritchek, co-founder and past president of One in Nine, an advocacy organization, said: "The phone has been ringing off the hook. Everyone is very excited."

"We're very, very impatient about the process," she added. "We hope to see it speeded up. We would like to see the pharmaceutical companies that are making this drug really make it a top priority so that clinical trials will begin. they're playing with people's lives here."

In California, Jack Fisher of the Sacramento Center for Hematology and Medical Oncology, said Monday that a woman with lymphoma in remission had asked him about the drugs after reading about them.

"She was very excited about it," he said, adding that he told her: "Maybe in three years, I'll have this available."

"What we're doing with chemo will look so crude" in 20 years if the tests are successful, Fisher predicted.

In Los Angeles, Dr. Derek Raghavan, chief of medical oncology at the University of Southern California and associate director of the Norris Cancer Research Center, said that several of his patients asked about the new cancer drugs during examinations Monday.

"They did not ask for them by name, but expressed interest in whether they ware useful in their situation, whether they are safe and whether they are cancer killers or cancer stoppers," he said. "Patients are interested and they are very educated these days."



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# TELEFAX TRANSMITTAL

Harold Varmus, M.D.
Director, National Institutes of Health
Building 1, Room 126
1 Center Drive, MSC 0148
Bethesda, MD 20892-0148
Fax No. (301) 402-2700
Confirmation Phone No. (301) 496-2433


**DATE:** 7 May 1998

**TO:** Jerry Mande
Office of the Vice President
White House

**FAX NUMBER:** (202) 456-6027

**PHONE NUMBER:** (202) 456-6018

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**REMARKS:** Attached is a list of past and current NIH awards to EntreMed.

Barry Bowman
Assistant to the Director, NIH

## NIH AWARDS TO ENTREMED, INCORPORATED -- ROCKVILLE, MARYLAND

| FISCAL YEAR / PROJECT TITLE | PRINCIPAL INVESTIGATOR | AMOUNT AWARDED |
|---|---|---|
| 1994 | FORTIER, ANN | |
| DEVELOP THERAPY TO INDUCE LONGTERM ENDOTOXIN TOLERANCE | | 61,958 |
| BUDGET START = 06-06-94 | BUDGET END = 12-05-94 | |
| (contract) | | |
| 1994 | NACY, CAROL A | |
| DETECTION OF INTRACELLULAR PATHOGENS BY FLOW CYTOMETRY | | 100,000 |
| BUDGET START = 08-15-94 | BUDGET END = 08-14-95 | |
| PROJECT START = 08-15-94 | PROJECT END = 08-14-95 | |
| (Small Business Technology Transfer Research Grant) | | |
| 1994 | SIM, KIM L | |
| PLASMODIUM FALCIPARUM MALARIA INVASION LIGAND AS A VACCINE | | 75,000 |
| BUDGET START = 09-30-94 | BUDGET END = 06-30-95 | |
| PROJECT START = 09-30-94 | PROJECT END = 06-30-95 | |
| (Small Business Innovation Research Grant) | | |
| 1995 | SIM, KIM L | |
| ANGIOSTATIN--RECOMBINANT THERAPEUTIC FOR METASTATIC CANCER | | 100,000 |
| BUDGET START = 06-15-95 | BUDGET END = 11-30-95 | |
| PROJECT START = 06-15-95 | PROJECT END = 11-30-95 | |
| (Small Business Innovation Research Grant) | | |
| 1997 | SIM, KIM L | |
| FALCIPARUM MALARIA INVASION LIGAND VACCINE | | 367,060 |
| BUDGET START = 05-01-97 | BUDGET END = 04-30-98 | |
| PROJECT START = 05-01-97 | PROJECT END = 04-30-99 | |
| (Small Business Innovation Research Grant) | | |
| 1998 | SIM, KIM L | |
| FALCIPARUM MALARIA INVASION LIGAND VACCINE | | 382,940 |
| BUDGET START = 05-01-98 | BUDGET END = 04-30-99 | |
| PROJECT START = 05-01-97 | PROJECT END = 04-30-99 | |
| (Small Business Innovation Research Grant) | | |

# Scientist says he was misquoted in cancer article

A week of stories from the Boston Globe's Washington bureau

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**By Reuters, 05/07/98**

EW YORK - The Nobel laureate who helped discover the structure of DNA, James Watson, is disputing a quote in The New York Times that had him predicting that two drugs would help cure cancer within two years.

The front-page article Sunday on the drugs angiostatin and endostatin spurred an explosion of interest in EntreMed, the Rockville, Md., biotechnology company that has licensed the rights to develop them.

The drugs are naturally occurring proteins that block growth of blood vessels that feed tumors. They were discovered in the laboratory of Dr. Judah Folkman, a cancer researcher at Harvard Medical School and Children's Hospital in Boston.

In the article, written by Gina Kolata, Watson is quoted as saying, "Judah is going to cure cancer in two years."

The article added that Watson said Folkman would be remembered along with scientists like Charles Darwin as someone who permanently altered civilization.

Some Wall Street analysts said the bold statement by Watson, a co-discoverer of the "double helix" structure of DNA, boosted interest in the drugs.

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Watson, director of the Cold Spring Harbor Laboratory on Long Island, submitted a letter to the editor of the Times challenging the quote, according to laboratory spokesman Wendy Goldstein.

Goldstein provided Reuters a copy of Watson's letter, which she said would be submitted to The New York Times yesterday for publication.

In the three-paragraph letter dated May 4, Watson wrote: "In the May 3 New York Times article, Ms. Kolata reported that I predicted that Judah Folkman would cure cancer in two years. My recollection of the conversation to which she refers, however, is quite different."

The letter continues, "What I told Ms. Kolata, at a dinner party six

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The letter continues, "What I told Ms. Kolata, at a dinner party six weeks ago, was that endostatin should be in NCI (National Cancer Institute) clinical trials by the end of this year, and that we would know about one year after that" whether the drug is effective.

A spokeswoman for the Times, Lisa Carparelli, said: "The Times is very confident of the accuracy of Ms. Kolata's story. Dr. Watson is a respected source and the New York Times stands by precisely what was reported."

EntreMed officials could not be reached for comment.

In his letter, Watson noted that the two drugs have not been tested in humans, only in mice - a point that the medical community and drug industry analysts have underscored as a reason for caution.

Goldstein said Watson was in California and could not be reached to comment.

"Dr. Watson feels very strongly about setting the record straight that he did not make such a statement," Goldstein said.

"He is contesting that quote primarily because he feels a statement as bold as this coming from him has offered what could very well prove to be false hope to a great many people" with cancer, she said.

Carl Gordon, a drug analyst for OrbiMed Advisors in New York, said he believed quotes by Watson and others in the article about the two drugs by Dr. Richard Klausner, director of the National Cancer Institute, were the biggest drivers of EntreMed's Wall Street rally Monday.

EntreMed's stock jumped from about $12 Friday to trade in the low $50 range Monday, after briefly hitting $85.

It lost $10.125 to $33 in heavy trading yesterday afternoon on the Nasdaq market.

This story ran on page A A10 10 of the Boston Globe on 05/07/98.


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THE WALL STREET JOURNAL INTERACTIVE EDITION
FRONT SECTION NEWS







May 6, 1998

# A New Revolution in Genetics Equips Cancer Fighters With Potent Weapons

By ROBERT LANGRETH
Staff Reporter of THE WALL STREET JOURNAL

The war on cancer, fought for three decades marked by failure and frustration, suddenly is in overdrive. Just a few weeks ago, reports rocked the medical world about two drugs that show promise in preventing breast cancer. This week, Wall Street and Main Street alike went wild over word of a bold experimental drug that wiped out tumors in mice.

These approaches are in very early stages of development and, even if all goes well, will require years of human testing before they can move into widespread usage. But they underscore a much bigger story: A quiet revolution in genetics has brought scientists closer than ever before to finding an actual cure for cancer.

One Approach: Cut the Blood Supply
Some Aim to Fix the Genes Themselves

The drugs that made headlines this week use the promising approach of blocking a tumor's blood vessels. Even farther along in development, however, is a whole new generation of gene-based drugs aimed at a strikingly broad range of cancers. Human testing is already under way for this new arsenal, which looks to be far more powerful and far less toxic than anything tried before.

## Targeted Precisely

Some of the biggest pharmaceutical companies are pursuing the drugs, which attack cancer in a way entirely different from chemotherapy or radiation, the standard therapies. Where chemo and radiation assault all cells, cancerous and healthy alike, causing severe and even lethal side-effects, the new gene-based chemicals are precisely targeted. They take direct aim at the genetic machinery inside malignant cells to disable defective or mutated genes that provide the marching orders for unchecked growth.

---

## Players and Progress

An arsenal of new gene-based drugs has begun human trials

| Target | Company | Status of Testing |
|---|---|---|
| HER2 | Genentech | Phase III human trials completed in breast-cancer patients. Submitted formal application for approval to the FDA and could win federal approval by year end. |
| RAS | Merck | Phase I human safety trials began in April 1998. |
| | Schering-Plough | Phase I trials began in late 1997. |
| | Johnson & Johnson (Janssen division) | Phase I tests began in early 1997. Phase II small-scale tests for effectiveness in humans may begin soon. |
| | Bristol-Myers Squibb | Preclinical testing. Phase I human trials could begin soon. |
| EGFR | Pfizer (with partner OSI Pharmaceuticals) | Phase I testing started in 1997. |
| | Zeneca | Beginning Phase II trials. |
| | Novartis | Close behind Pfizer and Zeneca. |
| | Warner-Lambert | Preclinical testing. |
| PDGF | Sugen | Phase III trials for treatment of brain cancer. Phase II trials for treatment of prostate cancer. |

**Note:** New drugs first go through safety tests in animals before moving through three phases of human testing to win government approval. Phase I tests for safety in humans. Phase II tests for effectiveness in a small number of people. Phase III tests are large-scale final trials for effectiveness and safety in humans.

---

Except for one far-along drug from Genentech Inc., it will still take several years to know whether these drugs can live up to their promise. But even guarded scientists are saying that the first new and highly effective therapy in decades is at hand, one likely to change forever the way cancer is treated.

"This is the dawn of the future of cancer therapy," says Richard Klausner, director of the National Cancer Institute. And J. Michael Bishop, a Nobel laureate in cancer research, says: "For the first time in my life, I believe we will eventually be able to conquer cancer."

## War on Cancer

The target genes that hold this promise were discovered over the past 25 years, largely the result of a surge in federally funded research

after President Nixon declared war on cancer in 1971. But only in the past five years or so have scientists unraveled enough details of how genes operate to try to turn them off with drugs. Now genetic targeting has become the focus for developing most kinds of drugs, and the new anticancer compounds are leading the way. It adds up to nothing less than a new golden age of biology.

The war is being waged by corporate drug giants in a race for profits, their crack research teams working in secret and often unaware of the progress at rival labs. For years, many drug makers left most cancer research to university and government labs because it was a costly crap shoot. Now even some companies that never focused on cancer before are in hot pursuit, among them Merck & Co., Pfizer Inc. and Johnson & Johnson.

The first of the gene-based drugs could win federal approval by year end. It is Genentech's Herceptin, which attacks a virulent form of breast cancer.

Other companies are tackling a far broader range of cancers. Human testing of gene-based weapons against cancers of the lung, colon, pancreas and other organs has begun at Merck, Schering-Plough Corp. and J&J. Bristol-Myers Squibb Co. and Warner-Lambert Co. are close behind. Drugs targeting tumors in the prostate, breast, head and neck, based on a different gene, have entered human testing at Pfizer Inc. and Zeneca Group PLC.

**Destroying Tumors**

Originally, scientists just hoped gene-based cancer drugs would be strong enough to hinder or halt tumors' growth. In a great surprise, several of the drugs have surpassed all expectations and shown an ability to kill cancer cells outright. In animal tests, experimental drugs from Merck and Bristol-Myers can destroy tumors of the breast, lung or colon.

Now researchers must determine whether the drugs are both safe and effective in humans, enduring the three phases of testing where so many promises have been dashed. They "will undeniably be a major advance," predicts Robert Kramer, who heads oncology research at Bristol-Myers Squibb. "The only question is how major." Even though some drugs are bound to falter, researchers clearly have turned a corner in their unending battle against cancer, thanks to a profound change in how their weapons are developed.

For decades scientists essentially wandered around in the dark, randomly testing thousands of natural chemicals for antitumor activity. Even when scientists found one that killed cancer cells, they often didn't know why.

In the past decade, researchers have flicked on a light illuminating the molecular processes by which cancer cells get the instructions needed for rampant growth. By identifying some of the defective genes at work, they have been able to spot vulnerabilities in the molecular mechanics. They try to disrupt these processes with newly designed drugs -- tossing a chemical monkey wrench into the tumor-making machinery.

This keener insight has helped researchers with other new approaches as well, including blocking formation of the blood vessels that large tumors must have to thrive. Another method in very early stages of study involves "suicide genes" that are otherwise disabled in cancer cells, aiming to turn them back on so they can tell the cell it is time to die.

"Traditional anticancer agents have been discovered through chance. We are now going after the fundamental mechanisms of cancer," says Allen Oliff, the top cancer researcher at Merck.

High hopes, however, have proved to be premature in the past. Cancer is a cunning foe, coming in more than a hundred different forms and traceable to as many different genetic defects. The list of disappointments and outright flops in the quest to cure cancer is long and storied: monoclonal antibodies in the late 1970s and again in the 1980s; tumor necrosis factor, a natural protein whose promise rose and fell in the mid-1980s; interferons, immune boosters that held out great hope a decade ago but have only limited uses; Interleukin-2, a natural cancer-fighting protein that made headlines in the late 1980s but proved to be violently toxic.

Tangible progress has been slow. Although survival rates for some childhood cancers have risen and leukemia, lymphoma and testicular cancer now can often be cured with radiation and chemo, for most other cancers the advances have been slight. Despite tens of billions spent on research, cancer remains the second leading cause of death after heart disease. Eight million Americans have cancer or have survived it. Each year it kills 560,000 people in the U.S., and 1.2 million more are diagnosed with it.

About 96% of those who get pancreatic cancer still die within five years. So do 94% of liver-cancer patients, 86% of lung-cancer patients and 79% of people who get stomach cancer.

The new gene-based drugs could change all that.

To understand them, a quick primer: In each of the body's billions of cells is a nucleus holding a genetic formula, 23 pairs of chromosomes. The chromosomes -- long strands of DNA -- each carry thousands of smaller segments of DNA called genes. In different types of cells, different sets of genes are active or inactive,

with each "on" gene holding an instruction telling the cell to produce a particular protein. The on genes in, say, a skin cell carry the code for producing the proteins needed to give it skin-like properties.

Only several hundred of the 50,000-plus genes hold instructions for producing proteins that regulate cell division. These are the ones involved in cancer. Scientists have identified at least 20 defective genes that sometimes tell cells to just grow and grow.

Their defects probably reflect a slow accumulation of genetic mutations over a lifetime. Molecular "typos" in just one or more of the thousands of genes in a cell can result from environmental toxins or exposure to radiation, or they can occur randomly during cell division as new copies are made. As more typos occur over many years, enough errors build up to overwhelm the body's defenses against unrestrained cell growth.

What to do? Researchers, for the most part, can't tinker directly with a flawed gene. Instead, they disable proteins that the genes order to be made.

To accomplish that, they copy the strategy of more-conventional drugs. Their molecules maneuver into tiny keyholes, or "active sites," that a protein or enzyme needs to function. Plug up the keyhole and the troublesome protein can't do its job.

When researchers first responded to the 1971 call for a war on cancer, no one knew what caused the disease. Millions of dollars initially were spent studying the wrong suspect, cancer-causing viruses in animals. The virus theory failed for most human cancers.

Then in 1975 Dr. Bishop and another biologist at the University of California at San Francisco, Harold Varmus, astonished fellow researchers by identifying the cause of a chicken cancer: a defective gene. Although the gene turned out to be restricted mostly to animal cancers, the work triggered a frenzied search for genetic cancer causes in people.

The next breakthrough came three years later when an ambitious young researcher at the National Cancer Institute, Edward Scolnick, discovered a cancer gene in rats. He named it RAS, for rat sarcoma. Other scientists eventually showed it played a central role in as many as 30% of human cancers, including major killers. They found that half of all colon cancers, 90% of pancreatic tumors and 25% of lung cancers involve defective RAS genes.

RAS now is one of three main genes the drug scientists are targeting. About nine others are getting earlier-stage attention.

In 1982 Dr. Scolnick moved to Merck, hoping research on RAS by a

giant drug company could lead to a new way to treat cancer. Now 57 and head of Merck's entire research operation, he vows to deliver a major new cancer drug by the time he retires. But in the early 1980s, for Merck and for others throwing money into the genetic approach, it was leap of faith.

The work proved far more difficult than expected. "We wasted a lot of time on things that were completely impossible," says Dr. Oliff, whom Dr. Scolnick hired to head Merck's cancer program. "The first five years were a total waste."

The problem was that they knew little about how the RAS gene actually worked. It was like trying to repair a car engine without knowing just what the parts did.

They know a lot more now. Normally the RAS gene carries instructions for making a protein that perches near the inner surface of all cells and acts as a central relay station for cell division. When growth hormones outside the cell send chemical messengers telling it to multiply, the RAS protein relays that directive to the cell's nucleus; otherwise, RAS stays quiet and the cell refrains from dividing.

In cancer cells, a single chemical bead among the thousands that make up the RAS gene is out of place; this turns the RAS protein into a monster. Stuck in the "on" position, it continuously conveys a phantom message telling the cell to divide and multiply.

Cancer researchers tried to create molecules that could interfere with the RAS protein and stop it from functioning, but they couldn't find the right spot for attack. In addition, RAS functions in all cells, so blocking it in cancer cells risked thwarting it in healthy cells where it was needed.

That has always been a major obstacle in creating cancer drugs. Bacterial, fungal and viral infections introduce a foreign intruder, posing a ready target for drug design, but in cancer the enemy comes from within. The differences between normal cells and cancerous ones are often so subtle that drugs can't distinguish them. This is why current cancer drugs cause such toxic side effects; they're hammering regular cells, too.

The new gene-based drugs, narrowly targeted at a cancer cell's innermost workings, may clear this hurdle.

In 1990 two Nobel-laureate chemists at the University of Texas, Michael Brown and Joseph Goldstein, found a promising target: a helper protein that the RAS gene needs for forwarding messages. Called farnesyl transferase, or FT, it is an enzyme that triggers a chemical reaction. The search was on for a drug that could block FT.

Merck had been winding down its RAS research, but it decided to take one last shot. By 1993, it had compounds that blocked the RAS helper protein. But then for five long years, one after another turned out to be toxic. "It's very frustrating because we've had compounds that [blocked RAS] since 1993," Dr. Oliff says.

Early this year, Merck finally completed successful safety tests in animals of a powerful anti-RAS drug -- so secret it won't even reveal the code name. Last month it began human safety tests. If the drug is found safe, a small efficacy test will begin, the phase II trial. If the drug clears that, the final, Phase III trial to test for efficacy in a large group of people could begin in a few years.

Other drug companies rushed into the fray, too, and Bristol-Myers Squibb found a chemical that could turn off the FT helper protein in test tubes. Animal tests showed it to be far more potent than anything the company had tested before against cancer. In one animal test of a colon-cancer strain that was resistant to existing drugs, the substance obliterated the tumors 100% of the time. Human trials could begin in a few months.

Unknown to these drug powerhouses, a neighbor also was hard at work. A mere three miles from Merck's main lab in West Point, Pa., a small group of scientists studied the RAS gene at Janssen Pharmaceutica, owned by Johnson & Johnson.

In 1990, a young scientist at Janssen, David End, had read a scientific article that led him to test for anti-RAS powers in a class of drugs that included J&J's toenail-fungus drug, Nizoral. It didn't work, so he tried related chemicals similar to J&J's cream for vaginal infections, Monistat. Bingo.

Janssen scientists in France later designed a compound 100,000 times more potent than the over-the-counter product. Safety tests in humans began more than a year ago, and the company hopes to begin efficacy tests soon.

RAS wasn't the whole story. Also becoming a key target at some drug companies was a gene called EGF receptor.

The EGF receptor plays a central role in division for all cells, acting as a chemical gatekeeper on their surface. In the early 1990s, scientists learned that the EGF receptor and the RAS protein are terminals on the same chemical relay system. The receptor gets signals from growth hormones secreted by other organs indicating it is time for cells to divide, then relays the message to RAS, which dispatches it to the cell nucleus.

Normal cells have 10,000 or so copies of the EGF receptor. But many lung, prostate and brain tumors have extra copies--as many as a

hundred times as many. That means a normal growth message is amplified tremendously, causing the cell to reproduce madly and grow into a tumor.

Pfizer attacked this gene through a biotech partner, now called OSI Pharmaceuticals Inc. Vastly speeding its search for a chemical to jam the EGF receptor was new robotic testing of compounds. Pfizer and OSI screened nearly 300,000 compounds, Pfizer's entire chemical collection at the time, and in 1993 isolated a group of related molecules that did the job.

But the EGF receptor strategy has a big obstacle. The risk of terrible side effects is high because this receptor is very similar to other receptors involved in nourishing the nerves, processing messages from insulin and handling other critical functions. A drug that blocked the EGF receptor might also thwart those processes, causing diabetes or even brain damage.

After years of searching, Pfizer now has a drug that can block the EGF receptor selectively. In early human tests, it looks safe. Zeneca has a similar EGF drug that has already moved into Phase II, the initial efficacy test.

The EGF approach may fail to kill tumors outright. But scientists hope it will stop them from growing and spreading, thus turning some cancers into chronic, manageable diseases.

"The enthusiasm here is incredibly high but so is the pressure, because Pfizer has spent millions on cancer research and we still don't have a drug," says Michael Morin, who heads Pfizer's cancer research at a huge lab in Groton, Conn. "It takes a long time to test a drug when you have a totally novel mechanism."

The third gene the drug companies are targeting heavily may be the first to yield a marketable drug. It is called HER2, and it is the one Genentech is aiming at. HER2 is a cousin of EGFr: a growth-message relay switch that is hyperactive in many patients with severe cases of breast cancer.

Genentech has taken on HER2 using monoclonal antibodies, the once-promising approach that faded with the 1980s and now is making a comeback. They are clones of human antibodies that target a single protein.

A lot of the credit for Genentech's drug goes to a researcher at the University of California at Los Angeles, Dennis Slamon. Genentech scientists exploring new genetic-splicing techniques in the 1980s sent him a clone they had produced of the HER2 gene, not knowing what its function was. Dr. Slamon, who was looking for genes that might be involved in cancer, compared the cloned gene and the protein

based on it with tumor samples from patients with breast cancer. He found abnormally large quantities of the HER2 protein in about 30% of breast-cancer tumors, including the most virulent.

He urged drug makers to attack this gene by designing a monoclonal antibody that would bind to the HER2 protein and block it. Most companies didn't bite. The monoclonal method had fallen from favor, and drug companies knew how easy it was to spend millions working on cancer drugs and get nothing.

Top officials at Genentech, too, were highly skeptical, but a handful of scientists there kept the research going for years. Finally, their work produced the genetically engineered drug that has now gone through all three phases of human testing. Herceptin has been given to about 400 women with a virulent form of breast cancer, and in combination with chemotherapy it helps at least some of the time. A few women on the drug remain alive and well several years after being told their breast cancer was terminal.

Detailed trial results will be released May 17. This week, Genentech applied to the Food and Drug Administration for approval to sell Herceptin, which the company's chief medical officer, Susan Hellmann, calls "a breakthrough by any criteria."

How much longer patients will live thanks to such gene-based drugs won't be clear for years. The new chemical weapons are so different that testing poses immense challenges in deciding what doses to use, for how long, and in which patients. Scientists may end up having to combine several types into a cocktail that blocks the products of several defective genes.

But even with all the caveats, legions of veteran cancer researchers have the palpable sense that a revolution in cancer treatment is at hand -- that the notion of an outright cure, someday, has become an attainable goal.

"It's unpredictable what will happen," says Merck's Dr. Scolnick. As he and other scientists repeatedly point out, many prototype drugs, once so full of promise, ultimately failed. But even the always-cautious Dr. Scolnick is hopeful. It is possible, he says, that under the attack of the new gene-based drugs "the tumors will just melt away." If that happens, "it would be a miracle."

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HEADLINE: THE NEW BIOTECH BOOM: A STAR IS BORN;
ONCE AGAIN BIOTECH IS ALL THE RAGE. BUT IT'S DIFFERENT THIS TIME. CONSIDER THE STORY OF ENTREMED, A COMPANY WITH REAL SCIENCE, REAL FINANCING, AND REAL PROSPECTS. WHICH ARE QUALITIES A BIOTECH COMPANY NEEDS TO GO PUBLIC THESE DAYS. REFRESHING, ISN'T IT?

BYLINE: ERICK SCHONFELD, REPORTER ASSOCIATE JOYCE E. DAVIS

BODY:

Whenever the name Judah Folkman comes up in conversation, it is shortly followed by the prediction that he will one day win the Nobel Prize for medicine. If such an announcement is ever made, it will probably do two things. It will spotlight Folkman's pioneering work in a field of cancer-related research called angiogenesis. And it will likely cause a blip in the stock of an amoeba-size biotechnology company called EntreMed.

Like most biotech companies, EntreMed's stock is valued more on news flow than cash flow, since it doesn't have much in the way of revenues and since earnings at this point are purely hypothetical. What it does have, though, is Folkman--more specifically, it has the rights, through the end of the millennium, to nearly all of the discoveries in applied research emanating from the scientist's tenth-floor laboratories at Children's Hospital in Boston. In other words, a Folkman breakthrough is also an EntreMed breakthrough. Indeed, this relationship is so important that it is the primary reason that pharmaceuticals giant Bristol-Myers Squibb was willing to sign a $ 76 million partnership agreement in December 1995 with EntreMed. That deal, in turn, gave EntreMed the credibility to go public last June, a mere six months later. But that's getting a little ahead of our story.

Perhaps you haven't noticed, but we're in the midst of a big biotech boom--the second such boom in the Nineties. The first biotech boom you undoubtedly did notice: It was a lot like the recent craziness in Internet-related companies. A sizzling industry had arrived on the scene, and everyone started grabbing for a piece of it: scientists who quit their jobs to start biotech companies; venture capitalists who threw outrageous sums of money at those scientists; and eventually the investing public, which gobbled up biotech IPOs as if they were a sure thing.

But of course they were far from a sure thing. They were so new that there was no real sense of how long they would take to make money or what kinds of products would eventually be viable. They burned through capital at an alarming rate. Many had been created on the flimsiest of rationales: "In that boom," recalls EntreMed CEO John Holaday, a veteran of the industry, "you could go public with a concept." In the subsequent haste to get products out the door, many biotech startups miscalculated the complexities of the underlying biology or launched poorly designed clinical trials that could not pass muster with

the FDA.

Inevitably, it all came crashing down: "Concepts" failed, money ran out, products never materialized, and boom turned to bust. In classic Wall Street fashion, investors who had once indiscriminately bought anything related to a recombinant protein were, by 1993, just as indiscriminate in their aversion to all things biotech.

In retrospect, the bust was probably healthy for biotech because it caused the industry to grow up fast. As venture capitalists became cautious about tossing money at biotech startups, scientist-entrepreneurs learned to do the arduous work of establishing credibility: of cutting deals with pharmaceuticals companies, of establishing links with brand-name scientists, of spending money in a smarter way. As companies discovered how to do that, it led to the second, quieter biotech boom, the one that began in 1995 and is still steaming ahead.

In this boom the companies that have been able to go public may not yet have real profits, but they do have real prospects. And in this boom the act of going public is not a first step, as it was in the early Nineties, but the culmination of a process in which each step leads inevitably to the next--and in which one misstep can cause the whole thing to blow up. The companies that have gone public this time are those that, through luck or skill or some combination of the two, have made all the right moves. Companies, that is, like EntreMed.

THE GUY FROM CENTRAL CASTING

It is both EntreMed's blessing and its curse that it was born at the tail end of the last boom. The year was 1991, a time when the money was still flowing and the standards were still low. Two men, Holaday and Steve Gorlin, were planning to take advantage of this happy circumstance--though of course they didn't think of it quite like that. Holaday, an accomplished academic scientist, was then at a small dermatology concern but had higher ambitions than to be a peddler of acne medicines and cleansers; Gorlin, an Atlanta financier and an early backer of the dermatology company, had found in Holaday someone with whom he felt he could start a business. They enlisted a third man, Bart Chernow, then (and now) the physician-in-chief at Sinai Hospital of Baltimore.

That all three were infected with the boom mentality seems, in retrospect, plain. They had no products or technology to speak of. Rather, they had a concept: EntreMed was to be a kind of clearinghouse for other people's science. Holaday and Chernow knew that many scientific projects sat languishing in university laboratories for lack of funding. Never mind what the particular projects would turn out to be; if they could use their contacts to identify promising science and develop it until it was ready for a larger partner to take over--well, surely there was a business opportunity in there somewhere. As for Gorlin, who had successfully funded several biotech companies, he was simply betting on Holaday. His philosophy: "Be sure you get the right jockey, then get out of the way and let him run it."

Naturally they planned to go public as soon as possible. In preparation for that task, Gorlin secured capital and helped to set up a board of directors. He did not, however, seek venture capital, which is ordinarily necessary to convince the public that a biotech company is for real. Seeing that the IPO market was so frenzied (indeed, the entire biotech market was a little juiced--biotech stocks rose 120% in 1991 alone), Gorlin did not want to share

the gains with too many people. Instead, he borrowed money from his friend Morty Davis, chairman of D.H. Blair Investment Banking, who backed many of the flightier biotech concepts during the boom. Together they put in $ 3 million and looked forward to a quick IPO. That's when the entire sector started to tank. So much for Plan A.

Plan B was simply to beg money from rich folks. As it turns out, this was something Holaday was very good at. Articulate, personable, and convincing, Holaday is a born teacher who would unveil the mysteries of science in presentations to prospective investors. When investors asked obvious questions, he would make them feel smart by noting what excellent questions they were. Yet he also exudes a Bill Clinton type of sincerity--so polished you don't know whether to believe it. When D.H. Blair's Davis first heard him speak, he asked Gorlin, "Where did you get this guy, central casting?"

Some potential investors were put off by Holaday's studied charisma, but a sufficient number found him persuasive enough that EntreMed was able to raise $ 7 million in a March 1993 private placement. Investors included Continental Airlines' controlling shareholder, David Bonderman; former drug industry executive Sam Dunlap; and two founding members of the mutual fund company Invesco Capital Management: Don Sallee and Chairman Wendell Starke. Dunlap and Starke joined the EntreMed board (it is the only board seat Starke holds outside Invesco). As for Sallee, let's just say his interest in EntreMed was preordained. Holaday, who was raised in Tuscaloosa, Alabama, would later discover that Sallee had gone to graduate school at the University of Alabama in his hometown. Not only that, but for two years back then, Sallee had rented a room over a garage behind the very house where Holaday grew up.

A LITTLE SCIENCE GOES A LONG WAY

Money in hand, EntreMed set up laboratories at its headquarters in the high-tech spawning grounds off Interstate 270 in Rockville, Maryland. Now it was time to find some science.

As planned, Holaday began looking for ideas in academia. He lined up deals for projects such as an anticholesterol vaccine, as well as a device to make blood more oxygen-efficient. The latter was licensed from Claude Nicolau at Harvard's Center for Blood Research and showed great promise for the millions of people suffering from cardiovascular diseases. Normally hemoglobin, a key component of red blood cells, releases only one of the four oxygen molecules it carries. Nicolau, however, invented a machine that electrically inserts a commonly found plant chemical into extracted red blood cells, which causes the hemoglobin to release three of its oxygen molecules, thus making blood three times more efficient.

EntreMed's biggest boost, though, came from the work of Judah Folkman, the father of research into angiogenesis, which is one of the ways the body creates new blood vessels. Angiogenesis occurs during early fetal growth, wound healing, women's menstrual cycles, and pregnancy. It also takes place in conjunction with certain diseases--most notably cancer. Folkman's work for the past 25 years has been aimed at showing, among other things, that malignant tumors can be attacked by cutting off their blood supply, which courses through angiogenically produced capillaries. Today Folkman's idea is widely accepted and is transforming the way scientists approach cancer treatment. But Folkman's story is really a story of scientific persistence, for it took him two decades to prove what he felt in

his bones to be true.

Folkman had known he was going to be a surgeon since he was 7 years old. His father, a rabbi in Columbus, Ohio, would visit sick congregation members in the area's hospitals on weekends. As a reward for good behavior, Folkman and his siblings were often allowed to accompany him and sit quietly in the rooms of the ill. "It began to dawn on me that the doctors coming in could actually do things that seemed better than prayers," he recalls. As a medical student at Harvard in the Fifties, he designed one of the first pacemakers. In the Navy he invented an implantable device that slowly releases drugs into the body, which he later donated, patent-free, to the Population Council. It is now known as Norplant.

In 1967, at the ripe old age of 34, Folkman became a full professor at the Harvard medical school and soon after was named surgeon-in-chief at Children's Hospital. There he began his effort to uncover the secrets of angiogenesis. Within a few years he had come to believe that the growth of cancerous tumors depended on their formation of thousands of tiny blood vessels that feed them oxygen and nutrients. Folkman's reasoning went against the prevailing wisdom: When surgeons removed tumors and witnessed massive bleeding, they assumed the bleeding was caused by the surgery rather than by a superabundance of blood vessels.

Folkman's problem was that he couldn't prove his theory because, try as he might, he was unable to identify the molecule that stimulates angiogenesis. Criticism and ridicule were heaped upon him. Rejected grants piled up in a file drawer. Colleagues went so far as to suggest to his wife that he had gone off the deep end.

Through it all, Folkman never lost faith. And in the early Eighties his lab finally struck pay dirt: a molecule that induced angiogenesis. The next task was to find molecules that would inhibit angiogenesis; that, Folkman thought, would be the way to, in effect, starve tumors. His lab quickly found molecules that had the desired effect, and he continued to search for more potent inhibitors. Meanwhile, his critics began to fall silent. Today drug companies like Bristol-Myers Squibb salivate at the prospect of cancer patients some day downing inhibitor pills rather than suffering through chemotherapy or radiation treatments. Explains Jerry Treppel, a Dillon Read stock analyst: "Angiogenesis inhibitors represent what could be the first change in the treatment of cancer in 50 years."

In 1992, at about the time EntreMed was coming together, one of Folkman's postdoctoral students, Robert D'Amato, made a startling discovery. D'Amato is an ophthalmologist, and he was interested in angiogenesis because blindness can sometimes be caused by a profusion of blood vessels in the eye. D'Amato was searching through a huge database of existing drugs, looking for some that might have been suppressing angiogenesis all along, unbeknown to anyone. Sitting in front of his computer late one evening, he looked up and down his body trying to think what side effects an anti-angiogenic compound might cause. He could think of nothing except a slowing of wound healing, which would be hard to notice. But what if he were a woman? Immediately, he thought, "My menstrual cycles would stop." He quickly searched for all known drugs that interfered with menstruation. Hundreds popped up. He knew angiogenesis also took place in the early stages of fetal growth. So what about drugs that could cause birth defects? Still too many candidates. But when D'Amato merged the lists, only six drugs remained. The one that floored him was thalidomide.

Thalidomide, of course, is one of the most reviled drugs of all time. Responsible in the early Sixties for the horrible deformation of thousands of European babies, it is the drug that spurred the FDA to tighten its approval guidelines in 1962. Even after three decades of research, no one knew why pregnant women who took thalidomide gave birth to babies with shortened, flipper-like limbs. Now D'Amato had inadvertently stumbled upon the long-sought reason: Thalidomide inhibits angiogenesis. When he saw it on his list, he reasoned that it was precisely this ability to stop blood vessels from growing--so tragic in newborns--that might give thalidomide the potential to improve the lives of people afflicted with blindness and cancer. Clearly, thalidomide was potentially a more powerful inhibitor than any previously unearthed. (Later, D'Amato did experiments proving that thalidomide does inhibit angiogenesis in animals.)

And whom did D'Amato call to talk about his discovery? None other than John Holaday, who is like a surrogate father to D'Amato. Every summer during college D'Amato had worked in Holaday's lab at the Walter Reed Army Institute in Washington, D.C., where Holaday spent most of his academic career. As D'Amato told him about what he had found, Holaday became intrigued. He liked the idea of "teaching an old drug a new trick," he would later say, and thought thalidomide would be a good candidate for EntreMed.

But why would Folkman even consider turning over his lab's discovery to a company like EntreMed? The answer is simple: Even prestigious scientists from Harvard need money--lots of it. Although Folkman's basic research was largely funded by the government, that money wasn't nearly enough to cover costly clinical trials, and Folkman was in the process of seeking a corporate sponsor to supplement his government grants.

By this time, Folkman thought he was close to finding another powerful angiogenesis inhibitor--a fact that he was mentioning to potential underwriters and that he felt might allow him to land a bigger fish than tiny EntreMed. But because he had not yet come up with a molecule, they weren't yet biting. The one Folkman most wanted to snag was the giant Swiss pharmaceuticals company, Hoffmann-La Roche.

Holaday and EntreMed, needless to say, were also interested in the prospect of a second angiogenesis inhibitor coming out of Folkman's lab--and not nearly so concerned that finding an actual molecule might take years. EntreMed desperately needed a catalyst to move its business forward, and it viewed Folkman as its best hope. In mid-1993, Gorlin heard that Folkman was about to fly to Basel, Switzerland, to meet with Hoffmann-La Roche. On a day's notice, EntreMed's patent attorney, its head scientist, Holaday, and Gorlin flew (in Gorlin's Learjet) to Montreal, where Folkman was receiving an award prior to his own flight. The EntreMed team told Folkman that if he went with Roche, he would be just another item on its shelf competing for attention with a dozen others. In the end, Roche decided not to sponsor Folkman anyway, and Harvard signed a contract with EntreMed in October 1993.

Harvard, unlike most other universities, bars professors from owning stock in companies with which it has a research relationship. So Folkman couldn't accept shares in EntreMed. He didn't care. He had the money he needed to keep his experiments moving forward. EntreMed had what it needed too: the rights to commercialize some of the most promising research being done by one of the world's best-known scientists.

Then EntreMed got lucky: Folkman found his second inhibitor, and it was twice as powerful as thalidomide. Another post-doc in Folkman's lab, Michael O'Reilly, had spent a year purifying microgram quantities of a protein, angiostatin, from over 40 liters of acrid mouse urine. (His poor wife would force him to air out on the porch before entering the house.) Angiostatin turned out to be the second inhibitor. Later, in the June 1996 issue of Nature Medicine, he and Folkman reported that angiostatin can suppress the growth of tumor volumes in mice with implanted human breast, colon, and prostate cancers, on an order of 95% to 100%. If it showed similar effects in humans, the protein would revolutionize cancer treatment. No assurance could be given that a bona fide drug would ever emerge. But with both thalidomide and angiostatin, EntreMed now had enough science to seek a partner of its own.

WALLETS OPENED WIDE

There is a natural marriage between biotech and major drug companies. At their core, pharmaceuticals companies are cash-generating manufacturers and marketers searching for innovative products to push through their factories and distribution channels. Biotech companies have those products but need the financial support, clinical-development expertise, and large-scale manufacturing skills that pharmaceuticals companies offer. During the earlier biotech boom, neither side fully appreciated how much it needed the other. There was plenty of easy capital floating around for the biotechs. As for the drug companies, they were still mired in an old strategy: producing me-too versions of popular drugs, which they could sell at hefty margins. But in the wake of the Clinton Administration's effort to reform health care and the speeded rollout of managed care that followed, tremendous pricing pressure was placed on the big drug companies, and that strategy began to crumble.

Not surprisingly, the number of deals between biotech and drug companies is increasing dramatically, as is their average size. Recombinant Capital, a San Francisco research firm, calculates that the money pouring in from major worldwide drug-biotech deals since 1991 has risen more than sixfold, to around $ 4 billion. Says Recombinant chief Mark Edwards: "The wallets of the pharmaceuticals have opened wide for biotech."

The payoff is already clear: While only 46 biotech drugs have been approved by the Food and Drug Administration in the past 15 years, the pipeline is brimming with compounds that are close to being ready for the marketplace. UBS Securities analyst Marc Ostro expects 43 new approvals in the next two years alone. There is another payoff too. On Wall Street there is a clear line of demarcation between those companies with approved drugs and those without. For obvious reasons, once a company has a drug approved by the FDA, its market capitalization soars: Ostro calculates that a biotech company awaiting such approval has a typical market cap of $ 350 million, while companies with approved drugs have market caps that run into the billions.

One pharmaceuticals giant that has actively pursued biotech deals--it signed ten in 1994 and 1995--is Bristol-Myers Squibb. Leon Rosenberg, its R&D chief, is very much of the new breed--"more like a venture capitalist managing a portfolio than a czar overseeing an empire," in the words of one industry watcher.

Rosenberg is also a friend of Folkman's. Perhaps not surprisingly, this was about to become yet another key connection working in EntreMed's favor. In April 1995, Rosenberg attended a dinner where Folkman was being presented the

Bristol-Myers Squibb Award for his work on angiogenesis. (One month later Folkman would join Bristol's scientific advisory board.) Over cocktails, Folkman mentioned his research on the angiostatin protein to Rosenberg. Later, Rosenberg called to ask for more information, and Folkman told him the protein belonged to EntreMed. Says Rosenberg: "I then decided that this was too interesting an opportunity to just refer it to the usual channels."

Holaday missed the award dinner because he and Sam Dunlap were trying to raise more money privately in Saudi Arabia. The Mideast turned out to be a dry hole, but when Holaday returned, there was a message waiting for him from Rosenberg. EntreMed was already in deep negotiations with other drug companies, including Germany's Boehringer-Ingelheim. So Holaday told Rosenberg they would need to speak quickly. Rosenberg flew down to EntreMed's headquarters in a helicopter to hear Holaday out. At the end of the meeting, Rosenberg told Holaday he wanted to deal.

Shuttling between Bristol and Boehringer-Ingelheim, EntreMed tested each to determine which would be the best reagent with which to combine. Both offered the financial backing of a large, credible company, but Bristol was special because treating cancer is among its most prized franchises. If anti-angiogenesis was the future of cancer therapy, the company that currently rakes in about $ 900 million a year from the chemotherapy drug Taxol certainly did not want to miss out on the Next Big Thing. And for EntreMed, says Holaday, "Bristol-Myers was so good, how could we go with anyone else?"

While the negotiations stretched on, EntreMed was burning over half a million dollars a month and had only about 60 days of cash left. An $ 8 million private placement in November provided enough money to tide the company over. When the Bristol deal was finally signed, the world's third-largest pharmaceuticals company agreed to pay EntreMed a combination of research, equity, and milestone payments that could potentially total $ 76 million over five years--more than most such deals.

A WINDOW ON WALL STREET

EntreMed had never abandoned its goal of going public. It had now jumped through all the necessary hoops: It possessed two drug targets (as well as other technologies in the works), an exclusive relationship with a renowned Harvard scientist, and a partnership with the world's premier cancer-drug company. The day of EntreMed's 1995 Christmas party, Holaday received notification of the first wire transfer from Bristol. He wasted no time. The following week he called Mark Randall, another board member recruited by Dunlap, to discuss IPO strategy. A London-based director of the private Swiss bank Sarasin, Randall then phoned Allen & Co.

It is highly unusual to see Allen & Co. listed as a manager on a biotech prospectus. Best known for its media deals, Allen has only a limited biotech practice. But the firm offered a final credential EntreMed lacked. As Volpe Welty & Co. analyst David Steinberg notes: "EntreMed was not on the radar screens of Wall Street because it was not backed by venture capital." Instead, it had Allen, a bank known as a shrewd investor that holds shares in the companies that are its clients. Since it has no research analysts who provide stock coverage, Allen compromised with co-managers Dillon Read and Volpe Welty by splitting the distribution of shares evenly but remained as lead underwriter.

Always trying to follow the smart money, Wall Street reacted to the pharmaceuticals-biotech alliances that were taking place by once again opening the window for biotech IPOs. From July 1995 to June 1996, public offerings brought in a total of $ 4.4 billion, an eightfold increase over the previous period, according to Burrill & Craves, a biotech consulting firm. Cynthia Robbins-Roth, editor-in-chief of BioVenture View, in San Mateo, California, opines: "Personally, I find Wall Street to be very silly. Investment bankers will never stop stampeding, even if they know it will crash the system in another three months." That was the predicament EntreMed now faced: Would it be able to get its offering out the door while the door was still open? Watching the daily money flows, price movements, and general overheating, Randall feared the market's receptivity would soon vanish yet again.

By midsummer, deals were overflowing, including the second-largest biotech IPO in history, a genomics outfit called Genset. Biotech firms that had sidled up to corporate partners during the IPO drought now pointed to those relationships in their road shows as a sign that they were less risky investments than their brethren of five years before. EntreMed was no exception. Says Robert Miller, its banker at Allen: "The financial markets were wondering where to place their bets and were looking for large relationships to be forged that validated one company over another." EntreMed's stock came out at $ 15, the middle of its initial pricing range, just as the window seemed to slam shut in June.

TOMORROW'S GENES

As it turns out, EntreMed needn't have worried quite so much. Although the number of biotech deals dropped from 19 in June to four in September, it quickly began climbing again: There were 12 in October, for instance. EntreMed's stock dipped as low as $ 9, but since has returned to its IPO level. And industry fundamentals are much sounder than the last time the market lost its appetite for biotech, when product and company failures were the norm. But Wall Street is in the story business, and it is very important that the tales it hears continue to be believable. For EntreMed, that means it needs to keep delivering news of successful clinical trials, new products, and new partnerships.

Folkman's lab has identified another protein inhibitor, which is at least as potent as angiostatin and perhaps even more so. More significantly, the two inhibitors appear to work especially well in combination. Meanwhile, thalidomide is in human clinical trials for breast, prostate, brain, and AIDS-related cancers, and for two types of blindness. As for angiostatin itself, Bristol is hitting some roadblocks in trying to scale up production of the protein for human clinical trials. A bigger blow to EntreMed, though, is that its strongest champion within Bristol, Rosenberg, is stepping down as head of R&D in January. EntreMed has troubles in its executive suite too: It recently lost its chief scientist and does not yet have a full-time CFO.

EntreMed has another key ingredient it is about to add to this biotech brew. The technology it licensed back in June 1993 from Harvard's Nicolau--the one that enhances the oxygen-delivering capabilities of blood--is still all EntreMed's. Flush with cash after the Bristol agreement and the IPO, EntreMed could afford to hold off finding a corporate partner for Nicolau's cell-permeation device. The longer EntreMed waited, the more completely it could develop the technology, and the higher price it could command for an eventual collaboration.

Holaday hopes crucial preclinical data will be available by February, which would allow human clinical trials to begin in the first half of 1997. He is also toying with another application for the device: inserting genes into white blood cells, effectively making the cells drug-delivery agents. Finally, he is close to signing an agreement with another large pharmaceuticals or scientific-instrument company for Nicolau's device (FORTUNE's guess: Johnson & Johnson or Perkin-Elmer). Meanwhile, the search for key ingredients never ceases, as this perpetual experiment requires constant replenishment.

REPORTER ASSOCIATE Joyce E. Davis

GRAPHIC: COLOR CHART: FORTUNE CHART/SOURCE: WWW.RECAP.COM, THE BIOTECH INDUSTRY'S WILD RIDE, AFTER PEAKING at $ 3.7 billion, biotech offerings plummeted to $ 1 billion in 1994. Now they're topping $ 4.5 billion. [Chart not available--line graph showing value of biotech public offerings from 1981 through 1996]; COLOR PHOTO: PHOTOGRAPHS BY CHRIS USHER, ENTREMED CEO John Holaday had the right mix of science and savvy to bring his company from speculative beginnings to a successful public offering.; COLOR ILLUSTRATION: ILLUSTRATION BY BRISTOL-MYERS SQUIBB/DR., STANLEY KRYSTEK, LI'L STRANGLER: HOW TO CHOKE A TUMOR, Drugs like angiostatin (above), to which EntreMed has the rights, may well be one of the best weapons yet in the battle against cancer. It inhibits angiogenesis, which is the birth of new blood vessels. In cancer, angiogenesis causes thousands of blood vessels to infiltrate the tumor and act like tiny feeding tubes (left). If angiogenesis can be stopped, the tumor will starve. [Diagram showing angiostatin molecule and process of angiogenesis]; COLOR PHOTO: PHOTOGRAPHS BY CHRIS USHER, IN BACKING Holaday's dream, EntreMed investors (left to right) Wendell Starke, Steve Gorlin, and Sam Dunlap will reap a bounty. [Wendell Starke, Steve Gorlin, and Sam Dunlap standing in cornfield]

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