

Bloom off Folkman's Rose *Tumor-fighting drugs suffer setbacks*

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Four years ago, two drugs discovered at Children's Hospital were electrifying cancer researchers and patients worldwide. In mice, the drugs appeared to melt tumors away and the National Cancer Institute made testing them in patients a top priority. Nobel laureate, Dr. James D. Watson, even predicted that the new medicines, called angiogenesis inhibitors, would cure cancer.

But the entire class of drugs built on Dr. Judah Folkman's work at Children's is proving much harder to perfect than expected. In recent months, two of the leading drugs flunked final tests in patients, showing no real benefit. The company developing a third contender decided to pull back from seeking government approval this year because its tests were not rigorous enough. And the two drugs from Folkman's lab that generated so much excitement, endostatin and angiostatin, have been little help to patients in early tests and remain years away from the market.

"This is not going to be a panacea," said Dr. George Yancopoulos, chief scientific officer of Regeron Pharmaceuticals, a company based in Tarrytown, NY, that is working on its own angiogenesis inhibitor. "It's not going to be such a simple thing that it will work for all comers."

Unlike chemotherapy and radiation, which attacks cancerous tumors directly, angiogenesis inhibitors block the growth of blood vessels that feed the tumors. Scientists had hoped the drugs would work in most cancers, adding years to patients' lives, if not curing their illnesses. But they are coming to believe that these drugs must be targeted to select diseases and patients, and combined with typical cancer treatments, even to stabilize the cancers.

Despite the setbacks, which are common in drug development, the first angiogenesis inhibitors could be approved by the Food and Drug Administration as early as 2004 for use in a small group of cancer patients. Folkman had suggested, however, it will be another 8 to 10 years before the class of drugs is widely available for patients.

"The principle is good," Folkman said, "but applying it is really hard."

Folkman began work on the concept behind the drugs more than 30 years ago. Since then, he and his colleagues have identified many substances that slow cancer growth in mice. At least one drug from his lab, TNP-470, was tested in patients in the early 1990's, but dropped when it caused seizures. Angiostatin and endostatin, discovered in the mid-1990s, seemed much more promising since they were more potent in mice and caused no side effects.

But Folkman and scientists around the world were working on angiogenesis inhibitors in relative obscurity until The New York Times published a front-page article in 1998, including Watson's prediction that "Judah is going to cure cancer in two years." Although Folkman was more cautious, expectations skyrocketed and patients clamored for the drugs.

So far, more than 10,000 patients have helped test dozens of angiogenesis inhibitors, according to the Cambridge-based Angiogenesis Foundation. For a few patients, the drugs appear to be lifesavers, and for hundreds, they have slowed the cancer's growth. But the results have not yet been consistent enough for any company to apply for FDA approval.

Six drugs that made it to final human testing have flopped. Most recently, Pharmacia Corp. of Peapack, NJ, pulled the plug in February on SU5416 when it didn't improve survival for patients with late-stage colo-rectal cancer. Many other inhibitors have not even made it that far.

The drug Thalidomide - the 1960s morning-sickness pill for pregnant women blamed for causing birth defects - has shown more promise as an angiogenesis inhibitor and its maker was poised earlier this year to become the first to seek FDA approval. But in March, Celgene officials announced they were delaying their application for two years because controlled studies of the

drug had not been rigorous enough, according to David Stirling, the company's chief scientific officer.

The most recent disappointment occurred two weeks ago when Genentech announced that its angiogenesis inhibitor, Avastin, didn't slow late-stage breast cancer or increase survival in its final round of testing. Scientists were particularly troubled because the drug flopped when used with chemotherapy.

"The sparkle has been taken off the field," said Dr. Douglas Figg, an angiogenesis specialist at the National Cancer Institute. Figg said he expects results to be "sporadic until we have a better understanding of the biology of angiogenesis."

Meanwhile, early tests of endostatin and angiostatin in cancer patients have dampened enthusiasm. In phase 1 testing, which focuses on safety, the drugs caused no side effects but only modestly shrank tumors or stabilized cancers in a few patients. The second phase, now under way, is two to three years behind many other inhibitors. Factors in the delay include a later start and the difficulty and expense of producing enough of the complex drugs to allow testing.

Some also say testing is hampered by lack of scientific understanding about how endostatin and angiostatin work. Most other inhibitors were bioengineered to target specific body chemicals that spur the growth of blood vessels, but angiostatin and endostatin are copies of complex natural proteins isolated from the body.

Folkman, however, said the way they work is becoming clearer every day. "What had held it up," he said, "is lack of knowing how to give it in humans."

In fact, scientists have been puzzling over the disappointing results for several drugs and believe they may have to do a better job of targeting the right cancers. In breast cancer, for example, some say Avastin failed because the cancer grew blood vessels using other growth factors after Avastin disabled just one. Alternately, they may need to target cancers earlier, when they are dependent on one growth factor for blood supplies. In addition, scientists suggest the drugs may work better in combination with each other or with low doses of chemotherapy given over long periods.

Despite the setbacks, three drugs remain in final stages of testing and could be on the market by 2004, if the tests go well.

Although Avastin flopped in breast cancer, the drug slowed renal cell cancer and appeared useful against colo-rectal cancers in early tests.

Likewise, Cellegene officials and many doctors remain bullish about Thalidomide, which has induced remission of the bone marrow cancer, multiple myeloma, in about a third of patients and halted the disease in another third. The drug, whose anti-angiogenic properties were discovered in Folkman's lab, is already approved for treating leprosy and is widely used "off-label" to treat myeloma.

And Neovastat, made by Aeterna Labs, might beat them both. The company expects results of final tests in renal cell cancer early next year and intends to apply directly for FDA approval. Earlier tests showed the drug doubled the number of months severely ill patients survived.

Behind these leaders, 63 other inhibitors are being tested in patients, with a new one beginning testing every two months, according to Dr. William Li, president of the Angiogenesis Foundation. Common drugs such as the painkiller Celebrex and cancer drug interferon-alfa are also being tested for anti-angiogenesis benefits. Folkman and other scientists are developing new drugs they think may be even more effective.

"We're still hoping to use this therapeutic approach to manage and control the disease for long periods of time," said Dr. Robert Kerbel, an angiogenesis specialist at the University of Toronto. "But we have a lot of work to do."