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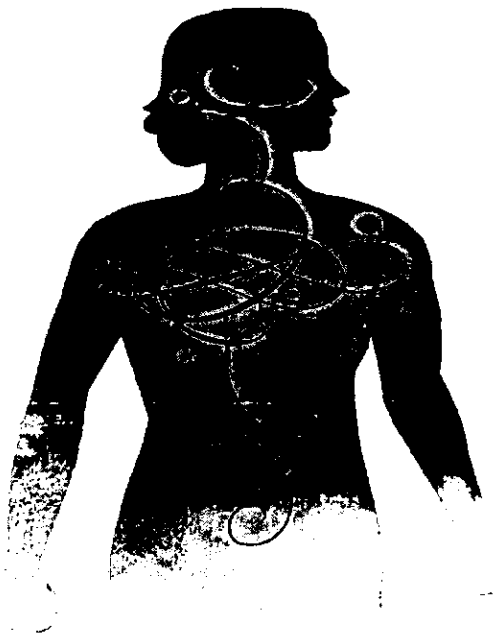
KILLSWITCH

IN ADDITION TO BLOCKING AN ENZYME RESPONSIBLE FOR TUMOR GROWTH AND MATASTASIS THE DRUG VEGLIN APPEARS TO SLOW THE GROWTH OF THE CANCER CELLS THEMSELVES.

by Lori Oliwenstien



About two years ago, renowned scientist James Watson—of DNA/double-helix fame—declared in the New York Times that a new class of drugs called antiangiogenesis agents was going to cure cancer. And although some of the results published since then have been disappointing, the U.S. Food and Drug Administration did recently approve the first such drug—Avastin—for the treatment of colorectal cancer.

Antiangiogenesis drugs have a very specific target: They stem the growth of new blood vessels in and around tumors. Cancer cells—like all cells—need a blood supply to get their much-needed fix of oxygen and nutrients. Without this supply, they will eventually die.

To get oxygen, cells give off a protein signal that prompts the creation of the necessary new blood vessels. One such signal is called vascular endothelial growth factor, or VEGF. So scientists reasoned that blocking the production of VEGF in tumor cells would block the growth of blood vessels and starve the cells of oxygen and nutrients, killing them.

This logic is what prompted a team of scientists from the Keck School of Medicine of USC and the USC/Norris Comprehensive Cancer Center to develop a drug to do just that. The drug is Veglin. And as the scientists working with it have shown, it is an antiangiogenesis drug, just like Avastin—except Veglin has a little extra kick.

As it turns out, in addition to its antiangiogenesis properties, Veglin appears to slow the growth of the tumor cells themselves. That gives Veglin two different ways to attack cancer—and, according to Keck School researchers, it seems to do so quite well.

In an early phase trial of the drug, Alexandra M. Levine, M.D., Distinguished Professor of

Medicine, chief of hematology at the Keck School of Medicine, the Ronald H. Bloom Family Chair in Lymphoma, and medical director of the USC/Norris Cancer Hospital, and her colleagues have shown that Veglin is safe for use in patients with a wide variety of cancers—and that it also seems to be effective in combating some cancers.

Veglin was developed in the laboratory of USC/Norris researcher Parkash S. Gill, M.D., Keck School professor of medicine and pathology. Los Angeles-based VasGene Therapeutics Inc., which was co-founded by Gill, is sponsoring further investigation and development of Veglin.

Veglin is a bit of DNA that binds directly to the gene that produces VEGF. By blocking the production of VEGF by the tumor cells, Veglin is potentially capable of blocking the growth and metastasis of tumors, while also killing the cancer cells themselves.

"VEGF serves as an autocrine growth factor for certain types of cancers," Levine says. "The analogy would be if a car were able to make its own gasoline, it would drive forever. The gasoline for the cancer cell is VEGF; it is made by the cancer cell, and comes back to work on the cancer cell that made it, causing the cancer cell to divide and proliferate."

It was that observation that spawned the Phase I trial, led by Levine, into which 37 patients have so far been entered. "These patients have had various types of cancers, all of which have failed all available treatment for their disease," Levine says. Among the cancers represented in the trial are lymphoma, melanoma and various sarcomas, as well as renal, lung and colon cancers.

Patients in the trial receive Veglin intravenously over two hours, five days a week. They then get a week off. This cycle continues for four months.

Overall, the trial consists of several dose levels, which escalate over time. "Three patients are entered at each dose level," Levine explains. "If no significant side effects are seen at that level, then the next three patients are treated at the next highest dose level." Currently, she says, they are at dose level 11. Levine reports, "Veglin appears quite easy for the patients to take, and has not been associated with decrease in blood counts, or any nausea or vomiting or hair loss, or other significant side effects."

Even better, Levine says, has been the noticeable response to the drug shown by a number of patients.

"Remarkably, we have seen some dramatic responses in some patients, despite the fact that we are using very small doses of the drug," she says. "One patient with AIDS-related Kaposi's sarcoma had a complete remission of his cancer, which lasted for four months, despite the fact that he only received five days of the drug. The original study design allowed us to treat only one time, for five days alone. That was amended when we saw real activity, and wanted to see if we could achieve more responses with more treatment than simply five days."

In addition, Levine says, a second Kaposi's sarcoma patient saw his cancer recede, though not as dramatically as the first patient. Levine and her colleagues also have seen major responses in patients with cutaneous T-cell lymphoma and renal cell cancer.

"It is unusual for a phase I agent, for which we don't yet even know the correct dose or schedule, to be associated with these responses in patients with such far-advanced disease. The results are quite impressive, and we are very pleased so far," she says.

These clinical results are backed up by laboratory measures as well, notes Levine. In 56 percent of the patients, for instance, blood levels of VEGF have fallen significantly, showing that the enzyme is indeed being blocked.

"This trial is already showing that shutting down the production of VEGF at the level of the DNA is a valid principle for future anti-cancer therapies," Levine says.

She adds, "We have shown that decreasing VEGF levels may be associated with the killing of cancer cells in various types of cancer, and we have shown that this approach appears to be safe. We have also shown that it is possible to develop an idea at the university, and to take that idea forward in the laboratory in order to make a drug that can then be tested in the patients referred to us at USC/Norris—patients who have been sent to us because they had no other treatment options available to them."

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