Taking Down Tumors: Vascular Disrupting Agents Entering Clinical Trials

A tumor’s support system—its existing blood vessels, or vasculature—nourishes the tumor by supplying oxygen and nutrients, allowing it to grow, spread, and often turn lethal. Antiangiogenesis approaches attempt to prevent the formation of these blood vessels, but researchers are also focused on targeting the established vasculature in hopes of destroying tumors by obliterating the blood vessel underpinnings that support them.

Vascular disrupting agents (VDAs) work by causing the endothelial cells, cells that line the inside of blood vessels, to change shape and collapse. This action shuts off blood flow to tumors, leading to cell death. “You don’t, by any means, have to affect all the endothelial cells in a vessel,” explained Dietmar W. Siemann, Ph.D., a radiation oncologist at the University of Florida in Gainesville. “All you have to do is cause a collapse by damaging some part of the vessel. Everything downstream will not get its nutritional supply or clear waste products, so the tumor cells will die.”

Researchers are pursuing two types of VDAs—small molecule and ligand directed. The intended result of both classes of VDAs is the same, but their approaches are different. Small-molecule VDAs damage the structure of endothelial cells by interfering with the cells’ cellular scaffolding, or tubulin. Tubulin is a protein composed of microtubules, a minute filament that helps cells maintain their shape. Some small-molecule VDAs cause the release of tumor necrosis factor, which leads to the collapse of blood vessels. Small-molecule VDAs have made the greatest progress in the clinic, Siemann said.

Ligand-directed VDAs use antibodies, peptides, or growth factors to target toxins or procoagulants to the tumor endothelium. The idea behind this approach is that endothelial cells in tumor blood vessels express receptors on their surfaces that are unique to the tumor vessels. Researchers are trying to identify these receptors to target them with drugs, monoclonal antibodies, or gene therapy, which would cause their collapse.

The overall goal of VDAs is specificity, something that is hard to come by in many of today’s cancer treatments. Rather than obliterate cancer cells and surrounding nonmalignant cells, VDAs would go straight to the endothelia of tumor blood vessels and destroy them, while leaving surrounding tissue untouched.

Several companies are conducting preclinical studies and early phase trials with VDAs. So far, research has shown that these agents alone do not have a substantial effect on cancer cells, but they deliver a bigger punch when combined with other therapies such as chemotherapy and radiation.

“Vascular disrupting agents kill the tumor from the inside out. What are left are the tumor cells on the outside,” said David J. Chaplin, Ph.D., chief scientific officer and head of research and development at Oxigene Inc., a pharmaceutical company in Waltham, Mass. “These tumor cells are living off normal blood vessels and are rapidly proliferating. This makes them sensitive to radiotherapy and to chemotherapy because these modalities are designed to kill rapidly proliferating, well-oxygenated cells.”

Oxigene is testing the small-molecule VDA combretastatin A-4 phosphate...
(CA4P), which triggers a change in the shape of the endothelial cells lining tumor blood vessels, blocking the flow of blood to a tumor and depriving it of oxygen and nutrients essential to its survival. In a phase Ib study that combined CA4P with the chemotherapy drugs paclitaxel or carboplatin, six of nine evaluable ovarian cancer patients had 50% tumor shrinkage. In early results—presented at the 2005 American Society of Clinical Oncology annual meeting—from another phase Ib study that combined CA4P with radiation therapy in 20 patients with non–small-cell lung cancer and or prostate cancer, the combination was well tolerated and showed antitumor activity. Oxigene plans to begin randomized phase II/III trials in the next year that will test CA4P with radiotherapy in patients with non–small-cell lung cancer or prostate cancer and a phase II trial of CA4P in ovarian cancer with two different chemotherapy drugs given at the same time.

London-based pharmaceutical company Antisoma has recently started a phase II trial of its small-molecule vascular disrupting agent AS1404 in patients with recurrent ovarian cancer. The randomized, controlled trial will include 70 patients from Europe, Australia, and New Zealand. Half the patients are receiving standard chemotherapy treatment and the other half are receiving the same treatment plus AS1404. Response rates, time to tumor progression, and survival will be assessed. Similar trials in lung and prostate cancer patients are ongoing. Data should be available from the lung cancer study later this year, according to Antisoma’s CEO Glyn Edwards.

**Other Targets for Therapy**

Beyond combinations with chemotherapy and radiation, VDAs may also work well when partnered with antiangiogenesis therapies. Siemann showed in mouse models that when a small-molecule VDA was given along with an antiangiogenesis drug, tumor growth was delayed for 55 days in mice with Kaposi sarcoma xenografts and for 86 days in mice with human renal cell carcinoma xenografts. When only the VDA was administered, tumor growth was delayed by just 23 days in the renal cell model and 26 days in the Kaposi model.

“Each therapy on its own had an effect on tumor growth, but the combination had far greater effects,” Siemann said. “There was prolonged animal survival and prolonged tumor responses.” The genes responsible for the development of the tumor vasculature may also be a potential target for therapy. “It has become apparent that there are genes expressed on the endothelium of tumors that are not expressed on endothelium in normal tissues,” said Roy Bicknell, Ph.D., lead researcher of the Molecular Angiogenesis Laboratory, Cancer Research U.K., at the Weatherall Institute of Molecular Medicine at the University of Oxford in England. “What we would like to do is use them as targets at which to aim antibodies or antibodies conjugated with radioisotopes or other toxins to destroy the tumor endothelium.”

At least one earlier study has shown that this approach could work in an animal model, though it has yet to be replicated in humans. However, researchers have identified four or five gene targets that show promise.

“What has revolutionized this field is the sequence data now available on the human genome. We know roughly how many genes there are, and we can now apply various screening technologies to identify genes that are upregulated in the tumor endothelium,” Bicknell said. “We need to keep up the search for more gene targets, because at this point it is not clear which the best ones are.”

**More To Learn**

Scientists look at the recent U.S. Food and Drug Administration approval and clinical use of the antiangiogenesis drug bevacizumab (Avastin) in patients with colorectal cancer as a signal that targeting tumor vasculature—whether the focus is on the prevention of new blood vessel formation or the destruction of existing blood vessels—is a potentially powerful approach to cancer therapy. Yet scientists have a lot more to learn about the human vasculature and how to best exploit it for cancer therapies. Wadih Arap, M.D., Ph.D., and Renata Pasqualini, Ph.D., researchers at the University of Texas M. D. Anderson Cancer Center in Houston, have come closer to understanding the human vasculature by creating its molecular map. Their research shows that blood vessel cells have different molecular signatures, or “ZIP codes,” depending on the tissue of the body that the cells are associated with. Blood vessels in the lungs are different from blood vessels in the kidneys, and blood vessels of tumors are different from blood vessels in nonmalignant cells. Arap and Pasqualini hope to develop drugs that would target and destroy the blood vessels at specific ZIP codes, those of tumors located at different organs and tissues of the body.

“The ability to hone in on the differences—this incredible vascular diversity—is where the beauty is,” Arap said. Other questions about vascular targeting remain. For example, if the blood vessels that support tumor cells are knocked out, will the tumor cells find another way to survive? Also, the drugs that are in use now may be supplanted by newer drugs that have lower toxicity profiles or may not have to be given in as high doses. “When we first started chemotherapy, some of the drugs we used then are no longer in use now because people have come up with much better agents,” Siemann said. “We are already seeing this in the vasculature targeting area. There are compounds coming along in the preclinical level that may have more promise.”

—Leslie Harris O’Hanlon