anyway, you can do it up front and then select the cohort that should go to surgery. The savings are potentially huge.”

The search for more effective treatment for pancreatic cancer has also led to a vaccine trial at Johns Hopkins. Later this year, the first of 15 patients will receive a whole-cell vaccine made from pancreatic cancer cells taken from a number of different patients.

“Originally, we started with the idea of a designer vaccine, developed from the concept that each patient has a unique set of proteins against which the immune system can react,” said Elizabeth Jaffee, M.D., an assistant professor of oncology and immunology. “However, we and others have found that there are probably a lot of shared antigens that the immune system recognizes among cancer patients.”

Each patient will receive the vaccine prior to resection, followed by a booster one month after adjuvant chemoradiation therapy. In a previous trial involving patients with renal-cell carcinoma, a similar vaccine led to a delayed hypersensitivity reaction against tumor cells but not normal cells.

Jaffee said patients enrolled in the phase I trial will probably be “average stages I-III pancreatic cancer patients, who have a long-term survival prognosis of about 20%.”

Considerable interest centers on agents that have the potential to manipulate ras oncogene expression, including one that is rumored to be ready for phase I testing before the end of the year. A spokesperson for the manufacturer declined to provide specifics about the ras modulator, but did say that the agent’s clinical trial readiness probably has been overstated by investigators familiar with the agent’s development.

— Charles Bankhead

Angiogenesis Research Enjoys Growth Spurt in the 1990s

Karen Olson, M.D., remembers attending cancer research meetings around 1984 and 1985 and finding few if any presentations on angiogenesis research. “At that time,” said the Harvard Medical School instructor in pathology, “no one was doing it.”

Now, it seems everyone is.

At the recent annual meeting of the American Association for Cancer Research, participants, including Olson, presented more than 40 papers. The last day was capped with a seminar led by angiogenesis pioneer Judah Folkman, M.D., of Children’s Hospital in Boston.

In the quarter-century since Folkman proposed that tumor growth is angiogenesis-dependent, researchers around the world have dissected the process and developed more than 25 anti-angiogenesis drugs that are in various stages of testing — some of them as far as phase II clinical trials. Certainty about their use in treatment is such that in conversation and oral presentations many researchers are dropping the usual cautionary words — “may,” “if,” and “should” — used in describing experimental compounds still in development.

“At some point, we’re going to be treating with them,” said Olson of the new drug candidates. A few members of the group are familiar agents already in use. Paclitaxel, approved for breast and ovarian tumor therapy, is under investigation for its anti-angiogenic properties at centers including the University of Milan Medical School and G. Mario Negri Institute in Italy. Suramin and cisplatin, agents used against prostate cancer, are under scrutiny for anti-angiogenic properties.

A group from the Veterans Affairs Medical Center at the University of Kentucky College of Medicine, Lexington, and University of Bonn in Germany, has found 15 suramin analogs that have exhibited anti-angiogenic activity equal to or greater than the original compound.

Olson and co-researcher James W. Fett, Ph.D., have found that the combination of cisplatin and suramin with an anti-angiogenic monoclonal antibody is strikingly more effective in tests with mice than either chemotherapeutic agent by itself. Said Olson, “Antiangiogenic agents may increase the amount of chemotherapeutic agents taken up by the tumor.”

Compounds Under Study

Glycomed, Inc., Alameda, Calif., recently absorbed by Ligand Pharmaceuticals, is seeking a partner to continue clinical testing of its Galardin (GM6001). The compound is in the midst of phase III trials in Japan with partner Sankyo Co. Ltd., said Patricia Williams, Ph.D., Glycomed’s vice president of preclinical development.

Remaining compounds under study fall into several broad categories, said James Pluda, M.D., senior investigator in the Investigational Drug Branch of
the National Cancer Institute. One of these categories is endothelial response inhibitors including such agents as interferon alpha, TNF-470, and vascular endothelial growth factor inhibitors.

Another category of agents that prompt the breakdown of the cellular matrix includes Vitaxin (human LM-609 antibody), produced by Ixsys Co., San Diego, and Metastas (Col-3), produced by CollaGenex, Newtown, Pa., both in preclinical studies, and British Biotech’s Marimastat (BB2516) in phase I and II trials. A third group targets blood vessels directly. The NIH’s CM-101, for example, which is derived from exotoxin of Group A Streptococcus antigen, binds to new blood vessels and induces an intense host inflammatory response.

Among the growth factor inhibitors is a drug that may seem like a dark horse. Thalidomide, developed in the 1950s as a sedative, gave birth to a generation of “thalidomide babies” with stunted, poorly developed limbs, the result of their mothers having taken the drug during pregnancy.

Thalidomide inhibits angiogenesis induced by basic fibroblast growth factor, but the mechanism by which it does so is unknown, according to researchers reporting in the Proceedings of the National Academy of Sciences in 1994. In the fetus, the drug is believed to prevent new blood vessel growth in the developing fetal limb bud.

Edward Gubish, Ph.D., director of regulatory affairs for EntreMed of Rockville, Md., which is developing the drug as a cancer treatment, noted, however, that “there are more potent teratogens being prescribed for women of child-bearing age, provided they use contraceptives. Accutane comes to mind.”

Four small clinical studies that will investigate the effects of thalidomide on hormone-refractory prostate cancer, metastatic breast cancer, Kaposi’s sarcoma, and glioma have been enrolling patients since the first of the year, Gubish said.

The question of side effects becomes even more important in the study of anti-angiogenic agents under consideration for use in long-term treatment. The idea of “dormancy therapy,” in which a patient takes a drug over many years — preferably orally — to keep a tiny clump of tumor cells quiescent, is already circulating in the medical literature.

Angiostatic agents in general interfere with menstruation, wound healing, and pregnancy, said Pluda, but neither

**Blocking Angiogenesis May Help Keep Tumors Dormant**

Why some tumors lie quiet for years, then suddenly resurface and explode as metastatic disease, has long puzzled researchers. Why did the cancer come back? And what were the cancer cells doing during those “dormant” years?

For Judah Folkman, M.D., the answer lies in angiogenesis — the process by which tumors establish the vascular tentacles that nourish them and provide their deadly access to other sites in the body. Folkman, a keynote speaker at last month’s American Society of Clinical Oncology meeting in Philadelphia, believes that cancer is regulated by a two-compartment system in which tumors cells and vascular endothelial cells stimulate each other as carcinogenesis takes hold. Treating both compartments instead of just the tumor cells, he told the capacity crowd, offers the best hope for therapeutic advances in the future.

“There is great synergy between angiogenic therapy and chemotherapy,” Folkman said, adding that such a strategy is more effective than either therapy alone and in mice brings high levels of “permanent cures.”

In an upbeat hour-long speech, Folkman noted that today there are at least 26 pharmaceutical companies making angiogenesis inhibitors, while animal models now exist for each of the four most common ways patients develop metastasis. These include not only the development of metastatic cancer after a long dormancy period, but also metastasis from an unknown primary tumor, metastasis at the time of initial diagnosis, and the rapid recurrence of disease after removal of a primary tumor.

By studying clinical patterns, Folkman said, his group and others have shown that tumors release angiogenic stimulators as well as angiogenic inhibitors that can hold a primary tumor in check. At least four tumor inhibitors, including angiostatin, have been identified. “Can a primary tumor then be treated with angiostatin?” Folkman asked. “In a mouse model, the answer is yes.”

Meanwhile, researchers continue to identify growth factors, such as fibroblast growth factor, vascular endothelial growth factor, and interleukin 8, which are produced by the rapid turnover of endothelial cells during angiogenesis, and further stimulate tumor growth. The presence of these peptides in the blood and urine often signals active disease.

“This is a work in progress,” Folkman stressed. “[But] now we have a unifying hypothesis.”

— Susan Jenks