Judah Folkman Leaves Expanding Legacy

By Vicki Brower

Known as the father of angiogenesis research, Judah Folkman, M.D., died suddenly on January 14, 2008, while traveling to a scientific meeting.

Folkman was a professor of cell biology and pediatric surgery at Harvard University and chair of vascular biology at Boston’s Children Hospital. He pioneered the field of angiogenesis research, taking it from hypothesis to clinic in the space of three decades. Though 74, he was nowhere near slowing down. His work on the role of blood vessel growth in cancer was advancing rapidly, along with the field that he inspired.

Colleagues and students called Folkman “an electrifying lecturer,” “extremely generous,” “a mensch,” and the reason they went into the field. Friends and associates remember his influence on cancer research and treatment, which continues to further his vision of making cancer a chronic, treatable disease.

“Folkman opened up a new area of cancer biology, broadening the focus beyond the tumor cell to the microenvironment, and spurred on a new generation of cancer researchers,” said David Lyden, M.D., Ph.D., of Weill Cornell Medical College and Memorial Sloan-Kettering Cancer Center in New York. “There are now over 1,000 labs worldwide focusing on angiogenesis research, and 50 new inhibitors identified, many of which are in clinical trials.”

Two angiogenesis inhibitors, bevacizumab (Avastin) and ranibizumab (Lucentis), were the first to be approved by the U.S. Food and Drug Administration and are now playing a major role in treatment. “In my student days in the mid-1990s, no one talked about using angiogenesis inhibitors to treat cancer; now, it’s a given,” said Roy Herbst, M.D., Ph.D., professor of cancer biology at the University of Texas M. D. Anderson Cancer Center in Houston.

He Asked Why

Folkman first presented his angiogenesis hypothesis—that tumors need new blood vessels to grow and metastasize—in a landmark New England Journal of Medicine article in 1971. His notion that endothelial cells, which form new blood vessels, were a more genetically stable and, therefore, better target than cancer cells represented a monumental shift of focus in cancer research. It drew much attention and criticism.

“Judah persisted in the face of great opposition, and 30 years later, it is well accepted that cancer is not just a disease of cancer cells but also of stroma and microenvironment,” said Larry Norton, M.D., medical director and head of breast disease management at Memorial Sloan-Kettering Cancer Center.

Although others may have observed that tumors need blood vessels, Folkman’s real genius is that he asked why, noted John Heymach, M.D., Ph.D., of M. D. Anderson. “It took someone from outside the field to punctuate the equilibrium.”

In the decades that followed, the field evolved steadily. “In the 1970s, Folkman laid out the notion that angiogenesis played an enabling role in cancer,” said Bruce Zetter, Ph.D., chief scientific officer at Children’s Hospital in Boston. “In the 1980s, he and others gave the field a molecular framework, observing that there were factors made by tumors that stimulated angiogenesis and could be studied; VEGF [vascular endothelial growth factor] and bFGF [basic fibroblast growth factor] were discovered then.”

In the 1990s, Folkman and others discovered several endogenous inhibitors. These findings led to experiments to understand the steps that some dormant cancers take to progress to a malignant phenotype, said Raghu Kalluri, Ph.D., of Boston’s Beth Israel Deaconess Medical Center, who discovered the endogenous inhibitors canstatin, tumstatin, and neostatin. As understanding of these mechanisms grew, Folkman and others tested his hypothesis that angiogenesis inhibitors could push cancer into dormancy, making it into a chronic, manageable disease.

Since 2000, angiogenesis inhibitors have entered an era of clinical trials, being tested in more than 30 phase II trials and more than 20 phase III studies. The ultimate vindication of Folkman’s ideas, Zetter said, is that every major pharmaceutical company now has an angiogenesis research program.

Working Out the Details

Once a fledgling field, angiogenesis research is now in its adolescence, said M. D. Anderson’s Heymach. With the 2004 approval of bevacizumab for the treatment of metastatic colorectal cancer, the FDA recognized angiogenesis therapy as “the fourth treatment” modality. “We are now just working out the details,” Heymach said. Many newer drugs, for instance, target multiple growth factors or signaling molecules that trigger angiogenesis and may prove to be more effective than those that hit only one, such as bevacizumab.

Many researchers are focusing on antiangiogenesis agents in combination
with chemotherapy. Research by Harvard's Rakesh Jain, Ph.D., indicates that, rather than killing a tumor's new blood vessels, VEGF inhibition normalizes these leaky blood vessels, actually restoring blood flow and enabling chemotherapy to reach areas deep in tumors previously untouched by drugs. Jain maintains that inhibitors should therefore be used with chemotherapy.

In support of this idea, one recent phase II study published in the New England Journal of Medicine last December demonstrated that bevacizumab and paclitaxel increased time to progression in advanced breast cancer patients compared with chemotherapy alone (11.8 months versus 5.9 months). However, the overall survival rates were not statistically significantly increased. Because VEGF is believed to be most active in early cancer, the investigators, led by Kathy Miller, M.D., of the Indiana University Simon Cancer Center in Indianapolis, expect the combination to work even better as adjuvant treatment. A new 5,000-patient trial will determine whether the same combination will raise the survival rate of early-stage breast cancer.

Reducing Resistance, Toxicity

Other approaches in angiogenic research abound. In the early 1990s, Robert Kerbel, Ph.D., of the University of Toronto, inspired by Folkman, theorized that conventional chemotherapy might also suppress angiogenesis, and he began designing low-dose, continuous—or metronomic—chemotherapy trials. His results indicate that this strategy may reduce drug resistance and lower toxicity.

Folkman also hypothesized that some existing drugs, including COX-2 inhibitors and thalidomide, had antiangiogenic activity. These and other drugs are being tested with antiangiogenic agents and chemotherapy, so far with mixed results.

Research with more specific inhibitors is also advancing. A new class of drugs targeting placental growth factor (PIGF), a homologue of VEGF, was recently described by Peter Carmeliet, Ph.D., of Belgium's University of Leuven. In preclinical models, anti-PIGF antibodies inhibited tumor growth and metastatic progression by attacking tumor blood vessel development without affecting healthy tissues; unlike VEGF, PIGF does not affect normal angiogenesis. Earlier this year, Leuven-based ThromboGenics began a phase I trial with its anti-PIGF drug, TB-403.

At Genentech in South San Francisco, Calif., Napoleone Ferrara, M.D., the developer of bevacizumab, is studying other mechanisms of tumor angiogenesis and new tissue-selective endothelial cell mitogens. He recently identified endocrine gland–specific VEGF, or EG-VEGF.

Biomarkers of angiogenesis are another burgeoning area of research. Folkman was working on biomarkers in platelets when he died (see sidebar). Studies using circulating endothelial cells as biomarkers are also showing promise. Preclinical research recently published in Science by Vivek Mittal, Ph.D., and colleagues at the Cold Spring Harbor Laboratory in New York showed that endothelial progenitor cells control the angiogenic switch to metastasis in a mouse model of lung cancer. This study built on research by Weill Cornell's Shahin Rafii, M.D., and Lyden, who demonstrated that some of these cells derived from bone marrow are recruited by tumors to the premetastatic niche—the site of metastasis to which cells are recruited from bone marrow.

The list of recent developments in angiogenesis research—new laboratory discoveries, new mechanisms, new drugs, and new theories—is long. Thirty-seven years after his first article on angiogenesis, Judah Folkman's imprint on cancer treatment and research is ubiquitous and indelible.

“He opened the door wide to the impact of angiogenesis in cancer formation and treatment. And while he was recognized during his lifetime, I predict that he will receive even greater acknowledgment as we move forward.”

—Vicki Brower

Folkman’s Most Recent Studies Focused on Platelets

Until his death, Folkman worked with a sense of urgency, said Harvard's Giannoula Klement, M.D., a coauthor with Folkman of two new studies published posthumously on February 1 in Blood.

The first study illustrates that endogenous angiogenic and antiangiogenic proteins are sequestered into two sets of platelet alpha granules. Until now, hematologists believed that there was only one set. Measuring angiogenic growth factors in the blood has not shown consistency as a biomarker because they are found in high concentration only in platelets, not blood.

The second study identifies one biomarker in platelets, platelet factor 4, which is associated with early tumor growth across many mouse models of cancer.

Forthcoming research will focus on other markers specific to particular cancers, said Klement, who will be taking over Folkman’s platelet research. “He has left a lot of other projects behind him, and a worldwide recruitment is going on looking for a person to lead the vascular biology division at Children’s Hospital,” she said. “As you can imagine, there is only a handful of people who could fill those large shoes.”

© Oxford University Press 2008. DOI: 10.1093/jnci/djn072