

# Dr. Folkman's progeny

RESEARCH IN A VARIETY OF INITIATIVES, TOUCHING MANY FIELDS, IS SHOWING EXTRAORDINARY PROMISE

By Robert Cooke

For a look into the future of angiogenesis research, read the handwriting on the wall in Judah Folkman's small conference room. Listed in his scrawl, now protected with Plexiglas (and pictured above), are problems not yet solved in 2007 and things he hoped might get done in 2008.

Unfortunately, the renowned surgeon and cancer researcher's personal role in solving those problems came to a sudden end in January, when he died en route to speak at a scientific conference. But part of Folkman's genius was to mentor and inspire generations of researchers who are carrying his pioneering work forward—many of them in the Vascular Biology Program he founded at Children's Hospital Boston.

"The program is strong and vital because Dr. Folkman created it that way," says Marsha Moses, PhD, a long-time member of Folkman's team who is interim co-director of the program with Donald Ingber, MD, PhD. "And we plan to solidify that."

There's great hope that the questions on the wall, and many more not yet thought of, will someday be answered. Below are

some of the most promising projects—and the people Folkman inspired to pursue them.

## TREATING THE BIOMARKER

One of Folkman's biggest dreams was to treat cancer like a chronic disease, using agents that block blood-vessel growth, or angiogenesis, to "starve" the cancer and keep it dormant. Moses and others have begun to realize that vision, discovering "biomarkers" that give early warning that a tumor is starting to expand or recur. Guided by biomarkers alone, doctors could begin immediate treatment with angiogenesis inhibitors.

Giannoula Klement, MD, a pediatric hematologist/oncologist from Dana-Farber Cancer Institute who does research in Folkman's lab, has discovered that blood platelets harbor some of the best biomarkers available.

"Platelets are the first responders to injury, inflammation or tumor growth," Klement says. "They continuously sequester, store and transport proteins that regulate blood vessel growth, and can deliver these regulators to an injury or tumor site in very high concentrations."

In mice seeded with human tumors, Klement has shown that angiogenesis regulators are indeed highly concentrated in platelets, and that elevated levels can be detected before they show up in plasma, and before the cancer becomes clinically evident. "Almost as soon as an angiogenic tumor is present, the platelet angiogenesis protein profile changes to reflect what the tumors may be secreting," she says.

Klement believes platelet profiling could provide a highly accurate way of staging and monitoring cancers over time, and hopes to test this idea in cancer patients. In a recent paper, she suggests that new cancer therapies might someday "instruct" platelets to selectively release predominantly anti-angiogenic factors and inhibit tumor growth.

"Dr. Folkman was very excited about this," she says. "He was keen on getting it all confirmed in humans."

## CONTROLLING METASTASIS

Metastasis—the migration of cancer cells to other parts of the body—is the most dangerous phenomenon in cancer, generally



GIANNOULA KLEMENT, MD  
Vascular Biology Program

the one from which people die. Doctors have known for years that tumors seem to select where their metastases grow; lung cancer often metastasizes to bone, for example. But no one knows what guides these selections.

Randolph Watnick, PhD, in the Vascular Biology program, has been finding that primary tumors prepare landing places in distant organs for their metastases by secreting certain proteins. Studying cells from various tumors that were known to be metastatic, he discovered a common thread: all had the ability to turn off thrombospondin, a natural angiogenesis inhibitor. Cells from tumors that didn't metastasize, never leaving the original tumor site, actually stimulated thrombospondin.

Using proteomics techniques, Watnick's team focused on the metastatic cells, hoping to isolate different proteins that steered metastases to different parts of the body. "I thought we'd come back to the suppressor later," says Watnick.

But Folkman, always thinking of patients' needs, had a different idea. "This is important," he told Watnick of his protein work, "but you might have a drug right here."

Watnick went on to find that the suppressor, called prosaposin, reduced metastasis in mice by as much as 20-fold. If it's confirmed to be a viable drug in humans, Watnick hopes doctors can someday tell patients, "We can't keep you from getting cancer, but we can potentially keep you metastasis-free."

### A MISSING INGREDIENT FROM THE WOMB

In February 2005, Anne Hansen, MD, medical director of Children's Neonatal Intensive Care Unit, gave a Grand Rounds presentation on complications in premature newborns, including hemorrhage in the brain, necrotizing enterocolitis (death of intestinal tissue), retinopathy (causing blindness) and the noncancerous tumors known as hemangiomas.

Folkman, in the front row, immediately thought of 2-methoxyestradiol (2ME2). 2ME2 was discovered in 1994 by Robert D'Amato, MD, PhD (see Profile, page 23), spurred by Folkman's interest in how blood vessels grow and regress during menstruation and pregnancy. A fragment of the estrogen molecule, 2ME2 is produced in large amounts during late pregnancy, and has



**RANDOLPH WATNICK, PHD**  
Vascular Biology Program

Photos: Patrick Bibbins

proved to be a powerful angiogenesis inhibitor. It is now being tested clinically against several cancers.

"After my talk," recalls Hansen, "Dr. Folkman stood up and asked: 'Did you realize that all of these complications of preterm infants are related to an imbalance between angiogenesis and anti-angiogenesis?'"

Hansen was puzzled; no one in her field was pursuing this idea. Thirty hours later, Folkman personally delivered a letter laying out his research proposal. He suggested that babies born before 32 weeks' gestation don't get adequate exposure to 2ME2, so their blood vessels grow and leak too much.

Today, Hansen is collaborating with Carmen Barnés, PhD, in Folkman's laboratory and Thomas McElrath, MD, at Brigham and Women's Hospital, to measure premature newborns' 2ME2

## IN THE PIPELINE

Two drugs developed in the Folkman laboratory, dismissed early on as failures, have recently re-emerged with new and greater promise.

TNP-470, discovered by Donald Ingber, MD, PhD, is a powerful angiogenesis inhibitor, shrinking a wide range of tumors by cutting off their blood supply. It entered clinical trials in 1992, and produced a number of dramatic cancer remissions—but also caused unacceptable neurologic side effects.

Fast forward 10 years. A young chemist Folkman had hired as a research fellow, Ronit Satchi-Fainaro, PhD, solved the neurotoxicity problem by modifying TNP-470 so that it couldn't slip into the nervous system. The new compound, Caplostatin, retains a strong anticancer effect. More recently, Ofra Benny-Ratsaby, PhD, another fellow in the lab, developed an oral version, called Lodamin, that would avoid the need for injection or infusion. (See "New anti-angiogenic drugs optioned," page 24.)

And Folkman's favorite anti-angiogenic drug, endostatin, has been reformulated by biochemist Kashi Javaherian, PhD, extending its half-life in the bloodstream to two weeks, rather than just two hours. Animal tests show it's now hundreds of times more effective and still non-toxic.

**JUDAH FOLKMAN, MD, and DONALD INGBER, MD, PHD,**  
around the time of TNP-470's discovery



Photo: Children's Hospital Boston Archives

levels. While Hansen collects umbilical cord blood samples from mothers, Barnés is working to develop a blood test to establish a minimum necessary 2ME2 level. "If we can find a threshold, maybe we could give preterm babies replacement therapy," Barnés says.

In early February, Barnés won an award from the Massachusetts Technology Transfer Center to support her 2ME2 work, which may also help doctors understand and treat preeclampsia, a life-threatening rise in blood pressure in late pregnancy. Sadly, Folkman died shortly before the award was made final. But the proposal won on its own merits, with Barnés as principal investigator.

### TURNING HYDROCEPHALUS ON ITS HEAD

In 2006, Folkman attended another Grand Rounds lecture, by neurosurgeon Joseph Madsen, MD. The topic was hydrocephalus, or water on the brain, which can lead to severe brain damage.

For decades, hydrocephalus treatment has involved installing a shunt to drain the excess fluid into the abdomen. But there are often problems, including the need to replace the shunts. Madsen discussed how hydrocephalus was being explored in terms of physics, with the idea that pulses in blood pressure might be involved.

Folkman approached Madsen afterward, suggesting that hydrocephalus might be an angiogenic problem: The excess fluid might be coming from abnormal, leaky blood vessels, a problem known to occur in some eye disorders. If so, a drug treatment might be possible. "He laid out two years' worth of research in that one encounter," Madsen recalls.

Within 10 days, Madsen's team was sending cerebrospinal fluid samples to Folkman's lab, which tested them for vascular endothelial growth factor (VEGF), an angiogenesis stimulator that

**JOSEPH MADSEN, MD,** Neurosurgery



**CARMEN BARNÉS, PHD,** Vascular Biology Program (left), and **ANNE HANSEN, MD,** Newborn Medicine

can also make blood vessels leaky. "He faxed me from Japan," Madsen says, "saying 'this is extremely important.'"

Many patients' fluid samples had markedly elevated VEGF levels, suggesting that leaky blood vessels might indeed contribute to hydrocephalus, and that an anti-angiogenic drug like Avastin, which specifically targets VEGF, might relieve the disorder. Madsen's Neurodynamics Laboratory is now exploring this "leakage" hypothesis.

### ANGIOGENESIS: AN ORGANIZING PRINCIPLE IN MEDICINE?

Folkman's most recent papers lay out the case for angiogenesis as an organizing principle in biology, medicine and drug discovery. Although his propensity to make creative connections was repeatedly criticized during his lifetime, he often turned out to be correct. As early as 1971, he proposed a connection between angiogenesis and certain eye diseases; today, hundreds of thousands of patients with the blinding disease macular degeneration are benefiting from the angiogenesis inhibitors Macugen and Lucentis, which are slowing or even reversing their vision loss.

Folkman loved to tell the following anecdote. A few years ago at a major cancer conference, he was in the audience when successful use of Avastin, the first anti-angiogenic drug to be commercialized for treating cancer, was announced to cheering and loud applause.

He overheard a nearby researcher tell a colleague, "If only Folkman were alive to see this!"

He was—and he enjoyed it immensely.

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