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At 9 A.M. on a hot, sticky Friday in the middle of June, the tiny conference room on the 10th floor of Children’s Hospital in Boston is packed with the eager faces of an ethnically diverse cast of young people munching bagels. Among the Birkenstocks, T-shirts and jeans of his 30-odd graduate students and postdoctoral fellows, Judah Folkman stands out because of three things: his age (65 years), his necktie and white lab coat, and his courtly but authoritative manner.

At this weekly laboratory meeting, several of the lab members stand to describe their most recent results studying the link between angiogenesis—the growth of new blood vessels—and cancer. Folkman offers everything from detailed remarks on the methods of a particular experiment to advice on how to make the best use of an overhead projector. He’s the consummate manager and mentor: one minute he’s upbrazing a cocky postdoc for not taking criticism as easily as he dishes it out; the next he’s commending the same young man for “good progress” and joking with him that it’s not yet time for him to give up and go to business school. The postdoc wraps up his presentation and sits down with a smile.

Folkman and his prolific laboratory hit the news in a major way this past May, when an overenthusiastic, front-page story in the *New York Times* trumpeted results by Folkman’s group using naturally derived angiogenesis inhibitors to cure cancer in mice by preventing the growing tumors from attaining a blood supply. The focus of the story was a scientific paper published in November 1997 that had already been the subject of a *Times* news story, though not on page one.

One of the most provocative aspects of the *Times* article was a quote attributed to Nobel laureate—and biology legend—James D. Watson: “Judah is going to cure cancer in two years.” Although four days later the newspaper published a letter from Watson saying his “recollection of the conversation” with the *Times*’s reporter was “quite different,” the damage had been done. Hordes of people with cancer were already rushing their physicians’ offices, demanding access to the impending “cure”—despite the fact that it has yet to be tested in a single human. Folkman’s office alone logged more than 1,000 calls a day from cancer patients and their loved ones the week after the *Times* ran the story.

Folkman says he is puzzled over why the *Times* decided to publish such a belated, breathless article on his group’s work. “Our published results have all been in mice,” he emphasizes. “Many different substances have been shown to inhibit cancer in mice over the years, but unfortunately, so far not all of them have worked as well in people.” Most of all, he says, he is concerned that the story might have instilled false hopes in so many of those desperately ill with cancer.

Folkman is a leading pediatric surgeon but shows none of the ego of the stereotypical topflight surgeon. Quite the opposite. He dislikes giving interviews (especially for television) to the point that this summer he even turned down a request by NBC morning anchor Katie Couric—who had recently lost her husband to colon cancer—to appear on the *Today* show. He also hates having his photograph published—not because he is vain about his looks, he says, but because he doesn’t want to seem to be taking sole credit for the dogged work of the many scientists who make up his laboratory. In addition, he says, he wants to avoid being thought the leader of the only laboratory in the world devoted to angiogenesis, because many other labs contribute to the field.

A cavernous, elaborate workspace is not for Folkman: his office, which he rarely uses, is small and furnished with tattered, 1970s-era furniture. Every horizontal surface is stacked with books, journals, files and papers, so that the room more closely resembles an attic.
Although his office has a computer, Folkman’s secretary says that when he needs to write something he usually pulls a chair up to a spare computer next to her desk, in a cramped corner in front of a mini-refrigerator, because there is more room there than in his own space.

Folkman’s lifework on cancer and angiogenesis began in circumstances not of his own making: he was drafted into the U.S. Navy in 1960. Although he had just finished his assistant residency in surgery at Massachusetts General Hospital in Boston, the navy set him up with a small lab at the National Naval Medical Center in Bethesda, Md., to help in the military’s drive to create blood substitutes for use on aircraft carriers, which often spend months at sea.

There Folkman conducted the pivotal experiments that focused him on angiogenesis. While studying the ability of a cell-free blood substitute to keep a rabbit thyroid gland alive in culture, Folkman and navy colleague Frederick Becker placed a few rabbit melanoma cells on the gland’s surface. To their surprise, the cells grew but stopped once they formed tumors the size of peas.

“Why did the tumors stop growing?” Folkman asks. “That question kept me going for years.”

After leaving the navy in 1962, Folkman returned to Mass General, where he became chief surgical resident two years later. As one of Harvard Medical School’s brightest young surgeons, by 1967 Folkman had attained tenure, going directly from associate (instructor) to full professor and chairman of the department of surgery at Children’s Hospital in just one year. Folkman had distinguished himself as a surgeon through his technical skill and his ability to train others. He had also participated in the early development of implantable drug-delivery devices, which eventually led to the commercialization of products such as the contraceptive Norplant.

Along the way, Folkman kept a small research lab going on the side to pursue his interests in angiogenesis. But when he tried to publish his animal results, he was turned down by dozens of journals. Many scientists scoffed at his idea that devising a way to block angiogenesis might keep growing tumors in check.

It was only through giving a lecture in 1971 that Folkman got his ideas into an important journal for the first time. That year he was asked to give a special seminar at Beth Israel Hospital in Boston that has often been invited for publication in the New England Journal of Medicine. Finally, Folkman had a well-read platform for describing his conclusion from the rabbit thyroid gland experiments: that tumors are incapable of growing beyond a certain size unless they have a dedicated blood supply and that finding a way to block the process of angiogenesis might nip emerging cancers in the bud.

But the NEJM article simply egged on Folkman’s critics. In 1973, for example, when Folkman and his co-workers reported that injecting human tumor cells into the eyes of rabbits prompted angiogenesis, some scientists argued that the observed blood vessel growth was simply part of an inflammatory reaction to foreign cells. One researcher subsequently showed that implanting a chemical irritant, a crystal of uric acid, in rabbits’ eyes also spurred angiogenesis.

It took years for Folkman and his colleagues to explain this finding by demonstrating that immune system cells called macrophages had entered the rabbits’ eyes to destroy the uric acid and had secreted substances that promote angiogenesis.

Folkman’s struggles for credibility affected all the factors crucial to the success of a biomedical researcher: his ability to obtain grants from the National Institutes of Health, his chances of publishing his ideas in leading journals and his capacity to attract scientists in training to work for him in his laboratory.

“In the 1970s professors dissuaded their best students from coming to work in my lab,” Folkman says matter-of-factly. The only way he could convince outstanding young scientists to join him, he says, was by reminding them that they were so good that even if things didn’t work out and they left after a year, their careers wouldn’t be harmed.

Throughout the 1980s, Folkman and the other scientists in his laboratory kept adding pieces to the puzzle of angiogenesis and slowly gaining adherents to the idea that inhibiting angiogenesis might be a key to keeping cancer in check. A significant break came in 1994, when Michael S. O’Reilly in Folkman’s lab isolated one of the most potent natural inhibitors of angiogenesis, which they named angiotatin [see “Fighting Cancer by Attacking Its Blood Supply,” by Judah Folkman; SCIENTIFIC AMERICAN, September 1996]. Folkman, O’Reilly and their co-workers isolated a second natural inhibitor, endostatin, in 1996.

Folkman and his colleagues have now published articles in all the most prestigious research journals, and the list of awards and honors Folkman has received takes up two full pages of his curriculum vitae. Although researchers are not yet clear exactly how angiogenesis inhibitors work, angiotatin is expected to be tested in humans beginning late this year. (Several synthetic angiogenesis inhibitors are already in clinical trials.)

When asked how he persevered despite his early critics, Folkman credits his wife of 38 years, Paula, an alto who sings as a full-time member of the chorus with the Boston Symphony. “I would come home at night so disheartened,” he says, “and she would ask, ‘Why do you care what they think? She has always been very supportive.”

Does Folkman believe that he will eventually cure cancer? “No, I don’t think angiogenesis inhibitors will be the cure for cancer,” he answers. “But I do think that they will make cancer more survivable and controllable, especially in conjunction with radiation, chemotherapy and other treatments. I’m very excited to see how they will work in people.”

—Carol Ezzell

DISAPPEARANCE OF A TUMOR
implanted in a mouse took place in 12 days when the mouse was treated daily with the angiogenesis inhibitor endostatin.
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