



Four decades of research have established angiogenesis as an organizing principle in biology and pathology.

Judah Folkman

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REVERSE-ENGINEERING VASCULAR PATHOLOGY

His inkling that neovascularization fuels cancer progression was casually dismissed, then grudgingly tolerated and, finally, embraced. Today, after nearly 40 years of research, Judah Folkman, MD, delivers the Keynote Address at the Academy's Annual Meeting as the internationally respected originator of angiogenesis theory.

Physician, researcher, rebel and hero are some of the descriptors applied to Dr. Folkman, but “teacher” is the quiet figure he calls to mind as he discusses the peaks and troughs of his career. Very early on he realized that his colleagues were literally

not seeing what he was seeing. “After you removed the tumor you handed it to the pathologist, but by then the blood had drained from it and the tumor was white as a sheet,” he said. The cold, pale specimens examined by pathologists and

oncologists left them skeptical of the ideas of Dr. Folkman, who, as a surgeon, could see that before excision tumors were very warm and generously vascularized.

ANATOMY OF A PARADIGM

“Angiogenesis” is the word Dr. Folkman employed to describe the neovascular requirements of neoplastic disease, and it was not a notion that endeared him to mainstream medicine in the 1970s. In the early years of his work, he said, many of his journal submissions and grant proposals were rejected, and he saw a lot of people walk out of his presentations.

Acceptance by his critics came in capillary-sized increments. Even after they began to accept the *principle* of angiogenesis-dependent tumor growth, they insisted that, if it happened at all, it couldn't be reversed. But Dr. Folkman's persistence paid off. In 1998, a front page report in *The New York Times* trumpeted his lab's discovery of two endogenous antiangiogenic proteins—angiostatin and endostatin, and it quoted Nobel laureate James Watson promising that “Judah is going to cure cancer in two years.” Overnight, the stock of endostatin's commercial developer, EntreMed, soared. But the pharmaceutical compound was still very early in development, and, as a protein, was very expensive to make. A mere five years later, EntreMed dropped the research.

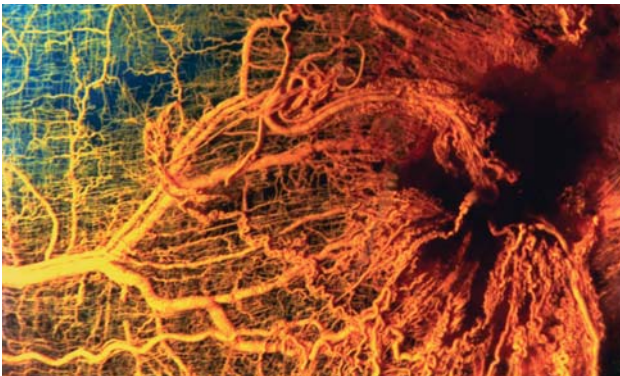
NO STOPPING A TRUE THING. Dr. Folkman has continued his intrepid study of angiogenic and antiangiogenic proteins as the director of the Vascular Biology Program at Children's Hospital in Boston and professor of

cell biology and pediatric surgery at Harvard University. His lab recently created a smaller molecular version of endostatin with the same potency of the larger one, and is pursuing commercial development for it. Meanwhile, another modified version of endostatin called Endostar is now manufactured in China.

Dr. Folkman seemed to handle his early adversity with magnanimity, and, in time, minds were changed with astonishing success: There are now 10 angiogenesis inhibitors approved by the FDA, and 43 more in development. The range of their intended uses shows that angiogenesis research may benefit many disciplines beyond oncology, including ophthalmology. Dr. Folkman outlined their bright future in an opinion published in *Nature Reviews/Drug Discovery* last April titled “Angiogenesis: an organizing principle for drug discovery?”¹

REMOTE MESSAGING TO METASTASES

Dr. Folkman's lab has clarified much of the once-opaque complexity of oncogenesis. Some cells in the primary tumor, for example, are essentially nonangiogenic, and grow side by side with angiogenic-prone cells. It is the latter that provoke new vascularization in primary tumors. “We learned to color-code the genes in tumor cells,” said Dr. Folkman. “What you see is that they're all mixed, and then the angiogenic cells attract the vessels, and the tumor grows and eventually metastasizes.” But the metastatic cells, both angiogenic and “non,” migrate singly. “It was always thought but not proven that they go as



A sarcoma in rat muscle—dark area, far right—promotes and attracts new blood vessel growth. Normal vessel distribution—upper left corner—is gridlike.

single cells, or clones. When you see them migrate randomly, they still behave characteristically—with the nonangiogenic cells unable to grow beyond the size of a pencil tip and the angiogenic cells ready to expand their population.” It is not until they resituate themselves, said Dr. Folkman, that the angiogenic immigrants can grow, and then only when they get proliferative messages.

TUMOR CELLS: CALL HOME. Amazingly, said Dr. Folkman, primary tumors that have metastasized are able to regulate the progression of their own remote metastases. This may seem bizarre on the surface, but a similar physiologic dynamic happens to women on a monthly basis: The dominant follicle in an ovary commands a generous blood supply for its own oocyte while hundreds of other follicles remain silent. Some primary tumors behave similarly, Dr. Folkman said, by using an array of angiogenic inhibitors. Endostatin is one example of a long-lasting, endogenous antiangiogenic protein. It can help ensure that a metastatic cell that migrated to another body site does not proliferate. In fact, if the primary tumor is removed, its angiogenic regulation goes with it, and, as surgeons over the years have observed, the metastases often then flourish.

VANQUISHING VESSELS OF THE FUTURE

A new generation of researchers and clinicians has expanded Dr. Folkman's work. In the early 1990s, Robert J. D'Amato, MD, PhD, a fellow in Dr. Folkman's lab, examined an old drug, thalidomide, that had caused thousands of birth defects in the 1950s and '60s, and he discovered that it actually had significant antiangiogenic and anti-inflammatory properties.² It was precisely the drug's antiangiogenic properties, sadly, that had impaired the development of extremities in first-trimester fetuses. But overnight, thalidomide made a comeback. Based on Dr. D'Amato's work, it became a valuable treatment for people with HIV infection, many of whom benefited from the drug's antivascular activity against Kaposi's sarcoma and its inhibition of tumor necrosis factor in



Harvard Medical School, Boston.

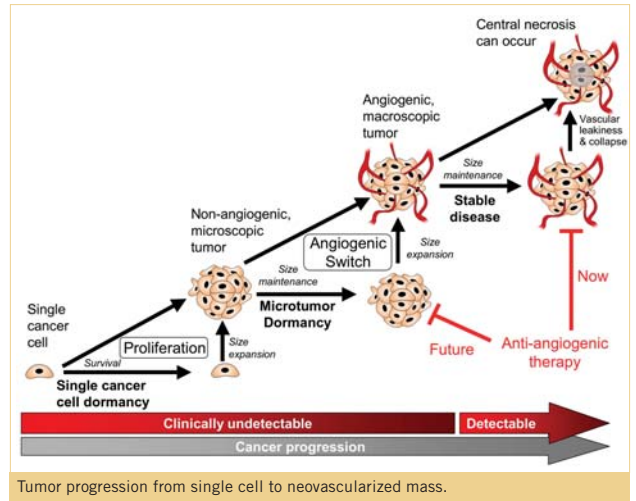
treating aphthous ulcers and wasting syndrome. Thalidomide is now used to treat multiple myeloma, and an analog is under study for other malignancies.

A retina specialist, Dr. D'Amato is now the Judah Folkman Chair in Surgery and director of the Karp Center for Macular Degeneration Research in the Vascular Biology Program at Children's Hospital in Boston. He describes Dr. Folkman's original vision as panoramic in scope. “Dr. Folkman has always considered angiogenesis work to be a platform to treat a large number of diseases: cancer, diabetic retinopathy, macular degeneration, arthritis, psoriasis. He's always thought that way—for decades. He's a very remarkable man, and it's been a real opportunity to work with him.”

Philip J. Rosenfeld, MD, PhD, has also advanced the boundaries of Dr. Folkman's work. He was the first ophthalmologist to inject the anti-VEGF drug bevacizumab (Avastin) into the eyes of patients with neovascular macular degeneration,³ and he was a lead investigator for ranibizumab (Lucentis) trials.^{4,5} “Directly or indirectly we can trace angiogenesis accomplishments to Dr. Folkman's lab,” said Dr. Rosenfeld, who is a retina specialist and professor of ophthalmology at Bascom Palmer Eye Institute in Miami. “He's left an indelible mark not only on ophthalmology but in all of basic science and clinical medicine. He is the father of angiogenesis research, and a dogged proponent of this research over the years, and he is single-handedly responsible for bringing it into the scientific and clinical mainstream.”

PROGRESS IS MEASURED. Are there situations wherein an angiogenesis inhibitor could be contraindicated? “Sure,” said Dr. D'Amato. “Wound healing, for example. If you are planning surgery, or treating diabetic ulcers, you would not want to impair the ability of blood vessels to grow in and heal the wound. But in the case of diabetic retinopathy, there could be the chance to administer the angiogenic inhibitor locally, and not impair the systemic wound-healing response. Conceivably, you could even put the diabetic patient on antiangiogenic eye drops. This is a great advantage over what we have to do to prevent or treat something like prostate cancer, which you pretty much have to do systemically.” Dr. D'Amato, in fact, imagines the day when physicians offer prophylactic therapy with antiangiogenic agents to individuals who are clearly at risk for a vascular proliferative disease. “Definitely. I think as antiangiogenic therapies are increasingly shown to be safe, and if, for example, you've got the gene for breast cancer, you could take an angiogenic inhibitor to suppress it.”

Dr. Rosenfeld is also proceeding with both caveats and optimism. “Completely curing something like macular degeneration is beyond our reach right now. But we can realistically get our patients to live with their chronic diseases, with malignancies and neovascular processes, having the best quality of life possible.” Like Dr.



D'Amato, Dr. Rosenfeld sees the Folkman legacy as spanning multiple disciplines. “I think the fields of immunology, oncology and angiogenesis are inextricably intertwined. When you think about immune cells and their regulation, the regulation of angiogenesis in cancer, and the role of the immune system and angiogenesis in macular degeneration, diabetes and other vasoproliferative and degenerative disorders, we find extensive interrelationships. It should be no surprise that their complicated pathways would overlap, and ophthalmology as well as all of medicine has benefited greatly from Dr. Folkman's groundbreaking research.”

MENTOR AND MENSCH

Dr. Rosenfeld likened Dr. Folkman to a Renaissance Man of Medicine. “Judah Folkman is a true triple-threat. He epitomizes what every physician-scientist strives to be: an innovative scientist, an outstanding clinician and a terrific teacher. He's trained at least two generations of scientists and opened up the whole field of angiogenesis. It all seems so intuitive now, but when he started, nothing was known about it at the molecular level. He had a belief that was supported by rational, defensible hypotheses. He was persistent. And he was right.”

Dr. D'Amato agreed. “Dr. Folkman is one of the great men of our era for his contributions in angiogenic research and what that research has culminated in, in terms of treatment for neovascular and exudative eye diseases. His contributions will go on forever because of the legions of scientists he's trained and the theories that he's proposed.”

A LONG AND WINDING ROAD. Dr. Folkman's four-decade journey from imagining angiogenesis to reversing it was often neither smooth nor straight. “This has been a very long and difficult road,” said Dr. D'Amato. “I'm sure it's quite a joy for him to see patients now benefiting at the end

of the tunnel.”

Dr. Folkman's own attitude throughout the ups and downs of his research might be described, ironically, as sanguine. In a 1999 interview with the Academy of Achievement, he expressed gratitude for the crucial support he was able to secure along the way. “A lot of credit goes to the Harvard Medical School. They gave me tenure very, very early . . . The joke at Harvard is that more people die waiting for tenure than for a liver transplant . . . I was only 33 and I was offered the position of professor. I jumped.”⁶ Dr. Folkman also credits the Children's Hospital in Boston, which offered him a lab and the position of surgeon-in-chief a year after his Harvard tenure began.

In that same interview, Dr. Folkman remembered the counsel offered by another colleague, Nobel laureate John Enders, to take neglect in stride. “This just proves that there are no experts of the future,” said Dr. Enders. “There are only experts of the past, and they sit on the study section.”

1 Folkman, J. *Nature Reviews/Drug Discovery* 2007;6:273–286.

2 D'Amato, R. J. et al. *Proc Natl Acad Sci* 1994;91:4082–4085.

3 Rosenfeld, P. J. et al. *Ophthalmic Surg Lasers Imaging* 2005;36(4):331–335.

4 Rosenfeld, P. J. et al. *N Engl J Med* 2006;355:1419–1431.

5 Brown, D. M. et al. *N Engl J Med* 2006;355:1432–1444.

6 www.achievement.org/autodoc/page/fol0int-1

For an in-depth interview with Judah Folkman, look for the November/December issue of *EyeNet* in your Annual Meeting bag and turn to “The Man Who Made Blood Flow Backward” on page 61.

The Keynote Address takes place today at 9:02 a.m. during the Opening Session, which runs from 8:30 to 10:07 a.m. in the Auditorium.