



Judah Folkman

1933–2008

BIOGRAPHICAL

Memoirs

*A Biographical Memoir by
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MOSES JUDAH FOLKMAN

February 24, 1933–January 14, 2008

Elected to the NAS, 1990

Moses Judah Folkman was born in 1933 in Cleveland, Ohio. He was the oldest child of a distinguished line of rabbis whose influence on the young man—particularly that of his father, Rabbi Jerome Folkman—is legendary. His mother, Bessie Schomer Folkman, instilled in him a love of science with bedtime stories about Newton, Pasteur, and Madame Curie.

A move to Columbus during high school put Folkman under the tutelage of Robert Zollinger, who spotted him working at Ohio State University Hospital as a volunteer aide and invited him to work in his laboratory afternoons and weekends. There in the Zollinger Laboratory, where he worked throughout college, Folkman had the opportunity to learn surgical skills and published a paper about liver cooling in the journal *Surgery*.



Judah Folkman, MD

By Patricia K. Donahoe

He was accepted at Harvard Medical School in 1953 and worked in the laboratories of Robert E. Gross, from whom he learned the “obsessive perseverance” required for his future life as a surgeon scientist. Folkman also helped to develop a heart-lung bubble oxygenator, which was initially used for repair of ventricular septal defects, and he designed a prototype transistorized pacemaker with Massachusetts Institute of Technology graduate student Fred Vanderschmidt. The heart lung machine and the pacemaker, though perfected in other laboratories, provided the tools to realize Gross’s dream of innovating and making cardiac surgery routine for infants and children (Cooke 2001).

In the Massachusetts General Hospital’s intense surgical training program, young Dr. Folkman progressively, meticulously, and creatively honed his surgical technique and patient-management skills, setting a gold standard that many future surgical residents thereafter strived to emulate. He chanced to meet and soon marry Paula Prial, an accomplished musician, and together they embarked on a lifetime journey during which she,

in parallel, pursued her profession, raised Laura and Marjorie, and firmly, but with sensitivity, influenced the lives of Folkman and a host of trainees and young faculty members over the ensuing years.

A hiatus in 1960, after being drafted by the U.S. Navy, brought Dr. Folkman to the National Naval Medical Center. Experiments there opened his eyes to the dependence of tumor growth on its ability to induce a vascular supply. He and Frederick Becker observed, while studying blood substitutes in an organ perfusion apparatus after the methods of Alexis Carrel, that melanoma cells that were injected into perfused thyroids grew uniformly to one millimeter and were viable; but when these cells were reimplanted in vivo, the resulting tumors grew to enormous size.

A prior 1947 paper from the laboratory of Glen Algire (Burk 1947) at the National Cancer Institute showed excess vascularity in tumor implants compared with normal tissue implants. Folkman's experiments, combined with intraoperative observations of highly vascularized tumors previously made by generations of experienced surgeons, germinated in his mind a concept that tumors secreted some factor that called forth blood vessels.



Folkman, with chicken eggs in lab. 1974.

Back at the Massachusetts General Hospital, a more seasoned Folkman finished a grueling senior and chief residency, becoming well regarded as a clinical surgeon and as an innovator. For example, he jury-rigged one of the early dialysis units to salvage, temporarily, a patient with terminal renal failure. However, he kept the tumor blood vessel image before him. William McDermott recruited him to the Boston City Hospital with a laboratory in which he could test his ideas, and this is where Folkman applied the term angiogenesis and antiangiogenesis to describe these phenomena.

Based on his considerable promise, Folkman was soon called to Children's Hospital in Boston as its youngest surgeon-in-chief, after serving a short hiatus of intense training in pediatric surgery at Children's Hospital of Philadelphia under the tutelage of C. Everett Koop, who later became our influential Surgeon General in the Reagan Administration.

To establish an assay to detect tumor angiogenesis, Folkman turned first to the subcutaneous air sac on the rat's pearly back; then to the rabbit cornea, working with Michael Gimbrone, which boosted his confidence in a diffusible tumor angiogenesis factor; and then to the chick chorioallantoic membrane.



Folkman, with his wife Paula.

Using human umbilical cord tissue, Ramzi Cotran, Gimbrone, and Folkman developed life-long collaborations as they tackled the then-impossible task of growing endothelial cells in culture, stimulated by thirty-percent fetal calf serum, which led to Folkman's first large grant from the National Institutes of Health and opened the field of vascular biology. One of the stimulatory factors that they found had previously been defined by Denis Gospodarowicz as fibroblast growth factor (FGF) (Gospodarowicz et al. 1976). Folkman then began a collaboration with Bert Vallee to isolate the "tumor angiogenesis factor," and realizing that scale-up was required, they turned to industry for funding.

In 1972, enter Monsanto and its champion Monte C. Throdel, resulting in the largest industrial-academic collaboration in history, at the time, with a ten-year agreement that included first licensing rights. The agreement, which took two years to execute, brought about a sea change in patent policy and industry relations for universities. The persistence of Harvard Medical School was inspired by the University of Wisconsin Foundation, with the hope of supporting academic basic research with upfront industrial funding. Monsanto's scale up went on for a decade, but an easy assay to detect tumor angiogenesis factor was still lacking.

Meanwhile, Robert Langer, a newly minted PhD from the Massachusetts Institute of Technology, came to the Folkman laboratory determined to isolate an antiangiogenesis agent. Reasoning that cartilage had few blood vessels, he purified from hundreds of pounds of cow and shark cartilage extracts that he studied in the rabbit cornea assay. Langer and Folkman also devised drug delivery systems, first from the silastic that

Folkman displayed in earlier work and later used to develop Norplant for contraception. Langer also discovered that by dissolving freeze-dried proteins of large molecular weight in alcohol, followed by evaporation, he formed a leaky polymer from which larger molecules could be released over time in a sustained fashion. A full circle would be completed if this technology for sustained release could be used for an antiangiogenesis factor.

After repeated discouragement using aortic endothelium, and believing that tumor angiogenesis factor might affect capillary endothelial cells differentially, Bruce Zetter and Folkman finally induced endothelial cells to grow on gelatin. When sprinkled with colloidal gold, Zetter could finally document factor-induced migration of capillary endothelial cells in vitro (Zetter 1980).

To augment its biological focus, Michael Klagsbrun, a young biochemist, was recruited to the Folkman laboratory in 1983. Frustrated by failure to isolate tumor angiogenesis factor (TAF) using size and charge characteristics, he made the paradigm changing observation that heparin enhanced angiogenic growth factor activity. He subsequently purified a factor from five hundred rat chondrosarcomas using heparin affinity chromatography, which yielded ninety-five percent purity in one step. Their chondrosarcoma derived growth factor turned out to be the same FGF that Gospodarowicz had discovered years earlier (Esch et al. 1985), but had not purified. Meanwhile, Napoleone Ferrara and William Henzel (Ferrara and Henzel 1989) also purified an endothelial factor by heparin affinity.

In 1985, as the Monsanto agreement was winding down, Vallee announced that his team had adapted tumor cells to serum-free media from which they purified angiogenin, reported its amino acid sequence (Strydom et al. 1985), and cloned its gene. Monsanto, however, never developed a product. In 1989, Rosaland Rosenthal in Folkman's laboratory purified a tumor angiogenesis factor and deciphered its amino acids. Meanwhile,



Folkman during surgery, at Massachusetts General Hospital.

Harold Dvorak at Beth Israel Hospital purified vascular permeability factor (VPF), which he had earlier proposed in 1977 (Senger et al. 1983), and Ferrara and Henzel at Genentech purified vascular endothelial growth factor (VEGF) from cow pituitaries, then they cloned its gene (Ferrara and Henzel 1989). All had unknowingly purified the same substance, and the name VEGF, which was proposed by Ferrara, perdured.



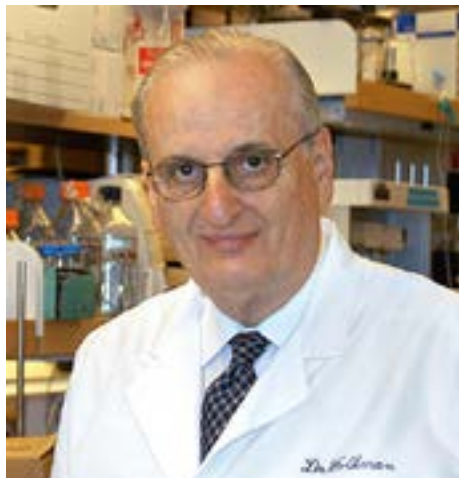
The grueling financial reality of keeping the laboratory doors open was a constant factor that pervaded all academic laboratories. Although the United States government took the lead in supporting the vast research enterprise that was growing across the country, competition for funding became increasingly difficult and is arguably now at its most fierce in the past fifty years. However, federal money is essential for the front end of research, while industry is crucial for advancing nascent concepts that can lead to prevention or treatment of human disease in the clinic. Folkman learned the necessity of garnering funds from both sources.

As the Monsanto agreement ended and rights were returned to the laboratories, Takeda Chemical Industries developed interest and supported the endeavor at one million dollars per year. Donald Ingber made a serendipitous discovery, reminiscent of Fleming, that a fungus, fumagillin, inhibited growth of capillary endothelial cells. Although inhibitory in mice, side effects of the fungus made it too risky for the clinic. Takeda scientists, however, screened four hundred analogs and produced TNP470, which had increased efficacy and decreased toxicity. They tested it as one of the first antiangiogenesis agents, with its first application as a treatment of lethal hemangiomas in a unique clinic led by John Mulliken and Alan Ezekowitz, along with Folkman at Boston Children's Hospital. They also treated these massive neonatal abnormalities with alpha interferon, an anti-angiogenic agent that was already available from Roche. After six months to achieve both institutional approvals and drugs supplied from Roche, a patient was treated with remarkable and lifesaving shrinkage of the hemangiomas, accompanied by decreased FGF in the urine as a marker.

Elevation of FGF in the urine of cancer patients was found to predict recurrence of tumors. The clinical observation that tiny tumors remained dormant in metastatic sites set the stage for understanding the on/off, ying/yang of tumor growth factors and tumor inhibitors, which had earlier been elaborated in the laboratory of Noel Bouck (Bouck 1990) at the University of Chicago. At the same time thrombospondin was found to be natural inhibitor of FGF and VEGF.

In 1991, Michael O'Reilly came from the University of Massachusetts as a surgical resident with no research experience, but after a labor-intensive first year, he found traces of an angiogenesis inhibitor purified from the urine of a large number of tumor-bearing mice. A small firm, EntreMed, funded the research, investing a full fifty-percent of its venture capital. O'Reilly purified angiostatin as an internal cleavage kringle-loop fragment of plasminogen in batches from forty cages of mouse urine, and then from commercial plasminogen, finding that the kringle fragment blocked growth of metastases when a Lewis primary lung tumor was resected from the back. Bristol-Myers bought out EntreMed, which had scaled up the purification of endostatin, and the field of anti-angiogenesis research exploded. NIH targeted angiogenesis in large requests for proposals. Genentech developed monoclonal antibodies to VEGF.

Joan Miller, now chief of ophthalmology at the Massachusetts Eye and Ear Infirmary, and Anthony Adamis, another young ophthalmologist in the Folkman laboratory, began to study diabetic retinopathy in primate models and found that VEGF could cause diabetic retinopathy, while monoclonal antibodies to VEGF could prevent the disease. They soon applied this therapy to macular degeneration. Robert D'Amato, yet another ophthalmologist in the Folkman laboratory, found that oral thalidomide, when processed in the gastrointestinal tract, was a potent antiangiogenesis agent, blocking new vessel growth in the eye. The impact of these findings and their subsequent development on the entire field of ophthalmology is incalculable. 2-methoxyestradiol (2ME2) was found to be another orally active antiangiogenesis agent. As the field further flourished, low-dose chemotherapeutic agents, when used metronomically, were also found to prevent angiogenesis.



Folkman, in lab. February 2004.

Folkman was a mile-a-minute, scientifically peripatetic “idea man,” yet he exhibited the patience and persistence necessary to develop and define a field with multiple clinical applications, which is now yielding untold corporate profits. Although he took out patents that funded his laboratory and institution, he made no personal profit. He loved to see “his critics become his collaborators” and revelled in the fact that his concepts were widely applied to an array of disease processes. After making scientific insights of considerable magnitude, he insisted on addressing the following inquiries: “What does it mean and how is it useful?” He also accepted the reality that he had to be equally as creative in funding the scientific enterprise as he was in contributing to its academic advancement.

Folkman derived profound insights from seemingly mundane observations. He saw the diamond where others saw coal. His most abiding influence was on his research trainees. He prodded, inspired, and set the example by always working longer hours than most mortals could sustain. Even if we stayed until midnight, there was always a directive note on the board indicating his presence before our arrival the next morning.

He acted as a lifelong advocate for his fellows and residents in quiet ways and in multiple venues that few realized. He became an advocate for women, mentoring such notables as Marsha Moses, who succeeded him as director of the Vascular Biology Program at Children’s Hospital, Boston; Patricia D’Amore, director of research at Schepens Eye Research Institute, Boston, and Joan Miller. He also advocated heavily for minorities. Those blessed with his mentorship will miss his example and tutelage, but vow to carry on his tradition.

Until the day he died, Folkman was the perennial student. Each meeting, local or national, would find him focused, in the front row, taking notes and asking insightful, pressing questions. While doing so, he found ways to compliment and encourage the speaker, particularly those speakers who were the most junior of his colleagues.

Folkman engendered loyalty and love from talented administrators and technicians, such as Wendy Foss and Paul Wesley, and a long gray line of hundreds of fellows and postdocs who made his legendary productivity possible. Touched by his ideals, many from this multitude of fellows have gone on to productive careers and academic prominence.

When analyzed in aggregate, new concepts emerged often because of his skill as the consummate physician, his involvement of both MDs and PhDs in the search for solutions, and his deep commitment to an early dream. He was truly characterized by prescience, perseverance, patience, and collaborative partnerships, and he built upon this his enduring role as a practitioner of the art of listening to the patient.

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