Judah Folkman, M.D.
February 24, 1933–January 14, 2008

The sudden death of Dr. Judah Folkman was tragic, not the least because he had so much left to do. Director of the Vascular Biology Program and former Surgeon-in-Chief at Children's Hospital Boston, he died while en route to address a scientific meeting in Vancouver. His laptop was open on his lap; he had an exhaustive list of investigations underway, all aimed at expanding the diagnostic and therapeutic possibilities of the field he had founded—angiogenesis research.

The story of how Judah persevered in the face of skepticism to prove that tumors require a blood supply to grow is legendary. On the long road to establishing angiogenesis as a major field, he always asked the next question, suggested the next experiment, made the unexpected connections of which discovery is born. He brought compassion and wisdom to his roles of healer, scientist, teacher, and mentor. Judah had an extraordinary dedication to his patients day and night.

Moses Judah Folkman was born in Cleveland, Ohio, and grew up in the Midwest. He knew by age 10 that medicine was his calling. The book *Dr. Folkman's War*, by Robert Cooke, vividly recounts his formative experiences, from visiting hospitalized congregants with his rabbi father to spending hours as a teenager practicing surgical knots and suturing the family's dish towels together, a foreshadowing of the single-minded focus and perseverance that would define his career.

Judah entered Harvard Medical School at 19, served his residency at the Massachusetts General Hospital, and, at 34, was appointed Surgeon-in-Chief at Children's, becoming one of the youngest full professors in Harvard Medical School history. Two pivotal events during Judah's residency years set his future course: he married Paula Prial, with whom he raised the family that rivaled science as his life's love, and he was drafted for a two-year stint in the Navy. While posted at the National Naval Medical Center in Bethesda, Maryland, Judah conducted experiments that stimulated the ideas that would mature into his angiogenesis hypothesis.

The scientific community first learned of Judah's angiogenesis theory in 1971, when he published a seminal paper in the *New England Journal of Medicine*. In it, he proposed that tumors could not grow beyond a certain size without a dedicated blood supply. He postulated that they secreted a protein to stimulate the ingrowth of capillaries, and that this process, angiogenesis, transformed a tumor composed of mutated but harmless cells into a potentially lethal neoplasm. Since physiological processes most often have checks and balances, he further proposed that naturally occurring substances that *inhibited* angiogenesis kept some tumors dormant despite their malignant potential.

The decade that followed was a challenging period spent identifying the molecular basis of tumor angiogenesis. Toward this end, Judah developed the assays and tools to study angiogenesis in vivo and in vitro. These assays remain in use today. They include long-term culture of capillary endothelial cells, the chick chorioallantoic membrane and corneal pocket bioassays, and the sustained-release polymers required to deliver angiogenic regulators to be tested.

In the early 1980s, the lab purified the first angiogenic stimulator, basic fibroblast growth factor (bFGF), which ushered in an era of discovery, validation, and refinement that established angiogenesis as the defining process in a tumor's ability to grow and metastasize. In the decades since, Judah's lab and others have identified more than 30 endogenous angiogenesis inhibitors, including angiostatin and endostatin, and over a dozen stimulators, and they have begun mapping multiple pathways through which pathological angiogenesis occurs. Drugs based on these discoveries are now benefiting more than 1.2 million people worldwide. Ten are approved in the US and other countries for cancer and the wet form of age-related macular degeneration (ARMD), which is also angiogenesis dependent; another 40-plus are in clinical trials. The ARMD drugs are the first ever to reverse blindness.

Judah was gratified but not satisfied with these advances. As always, his vision was bigger. In 1989, he proposed the concept of the "angiogenic switch," the point in a tumor's development when the balance of stimulators and inhibitors is altered in favor of angiogenesis stimulation, triggering the transition to the angiogenic phenotype. He theorized that blocking the switch would keep cancer from developing. The key would be to identify biomarkers of the switch, then "treat the biomarker" with nontoxic angiogenesis inhibitors, akin to using statins in response to high choles-

terol levels. He had begun clinical trials to evaluate the efficacy of biomarkers in detecting recurrent cancer before the tumors could be imaged or palpated, a first step toward his vision of "cancer without disease."

His vision for angiogenic therapies did not stop there, however. He viewed angiogenesis as an organizing principle of biology and pathological angiogenesis as a common factor in many disparate diseases. He pointed out that angiogenesis is necessary to support the growth of any mass—be it an arthrosclerotic plaque, adipose tissue, or a malignancy, and that it characterizes conditions as different as retinopathies and endometriosis. This shared characteristic led Judah to propose that angiogenesis-based biomarkers could be used to monitor the progression or regression of a number of these diseases. Further, drugs developed for one angiogenesis-dependent disorder could potentially treat another. This had already happened with Avastin, the cancer drug some ophthalmologists used to successfully treat wet ARMD before the more targeted eye drugs Lucentis and Macugen received approval. Judah envisioned a time when a single, broad-spectrum angiogenesis inhibitor or a combination of antiangiogenic drugs would be used to treat a wide range of conditions.

Judah Folkman authored some 400 peer-reviewed papers and more than 100 book chapters and monographs. He had been elected to the National Academy of Sciences, the American Academy of Arts and Sciences, the American Philosophical Society, the Institute of Medicine, and the President's Cancer Advisory Board. The research lab he founded with a single assistant when he came to Children's Hospital Boston in 1967 had, by the time of his death, grown into a 100-scientist-strong Vascular Biology Program. More than 1000 labs around the world are now pursuing angiogenesis research, yielding thousands of angiogenesis-related publications each year.

That the challenge Judah Folkman faced in 1971 had been met was nowhere more apparent than in the awards and honorary degrees crowding every inch of the walls of one of the Vascular Biology Program's conference rooms. But the display in a second conference room was even more meaningful to him. There, the walls exhibit journal covers reflecting the achievements of all 13 of the Vascular Biology Program's labs, many of which are now run by scientists who began their careers as Folkman post-docs. Judah was intensely proud of his scientific progeny.

Judah Folkman's fiercely original and courageous intelligence, his gift for focusing on big, important questions that could make a difference in people's lives, and his delight in discovery inspired hundreds of scientists, clinicians, and patients all over the world. We are honored and grateful to have been witness to his genius and his selflessness.

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