

RETROSPECTIVE

Judah Folkman (1933–2008)

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Judah Folkman died on 14 January 2008 en route to a scientific conference on angiogenesis, the field he fathered and championed. His loss has resonated throughout the biomedical research community, where he was celebrated for his boundless creativity, indefatigable optimism, a warm and humble personality, inspirational teaching and advocacy, and empathy as a clinician.

Trained at Harvard Medical School, Folkman had a remarkable intuition for organ biology. In the early 1960s, while serving in the U.S. Navy and stationed in a laboratory investigating blood substitutes, he began studying (and observing limitations to) the growth of explanted tumors, sowing seeds of inquiry that led to his landmark 1971 theoretical paper in which he proposed that tumors depend on the active induction and continuous growth of new blood vessels (angiogenesis) to survive and expand. He envisioned that such tumor-associated angiogenesis is not a passive physiological response, but is regulated by specific factors. He postulated that tumors express angiogenesis-inducing molecules, and that pharmacological inhibitors of tumor angiogenesis could be developed into useful drugs to treat human cancers. He subsequently substantiated early clues that tumors were angiogenesis dependent and developed innovative experimental systems to investigate the biology of angiogenesis.

In 1981, Folkman stepped down from his position as surgeon-in-chief at Children's Hospital, Boston, to focus on angiogenesis research. Since the late 1960s, he had sought to identify the postulated regulatory factors governing tumor angiogenesis, but the task proved challenging. In 1984, his team reported that a growth factor expressed by tumor cells—fibroblast growth factor 2 (basic fibroblast growth factor)—could induce angiogenesis. Their work on purification and bioassays set the stage for others to isolate vascular endothelial growth factor (VEGF), another potent (and more specific) angiogenic protein. VEGF proved to be the same vascular permeability factor discovered earlier by Harold Dvorak, Folkman's colleague at Harvard Medical School.

Folkman's frustration as a clinician with

the inadequacies of conventional cancer therapies, and his conviction that blocking angiogenesis would yield therapeutic benefit, led him to focus increasingly on angiogenesis inhibitors, beginning with the discovery in 1975 of an inhibitory activity in cartilage tissue. This was followed by the demonstration in 1982 that two cellular proteins, protamine and platelet factor 4, could inhibit angiogenesis. Later, buoyed by Noël Bouck's 1989–1990 reports of a tumor-derived inhibitor, the protein thrombospondin-1, Folkman's group discovered angiostatin (in 1994) and endostatin (in 1997), cleaved fragments of plasminogen and type XVIII collagen, respectively. These discoveries helped establish a principle that endogenous angiogenesis inhibitors serve as physiological modulators of angiogenesis.

Folkman's contributions and impact on the field are impressive for their breadth. Working with one of us, he demonstrated in 1989 that induction of tumor angiogenesis was not a mere consequence of oncogene-induced hyperproliferation, but rather a discrete event occurring during multistage tumorigenesis, subsequently called "the angiogenic switch." He and his colleagues conceived of a new way to use cytotoxic chemotherapy to inhibit angiogenesis involving a low-dose "metronomic" regimen that is now showing encouraging results in clinical trials. The notion of continuous, rather than bolus, drug delivery had its roots in another Folkman innovation. In the 1960s, he recognized the need for continuous delivery of steroids and performed studies with silicone-tube implants that led to timed-release implant technology for birth-control drugs. These are but examples of a remarkable set of accomplishments.

Folkman's passionate advocacy was not always evenly counterbalanced by the scientist's healthy skepticism. Thus, although his discoveries of endostatin and angiostatin were clearly important scientific achievements, they have not yet proven to be the breakthrough drugs he envisioned. Inspired by a

An innovative and inspirational pioneer in the field of angiogenesis research and its medical applications is remembered.

provocative study from Folkman's lab on their effects in tumor-bearing mice, James D. Watson proclaimed in an unguarded moment that "Judah is going to cure cancer in two years." Watson, already a legend for his broad impact on the development of modern biology, saw his prediction emblazoned on the front page of the *New York Times* in May 1998, creating a firestorm. Folkman was suddenly in the public eye, on prime-time TV, and in major news magazines, explaining his theories about angiogenesis and cancer and the potential therapeutic benefits of angiogenesis inhibitors. This publicity produced great expectations to provide these new miracle drugs to

patients. Delivering on their promise, however, has not been straightforward. Although angiostatin and endostatin have evident activity as anti-angiogenic agents, neither showed substantial benefit in early-phase clinical trials. Regrettably, the drugs proved expensive to produce and their clinical development was shelved largely for economic considerations, without their therapeutic efficacy being fully tested. Interestingly, however, a formulation of endostatin has been approved for treating lung cancer in China, suggesting its potential. Folkman remained an optimistic advocate of endostatin's pro-

spects, and his vision may yet be realized.

Folkman deeply believed that angiogenesis inhibitors would come to occupy an important place in the treatment of cancer and other diseases with angiogenic etiologies. Recently, three drugs that inhibit VEGF signaling were approved for treating certain cancers, and two more for angiogenic macular degeneration. Their demonstrable but often transitory efficacy represents important proofs of concept. Dozens of other angiogenesis inhibitors are in the drug pipeline, with prospects to further improve clinical responses. The benefits of anti-angiogenic therapy—and more will surely come—will serve as an enduring testament to Folkman's legacy as an innovator and inspiration for the future of angiogenesis research.

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