THE FACULTY OF MEDICINE
Harvard University

Michael Klagsbrun

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Michael Klagsbrun, PhD, was born into a family of diamond merchants in Antwerp, Belgium on January 16, 1939. At the age of 6 months, he left Belgium with his family as the Nazis advanced on the country and embarked on a journey with his family, largely on foot, across the European continent with stops in France and Spain. The trip was financed with diamonds sewn into the clothing that Michael wore as a child. They later found passage on a boat to Cuba and after some time on that island they eventually arrived in New York, where they settled in New York City (Queens). Michael attended public school in New York and shared vivid memories of playing stickball on the street in front of his family's apartment building. Perhaps as a result of his early travels, he was, as an adult, fluent in seven languages.

Michael attended the City College of New York where he majored in Biology. He then enrolled as a Ph.D. candidate at the University of Wisconsin, although much of his thesis research was conducted in the laboratory of Dr. Alex Rich at M.I.T. where he studied protein biochemistry. He then spent two years, from 1968-1970, as a commissioned officer in the U.S. Public Health Service, conducting research at the National Institutes of Health (N.I.H.) and continued as a staff scientist at the N.I.H. for 3 more years. He then joined the Surgical Research Laboratory, now the Program in Vascular Biology, at Boston Children's Hospital which was directed by Dr. Judah Folkman. Michael began as a postdoctoral fellow in 1973 and advanced to Assistant, Associate and Full Professor in the Departments of Surgery and Pathology at Harvard Medical School. His work over this time, both in his own lab and in collaboration with other members of the program, changed the course of research in the field of vascular biology. He was a creator and innovator, both in terms of technical advances and novel discoveries, that led to totally new concepts in the field.

Over his career, Dr. Klagsbrun published more than 280 papers, gave more than 300 lectures and co-

In tribute to their dedicated efforts to science and medicine, deceased members of the Harvard Faculty of Medicine (those at the rank of full or emeritus professor) receive a review of their life and contributions with a complete reflection, ***a Memorial Minute****.*

edited the definitive book at the time on Angiogenesis: Biology and Pathology. His research was funded continuously by the NIH for 35 years and was awarded a National Cancer Institute MERIT Award. Yet, as is often the case, it is not the number of his contributions that matters most, but rather the impact and legacy of his seminal discoveries. Michael Klagsbrun is best known for his pioneering work discovering novel growth factors and receptors, many of which form the underpinnings of our current understanding of contemporary vascular biology. He was among the first to show differences between the vascular endothelial cells that line normal blood vessels and their counterparts in tumors, a dogma-reversing finding. Perhaps most importantly, his discovery of the role of neuronal effectors such as neuropilins, semaphorins and netrins as mediators of vascular growth and guidance demonstrating the molecular cross-talk between nerve and blood vessel patterning has reset doctrines in both fields.

A classically trained biochemist, Michael was an expert in protein purification in the time before gene and protein sequencing were readily available. His published work is a testimony to his skill and ingenuity in the purification of novel growth factors and the determination of their function. He published a series of seminal papers describing polypeptide growth factors in human and bovine breast milk and their benefits to the newborn. In particular, his laboratory identified a number of factors that regulate both physiological angiogenesis, such as occurs in embryonic development or wound healing, and in pathological angiogenesis, as occurs in cancer or other diseases. In 1984, he and Yuen Shing reported the purification and characterization of the first identified angiogenesis stimulator, basic fibroblast growth factor (FGF-2), based on its strong affinity for heparin. Furthering this relationship, his lab later found that FGF-2 activity is dependent on cell surface heparan sulfate proteoglycans (HSPG) in addition to FGF tyrosine kinase receptors. His group subsequently purified and identified another growth factor called heparin-binding EGF-like growth factor (HB-EGF), a potent vascular smooth muscle growth factor and a receptor for diphtheria toxin in humans. Together, Dr. Klagsbrun's discoveries cemented the importance of heparin-related moieties as both a physiological component of vascular homeostasis and chemo-guidance as well as a tool for identification of molecules involved in these processes. He became internationally recognized for his outstanding contributions to vascular biology and cancer research and as a pioneer in the field of vascular growth factors and their cognate receptors.

In subsequent work, Michael and his colleagues continued to investigate factors that modulate blood vessel growth with this work resulting in the purification and identification of two neuropilin proteins (NRP1 and NRP2) as novel receptors for vascular endothelial growth factor (VEGF), a potent stimulator of angiogenesis. NRPs had previously been shown to be regulators of axonal guidance by mediating repulsion from class 3 semaphorin (SEMA3) ligands. The finding of NRP receptors on blood vessels and neurons and the competition between VEGF and SEMA3 ligands established the principle that similar molecular mechanisms regulate both neuronal guidance and vascular patterning. The Klagsbrun Lab went on to show that NRPs are expressed in carcinoma cells and therefore the SEMA3 proteins, which act to collapse the cytoskeleton of cells, can inhibit tumor cell migration and invasion. In fact, his group demonstrated that overexpression of SEMA3F inhibits tumor progression and metastasis *in vivo*. In a later series of papers, his lab characterized and highlighted the role of Netrin-1, another

axon guidance factor, as a modulator of cancer cells, vascular cells and immune cells within the tumor microenvironment. These pioneering molecular studies have led to an entire new field of investigation into the commonalities between processes of neuronal and vascular development and pathogenesis.

Dr. Klagsbrun was one of the first scientists to fully appreciate the difference between normal endothelial cells and those in tumors (the tumor endothelium). Most of those working in the field thought that they were very similar. He and his colleagues were among the first to isolate endothelial cells from tumors and to show that they differed in several ways including: lack of chromosomal integrity, increased expression of growth factors and receptors, and abnormal calcification. These studies revealed that tumor endothelium had unique properties that could potentially be exploited to target and inhibit these cells, but not normal endothelial cells, with the goal of halting cancer progression.

Michael was a colleague, collaborator, and friend to Dr. Judah Folkman for nearly 40 years. They began working together in 1973 when Michael was a post-doctoral fellow in the Folkman Lab and Dr. Folkman was Surgeon-in-Chief and Chairman of the Department of Surgery at Boston Children's Hospital. Their relationship was marked by a mutual devotion to furthering the study of vascular biology and a shared curiosity as to how work in other fields could be incorporated into their own. They shared enormous mutual respect and their collaboration spurred the field forward over four decades. After Dr. Folkman passed in 2008, Michael was selected to deliver the First Annual Judah Folkman Lecture at Boston Children's Hospital.

A recipient of many awards and honors, there were two of which he was most proud. One was to be named the Patricia K. Donahoe Professor of Surgery. Michael knew and admired Dr. Donahoe both personally as well as for her pioneering advances in research. He also appreciated the hurdles that she overcame as one of the pioneering women in the field of Pediatric Surgery. Another recognition that he felt particularly honored and proud to receive was the 2013 Earl P. Benditt Award from the North American Vascular Biology Organization, NAVBO, as this was awarded by his peers for the significance and impact of his work in the field of vascular biology.

Beyond science, Michael was passionate about his family, about history, politics, good discussions and especially the Red Sox. Michael married Deborah Kalin in 1982 and they had a daughter, Arielle. He was supremely proud of both of their accomplishments and their strong sense of activism. Michael remained close throughout his lifetime with his many cousins sharing many dinners, calls and conversations with them. He was a frequent visitor to Fenway Park and when he could not be there, would catch the games on TV or on the radio. He was at a conference in St. Louis the night that the Sox won their first World Series in 85 years and he immediately ran over to the park as the game ended and entered the stadium to celebrate with the faithful Sox fans who were there.

Michael had ties to several continents. Many members of his family, including his parents, returned to Belgium after the war and he visited there frequently. Michael was well known for his quick wit and

he had a unique ability to tell jokes that succeeded with both Europeans and North Americans. In his research, he developed strong ties with scientists in Israel and in Japan and his lab was often populated with young scientists from those two countries. At any moment, one could here conversations in English, French, Hebrew and Japanese going on simultaneously.

Michael was diagnosed with Parkinson's disease in 2010 and fought valiantly to remain independent and continue his lab work. When this became no longer possible, he moved to Newbridge on the Charles to receive extended care. He passed away there, on May 7, 2020 at the age of 81. He is missed immensely by his colleagues and former trainees, by his family, and by everyone who had the privilege to experience his keen scientific mind and terrific wit. His legacy lives on in the more than 100 students and fellows that he personally trained and in his pioneering and enduring scientific accomplishments.

Respectfully submitted,

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