

## Enrico Mihich, MD: In Memoriam (1928–2016)

Margaret Foti<sup>1</sup> and Youcef M. Rustum<sup>2</sup>



Enrico "Henry" Mihich, MD, scientist, educator, administrator, cosmopolitan, American Association for Cancer Research (AACR) past president, and Fellow of the AACR Academy, died December 29, 2016, at the age of 88, after an impressive career in cancer research that spanned more than 60 years. We are honored to memorialize this great man, scientist, and visionary leader with whom we were proud to work professionally and whom we were also privileged to know as a friend, colleague, mentor, and advisor for the better part of our careers.

As the first director of the newly established Grace Cancer Drug Center (GCDC) at Roswell Park Cancer Institute (RPCI, Buffalo, NY), Henry Mihich, together with 25 newly recruited faculty members, pioneered the development of drugs and cancer therapies, with a major focus on mechanisms of drug efficacy, resistance, selectivity, and the interactions of anticancer drugs with the immune system. His scientific focus on cancer immunology was prescient in that, early on, when others had abandoned the field as being a nonstarter, he was determined to keep it alive and to investigate the dual effects of anticancer drugs—to boost the immune systems of patients to help them fight their own cancers and to exert selective cytotoxic effects on cancer cells. Clearly, he was a trailblazer for the development of a rational approach for combining immune modulating agents with the appropriate doses and schedules of chemotherapy. As we all know now, cancer immunology and immunotherapy are revolutionizing the treatment of cancer; indeed, this is one of the most exciting and promising areas of research in the cancer field today.

Henry Mihich was the first to demonstrate that the therapeutic effects of certain anticancer drugs and cytokines are dependent upon the drug-induced modulation of the immune responses against the tumor. He was also the first to show that resistance to certain anticancer drugs was associated with increased immuno-

genicity of the resistant cells. He later discovered a protein, which he named TIP-B1, that inhibited cell death when incubated with TNF $\alpha$ . He also showed that inhibition of polyamines resulted in antitumor effects. In addition to these fundamental studies, he is well known for his work in experimental therapeutics and brought several drugs into clinical trials, including methylglyoxal-bis-guanylhydrazone.

Born January 4, 1928, in the Italian town of Fiume (present-day Rijeka, Croatia), Henry narrowly survived the Nazi occupation of his homeland during World War II. After the war, he and his family escaped the Yugoslavian communists' takeover of the region by fleeing to Milan, where he received his medical degree from the University of Milan (Milan, Italy) in 1951. He then went to Memorial Sloan Kettering Cancer Center (New York, NY) in 1952 for postdoctoral work and moved to the United States permanently in 1957 when he joined RPCI in Buffalo, NY, where he spent most of his long career.

Henry became interested in cancer research at an early age. His education at the Institute of Pharmacology in Milan, and the death of his mother from cancer in 1955, confirmed his resolve to devote his career to the pursuit of a cure for cancer. Two researchers who had important formative influences on him were Emilio Trabucchi, chairman of pharmacology in Milan, a generous and supportive mentor during his studies there; and Frederick S. Philips, with whom he did postdoctoral research at Memorial Sloan Kettering Cancer Center. He credited Fred Philips with teaching him how to perform experiments with precision and accuracy, and Fred credited himself with introducing Henry to his future wife, Marisa Mustacchi, whom Henry married in 1954.

In 1971, Henry was appointed to establish a research center at RPCI for the development of drugs and therapies for cancer patients. Within 5 years of its establishment, the GCDC, with almost 200 researchers, staff, and graduate students, became a recognized innovative center for basic and translational cancer research, and a center for advanced training of national and international graduates. Under Henry's 30-year leadership, the center was well funded by the NCI (Rockville, MD) and by industry and was instrumental in bringing new drugs and therapies into clinical trials. In fact, for a number of years, RPCI held two comprehensive cancer center support grants from NCI, one for the institute at large and one for the GCDC.

From 1969 to 2006, Henry also held the position of chair of the Program of Molecular Pharmacology and Cancer Therapeutics at the Roswell Park Division of the Graduate School of the State

<sup>1</sup>American Association for Cancer Research, Philadelphia, Pennsylvania.

<sup>2</sup>Roswell Park Cancer Institute, Buffalo, New York.

**Corresponding Authors:** Margaret Foti, American Association for Cancer Research, 615 Chestnut Street, Philadelphia, PA 19106. Phone: 215-440-9300; Fax: 215-440-9322; E-mail: margaret.foti@aacr.org; and Youcef M. Rustum, Roswell Park Cancer Institute, Pharmacology & Therapeutics, Elm and Carlton Sts, Buffalo, NY 14263. Phone: 716-845-2389; Fax: 716-845-7609; youcef.rustum@roswellpark.org

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University of New York at Buffalo. He was a mentor to many young scientists from the United States and from all over the world. He devoted his life to good science, leading the training of hundreds of graduate students. He established a first-class graduate education program in molecular pharmacology and therapeutics; many graduates later assumed leadership positions in academia and the pharmaceutical industry.

From the beginning of Henry's tenure as director of the GCDC, he established and implemented a policy that, prior to final submission, every manuscript and grant must be reviewed and signed off on by two independent reviewers and receive a final review from Henry himself. He insisted on meeting with the senior author to go over the changes line by line. His changes usually exceeded what had originally been typed. Henry's hands-on input may not have been appreciated or recognized at the time, but it had a very deep and profound impact on the scientific development of those who worked with him. Henry helped to build the careers of many; he never tried or agreed to have his name on any manuscript to which he did not make a direct scientific contribution, a valuable lesson for all. To effectively advance the implementation of bench to bedside research and vice versa, Henry was the first at the institute to recruit a full-time senior clinical scientist, a novel concept in the 1970s. This appointment facilitated the monthly meeting with medical and surgical oncologists at the institute and resulted in the development of the so-called "Roswell Park regimen" of weekly 5-fluorouracil efficacy modulation by leucovorin in patients with advanced colorectal cancer.

Henry viewed the GCDC as a second home; he was the first to arrive and the last to leave. He was a highly effective administrator, respected worldwide as an educator and cancer researcher, yet he was very kind, modest, and helpful, and freely accepted suggestions and criticisms. With the support of his wife, Marisa, Henry had frequent gatherings at their home with members from throughout the institute, especially when a guest speaker was in town. These gatherings facilitated the many national and international collaborations that were established under his leadership. The annual Dr. Enrico Mihich Lecture was created at RPCI in 2007 to honor his lifetime of achievements in cancer research.

Henry authored more than 400 scientific publications and served on the editorial boards of 16 scientific journals. He was instrumental in bringing the journal *Cancer Immunology, Immunotherapy* into existence and served as its distinguished Editor-in-Chief from 1982 to 2012. He was a member of the National Cancer Advisory Board from 1984 to 1990 and served on the NCI Board of Scientific Advisors from 1996 to 2004. He was also appointed a member of the Scientific Advisory Council of the University of Pittsburgh Cancer Institute in 1986, and a member of the International Advisory Board of Chulabhorn Research Institute, Bangkok, Thailand, in 1991.

Upon retiring from RPCI in 2007, Henry became Presidential Scholar and Special Assistant to the President for Sponsored Research at Dana-Farber Cancer Institute in Boston, Massachusetts, where he remained until his death.

Henry became a member of the AACR early in his career in 1958 and gave generously of his time and wisdom to its programs and initiatives. He served as a member of the AACR Board of Directors from 1985 to 1990, and as chair of the Program Committee for the 1978 AACR Annual Meeting. He also served on the *Cancer Research* editorial board (1981–1988), on numerous other AACR

committees, and as the AACR representative to the International Union Against Cancer (1998–1999).

He helped shape the AACR into the organization that it is today by enlarging its scientific and international scope. His activities as president (1987–1988) were particularly memorable. He was always thinking ahead in an effort to "push the envelope" and stretch established limits to advance the field. There was a constant stream of new concepts for all to consider, which, once analyzed and implemented, resulted in a broadening of the AACR's programs and in a new vision for the future.

It was important to Henry to play a vital part in infusing excitement and innovation into AACR scientific programs, and during his AACR presidency, he decided to form five task forces, in experimental therapeutics, endocrinology, clinical investigations, molecular biology, and virology, to consider what should be done by the organization scientifically and programmatically to accelerate progress against cancer. All five task forces of experts in these different scientific areas put forward the same recommendations: expand the cancer science and medicine presented at the AACR Annual Meeting, increase programs for young investigators, and hold focused scientific conferences in specialty areas. These ideas that were implemented in the late 1980s transformed the AACR, offered opportunities for scientific leadership, increased membership, and excited the cancer field as a whole.

Henry chaired a steering committee to develop the concept of small AACR scientific meetings. As a result of the committee's work, the first AACR Special Conference was held in the fall of 1988 on the subject of gene regulation and cancer. Under the brilliant chairmanship of Nobel Laureate Phillip A. Sharp, it was a "watershed" scientific event of monumental consequences. With this extraordinary meeting, the Special Conferences series was launched and has since become a highly popular, signature program of the AACR.

Mihich's visionary worldview of cancer research led him to advocate for global collaboration long before it became an established practice in the cancer research community. Two of his lasting legacies to the AACR in this area are worthy of mention. Because of Henry's close relationship with Japanese scientists and the Japanese Cancer Association (JCA), the first jointly sponsored triennial AACR-JCA international meeting was held in Hawaii in 1989. This series continues to this day to be a special collaboration with Japanese colleagues and, through this program, the AACR has further expanded its interactions with the JCA, with frequently held cosponsored events in the United States and Japan as well as joint sessions at each other's Annual Meetings.

His other important legacy to the AACR in the global arena is the partnership he forged between the AACR and the Pezcoller Foundation in Trento, Italy. By conceptualizing the importance of bringing together the AACR and the Pezcoller Foundation to offer the Pezcoller Foundation-AACR International Award for Cancer Research, he initiated an international dialog that continues to shape cancer research around the world today. Henry served on the Pezcoller Award Selection Committee from 1997 to 2001 and 2011 to 2012, and as chair of the Pezcoller Symposium Committee from 1989 to 2008. The fact that AACR's partnership with the Pezcoller Foundation thrives to this day is a testament to Henry's vision, passion, and enthusiasm for collaborations among cancer researchers throughout the world, and his international goals continue for the good of the field and cancer patients.

Henry's extraordinary contributions to cancer research were recognized by his induction into the inaugural class of Fellows of

the AACR Academy in 2013. Other prestigious honors throughout his career included the Director's Service Award from the NCI, the Thomas B. Tomasi Achievement Award from Roswell Park Cancer Institute, the Lifetime Science Award from the Institute of Advanced Studies in Immunology and Aging, and an honorary medical degree from Aix-Marseille University in France. He was also a Fellow of the American Association for the Advancement of Science, an honorary member of the Japanese Cancer Association, and a Fellow of the Royal Society of Medicine (London, United Kingdom).

Henry was a compassionate friend and mentor to many in the cancer field. Inspired by his indefatigably determined spirit, relentless hard work, and dedication to the cause, we followed

his sage recommendations that have contributed greatly to our own professional careers.

Henry will be remembered always by those who knew him not only for his significant professional accomplishments, but also for his warmth and generosity, and a level of energy, enthusiasm, and drive that few can equal. Our deepest sympathies are with Henry's loving family. He leaves behind Marisa, his wife of 62 years; his daughter Sylvia Mihich and her husband Tom Harden; grandchildren Sara Mihich Harden and her husband So'ud Habbas, and Jaye Mihich Harden; numerous family members who reside in several countries; and a host of admiring international colleagues and devoted friends.

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The Journal of Cancer Research (1916–1930) | The American Journal of Cancer (1931–1940)

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