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In memoriam: Soldano Ferrone, MD, PhD (1940–2023)

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Dr Soldano Ferrone died on January 10, 2023, at the age of 82, after an 8-week-long battle with COVID-19. At the time of his death, Soldano was a Professor in Residence, at the Department of Surgery at Massachusetts General Hospital. He had previously held leadership positions in multiple academic institutions, including the Scripps Clinic and Research Foundation, Columbia University, New York Medical College, Roswell Park Cancer Institute, and the University of Pittsburgh Hillman Cancer Center.

Soldano was a pioneer in the field of cancer immunology and immunotherapy. He devoted his life and efforts to developing novel, more effective cancer therapies for 60 years. His productive research has paved the way for translating many immune therapies, including monoclonal antibodies, adoptively transferred activated T cells, natural killer (NK) cells, and most recently, chimeric antigen receptor T (CAR-T) cells, to the clinic. He was internationally renowned as an outstanding investigator in immuno-oncology, physician, educator, and mentor to numerous young scientists and clinicians. As a scientific community, we deeply mourn his loss and want to remember his enormous contributions to science and honor his memory.

Soldano began his life-long quest for novel treatments of human diseases as a medical student in Milan, Italy. Dr Ferrone played a significant role in developing and characterizing human red blood cells, which mimic red blood cells' behavior in paroxysmal nocturnal hemoglobinuria (PNH). Specifically, he showed that human red blood cells treated in vitro with the sulfhydryl compound 2-aminoethylisothiouromium bromide become abnormally sensitive to the lytic action of complement, have a reduced acetylcholinesterase activity, have a shortened survival in vivo, and display structural abnormalities similar to PNH red blood cells.[1 2]

Soldano's early work as a young investigator improved our understanding of interactions between lymphocytes, human leukocyte antigen (HLA)-specific antibodies, and complement by demonstrating that false-negative results in the lymphocytotoxic reaction used for HLA typing were caused by anticomplementary factors present in HLA-specific alloantisera. He showed that natural antibodies reacting with human lymphoid cells represent one of the mechanisms underlying the superior cytolytic activity of rabbit complement in the complement-dependent cytotoxicity assay with human lymphoid cells.[3] This work represented a major contribution to the burgeoning field of HLA typing.

In the late 1970s and with Dr Ralph Reisfeld, Soldano successfully applied the hybridoma methodology to developing monoclonal antibodies reacting with HLA class I, HLA class II, and human melanoma-associated antigens.[4] These reagents proved to be hugely valuable for studies of the expression and functional properties of HLA in normal and malignant cells. He demonstrated that the malignant transformation of cells is frequently associated with the reduction in HLA class I expression. He identified the molecular mechanisms underlying these defects and showed their role in driving resistance to antitumor T-cell-mediated immunity. Dr Ferrone developed a unique set of monoclonal antibodies, which recognized the components of the HLA class I antigen processing machinery (APM). Using these unique reagents in collaboration with Dr Barbara Seliger, he analyzed the expression of APM components in normal and malignant cells and showed that defects in the HLA class I APM components were frequent in malignant cells and associated

with poor prognosis and survival in various malignant diseases.[5]

Furthermore, he showed that defects in APM component expression were most often caused by functional mechanisms rather than structural defects. Only rarely was the loss of APM components caused by structural defects such as, for example, loss of the APM component TAP1 detected in a melanoma cell line. Also, Dr Ferrone was among the first to show that immunologically functional HLA class II molecules were frequently expressed on melanoma and malignant cells of epithelial origin. Using both polyclonal and monoclonal antibodies, Dr Ferrone went on to analyze the structural profile of HLA class II antigens and the antigenic profile of human melanoma cells. Furthermore, he showed that the adhesion molecule ICAM-1 (intercellular adhesion molecule 1) was expressed not only on lymphoid cells but also on melanoma cells and that ICAM-1 expression in primary melanoma lesions was associated with poor prognosis.

Soldano identified several tumor antigens expressed by melanoma cells. Among them was the high-molecular-weight-melanoma-associated antigen (HMW-MAA), also known as chondroitin sulfate proteoglycan-4 (CSPG4).[6] He showed that CSPG4 was overexpressed in a high percentage of melanoma lesions with limited heterogeneity and had a restricted distribution in normal tissues. These criteria indicated that CSPG4 could be used as a marker for immunoscintigraphy and as a target for immunotherapy. Dr Ferrone was the first to conduct a phase I–II clinical trial in patients with advanced melanomausing mouse anti-idiotypic monoclonal antibodies, which mimic the HMW-MAA as immunogens and which elicit HMW-MAA-specific cellular and humoral immune responses in patients with advanced melanoma.[7] This response had a beneficial effect on the clinical course of the disease. More recently, Dr Ferrone working with Dr Gianpietro Dotti showed that CSPG4 helps target tumor cells with transduced CAR-T cells. The anti-CSPG4 antibody proved to be useful for the isolation from melanoma plasma of exosomes produced by melanoma cells, and its use led to a discovery of the protein profile selective for melanoma cell–derived exosomes.

In the last decade, Soldano continued to develope novel anticancer therapies. In particular, he focused on the mechanisms of tumor-induced immune suppression responsible for tumor immune escape. These studies, all based on insights previously gained and the reagents he had in hand, motivated Dr Ferrone to establish a series of successful collaborations with colleagues engaged in the treatment of patients with cancer, especially melanoma, with immune checkpoint inhibitors. To address mechanisms of tumor resistance to immune therapies, he studied impaired functions of T cells and NK cells in the tumor microenvironment, defects of the APM in dendritic cells that interfered with antigen presentation, the role of cancer stem cells in the modulation of antitumor responses, HLA class I downregulation in metastases of patients with advanced melanoma, and lately, the role of tumor-derived exosomes in cancer progression.[8] Permeating his work was the theme that the tumor-induced impairments in HLA class I antigen processing and presentation represented the central underlying mechanisms of tumor resistance to immune therapies. Another favorite theme was the need to identify new therapeutic targets that are not dysregulated by tumors; hence, he intensively explored the possibility that B7-H3 may be a valuable target for CAR-T cells in cancer.[9] In aggregate, these studies represent an invaluable reservoir of information that Soldano shared with scientists and clinicians worldwide in many insightful reviews he penned and lectures he delivered. These reviews and lectures have guided us and have allowed us to formulate, translate, and introduce novel immune therapies to the clinic.

Throughout his scientific career, Soldano was continuously supported by grants from the US National Institutes of Health, and his service on study sections and review panels was exemplary. He remained an active member of the scientific community and conducted laboratory experiments almost until the day he succumbed to COVID-19. While the scientific, translational, and clinical significance of Dr Ferrone's research is impressive, Soldano will be remembered for his creativity, tenacity, generosity, warm, and friendly demeanor. He had an immense passion for science, which he expressed, often forcefully and with great humor, whether in English or Italian. Those of us who were privileged to work with Soldano cherished the times spent with him. We remember his insightful perceptions and thoughts on life in academia, scientific enterprise, and insistence on excellence in our work. Soldano was also a devoted husband to his wife, Agnes, a proud father of Dr Cristina Ferrone and Dr Marco Ferrone, both physicians, and a loving grandfather to Peter, Annamaria, Joseph, and Andrew.

We have lost one of our community's most valued and productive members. We honor his memory and hope to emulate his example in our work.

Contributors Both authors contributed equally.

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