Zena Werb (1945–2020): Mourning the loss of a tissue microenvironment icon

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The science community has lost a unique voice, a fierce advocate for women in science, and a beloved mentor. Zena Werb, PhD, who was a Professor and Vice Chair in the Department of Anatomy for over 40 years, Associate Director for basic science at the University of California, San Francisco (UCSF) Helen Diller Family Comprehensive Cancer Center, and National Academy of Science member since 2015, died unexpectedly on June 16th, 2020 at the age of 75.

Zena was an uncannily insightful, impressively intelligent, consistently honest, and refreshingly unpretentious scientist. These attributes can be traced back to her humble beginnings. Zena was born in early 1945 to Polish–Jewish parents in the Nazi concentration camp Bergen-Belsen in Germany. After the camp was liberated Zena's mother carried her over the Swiss–Italian Alps to reunite with her father in Italy. Shortly thereafter the family joined countless refugees fleeing Europe to emigrate to Canada, where they initially settled in northern Saskatchewan. After a short stint in Saskatchewan the family relocated to a farm in southern Ontario, where Zena received her early education in a one-room schoolhouse. Notwithstanding these inauspicious beginnings, and no doubt due in large part to the fact that Zena's parents were strong advocates of education, Zena developed an early love of math and science. Encouraged by her father Zena chose to study biochemistry at the University of Toronto, where she excelled and was encouraged to pursue graduate studies.

After finishing her undergraduate degree, Zena joined the Zanvil A. Cohn laboratory at The Rockefeller University, where she studied macrophages and cholesterol regulation. Zena's thesis work laid the foundation for her later research into immune regulation of organ development and inflammation and cancer. Furthermore, during her graduate studies, she became captivated with live-cell imaging. Watching macrophages moving in real time under the microscope impressed upon Zena the utility of live-cell imaging, which she eventually incorporated into her research program with great effect exploring the interplay between tumor cells and infiltrating immune cells in breast cancer progression using intravital imaging and genetically engineered fluorescently tagged mice. For her postdoctoral training, Zena switched fields and moved to the United Kingdom to work with Dr. John T. Dingle at the Strangeways Research Laboratory, Cambridge, England. It was here that she began studying fibroblasts, the collagen-producing

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cells that synthesize, deposit, and remodel extracellular matrix (ECM) proteins. It was during her tenure at Cambridge that Zena began her work on matrix metalloproteinases (MMPs) that would later be a cornerstone of her scientific career. These early research experiences prepared Zena for a lifetime of research exploring the role of the cellular and noncellular microenvironment in tissue development and malignancy.

After an initial start at Dartmouth College in New Hampshire, in 1976 Zena was recruited to UCSF to the Department of Anatomy, where she remained throughout her distinguished academic career. Her postdoctoral studies on fibroblasts informed Zena's early discoveries demonstrating that the ECM is not merely a passive tissue entity, rather, that cells use cell surface receptors, such as integrins, to "read" cues from the ECM that guide their behavior. Zena also pioneered the field of ECM remodeling. Under her leadership, Zena's group identified and characterized MMPs and showed how these enzymes were key regulators of tissue development, including embryonic implantation, bone development, and blood-vessel formation. In addition, her graduate studies on macrophages and live-cell imaging provided important insight into her work studying innate immunity in wound healing, bone development, and malignancy. She discovered that the state of macrophage activation strongly affected the molecules secreted by the macrophages, and in particular, that macrophages in tissues were very important sources of MMPs, thereby bringing her thesis and postdoctoral research work full circle and placing her findings in physiological context.

In the mid-1980s a fortuitous collaboration began between Mina Bissell, who is a senior scientist at Lawrence Berkeley National Laboratory, and Zena Werb, that undeniably left a lasting imprint on the cell biology and cancer communities. Mina introduced Zena to the field of mammary gland development and cancer. Together, Mina and Zena published over 30 highly cited articles that established the field of the tumor microenvironment. The partnership leveraged Zena's formidable background in MMPs and ECM biology and her arsenal of methods and models and data-driven focus with Mina's creativity and integrative thinking. Together, Mina and Zena made a series of seminal discoveries demonstrating the critical role of ECM remodeling in mammary development, focusing on branching morphogenesis and involution. They then went on to produce a series of seminal studies that showed how disrupting ECM structure and function can initiate cancer and promote tumor progression and aggression. Their work challenged the then and sadly current dogma that oncogenes and tumor suppressors are the primary initiators and regulators of cancer.

Zena's early training in myeloid cell biology also informed her ability to make novel discoveries regarding the role of the innate immune system in tumor initiation, progression, and metastasis. She published several seminal articles years before the role of inflammation in cancer was accepted as mainstream dogma. In collaboration with Lisa Coussens, who at the time was a postdoctoral fellow at UCSF who was training with Doug Hanahan, Zena orchestrated a set of studies demonstrating the critical role of mast cells in squamous cell carcinoma that resulted in a highly cited research article (1). Thereafter, Zena and Lisa published a highly cited review article on inflammation in cancer that helped establish the field of inflammation and cancer (2). Over the years, Zena continued studying the role of myeloid cells in malignancy and metastasis, and has been credited with helping to inform the recent development of cancer immunotherapies.

To those who knew Zena, they understood well her dedication to data-based, fact-directed research, despite sometimes yielding unpopular discoveries. Throughout the 1990s and early 2000s the cancer community zealously promoted the use of MMP inhibitors to treat aggressive tumors. Zena's studies, however, highlighted their complexity, demonstrating instead how some MMPs restrict while others promote cancer. These findings presaged the catastrophic clinical trial results with wide spectrum MMP inhibitors. More recently, Zena's group published an article in PNAS describing the identification of metastasis inhibitory neutrophils that challenges current dogma (3). It is a tribute to her strong belief in fact-based science that she did not shirk from these unexpected data. Instead, Zena fearlessly initiated a series of studies aimed at clarifying the molecular basis of these observations that will be continued by her collaborators and trainees.

In conclusion, Zena's seminal discoveries on MMPs, the ECM, tissue development, and myeloid cells and inflammation in cancer established her as a world leader in the life sciences. She was an original, fearless voice in science whose many contributions made a lasting imprint on the cell biology community and forever changed the field of tumor microenvironment. Importantly, she was also our brilliant collaborator, who freely shared her honest and insightful opinions. Most of all, however, she was our big hearted, and loyal friend, and she will be genuinely missed.

1 L. M. Coussens, C. L. Tinkle, D. Hanahan, Z. Werb, MMP-9 supplied by bone marrow-derived cells contributes to skin carcinogenesis. *Cell* **103**, 481–490 (2000).

2 L. M. Coussens, Z. Werb, Inflammation and cancer. *Nature* **420**, 860–867 (2002).

3 C. Hagerling *et al.*, Immune effector monocyte-neutrophil cooperation induced by the primary tumor prevents metastatic progression of breast cancer. *Proc. Natl. Acad. Sci. U.S.A.* **116**, 21704–21714 (2019).