

Zena Werb 1945–2020

Unlike 30 years ago, when the notion of tumor cells being regulated by cell-extrinsic mechanisms was akin to heresy, the tumor microenvironment (TME) is now recognized as a hallmark of cancer, with a broad community of researchers focusing on how it regulates malignant transformation, metastasis and therapy response. We owe this evolution in thinking to several scientific giants, but perhaps none more impactful in changing the storyline than Zena Werb, our intellectually fearless colleague, beloved mentor and generous friend, who died suddenly on 16 June 2020 at the age of 75.

Zena was a professor and vice chair in the Department of Anatomy at the University of California San Francisco (UCSF) for over 40 years and was the associate director for basic science at the UCSF Helen Diller Family Comprehensive Cancer Center. Her foundational work on macrophage physiology, the extracellular matrix (ECM), mammary gland development, breast cancer and tumor-associated inflammation made her one of the most respected researchers in the world. Zena's contributions led to numerous awards and honors, including election to the National Academy of Sciences and the American Association for Cancer Research, presidency of the American Society of Cell Biology, the E.B. Wilson Medal from the American Society of Cell Biology and the Paget-Ewing Award from the Metastasis Research Society. However, Zena, as a devoted mentor and a fierce advocate for junior faculty and particularly women, took special pride in the UCSF Lifetime Achievement in Mentoring Award, which she received in 2015. Thus, the story of Zena Werb and the TME is also the story of her dedicated mentoring.

Zena was born in 1945 in the Bergen-Belsen Nazi concentration camp in Germany. After the war, her family emigrated to Canada, and she grew up in a rural community, where she attended a one-room schoolhouse. Following her undergraduate studies, Zena conducted her graduate research with Zanvil A. Cohn at Rockefeller University, focusing on lipid metabolism in macrophages. Despite being biochemically inclined, Zena was enthralled when she first observed macrophages moving in real time under the microscope — an experience that laid the foundation for her later love of cell biology, innate immunity and intravital microscopy. During her postdoctoral training with



Zena Werb as a graduate student at Rockefeller University, circa 1971. Credit: Rockefeller Grad – News and Notes. June 1971 Vol 2. No 10.

John T. Dingle at the Strangeways Research Laboratory, in Cambridge, England, she began investigating a new (at the time) family of proteolytic enzymes secreted by fibroblasts, called matrix metalloproteinases (MMPs). This class of ECM-remodeling enzymes would comprise another cornerstone of her life's work. After starting her own lab at Dartmouth Medical School, Zena relocated to UCSF in 1976, where she quickly established her reputation as a rigorous and prolific scientist. Much of her early independent research focused on fibroblast and macrophage MMPs, and she and her first postdoctoral fellow, Michael J. Banda, were the first to purify and characterize MMP12.

Her research on MMPs and their targets led her to study ECM remodeling and resultant cellular behavior, including cell proliferation and survival. Some of her seminal work laid the framework for new fields of research investigating the microenvironmental regulation of developmental processes, tissue homeostasis and disease pathogenesis, including cancer. Establishing these new areas was interwoven with launching the careers of some of her other early trainees, including James McKerron, Steven Frisch and Caroline Alexander. It was also during this time frame

that Zena forged an enduring collaboration with Mina J. Bissell, who introduced her to mammary gland development and cancer. Together they published innovative research that changed the fields of cell biology and cancer, including studies on how ECM remodeling regulates mammary gland branching morphogenesis and involution, stem cell behavior, and cancer cell invasion and metastatic dissemination. This pivotal collaboration also launched the careers of numerous trainees, including Nancy Boudreau, Leif Lund, Andre Lochter, Farrah Kheradmand, Derek Radisky, Bryan Welm, Mark Sternlicht, Laurie Littlepage and Valerie M. Weaver, many of whom are recognized as leaders in their fields. Zena and Mina loved to challenge prevailing dogma. Among their notable work from this period was demonstrating that collagenolytic enzymes lead to the generation of oxygen radicals, and that ECM remodeling regulates growth factor receptor and integrin signaling and controls cell polarity, differentiation, proliferation and death. Among their more groundbreaking discoveries were the findings that MMP overexpression causes epithelial mesenchymal transition and genomic instability in non-transformed mammary epithelial cells, and that MMP

overexpression is sufficient to induce tumors in the normal mouse mammary gland.

Another critical collaboration was with Douglas Hanahan. Together with their trainees Thiennu Vu, Gabriele Bergers and Lisa Coussens, they published a series of highly influential papers showing that when MMP9 is secreted by macrophages, mast cells or osteoclasts, it promotes angiogenesis during normal development and cancer. These reports coincided with the development of MMP inhibitors for cancer therapy. Nevertheless, Zena recognized early that some functions of MMPs also paradoxically protect against malignancy, and that the same is true for many TME-derived factors that both promote and inhibit neoplastic progression by context-dependent mechanisms. When MMP-inhibitor efficacy was not realized in the clinic, Zena turned to using MMPs as tools for understanding biology rather than as therapeutic targets. This strategy served as the foundation for mechanistic studies addressing the role of chronic inflammation in cancer, as discussed in a highly cited *Nature* article coauthored by Lisa Coussens and Zena in 2002.



Zena was scientifically fearless, routinely reinventing herself, while basing her research decisions on rigorous scientific facts. She was excited when findings were contrary to accepted dogma and especially when they went against her own expectations. She often said “the data are the data, and you follow the data.” Beyond steadfastly urging her mentees to follow their data wherever they led, she encouraged them to adopt or develop new technological approaches as needed. One such example was her early adoption of intravital imaging, which she used with

Bryan Welm, Andrew Ewald and Mikala Egeblad to study cell invasion during mammary gland branching morphogenesis and cancer. This work yielded new insights into underlying mechanisms and striking similarities between the invasive programs of normal mammary epithelial cells and those of breast cancer cells, as she predicted. When intravital imaging of tumors revealed that non-tumor cells were far more motile than neoplastic cells were, Zena realized that the highly motile cells were monocytes and neutrophils. With Mikala Egeblad and another instrumental collaborator, Matthew Krummel, she refocused her work toward understanding the contributions of innate immune cells to the resistance of tumors to therapy.

In the past several years, Zena was increasingly determined to understand the mechanisms that regulate metastasis. With postdoctoral fellows Devon Lawson and Kai Kessenbrock, she embraced single-cell sequencing to reveal that breast cancer metastases are initiated by stem-like cells, while also using the technique to compare cancer cells with normal breast epithelial cells — an ever-present theme in her research. Until the end, Zena remained highly focused not only on understanding metastasis but also on identifying new biomarkers and therapies, using her encyclopedic knowledge of the ECM and inflammation, and her understanding of normal development.

Zena’s quirky personality endeared her to mentees, whether they were lab members, junior faculty or senior colleagues. Many were treated as family and were nurtured with scientific wisdom and witty remarks (“stressed is desserts spelled backwards” was a favorite line

to worried senior trainees), as well as tickets to local museums, the symphony or opera, and Zena’s exceptional cooking. She maintained contact with her mentees as they transitioned into independent positions, and in many instances the mentoring relationships blossomed into deep kinships and productive collaborations — such as those we three experienced with her. With her passing, we grieve the loss of our cherished mentor and collaborator, and our loyal and unfailingly honest friend. Science has lost an original, indefatigable cell biologist and TME researcher. But we remind ourselves that although Zena was big-hearted, she was not sentimental. We can picture her telling us “Now, get on with it! Science needs you, and there’s a whole new generation of trainees who need mentoring.” So we will listen to our dear mentor, roll up our sleeves, nurture our mentees (sadly with our more pedestrian cooking) and follow the data. We — and so many others — carry some of her within us, ensuring that her wisdom, fearlessness and kindness remain, to become part of the fabric within which we pursue the scientific questions we seek to answer. □

Mikala Egeblad ¹, Lisa M. Coussens² and Valerie M. Weaver ³✉

¹Cancer Center, Cold Spring Harbor Laboratory, Cold Spring Harbor, NY, USA. ²Department of Cell, Developmental and Cancer Biology, Oregon Health Sciences University, Portland, OR, USA. ³Department of Surgery, University of California, San Francisco, San Francisco, CA, USA.

✉e-mail: valerie.weaver@ucsf.edu

Published online: 3 August 2020
<https://doi.org/10.1038/s43018-020-0101-z>