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IN MEMORIAM

Zena Werb (1945–2020): Cell biology in context

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Zena Werb, PhD, the world-renowned cell biologist and professor at the University of California, San Francisco (UCSF), died at the age of 75 on June 16, 2020. Zena was a leader in understanding the crosstalk between cells and their surrounding microenvironment. She was also a leader in her support and mentorship of scientists in training both in her laboratory and beyond, with a particular focus on supporting women in science. This untiring activity as a leading scientist and mentor was recognized through numerous awards, including the American Society of Cell Biology Women in Cell Biology Senior award in 2010 and the E.B. Wilson Medal in 2007.

We had the great fortune to be influenced and guided by Zena at distinct stages of our careers. During early postdoctoral training, as a naive physician scientist interested in cell biology and inflammation, Anna had the opportunity to work with Zena as a first-year postdoctoral scientist. Zena was at first skeptical about taking a physician scientist into her group but then embraced the challenge with regular invitations to talk about science in her office at UCSF. These office debates were engaging and covered broad areas from philosophy to specific discussions about data. After entering her office confused, one would leave feeling excited about the science and with a specific plan for experiments. Michael met Zena when she was on sabbatical at the Max Planck Institute of Biochemistry, where Michael was a junior group leader. Zena spent most of her time talking to the "youngsters," the scientists in training or investigators just starting their research groups. During her sabbatical, almost every day started with a scientific, philosophical, or any other kind of discussion. No matter the topic, Zena knew how to make it interesting.

For both of us, it never happened that Zena did not have a comment that made us think about our plans from another perspective. Zena trained us all to think critically. While she was very critical of what we said and of the data we showed to her, her mind was always open and constructive. Most importantly, her criticism was honest and bold. When proofreading a manuscript, it happened that she simply commented "boring" on the introduction in large red letters—and she was correct; it was boring. But not many people tell you that, despite the importance of honest input. She helped us to think critically and learn to openly examine our own thinking. Ultimately, it was all about the data and how to put the data into context.

Zena Werb at a Banbury conference. Photo courtesy of Cold Spring Harbor Laboratory.

Zena was not all talk; she always had an experiment in mind. The group at Max Planck, so deeply impressed with her breadth and originality, one day decided to challenge her practical skills. The goal was to get a fluorescent peptide into primary cells, and all transduction protocols had failed. When asked about advice, Zena responded in her typical mix of little child, mother, and commander-in-chief: "Type 'scrape-loading' in Google." Despite being away from the bench for decades, she accepted the challenge to do the experiment herself, and that same day, everyone watched as Zena was scrape-loading some cells. Cell culture dishes flipped, a lot of medium was spilled, and everything looked quite messy—but the experiment worked and the cells could be imaged (Riedl et al., 2008). Notably, it took the youngsters more than four weeks to find the precise conditions

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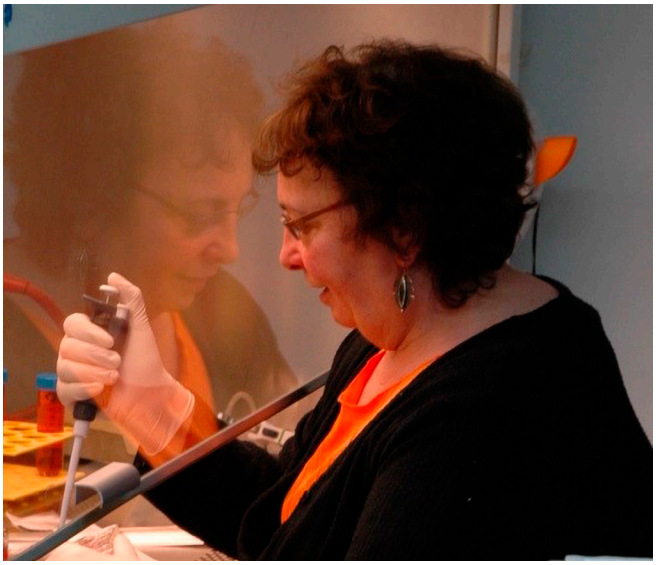
to reproduce Zena's success—so she also had a green thumb in the laboratory, even as a senior scientist.

Indeed, Zena herself did the groundbreaking experiments in her own laboratory in the 1980s that showed that the 3D matrix environment communicated with cells through cell surface integrin receptors to regulate the expression of genes that degrade the ECM, known as matrix metalloproteinases (MMPs; Werb et al., 1989). This supported the fundamental and far-reaching idea that the matrix was not simply a scaffold but that it had a signaling function.

Zena was all science. Her interests started as a young child growing up on a farm in Ontario, Canada. She trained at the University of Toronto and Rockefeller University for her PhD, then received postdoctoral training at the University of Cambridge, where she initially developed her interest in the ECM. Progression in her career was not without challenges. In the era when she trained and started her laboratory at UCSF, it was not always easy to be a woman in science. But despite many hurdles, Zena continued to live her credo: "Data wins." She had a remarkable ability to focus on the challenges ahead rather than the challenges behind her and always kept her eyes on the thing that she could control: doing the science.

Zena's contributions to science have been highly influential. Her work on MMPs demonstrated that these enzymes play a key role in regulating the extracellular microenvironment, in addition to being regulated by the ECM. In collaboration with Mina Bissell, she showed that MMPs are produced by breast cancer cells, influence tumor progression, and can drive invasive growth (Sternlicht et al., 1999). In more recent work, Zena had played a key role in making the link between inflammation and cancer. Zena has been highly collaborative and played a key role in mentoring leading scientists in cancer biology, including Lisa Coussens, Andy Ewald, and Val Weaver.

Because Zena was fearless in her approach to science, her work over the years evolved and continued to drive fields forward. She always believed in "the data," even at times when nothing made sense and unexpected results confused the mind. In more recent years, she developed a fascination with how the innate immune system can prevent the spread of cancer. It was with this new excitement that she gathered with us at a Banbury



Zena Werb at the Max Planck Society. Photo courtesy of Michael Sixt.

meeting of 30 scientists focused on understanding the role of neutrophils in cancer. The focus of these meetings is always scientific dialogue and debate, and Zena was a force at that meeting, driving this nascent field toward the challenges that she saw ahead (Hagerling et al., 2019). Even as we became senior scientists, she continued to mentor us. As Zena said, the "legacy will be the people that we have mentored." This is certainly true. She was a mentor but also a groundbreaker as a research scientist, advancing our understanding of the crosstalk between cells and their surrounding microenvironment. Thank you, Zena Werb.

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