



Zena Werb

1945–2020

BIOGRAPHICAL

Memiors

*A Biographical Memoir by
Fiona M. Watt*

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NATIONAL ACADEMY OF SCIENCES

ZENA WERB

March 24, 1945–June 16, 2020

Elected to the NAS, 2010

Zena Werb led the field of cell and molecular biology of matrix metalloproteinases (MMPs) and the extracellular matrix (ECM). She discovered that ECM receptors, integrins, signal to regulate cellular gene expression. Her experiments demonstrated that MMP-mediated extracellular remodelling is a central switch in programs of development, stem cells, inflammation and tumor progression and metastasis, integrating pathways in morphogenesis, invasion, and angiogenesis. Her studies on inflammation and stromal regulation of homeostasis and cancer were central to demonstrating the importance of innate immune cells in tumor development and metastasis. This pioneering work laid a mechanistic foundation for the field of tumor-microenvironment interactions. Her studies showed the power of using mechanisms arising out of studies in development to shape our thinking about diseases such as arthritis, asthma, and cancer.



By Fiona M. Watt

She was a professor and Vice Chair of Anatomy at the University of California, San Francisco (UCSF), where she served on the faculty for over forty years. She co-led the Cancer, Immunity, and Microenvironment Program at the Hellen Diller Family Comprehensive Cancer Center and was a member of the Executive Committee of the Sabre-Sandler Asthma Basic Research Center at UCSF. Zena was a former president of the American Society of Cell Biology and winner of numerous national and international awards. She mentored many students and postdocs in her own lab and had many friends and colleagues in the wider research community, receiving the UCSF Lifetime Achievement in Mentoring Award in 2015.

Early Life and Family

Zena was born on March 24, 1945, in the Bergen-Belsen concentration camp (KZ Bergen-Belsen). After World War II, her Polish-Jewish family lived in Poland and Italy before emigrating to Canada in 1948, where she was raised on a farm in Ontario with her younger siblings, Marsha and Michael. Her wisdom and determination were evident

from a young age, as this quotation from her valedictory address from South Lincoln High School on December 7, 1962, illustrates: "... the possession of an Upper School Diploma does not necessarily signify an educated person. It takes a lifetime to become educated."

Zena was from a close and loving family. Her parents instilled the sense that family—above all else—is of the greatest importance. Although she had no children of her own, she took great pleasure in her nieces and their children. Speaking at Zena's eulogy on June 28, 2020, her niece Debra Hamer said,

She modelled for us how to work hard and play hard—to make the best out of what life offers you. She was sarcastic, quirky, blunt, kind, generous, productive, curious, and unapologetically herself.

Her niece Naomi Hamer said,

"To my sister and I, our Auntie Zena was also the very definition of the eccentric, mythical aunt from a children's book. She loved colourful clothes and too-large jewellery; elaborate capes and unmatched earrings. She was a connoisseur of fine art, museums, and classical music. She had no patience for musical theatre or trashy television shows. Her baking and cooking skills were far beyond advanced whether it was rugelach or the most elaborate deliciously rich seafood dish."

Career

Zena received her bachelor of science with honors in biochemistry and physiology from the University of Toronto in 1966. She changed her major from geophysics when she was told that there was no accommodation for women at a field site she was planning to visit. Zena then moved to Rockefeller University in New York City and received her Ph.D. in cell biology in 1971, working under the supervision of Zanzvil Cohn. The title of her thesis was "Dynamics of Macrophage Membrane Cholesterol." After graduation she worked at the Strangeways Research Laboratory in Cambridge, United Kingdom, as a postdoctoral fellow with John Dingle from 1971 to 1973. She stayed on at Strangeways as a research scientist until 1975.



Zena as a young child.



Astride a cannon at Ely Cathedral during her time in Cambridge.

After a year as a visiting assistant professor at Dartmouth Medical School in New Hampshire, Zena moved to UCSF in 1976. She was an assistant professor until 1980, associate professor from 1980-83, and full professor from 1983 onwards. Although Zena remained at UCSF for her entire career, she took several academic sabbaticals that enriched her research and expanded her international network of colleagues and friends. From 1985 to 1986, Zena worked at the Sir William Dunn School of Pathology, University of Oxford, United Kingdom. She spent a sabbatical in 1998 at the Institut

Curie, Paris, France, and in 2006-2007 Zena was a visiting professor and Alexander von Humboldt Fellow at the Max Planck Institute of Biochemistry, Martinsried, Germany.

I first met Zena in the 1980s when I was establishing my own research group, which was first located at the Kennedy Institute of Rheumatology and subsequently at the Imperial Cancer Research Fund (ICRF), now part of the Francis Crick Institute in London.

If Zena had not been some years older than me, our paths would have crossed sooner, as I was a Ph.D. student at the Dunn School and was recruited to the Kennedy Institute by Helen Muir, a close competitor of John Dingle in the field of arthritis research. When I was at the Kennedy Institute, Helen would organize occasional visits of Kennedy Institute staff to the Strangeways labs for discussions on the proteoglycans of cartilage.

Zena enjoyed a long and close collaboration with Mina Bissell, of the Lawrence Berkeley National Laboratory, and I met Mina when she was on sabbatical at ICRF. Caroline Damsky of UCSF made up the trio of women studying different aspects of cell adhesion who had a profound influence on my early work on how extracellular matrix adhesion regulates the behaviour of stem cells. I saw them often at conferences, where they



Zena and Mina.

not only shared their research results but also their survival tips as women in science. I thus had the privilege of knowing Zena as the different phases of her research came to fruition.

Inflammation in Development and Disease

As a Ph.D. student with Zanvil Cohn, Zena published five papers that examined cholesterol metabolism in macrophages, including the subcellular compartments in which cholesterol was distributed. This early training in biochemistry and cell biology was to stand her in good stead, and throughout her career she made many important discoveries about the biology and function of inflammatory cells, particularly macrophages.

Zena was one of the first scientists to propose that macrophages are not only phagocytes, but also important secretory cells, and she discovered a number of key secreted products of macrophages, including MMP12, apolipoprotein E, and several growth factors and cytokines. Her studies culminated in the demonstration that macrophages *in vivo* in healing wounds express these factors² and that MMPs regulate inflammatory cell migration. A surprising finding was that the adaptive immune system regulates normal mammary gland organogenesis. Zena's seminal studies provided compelling evidence that innate inflammatory cells, including mast cells, macrophages, and neutrophils, contribute to tumorigenesis. These studies helped lay the groundwork for current interest in inflammation in cancer.

Studies on Matrix Metalloproteinases

Zena is probably best known for her pioneering studies of matrix metalloproteinases (MMPs), proteases that remodel the ECM. The prevailing wisdom that the ECM is inert and structural in nature had been debunked by the work of Betty Hay² at Harvard, and Zena championed the view that the ECM and its modulators regulate cell behavior. Zena hypothesized that the stromal microenvironment, in general, and ECM, in particular, carries information through interaction with adhesion receptors and is a signaling unit, and that ECM remodeling by proteases is a central switch in altering homeostasis (normalcy vs. malignancy, apoptosis, and growth). Zena's work was crucial in establishing the role of MMPs in remodeling the ECM, building on earlier studies of Jerome Gross at Harvard Medical School in the 1960s.¹

One of the most impressive aspects of Zena's research was her ability to bring cell biological and genetic approaches to bear on the problems that she attacked. She brought the tools and ideas of cell biology to a field that up to that point was mainly old-fash-

ioned biochemistry. She observed that fibroblasts were the cellular source of collagenase (MMP1), the founding member of the MMP family, and that a critical control point in the extracellular function of these enzymes was the activation of the secreted zymogen precursors of MMP1 by a protease cascade. Her studies led to discovery of several members of this new family of proteases. She discovered macrophage metalloelastase (MMP12) made by stimulated macrophages and showed its role in pericellular proteolysis.

Zena hypothesized that there was a fundamental link between cellular morphogenesis, ECM, and the regulation of gene expression. Exploiting this concept, she identified stromelysin-1 (MMP3) and subsequently cloned stromelysin-1 and MMP1. Zena then went on to establish that MMP functions extend far beyond degrading ECM. She systematically developed functional model systems in culture and *in vivo* to test this hypothesis. She was one of the first to demonstrate regulation of gene expression through integrins and to suggest that extracellular proteases have signalling properties. In a set of brilliant experiments, she analyzed the role of MMPs in the regulation of angiogenesis in bone development. She discovered that proteolysis mediated by MMPs is a discrete event in vascular development because it regulates vascular endothelial growth factor (VEGF) bioavailability. VEGF coordinates a complex set of events, including recruitment not only of endothelial cells, but also ECM-degrading cells and ECM synthesizing cells.

Zena also demonstrated the functional significance of the tissue inhibitors of metalloproteinases (TIMPs) in regulating MMP activity. She went on to show that the modulation of TIMP-1 levels or other modes of abrogating MMP activity *in vivo* have substantial effects in various developmental and pathological processes.

Technical Advances

Zena not only formulated important hypotheses that challenged prevailing dogma, but was also responsible for technological advances that enabled her to test those hypotheses. She was amongst the first to develop the reverse transcription polymerase chain reaction (RT-PCR) test on single cells as a useful technology, enabling observations that set the stage for the subsequent work by others on the cytokines and chemokines made by a variety of cell types. Zena also developed video microscopic technology for visualizing the behavior and interactions of tumor cells, immune cells, and vascular cells in real-time at the cellular level in living animals. These studies changed the way that both scientists and non-scientists view cancer.

Stem Cells in Mammary Development and Cancer

In the late 1980s, Zena began her hugely productive collaboration with Mina Bissell, which led to the first description of proteinases in the mammary gland. Valerie Weaver, a postdoc in Mina's lab at the time, recalls how Zena co-mentored her. Valerie noted, "We remained close and when I came to UCSF late 2006 my lab was down the hall from her and we'd hang out. I also lived for a few months in the small apartment in her house and she'd entice me upstairs to hang out and feed me like a little sad bird!"

Zena's publications on mammary gland biology and breast cancer formed the basis for understanding how the gland remodels during involution and is remodelled during neoplastic progression. She drew the parallel between mammary gland branching morphogenesis and invasive cancer using state-of-the-art imaging and organotypic cultures. This is exemplified by her work on the transcription factor GATA3, in which she showed how GATA3 maintains the luminal compartment of the mammary gland and acts as a suppressor of metastasis.

Zena also made fundamental contributions to our understanding of stem and progenitor cells during development and as an origin of cancer. Her research on proteases helped to elucidate the nature of the stem-cell niche because proteases are the key factors in regulating the transfer of stem cells from the quiescent niche to the proliferative niche in developing mammary gland and breast cancer. With colleagues, Zena also found that MMPs regulate the bone marrow niche for hematopoietic stem cells, endothelial progenitors, and bone mesenchymal precursors. Indeed, the niche is also critical for maintaining the stem-cell characteristics of tumor cells.

Zena also discovered a major non-proteolytic function of MMPs. MMP3 up-regulates the canonical Wnt-signaling pathway by binding and inhibiting the non-canonical Wnt5b, thus affecting mammary stem-cell function. Subsequently, using single-cell transcriptome analysis, she showed that normal breast tissue contains a subpopulation of basal cells that express stem-cell markers, and that the cancer cells in early and indolent breast cancer metastases have a stem-cell-like phenotype. These studies have had a significant influence on the field.

MMPs and Cancer

Zena's studies of angiogenesis in bone development suggested that MMPs also regulate tumor angiogenesis. Zena deciphered the mechanisms by which extracellular matrix signaling processes take place and found that ECM controls cell survival. Her laboratory

was among the first to point to reactive oxygen radicals as important signaling molecules. She found that the cytoarchitectural changes downstream of integrins and MMPs result in activation of small GTPases and reactive oxygen species followed by activation of the NFkappa-B transcription factor and, subsequently, cytokine and MMP gene expression. These observations showing that ECM signals through adhesion receptors to change gene expression formed the basis of further studies showing that they are the principal effectors of the changing microenvironment of cells during development and in tumorigenesis. The altered stromal microenvironment then acts as a provocateur of epithelial carcinogenesis.

In the area of breast cancer, Zena's studies on the role of MMP3 validated her early theories about the importance of the stromal environment in regulating cell behavior, even to the extent that ECM remodeling by proteases can lead to the development of mammary tumors and the activation of angiogenic growth factors. She showed that MMP3 regulates branching morphogenesis, apoptosis, stromal phenotype, and neoplastic progression in the mammary gland. Her studies on the physiological consequences of MMP3 production, from the generation of tetracycline-inducible production of MMP3 in culture to the generation of MMP3 transgenic mice, provide a beautiful example of the diversity of her expertise.

Intriguingly, MMP3 transgenic mice develop cancer through evident stages in a pathway of tumorigenesis. This particular model unambiguously demonstrated the causal role of MMPs in cancer, in that almost all mice expressing the MMP showed some degree of premalignant or malignant lesion in their mammary glands and this was blocked by transgenic expression of TIMP1. To identify the critical control points, Zena established that as these cells progress towards malignancy, they sustain a progressive loss of growth control, striking alterations in tissue structure, and genomic instability, all of which eventually give rise to tumors. By manipulating signaling at the cell surface by proteolysis, cells reorganize their cytoarchitecture, undergo epithelial to mesenchymal transition, and become invasive.

Zena applied these insights in a mouse model of multistage carcinogenesis. She showed a novel role for proteolysis in angiogenesis in mouse models of de novo carcinogenesis.³ In tumor progression, the normally quiescent tissue microvasculature is activated to produce new blood vessels in the premalignant phase prior to formation of solid tumors. Zena revealed that the recruitment of inflammatory cells that make MMPs was the key event in the angiogenic switch, which precedes progression to solid tumors. However, these studies also indicated that blocking MMPs was effective during early events in tumor progression. Later, the tumors that develop in the absence of MMPs are more aggressive. Thus, Zena's

observations presaged the failure of the early clinical trials of MMP inhibitors in late-stage cancers and provided a basis for designing new trials.

At the time of her death, studies in Zena's laboratory were focused on the molecular processes of tumor metastasis, the heterogeneity of myeloid inflammatory cells in mammary development and breast cancer, the nature of adult stem cells that mediate tissue regeneration, and how to individualize therapy for intractable cancers. Intriguingly, she showed that the signaling from the stroma to tumor cells can facilitate tumor progression and metastasis or block it, depending on the receptor used and the target cell. By combining animal models for these processes with functional genomic approaches, she was hoping to develop new therapeutics for pathological processes and for tissue regeneration.

Public Service

Zena was not only an outstanding scientist, but also an outstanding public servant, organizing highly successful conferences and serving on important national and international committees. From 1980 to 1982, she was a member of the advisory committee of the Cell Physiology Program at the National Science Foundation. From 1990 to 1991, she was a member of the Cell and Molecular Biology Panel of the National Cancer Institute of Canada, and from 1991 to 1995, she was a member of the Board of Scientific Counsellors, National Institute of Arthritis and Musculoskeletal and Skin Diseases. Zena was a member and chair of the Intercellular Interactions Study Section, Cell Biology IRG, NIH (2007-10) and chaired the Special Emphasis Panels, NIGMS R35 (MIRA), NIH (2015-16). She also served on the membership selection committee of the American Academy of Arts and Sciences (2005-08) and from 2011 to 2014 was a member of the National Academy of Sciences Search and Screening Committee. In 2018, she was elected to the Council of the National Academy of Sciences.

Zena's advice was widely sought after, and she was a member of several scientific advisory boards, including the board of the Massachusetts Institute of Technology's Center for Cancer Research (2003-2011) and the Scientific Advisory Committee, Children's Hospital Boston, Harvard Medical School from 2004 to 2012, serving as chair from 2008. She became a member of the International Advisory Board of the Cancer Research UK Cambridge Research Institute, UK, in 2006, when I was deputy director. I remember that she was always well briefed and had a knack for both getting to the heart of issues and offering solutions. From 2010, Zena sat on the External Advisory Board of the University of Colorado's Comprehensive Cancer Center. She was also a member

of the Scientific Advisory Board of the Max Planck Institute for the Biology of Ageing, Cologne, Germany (2011-19) and a member of the International Board and Scientific and Academic Advisory Committee, Weizmann Institute of Science, Rehovot, Israel (2013-17). She was a member of the External Advisory Board (EAB), Knight Cancer Center, Oregon Health & Science University from 2012, the EAB of Maverick Therapeutics, Inc., Brisbane, California, and the Stanford Center for Cancer Systems Biology, Stanford University from 2017.

Zena organized a number of highly successful meetings that advanced the field. She was the 1984 chair of the Program Committee for the American Society for Cell Biology's Annual Meeting and served as the society's president in 2005. She also organized Keystone symposia and Gordon Research Conferences.

Zena was also active in scientific publishing. She served on the editorial board of the *Journal of Cell Biology* from 1983 to 1985 and on the Board of Reviewing Editors at *Science* from 1990 to 2001. I invited her to join the editorial board of the *Journal of Cell Science*, and she served with energy and distinction from 1999 to 2012. She also served as Consulting Editor for *Cell* (2000-09), *Developmental Cell* (from 2001), and *Cancer Cell* (from 2001). This experience enabled her to provide sound advice on papers—not always what would-be authors wanted to hear, but sound nonetheless.

Given her tremendous research contributions, it is not surprising that Zena received many honors and awards in her career. She received honorary degrees from the University of Copenhagen (Doctor in Medicine honoris causa, 2003) and the National Cheng Kung University, Tainan, Taiwan (Doctor of Medical Science honoris causa, 2016). She was elected a member of the Institute of Medicine (National Academy of Medicine) in 2002 and Fellow of the American Academy of Arts and Sciences in 2003. In 2010, she was elected a member of the National Academy of Sciences and in 2019 was elected Fellow of the American Association for Cancer Research Academy.

Zena received the FASEB Excellence in Science Award in 1996, the Charlotte Friend Lecture Award of the American Association for Cancer Research in 2001, and the Colin Thomson Memorial Medal of the Association for International Cancer Research in 2009. Zena obtained the WICB Senior Award of the American Society for Cell Biology (ASCB) in 2010 and in 2018 received the Distinguished Role Model Award of Northwestern University, Evanston, Illinois. In 2018, she also received the AACR Distinguished Lectureship in Breast Cancer Research Award, SABCS, San Antonio, Texas.

At the time of her sudden death, Zena had been awarded the 2020 Life Sciences Suffrage Science Award and the 2020 Paget-Ewing Award of the Metastasis Research Society. She had also been elected to the Royal Society of Canada Class of 2020. She was at the height of her powers and showed no sign of slowing down.

Women in Science

At ASCB, Zena was active in the Women in Cell Biology (WICB) group. WICB was founded in 1971 by Virginia Walbot, who brought together a group of women scientists who were unhappy with the lack of recognition for women within ASCB. WICB developed into a major force in cell biology, establishing awards to recognize women and disseminating career advice through the ASCB newsletter and conference sessions, a very valuable resource for men and women scientists around the world. Richard Hynes, a colleague and friend of Zena's at MIT recalls: "As a WICB participant 20-some years ago, Zena also maintained a list of women scientists, which I found very useful when setting up meeting programs. This was typical of Zena's proactive and constructive attitude to improving representation at scientific meetings."

As a newly independent woman scientist, I was shocked by some of the stories that Zena, Mina, and Caroline told me about the obstacles they had encountered in their careers. This prompted me to interview twenty-four women from different backgrounds for the *Journal of Cell Science*, which were published in 2004 and 2005. I asked each woman the same four questions, and once the series was complete, I summarised the findings in two reviews that were published in *Nature Reviews Molecular and Cell Biology*.^{3,4} Some of my interviewees were rather coy, and one admitted some years later that her comments about being supported by her husband were simply untrue. However, Zena was the perfect interviewee and spilled the beans with characteristic gusto.

In response to the question "What changes for women in science have you observed during the course of your career?" Zena talked about the sexist and inhospitable environments she encountered while in college and graduate school. The interview is well worth reading in full, but I quote some snippets: "In graduate school the prevailing attitude was that women students were there primarily to keep the male students from becoming too randy... Pressure for sexual favors was frequent and exploited—by both men and women." She went on to say that although by 2004 there were many more women in science, "Sexism has not disappeared, but since officially it is not tolerated, it has gone underground." She also said, "Gender differences in style and personality still work

against women. Forcefulness is often equated with a lack of collegiality. Women tend to feel less entitled, which is equated with weakness, rather than strength.”

When I asked Zena how her research career had affected her personal life and vice versa her reply was very touching. She said that if she had not become a researcher, she would probably have had a family: “I never thought that I was anything but superwoman. But finding a partner, who would accept that, proved less than successful. I found I could control my access to great science, but not to great men!... My career has given me a great scientific family. My students have become the children I never had.” These comments align very well with the feelings of those who passed through her lab—the affection was completely mutual. In addition, Zena’s support was practical—she did not simply accept the awards bestowed on her but also nominated her colleagues and mentees.

When I asked whether being a woman is an inherent advantage/disadvantage for a career in science, Zena replied:

The greatest advantage for women in a scientific career is that they can take chances, since there is nothing to lose. Lacking patrons, there has never been any benefit to women to work on the hottest topic, since they can only be followers....The greatest disadvantage is that it is rare for a woman to have a patron, and many more lack the mentorship needed to navigate the waters of science politics.

Finally, I asked Zena about her remaining career ambitions. She replied that most research lasts less than five years and that it is the next generation that you train that lasts. “I want to train terrific scientists for the future.... Finally, I still hope to attend a conference where several of the sessions or symposia are all women and no one finds that curious.”

Re-reading Zena’s interview now, it is good to see that through her efforts, and those of a small number of other women scientists, mentorship—of men and women—is now accepted as important. And, of course, the gender balance at conferences has improved significantly. However, Zena did not rest on laurels and nor should we—for science to flourish we must continue to strive to make it inclusive of everyone.

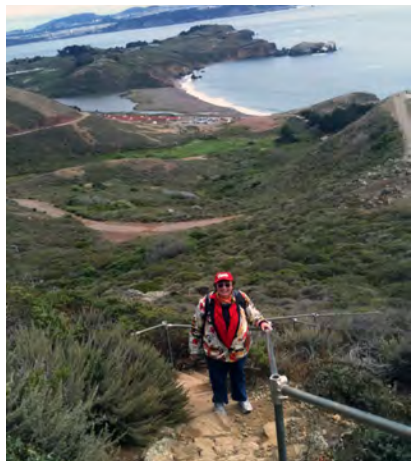
Conclusion

Zena was a creative and innovative scientist and a risk taker. Her extraordinary ability to see the connections between seemingly disparate observations was coupled with her courage and insight in putting forward new hypotheses and nurturing productive collaborations. Her work established the critical role of extracellular remodeling and signaling in development and disease. These studies provide a molecular mechanistic framework for understanding tissue morphogenesis and remodeling.

I remember her as a warm and uncompromising colleague, a stylish dresser with a great appreciation for art and music who loved to travel. Each year Zena would circulate an end of the year round-up of her thoughts and activities—it was a regular reminder of her tireless energy and the importance of friendship. But I leave the last words to Mina and Valerie.

Mina recalls, “Zena always would come to her group meetings with a box of cookies or special Jewish treats that she would cook herself. She had two subscriptions to *Symphony* and would invite one person of her group or her friends.”

Valerie Weaver sums up Zena very well: “Zena had a practical streak and an indomitable will—when she set her mind to doing something she just kept going forward until she achieved her objective. This of course percolated into her personal behavior and made for some memorable moments.” This included an outing to Point Reyes National Seashore that culminated in Valerie and Zena sitting in a pub “where we all had a good laugh and a pint and waited for her friends to join us. Now I feel this epitomizes the Zena I knew and loved.”



The trek to Point Reyes.



Zena and members of her lab.



With her great nephew.

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