Title

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Journal

Molecular Biology of the Cell, 27(21)

ISSN

1059-1524

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Publication Date

2016-11-01

DOI

10.1091/mbc.e16-06-0440

Peer reviewed

Thinking in three dimensions: discovering reciprocal signaling between the extracellular matrix and nucleus and the wisdom of microenvironment and tissue architecture

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ABSTRACT **I thought long and hard whether I could avoid talking about family and personal life, and just share the excitement of being a scientist and how science continues to sustain us all. But so many people, especially younger scientists, want to know—and always ask—How did you do it? A woman from Iran, a Middle Eastern country and essentially Muslim, now considered backwards and misguided if not downright scary, traveling very young and alone to the United States, finishing college and graduate school together with having children, first-year graduate school and second-year post doc—years ago, going against a number of entrenched dogmas, and yet succeeding against many odds and obstacles, and all the while on soft money? Below is my personal narrative answering some of these questions.**

> If there is one generalization that can be made from all tissue and cell culture studies with regards to the differentiated state, it is this: Since most, if not all, functions are changed in culture, qualitatively and/or quantitatively, there is no constitutive gene expression in higher organisms; i.e. the differentiated state is unstable and the (micro)environment regulates gene expression.
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> *Mina J. Bissell*
> *International Review of Cytology, 1981*

That was then….After more than 35 years of probing, I know this to still be true.

But now I feel a huge sense of responsibility and awe: the honor of winning the E. B. Wilson Medal is truly humbling. There are scores of deserving individuals who have spent their lives to discover the secrets of the cell and to enlighten and educate with generosity and kindness. My heartfelt thanks to all who provided moral support and funding, especially in early days of my career, and to those who kept an open mind and considered my laboratory's contributions seriously. To my family, who may have made peace with my constant grant writing and work ethic, and still seem to like me! To my many collaborators, especially to my fellows and students for their hard work, passion, and original ideas, and also for putting up with my excessive mentoring and in the process teaching me many things themselves. This singular honor is possible because of you. For students and fellows who are willing to be mentored still: If you are reading this, I hope you will go back and read many more essays by Wilson medalists since each of us is unique; we choose to advise and mentor in our own ways and this is the way it should be.

For all of you, and also for myself, I will continue to teach that we must be bold and speak without fear, exposing mediocrity, injustice, and greed, and questioning conclusions and mindless authority. I will continue reminding myself and others that scientific results are not written in stone: well-designed experiments and unexpected data that lead to new paradigms, and maybe even beget medals and prizes, sooner or later will have to be reexamined as we become wise enough to admit how much more remains to be discovered. I believe deeply that the pull and the beauty of science is its humbling complexity, which leaves no room for arrogance, and that looking at new data with unbiased eyes and awe is the sacred duty of science and scientists.

WHAT ARE THE QUESTIONS TO ANSWER AND WHY?

I thought long and hard whether I could avoid talking about family and personal life and just share the excitement of being a scientist

DOI:10.1091/mbc.E16-06-0440

Mina J. Bissell is the recipient of the 2016 E. B. Wilson Medal awarded by the American Society for Cell Biology.

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Abbreviations used: AFME, American Friends of the Middle East; ECM, extracellular matrix; STEM, science, technology, engineering, and mathematics; TME, tumor microenvironment; UCSF, University of California–San Francisco.

and how science continues to sustain us all.

But so many people, especially younger scientists, want to know, and always ask, "How did you do it? A woman from Iran, a Middle Eastern country and essentially Muslim, now considered backward and misguided, if not downright scary, traveling very young and alone to the United States, finishing college and graduate school together with having children in your first year of graduate school and during your second postdoc year, going against a number of entrenched dogmas, and yet succeeding against many odds and obstacles, and all the while on soft money?" First, a few facts: Iran used to be called Persia, which confuses many in the United States, who also don't know that Iranians are not Arabs and before the seventh century were Zoroastrians—one of the first monotheistic religions before Christ—and the name has been Iran for thousands of years—it means "the land of Aryans." It was Alexander the Great who brought his army to the capital of Iran in the province of Pars (hence Persia) and burned the Persepolis, the palace of the kings of Iran.

Photo credit: Shoey Sindel (shoey@shoeysindel.com), Berkeley, CA, 2016

Mina Bissell (wearing hat), her husband Monty, and their children and grandchildren.

So, when people ask, "How?!," the answer I give is: "Badly!" I am not being coy when I say that. Almost no one does it perfectly or even well, but the trick is to choose what you love to do and persist! I persisted. But I believe it is precisely because of my background in Iran that I could persist in the era of *Mad Men* in the 1960s and 1970s, even in the face of some amazingly bad behavior from a number of men in charge. My daughter and son are well educated, are "spreading good" in ways other than typical academia, and have happy families.

NOW FOR SOMETHING COMPLETELY DIFFERENT: FAMILY BACKGROUND!

I was born into a highly educated and unusual paternal family in Tehran. My father was the first of 10 children, a lawyer with a PhD from France. Three of my five uncles were judges, prosecutors, and attorneys, and one was a medical professor who spoke seven languages fluently and was also an accomplished poet! Almost 100 years ago, all my aunts were college educated, and one had a PhD from the Sorbonne in French literature. One was a principal of a school, and three were not professionals, but all were socially and politically involved, and two of their daughters were still playing in repertory theater despite being married. I never saw one of them with even a scarf over her head, let alone what is referred to as a "hijab," despite the fact my grandfather was a highly respected ayatollah (not a "mullah") and a descendant of at least five generations of ayatollahs! First sons were supposed to go to divinity school, become well educated in all forms of religion, and follow in their fathers' footsteps. But my father not only had zero intention of joining the clergy, he had no use for religion. Yet he and my grandfather were great friends; they looked upon one another as equals. My grandfather was a scholar, like many in those days, an amazingly educated and thoughtful man. He despised intolerance, and one of his closest friends and advisers was a well-educated Iranian, Mr. Shahabi, who happened to be Jewish. Zoroastrians, Muslims, Jews, Christians, Armenians, and many other religions were well integrated in Iranian society and had been since the times of Cyrus the Great, and the Shahabi family remained very close friends of our family and helped my mother for a year when my father became very ill with typhoid fever, in those days a deadly disease. My grandfather was one of the reasons I ended up in United States rather than England, which was where my father wanted me to go for my education.

COULD THERE BE ONE OR MORE LESSONS HERE FOR ALL OF US, ESPECIALLY OUR POLITICIANS?!

My father believed all religions are sources of much exploitation, wars, and misery. He held either we were reasoning humans, understood our responsibilities to our fellow humans, including our families and ourselves, or we weren't! He also believed that, whereas some clergy all over the world do "good" (as did his father, and now best exemplified by the magnificent current pope), most did more harm than good. He would debate my sister and me across the lunch table and would tell us we could join any profession we wanted as long as we could maintain our integrity. He was a fantastic orator and was known to defend people from all levels of society if they were victims of injustice or victims of the regime in charge at that moment! This meant helping both the Shah's enemies and the Shah's supporters, even if they were on opposite sides! In retrospect, my father was one of my early heroes and the reason I have lived my life the way I have. One of my mentoring points to mothers of sons and young men: if fathers believe in their daughters and have high expectations for both sexes, many of their daughters will succeed in having productive and satisfying lives.

On the maternal side, there was less interest in scholarly pursuits and no interest in politics, but one aunt was a U.S.-educated medical doctor and the chair of immunology at Tehran University, and the other was in public health; one uncle was in government, and the other was a professor of mathematics in the United States. The only member of this extended family who had not finished college was my mother. Her father was assassinated at the age of 27 in the Ghajar dynasty court, and despite being loved by all, including her two daughters, she felt inadequate and wanting in holding her ground intellectually, and at times was deeply unhappy. She found it degrading to be financially dependent on my father but was too proud to ask her mother for money. She drilled my sister and me to pursue

higher education and become independent no matter what. I think, even without reading Virginia Woolf's *A Room of One's Own* (1921) (a book to read by both sexes, even though it was written in the 1920s), she had arrived at the same conclusion: "For a woman to succeed, she must have a room of her own and 500 pounds a year" (Bissell, 1981). Hence, one of my other key mentoring refrains is: there is huge dignity in work and earning your own living.

CHILDHOOD

I had a happy childhood despite one very traumatic experience. I was born with what could be called a photographic memory for written and spoken words, a trait that surprised some grown-ups, who kept testing me for their amusement. This made me uncomfortable and separated me from my many cousins and friends in school. However, I lost quite a bit of this "gift" at age 8, being a bit of a tomboy, climbing trees and engaging in sports and other unseemly behavior for girls in those days. While jumping over a high bar set between two columns with nothing but hard ground underneath (a contrivance of one of my boy cousins who was 15 years old), I fell hard and was bedridden for months but survived and recovered against all odds. The result was essentially complete loss of hearing in my left ear and loss of most of my photographic memory. Despite the injury, I felt better integrated after recovery! Persians have a saying that I often still repeat: Enemy can bring "good," if goodness is willing!

My mother, who I adored, never seemed to be interested in books and politics but understood quite early that I would be able to amount to something when I grew up; she also understood how easily I would get hurt and how easily I cried when there was any kind of perceived injustice or unkindness, and she felt I needed some protection. (I used to be teased mercilessly by my sister, who I looked up to and loved and who is still my best friend, and cousins alike, who would make me cry by making fun of my crying!) I liked nothing more than hiding and reading books, and she tried to help me become more integrated socially, including sending me to a ballet class (although I was a bit too old at 10). I loved it—even if I never could do the split no matter how hard I tried! Nevertheless, it actually allowed me to become more at ease, and made me more open, socially and otherwise. When talking about the significance of form and function in my studies, I often show slides of dancers and quote Yeats's "Among School Children," as I did in a TED Talk: "How can you tell the dancer from the dance?" If you decide to have kids, try harder with them if they are loners, and don't be a loner yourself; there is wisdom in group activities, in scientific collaboration and team sports: we are born to be social creatures, and almost all of us have inherited the capacity for empathy from our ancestors and fellow creatures (de Waal, 2013).

SCHOOL YEARS AND MAKING A FAMILY

I loved school; it was effortless, and I was a top student in my primary and secondary schools for 12 years. In the last year, in the countrywide exams, I became the top student in the country. I was not particularly "special"—everyone is special—but I was lucky in the (micro)environment of my childhood. There are scores of children all over the world who could and will do many things better than I did in all areas if they have the opportunity. I received a medal and award from the Shah of Iran (there are a couple of pictures of me with the Shah, with me getting the medal and a book), and my fellowship for going abroad was not from a college in the United States but was earned by taking an exam for a special award given to five students in science, technology, engineering, and mathematics (STEM) fields in that year in Iran. My father felt the United States was too young a country to educate women, but I wanted to go to the United States, and as I said earlier, my grandfather—the Ayatollah Haeri Mazandarani—explained to my father, "She has earned it, she is good, and she deserves to go wherever she wants!" My father consented. I applied to a few universities in the United States by sending applications to the American Friends of the Middle East (AFME)—a branch of the American government—where we had to send my application for a U.S. visa. When the head of AFME saw my application, he called my father (who spoke reasonable English and, of course, French) and asked for me to come see him. He suggested I should go to Bryn Mawr, one of the Seven Sister colleges in the United States (analogous to the seven Ivy League schools, which then accepted only male students), since to his mind—and later to my mind—Bryn Mawr was and remains one of the best colleges in the United States. I knew nothing about the place, and luckily I was never asked to take the college entrance exam! At this point, my English was quite elementary, but they let me in!

After a short stay in New York City to take a perfunctory English course, arranged with the help of my uncle, the math professor, I spent an enchanting two years at Bryn Mawr. Math and chemistry were easy for me, due to my high school classes. But I did not enjoy English and Arabic at all in high school, partly because, apparently along with the hearing loss in my left ear, I had also damaged the "nomic gland" behind the left frontal lobe and had difficulty even then remembering names, places, or anything to do with the left side of the brain that I had to memorize. But I liked literature in Iran, and fell in love with English literature, because I love well-written words. I had an amazing and brilliant freshman English professor, Ann Berthoff. To this day, she is my favorite teacher and at age 93 is one of my most beloved friends. I debated between majoring in English literature or chemistry, and the latter won out, mainly for practical reasons. I will always remain grateful to the head of the AFME, the gentleman who cared enough and took the time to meet up with my father and me, and showed me the way. I never learned his name, since he died shortly after I had left for the United States, and I also found out much later from American newspapers that the AFME was a front for the CIA and behind a coup that toppled Mossadegh, then the most popular, beloved, and democratically elected prime minister Iran had ever had. For the young: politics matter in a democratic society. Get involved if you want to keep democracy alive—please vote! If you want to understand the times we live in now, please read and understand the history of different regions more deeply, particularly that of the Middle East.

In my sophomore year in college, in short order, I met a graduate student from Harvard University who was Iranian and was getting a PhD in political science and economics; he proposed and I said *yes*. I declared chemistry as my major, moved as a junior to Radcliffe/Harvard University, won the Medal from the American Institute of Chemists as a junior, married in my senior year, and ended up being a vanishing "Cliffie," since I received my bachelor's degree in chemistry as one of the inaugural members of the "integrated" Harvard class along with people like David Botstein. The degree was written in English. I had hoped for a classy Latin!

My husband was still a graduate student, so I opted to stay in the area to get a PhD in bacterial genetics from Harvard Medical School. Do not ask why—I am not sure I know myself! No sooner had I started graduate school than I got pregnant. This was eons ago, and at that time, there were 200 men and three women in the Harvard Medical School class that year, and the entire place had *one* woman faculty member. In the entering class in bacteriology, there were three men and three women (the latter all Cliffies!). Despite this early balance, after the first year, all three men left—they found HMS to be too ingrown, too arrogant toward "outsiders," and too wanting in

humanity. The women finished. I had chosen to do my thesis with a progressive Italian professor, Luigi Gorini, or rather, he chose me after I answered a difficult physics question in a high-resolution microscopy class! He was already almost 70 years old but very active and a real wiz in bacterial genetics. But he still felt I should quit, because I was pregnant—"What would your mother say?" My mother (and father) called quickly from Iran to make sure I would not be quitting—so much for the Iranian parents who more than 50 years ago were more understanding than most Western ones. I discussed some of the events surrounding my thesis in a "Turning Point" essay in NCB (Bissell, 2011).

When my daughter was two-and-a-half years old, I left my husband—a nice man, but somewhat incompatible with me as a life partner. It was a hard decision with a baby, but I felt I could raise her better by myself. I met my future husband, Monty Bissell, arguing over a centrifuge—he was a medical student who was doing a year of research in the bacteriology department and learning to play the cello, not necessarily in that order! We married a year later and will be celebrating our 50th anniversary this coming July. I think he liked me because I was the size of his cello and talked back! And I liked him because he was an English major in college, wrote beautifully written phrases, and towered over me! Deep down, he was also a poet and romantic. I am not even speaking of the fact that we could talk science—more so now than early on; we had some aspect of our science in common but had entirely different styles in running labs. Monty became the head of the Liver Center at University of California–San Francisco (UCSF) and later the chief of the GI Department and was admired not only for his science but also because he was successful in hiring terrific faculty. I was so proud that quite a few were outstanding women and that almost all his fellows loved him as a mentor.

Of course it is not easy to live with a guy who is a perfectionist in everything he does (he even has perfect pitch!), but making any marriage work is like science; it takes patience and perseverance, originality and empathy, and the willingness to talk frankly with each other. Do give it a shot and don't expect all will be rosy. But when it lasts by choice, it can be worth the effort, sometimes it even may feel like drinking a good aged wine. But get out fast if the other side is not capable or worth hard work and often makes your life miserable. Alone does not mean lonely, and it often is the preferred course—another reason for having your own career.

ADVENTURES IN VIROLOGY AND CELL AND CANCER BIOLOGY: DISCOVERING THAT HALF THE SECRET OF THE CELL IS OUTSIDE THE CELL!

> Based on the existing literature, a model is presented that postulates a "Dynamic Reciprocity" between the extracellular matrix (ECM) on the one hand and the cytoskeleton and the nuclear matrix on the other hand. The ECM is postulated to exert physical and chemical influences on the geometry and the biochemistry of the cell via transmembrane receptors so as to alter the pattern of gene expression by changing the association of the cytoskeleton with the mRNA and the interaction of the chromatin with the nuclear matrix. This, in turn, would affect the ECM, which would affect the cell, which …
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> *Bissell et al.,*
> *Journal of Theoretical Biology, 1982*

When I wrote the above article, even my close colleagues who were my friends asked what I was smoking! I had no intention of just postulating; my students and fellows (and often many undergraduates) and I worked long and hard for more than three decades, essentially on one organ, the mammary gland, to unravel how the extracellular matrix (ECM) may talk to the nucleus and vice versa. The majority of the critics have come around, and the number of papers in the area of tumor microenvironment (TME) has increased logarithmically. The model I proposed—not the name, but the concept of ECM regulating gene expression at many levels and the roles of basement membrane and tissue architecture—is here to stay. Many are working in these areas all over the world. Dozens of our own papers have shown the significance and mechanism of interaction between the ECM and cytoskeleton and the nuclear matrix and chromatin. We showed in the early 1990s that the promoters of milk protein genes contained ECM-response elements and that loss of interaction of laminin 111 with integrins leads to loss of milk function and induction of apoptosis. In the presence of laminin-rich gels (a 20% pure laminin 111 and rat-tail collagen gel can substitute for Matrigel) and certain oncogenic pathways, inhibitors can "revert" the malignant cells to a normal phenotype, despite the tumorigenic genome. Together with a number of outstanding collaborators, including Zena Werb (UCSF), Ole William Petersen (Copenhagen), Cathy Park (UCSF), and more recently David Lyden (Weill Cornell Medical College), we have explored many aspects of mammary gland morphogenesis, function, and homeostasis and breast cancer and exosomes, and have dared challenge other paradigms.

My apologies for short-changing the science I so love. But I have used up my print space here. There are, however, more than 30 interviews and write-ups listed on my website (www2.lbl.gov/LBL-Programs/lifesciences/BissellLab/main.html), a few of which I note in the reference list (Vaughan, 2002; Abbott, 2003; Flintoft, 2003; Friedrich, 2003; Graebner, 2003; Bissell and Devine, 2005; Bonetta, 2005; Novak, 2005; Pon, 2005; Cohen, 2006; Klein, 2006; Mason, 2006; Schuldt, 2006; Arry, 2007; Blow, 2007; Mervis, 2007; Platoni, 2007, 2008; Shekhar, 2007; Wong, 2007; Beishon, 2008; Marx, 2008; Fleischman, 2009; Kolata, 2009; Lako and Daher, 2009; Short, 2009; Yarris, 2009; Hayden, 2010; Zagorski, 2010; Claiborn, 2011; Bissell, 2015). There are also scores of write-ups on our publications and press releases in the Lawrence Berkeley National Laboratory archives (Today at Berkeley Lab, https://today.lbl.gov), and then there are more than 400 publications from our laboratory (also on the website).

I have been asked a few times: "Do you have any regrets?"

But of course! Even though I look at the bright side more often, and I am blessed with much, it takes extreme indifference and arrogance not to have regrets. Indeed, only idiots have no regrets! So I would like to leave you with a sentiment that has resonated with me deeply. It is in a tiny, tiny book, may be even still on the Web. It is the text of a convocation address to a graduating class at Syracuse University given by George Saunders. It brought tears to my eyes, and I envied him for putting it so well. I quote: "Here's something I know to be true, although it's a little corny, and I don't know what to do with it: What I regret most in my life are failures of kindness" (Saunders, 2014).

ACKNOWLEDGMENTS

I am indebted to the National Science Foundation, the granting agency that funded my first successful grant in 1980, followed by the Department of Energy, the first Innovator Award from the Department of Defense (after I stepped down as the Director of all Life Sciences at LBNL), and later, during another crisis, from the Breast Cancer Research Foundation, New York. Thank you! I will always be indebted to Marvin Frazier of the Office of Biological and Environmental Research of the Department of Energy Office of

Science, who not only was one of a very few scientists in granting agencies who was open to unorthodox ideas, but was modest, intuitive, and kind—in short a hero to many! He was willing to take chances. He also understood concepts and the significance of what we were trying to do. He overruled a number of scientists in his division and allowed our grant to be reviewed in the Post Genome Committee. The grant received the top score and was funded until the program was discontinued. It took 20 years to receive similar scores and acceptance as well as a Merit Award from the NCI. The Merit Award never materialized, because the program was abolished altogether at the NCI, even those few of us who had already been granted the Merit Award by the council were denied.

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